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Bertrand Gakière, Jingfang Hao, Linda de Bont, Pierre Pétriacq, Adriano Nunes-Nesi, et al.. NAD+ Biosynthesis and Signaling in Plants. Critical Reviews in Plant Sciences, 2018, 37 (4), pp.259-307. 10.1080/07352689.2018.1505591 . hal-02623583

HAL Id: hal-02623583
https://hal.inrae.fr/hal-02623583

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Critical Reviews in Plant Sciences

ISSN: 0735-2689 (Print) 1549-7836 (Online) Journal homepage: https://www.tandfonline.com/loi/bpts20

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To cite this article: Bertrand Gakière, Jingfang Hao, Linda de Bont, Pierre Pétriacq, Adriano Nunes-Nesi & Alisdair R. Fernie (2018) NAD$^+$ Biosynthesis and Signaling in Plants, Critical Reviews in Plant Sciences, 37:4, 259-307, DOI: 10.1080/07352689.2018.1505591

To link to this article: https://doi.org/10.1080/07352689.2018.1505591

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Published online: 05 Nov 2018.

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CRITICAL REVIEWS IN PLANT SCIENCES
2018, VOL. 37, NO. 4, 259–307
https://doi.org/10.1080/07352689.2018.1505591

NAD$^+$ Biosynthesis and Signaling in Plants

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ABSTRACT

Many metabolic processes that occur in living cells involve oxidation-reduction (redox) chemistry underpinned by compounds, such as glutathione, ascorbate, and/or pyridine nucleotides. Among these redox carriers, nicotinamide adenine dinucleotide (NAD$^+$) represents one of the cornerstones of cellular oxidation and is essential for plant growth and development. In addition to its redox role, compelling evidence of a role for NAD$^+$ as a signal molecule in plants is emerging. In non-plant systems, NAD$^+$ biosynthesis can be the product of two independent pathways—the *de novo* and the salvage pathway. Despite the fact that homologous plant genes exist for the composite enzymes of most, if not all, of these pathways research into plant NAD$^+$ biosynthesis *per se* has lagged behind that of microbial and mammalian systems. Indeed, much plant work has been focused on additional roles of the composite enzymes in processes, such as DNA repair or post-translational modification of proteins. That said, in recent years, a number of studies, mostly in *Arabidopsis*, have been carried out in order to fill this knowledge gap. Therefore, in this review, we intend to present a synthesis of such molecular genetic studies as well as biochemical analyses that have begun to elucidate the regulatory hierarchies both of NAD$^+$ biosynthesis and the parallel activities of the enzymes that are involved in these pathways.

KEYWORDS
Cellular signaling; defense response; DNA repair; growth; nicotinamide adenine dinucleotide; post-translational modification of proteins; redox; senescence

All living cells use nicotinamide adenine dinucleotide (NAD$^+$) as an energy transfer cofactor. NAD is a pyridine nucleotide involved in the transport of electrons within oxidation-reduction reactions (redox) as well as being a highly important component of cellular signaling (Hunt *et al.*, 2004; Noctor *et al.*, 2006; Pétriacq *et al.*, 2013). The pyridine nucleotides are composed of two nucleotides connected by a diphosphate group. One of the nucleotides contains an adenine base and the other a nicotinamide molecule (Figure 1). NAD exists in the following two forms: an oxidized and reduced form abbreviated as NAD$^+$ and NADH, respectively (Pollak, 2007a). NAD$^+$ also exists as a phosphorylated intermediate with the phosphate group attached at the 2′hydroxyl ribose of the adenine moiety. Despite their structural similarity, these molecules have very distinct biological roles with NADP$^+$ being more involved in biosynthetic processes, such as photosynthesis and fatty acid synthesis, where it acts as a reducing agent (Kramer *et al.*, 2004; Rawsthorne, 2002), whereas NAD is most often involved in catabolic processes as an oxidant (Geigenberger, 2003).

NAD is a 664-Dalton (Da) molecule discovered in yeast over a century ago (Harden and Young, 1906), and initially named "cozymase" for its stimulation of alcoholic fermentation. The subsequent elucidation of the structure of the dinucleotide "cozymase" by von Euler, earned the author the Nobel Prize in Chemistry in 1929 (von Euler, 1930). Subsequently, Warburg won the Nobel Prize in Physiology or Medicine for his work on "respiratory enzyme" (Warburg and Christian, 1936), and Kornberg, who was a Nobel Laureate in Physiology or Medicine in 1959 for isolating DNA polymerase I, was the first to discover a step

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Figure 1. The structure of NAD^+.

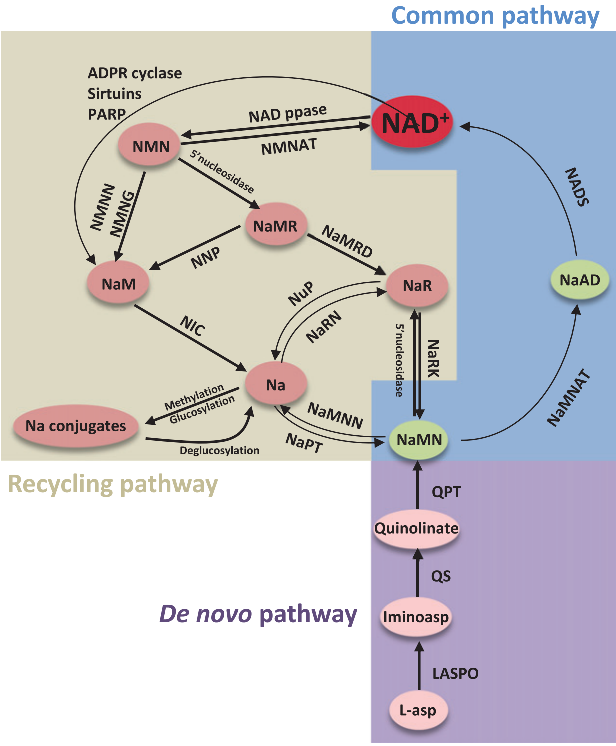

Figure 2. NAD biosynthetic pathways in plants. L-asp: L-aspartate; LASPO: L-aspartate oxidase; Na: nicotinate; NaAD: nicotinate adenine dinucleotide; NADS: NAD synthetase; NaMNAT: nicotinate mononucleotide adenylyltransferase; NaM; nicotinamide NaMN: nicotinate mononucleotide; NaMNN: nicotinate mononucleotide nucleosidase; NaMR: nicotinamide riboside; NaMRD: NAMR deaminase; NaPT: nicotinate phosphoribosyltransferase; NaR: nicotinate riboside; NaRN: NAR nucleoside; NaRK: NAR kinase; NMN: nicotinamide mononucleotide; NIC: nicotinamidase; NMNG: NMN glycohydrolase; NMNN:NMN nucleosidase NMNAT: nicotinamide mononucleotide adenylyltransferase; NNP: nicotinate nucleoside pyrophosphatase; NUP: nucleoside phosphorylase; PARP: poly(ADP-ribose)polymerase; QPT: quinolinate phosphoribosyltransferase; QS: quinolinate synthase.

in the biosynthesis of NAD (Kornberg, 1948). In 1949, Friedkin and Lehninger (1949) provided links between the NADH bound oxidative phosphorylation and the tricarboxylic acid cycle, prior to Preiss and Handler (1958a, 1958b) discovering three enzymes and two stable intermediaries in the synthesis of NAD from nicotinic acid. More recent discoveries suggest other important roles different from those related to its redox properties, including the involvement in cellular signaling. These functions include cleavage of the molecule, synthesis of cyclic ADP-ribose, deacetylation of proteins, and formation of ADP-ribose polymers, mechanisms which are all important in DNA repair (Hunt *et al.*, 2004; Vanderauwera *et al.*, 2007; Wang and Pichersky, 2007). In the following review, we will detail the pathways underlying the biosynthesis and metabolism of NAD^+ and describe the critical role of NAD in redox biology before discussing the more recently established roles of the constituent enzymes. Finally, we describe the phenotypes of plants deficient in the expression of enzymes of NAD metabolism and attempt to unravel the metabolic and developmental hierarchies which they control.

I. NAD^+ biosynthesis and metabolism *per se*

Considerable advances in the understanding of NAD^+ biosynthesis in plants were made by research teams involved in elucidating the synthesis of nicotine (*Frost et al.*, 1967), ricinine (Waller *et al.*, 1966; Mann and Byerrum, 1974), and trigonelline (Wagner *et al.*, 1986a), respectively. Following these early studies, investigations using radiolabeled carbon provided a wealth of information concerning the biosynthesis of NAD^+ and its derivatives (Katahira and Ashihara, 2009; Ashihara *et al.*, 2010; Ashihara and Deng, 2012) ultimately leading to our current understanding that NAD^+ biosynthesis is actually achieved by the combined function of both *de novo* and salvage pathways. In this section, we initially describe the pathways independently before detailing how they interact and cataloging our understanding of the enzymes involved in NAD^+ metabolism.

A. The *de novo* pathway of NAD^+ biosynthesis

In the *de novo* pathway, the amino acid aspartate serves as the precursor for NAD^+ biosynthesis (Katoh *et al.*, 2006; Takahashi et al., 2006; Schippers *et al.*, 2008). Following the conversion of aspartate to quinolate by aspartase oxidase and subsequent transformation to dihydroxyacetone phosphate by quinolate synthase, quinolate is converted to nicotinate mononucleotide (NaMN) by quinolate phosphoribosyltransferase. NaMN is thereafter transformed via

adenlyation to nicotinate adenine dinucleotide (NaAD), followed by amidation of NaAD to NAD^+, as the fifth and final step in *de novo* NAD^+ biosynthesis (Figure 2).

1. L-aspartate oxidase

The enzyme L-aspartate oxidase (LASPO, EC 1.4.3.16) is a Flavin Adenine dinucleotide (FAD)-dependent flavoprotein belonging to the oxidoreductose class of enzymes, which catalyzes the interconversion of L-aspartate to iminoaspartate. In bacteria, L-aspartate oxidase, sometimes still called synthase quinolinate B, is able to use either oxygen or fumarate as an electron acceptor according to the conditions of aerobic or anaerobic in which they are found (Nasu *et al.*, 1982). In *Arabidopsis thaliana,* L-aspartate oxidase is encoded by a single gene (At5g14760; Katoh *et al.,* 2006; Noctor *et al.*, 2006). Both plant and bacterial proteins are comprised of similar functional domains, namely an N-terminal L-aspartate oxidase domain and a C-terminal succinate dehydrogenase domain (Mattevi *et al.*, 1999; Noctor *et al.*, 2006). However, in plants, the enzyme has been sparingly studied. It has been documented that the purified enzyme from cotton contains a cofactor with an apparent molecular weight similar to that of FAD (Hosokawa *et al.*, 1983). Crystallization and site-directed mutagenesis studies of the bacterial enzyme revealed the amino acids involved in the binding of aspartate, FAD, and fumarate (Mattevi *et al.*, 1999; Tedeschi *et al.*, 2001; Bossi *et al.*, 2002; Rizzi and Schindelin, 2002). The very high sequence homology of these residues in plant proteins suggests that they likely exhibit highly similar catalytic properties.

When the FAD cofactor binds to L-aspartate oxidase, a change in conformation of the enzyme is observed. This is anticipated to protect the unstable reaction product, iminoaspartate, from degradation (Rizzi and Schindelin, 2002). Indeed, the half-life time of the iminoaspartate in solution is estimated at 144 s at pH 8 and 37 °C (Nasu *et al.*, 1982). However, iminoaspartate would itself inhibit the reaction catalyzed by L-aspartate oxidase, and this inhibition is suspended by addition of quinolinate synthase in the reaction medium (Mortarino *et al.*, 1996). In addition, it has long been suggested that these two enzymes could form a complex for transferring the unstable iminoaspartate from the first to the second enzyme. Indeed, on attempting to purify the L-aspartate oxidase from bacteria, Griffith and colleagues in 1975 obtained a co-purification of L-aspartate oxidase and quinolinate synthase. However, no further demonstrations have been presented, and thus the hypothesis of an L-aspartate oxidase and quinolinate synthase complex remains relatively weak (Sakuraba *et al.*, 2005). Some organisms are capable of oxidizing aspartate using enzymes other than L-aspartate oxidase. For example, the archaeon *Thermotoga maritima*, whose NADB gene encodes an aspartate dehydrogenase (EC 1.4.1.-), the primary protein sequence of which differs significantly from that of L-aspartate oxidase (Yang *et al.*, 2003). Mammals have a D–aspartate oxidase (EC 1.4.3.1), which synthesizes iminoaspartate and it has been demonstrated *in vitro* that this enzyme could replace the L-aspartate oxidase in the quinolinate bacterial synthase complex (Nasu *et al.*, 1982). The physiological role of the mammalian enzyme would not be to produce NAD^+, but rather to regulate the level of D-aspartate, a highly abundant compound in neuroendocrine tissue, by converting it into iminoaspartate, which decomposes spontaneously into oxaloacetate (Wang *et al.*, 2000; Wolosker *et al.*, 2000). Recently, an L-aspartate oxidase was characterized in *A. thaliana*, which displayed the fine-tuning regulation in NAD metabolism (Hao *et al.*, 2018).

In silico analysis of plant L-aspartate oxidase sequences, revealed the existence of a conserved N-terminal transit peptide suggesting a chloroplast localization of enzyme (Noctor *et al.*, 2006), which was experimentally confirmed by green fluorescence protein (GFP) fusions in *A. thaliana* (Katoh *et al.*, 2006). The gene encoding L-aspartate oxidase is expressed throughout the plant with the exception of epidermal cells and highly expressed in guard cells in young buds (9–11 stages) and stamen (*Arabidopsis* database VET Browser, Schmid *et al.*, 2005). A strong transcriptional regulation of this enzymatic step has also been documented under stress conditions (Genevestigator database; Hruz *et al.*, 2008). Additionally, induction of the gene encoding L-aspartate oxidase was observed in response to biotic stress caused by *Pseudomonas syringae* PV. *tomato* (Pétriacq *et al.*, 2012, 2013).

In bacteria, NADH acts as a competitive inhibitor of the FAD-binding site of the L-aspartate oxidase (Tedeschi *et al.*, 1999), as well as a transcriptional regulator (Penfound and Fraser, 1999). However, as yet transcriptional control of NAD^+ biosynthesis by NADH itself has not been reported in plants. That said, NAD^+ regulates the activity of L-aspartate oxidase with 50% inhibition of the cottonseed enzyme by 1 mM NAD^+ (Nasu *et al.*, 1982; Hosokawa *et al.*, 1983).

2. Quinolinate synthase

In bacteria, quinolinate synthase (QS, EC 2.5.1.72) is a copper-containing iron-sulfur center [Fe-S] enzyme that is the product of the nadA gene (Cicchillo *et al.*, 2005; Ollagnier-de Choudens *et al.*, 2005; Rousset *et al.*, 2008). In *A. thaliana,* cysteine desulfurylase is encoded by a single gene (At5g50210, Katoh *et al.*, 2006) and this is seemingly a common feature of plants (Noctor *et al.*, 2006). The three-dimensional structure of the *Pyrococcus* enzyme was determined, revealing a triangular architecture in which the conserved amino acid residues constitute a "three-layer sandwich triple repetitions" (Sakuraba *et al.*, 2005; Soriano *et al.*, 2013). The sequence alignment of plant and bacterial proteins indicates the presence of highly conserved amino acid residues including conservation of this structure, however, in plants is complemented with a C-terminal extension (Noctor *et al.*, 2006).

In *A. thaliana*, QS is localized in plastids (Katoh *et al.* 2006) and encoded by a single gene (At5g50210). A T-DNA insertion mutation into QS gene has been reported to be lethal in the homozygous state (Katoh *et al.*, 2006). However, another mutation in the same gene but affecting the cysteine desulfurylase domain does not alter the QS activity and is not lethal (Schippers *et al.*, 2008). That said, plants show an accelerated aging suggesting that the fall in cysteine desulfurylase activity affects the catalytic competence of the enzyme. Indeed, the authors demonstrated that this lesion in the *de novo* biosynthesis pathway could be compensated for by an increase in enzyme activities of one of the NAD recycling pathways resulting in a slight increase in cellular NAD levels (Schippers *et al.*, 2008).

3. Quinolinate phosphoribosyltransferase

Quinolinate phosphoribosyltransferase (QPT, EC 2.4.2.19) catalyzes the conversion of quinolinate to NaMN (Figure 2), by the irreversible transfer of a phosphoribosyl phosphonate (PRPP) moiety, which is derived from ribose-5-phosphate an intermediate of the pentose phosphate pathway. This metabolic pathway shares glucose-6-phosphate as a substrate with glycolysis and, in addition to ribulose-5-phosphate, generates NADPH. The reaction catalyzed by QPT requires the presence of a bivalent Mg^{2+} ion and releases carbon dioxide (CO_2) and inorganic pyrophosphate (PPi). Characterization of the purified castor albumen enzyme allowed determination of K_m values for quinolinate and for phosphoribosyl pyrophosphate of 12 and 45 μM respectively (Mann and Byerrum, 1974).

This enzymatic step is common in the *de novo* biosynthesis pathway of animals, fungi, plants, and prokaryotes (Foster *et al.*, 1985; Bhatia and Calvo, 1996). A unique gene homologous to the *nadC* bacterial gene encodes QPT in plants (*At2g01350* in *A. thaliana*, Noctor *et al.*, 2006), with the exception of tobacco, where a second isoform is additionally involved in nicotine production (Ryan *et al.*, 2012). Interruption of this gene by insertion of a T-DNA is lethal in the homozygous state in *A. thaliana* (Katoh *et al.*, 2006). Bioinformatics approaches predict that the enzyme resides in mitochondria and the cytosol in both *A. thaliana* and tobacco; however, *in vivo* studies have shown the presence of the protein in the chloroplast (Sinclair *et al.*, 2000, Katoh *et al.*, 2006). An inducible NAD enrichment system by overproducing *Escherichia coli* QPT in *A. thaliana* has demonstrated the involvement of NAD in specific mechanisms of defense which govern plant-pathogen interactions (Pétriacq *et al.*, 2013, 2016a, 2016b). Furthermore, deregulation of NAD synthesis by altering endogenous QPT production underlines the critical role of NAD for the coordination of C and N metabolisms under photorespiratory conditions (Pétriacq, 2011).

B. The common NAD biosynthesis pathway shared by both the *de novo* and salvage routes

The conversion of NaMN to NAD^+ is achieved in two steps; the adenylation of NaMN to yield nicotinate adenine dinucleotide (NaAD), followed by an amidation of NaAD to give NAD^+ (Ashihara *et al.*, 2005; Noctor *et al.*, 2006). The first step is catalyzed by the nicotinate mononucleotide/nicotinamide mononucleotide adenyltransferase (NaMN/NMNAT), and the second by NAD^+ synthetase (NADS; Figure 2). These enzymatic steps are common to both to the *de novo* biosynthesis of NAD^+ and one of the recycling routes of NAD^+ production.

1. Nicotinate/nicotinamide mononucleotide adenyltransferase (NaMN/NMNAT)

Mononucleotide nicotinate nicotinamide mononucleotide adenyltransferase (NaMN/NMNAT; EC 2.7.7.18) is the product of the *nadD* gene in bacteria. The reaction catalyzed by this enzyme requires ATP, Mg^{2+} ion and involves nucleophilic attack of the 5′ phosphate groups of NaMN and ATP. In *E. coli*, yeast and humans, this enzyme is able to use both NaMN and nicotinamide mononucleotide (NMN) as substrate albeit with a thousand times higher affinity for NaMN

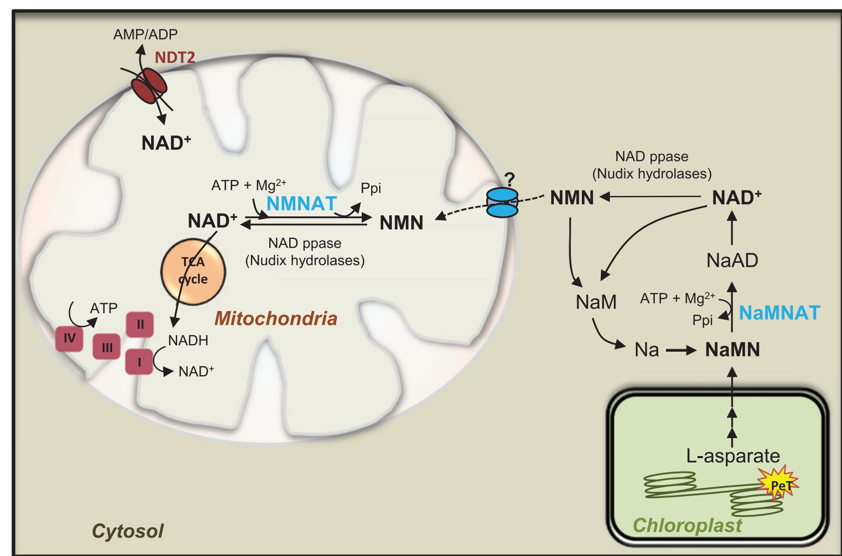

Figure 3. NAD biosynthesis in mitochondria via NMNAT and in cytosol via NaMNAT. ADP: adenine diphosphate; AMP: adenine monophosphate; ATP: adenine triphosphate; Na: nicotinate; NaAD: nicotinic acid adenine dinucleotide; NAD ppase: NAD pyrophosphatase; NaM: nicotinamide; NaMN: nicotinic acid mononucleotide; NDT2: NAD^+ carrier; NMN: nicotinamide mononucleotide; NaMNAT: nicotinate mononucleotide adenylyltransferase; NMNAT: nicotinamide mononucleotide adenylyltransferase; PeT: photosynthetic electron transport chains; Ppi: pyrophosphate.

(Dahmen *et al.*, 1967; Magni *et al.*, 2004; Lau *et al.*, 2010). In plants, NMNAT activity was measured in tobacco roots and Jerusalem artichoke tubers. The enzyme purified from tobacco displayed a much lower specific activity in the presence of NMN compared to that measured with NaMN as substrate (0.67 nmol.min^{-1}.mg^{-1} for NMN against 3.58 nmol.min^{-1}.mg^{-1} for NaMN; Wagner *et al.*, 1986a). More recently, NMNAT activity was detected in mitochondria of Jerusalem artichoke tubers (Di Martino and Pallotta, 2011). In this case, the activity preferentially used NMN (3.8 nmol.min^{-1}.mg^{-1} for NMN against 0.9 nmol. min^{-1}.mg^{-1} for NaMN; Di Martino and Pallotta, 2011). This NMNAT activity which is specific to the mitochondrial fraction, likely plays an important role in the metabolism of mitochondrial NAD in plants, most probably being involved in the recycling of NMN produced by the catabolism of NAD^+ in this compartment (Figure 3).

In contrast to plants, human mitochondria cannot import NAD and mitochondrial NAD derives directly from NMM transport and NMNAT3 activity (Palmieri *et al.*, 2009; Nikiforov *et al.*, 2011; Van Linden *et al.*, 2015). Recently, an additional chaperone function, as shown via protein-protein interaction studies (Zhai *et al.*, 2009), has been reported for Drosophila NMNAT that includes a potential role in the neuron repair process. This new function relies on alternative splicing of the unique Drosophila N(A)MNAT gene that occurs under stress conditions.

In humans, the three different isoforms of NaMNAT are localized in the nucleus, cytosol, and mitochondria (Berger *et al.*, 2005). The NaMNAT-1 isoform is localized in the nucleus and allows recycling of NMN produced by the catabolism of NAD^+ (Zhang *et al.*, 2012). In *A. thaliana*, only a single gene (*At5g55810*) which encodes NaMNAT has been identified and its product uses NaMN as a substrate (Hashida *et al.*, 2007). If plants encode a single NaMNAT gene, this does not exclude the existence of splice variants that could be responsible for the cytosolic NAMNAT activity and the mitochondrial NMNAT activity detected in *Helianthus tuberosus*. Strong NaMNAT expression was detected in the male gametophyte, and it appears to be involved in microspore development and pollen tube growth, suggesting that NaMNAT-mediated NAD biosynthesis is activated during pollen maturation (Hashida *et al.*, 2007, 2013a). NaMNAT is also essential for seed germination (Hashida *et al.*, 2009, 2013a). Furthermore, very high expression of NaMNAT was also observed in *Arabidopsis* differentiated guard cells (Hashida *et al*, 2010), where it contributes to ABA-induced stomatal closure (Hashida *et al.*, 2010).

2. NAD synthase

Subsequent to the reaction catalyzed by NaMN/NMNAT, NAD^+ synthetase (NADS, EC 6.3.5.1) transforms the NaAD into NAD^+ converting the acid functional group of the nicotinate moiety of NaAD

into an amide. Mg^{2+} is essential in this process because it enables the phosphate group of ATP, stabilizes the leaving group pyrophosphate (PPi), and facilitates the attack of ammonia (NH_3; Ozment *et al.*, 1999). *Mycobacterium tuberculosis* and *Helicobacter pylori* are assumed to lack NAD^+ recycling pathways; therefore, both NADS and NaMNAT have been prime targets in the search for new antibacterial agents (Warren *et al.*, 1983; Boshoff *et al.*, 2008). In *Arabidopsis*, NADS, which is the product of the *nadE* gene in bacteria and encoded by the *At1g55090* gene, lacks a target peptide, suggesting that it is cytosolically localized (Hunt *et al.*, 2004; Katoh *et al.*, 2006; Noctor *et al.*, 2006). According to the species, NADS either uses NH_3 and/or an amino acid amine donor as substrate. In *E. coli*, NADS accepts only NH_3 as substrate ($K_m = 65$ μM for NH_4Cl; Spencer and Preiss, 1967), whereas yeast and rat enzymes accept both NH_4Cl ($K_m = 140$ mM) and glutamine ($K_m = 35$ mM) although glutamine (Gln) would clearly be the preferential physiological substrate (Preiss and Handler 1958b). The plant enzyme preferentially accepts Gln and can use asparagine (Asn) but not NH_3 (Wagner *et al.*, 1986a). The appearance of the protein's ability to utilize Gln as an amine donor likely results from the acquisition of an additional nitrilase type domain in the C-terminus of the protein (De Ingeniis *et al.*, 2012) that was previously only found in eukaryotes and cyanobacteria (Gerdes *et al.*, 2006).

In *Arabidopsis*, NADS overexpression increases the amounts of some NAD biosynthesis intermediates but not the contents of NAD(H) and NADP(H), suggesting that NAD metabolism is increased. The imbalance between NAD generation and consumption in NAD-overexpressing plants results in the oxidation of NAD pools. As the consequence, the TCA cycle flux is enhanced and oxidative stress resulted in the early wilting of the flowers and the shortening of plant longevity (Hashida *et al.*, 2016).

C. Interconversion of NAD(H) and NADP(H)

1. NAD(H) kinase

NAD(H) is converted to NADP(H) by an ATP-dependent phosphorylation reaction catalyzed by NAD kinase (NADK, EC 2.7.1.23; Hunt *et al.*, 2004). While a single gene encodes the NADK in human and bacteria, three genes have been identified in *Arabidopsis* (Hunt *et al.*, 2004; Kawai and Murata, 2008; Waller *et al.*, 2010), four in monocotyledons, and up to six in *Brassica rapa* (Li *et al.*, 2014). In many species, NADK isoforms differ according to their calmodulin dependence—or lack of (CaM, Cormier *et al.*, 1981; Allan and Trewavas 1985; Gallais *et al.*, 2000). For example, spinach has a CAM-dependent cytosolic isoform but an independent chloroplast isoform. Similarly, two CaM-dependent NADK have been described in oats but a third isoform is independent of CaM (Gallais *et al.*, 2000). Finally, in maize, an NAD^+ activated CaM kinase is localized at of the outer mitochondrial membrane allowing a rapid response to changes in cytosolic calcium levels (Dieter and Marmé, 1984). In *A. thaliana*, NADK1 (encoded by *At3g21070*) and NADK3 (encoded by *At1g78590*) are located in the cytosol, whereas NADK2 (encoded by *At1g21640*) is targeted to the chloroplasts (Turner *et al.*, 2004; Berrin *et al.*, 2005; Chai *et al.*, 2005, 2006). If NADK1 and NADK2 use NAD^+ as a preferred substrate, NADK3 displays a very strong preference for NADH than NAD^+ (Turner *et al.*, 2004, 2005). One of the functions of NADK2, when activated by CaM under the effect of light, is to increase the NADPH/NADP ratio, which results in a change in C and N metabolisms (Heineke *et al.*, 1991, Takahashi *et al.*, 2009). Recently, the chloroplast-NADK2 was reported to be a positive regulator in guard cell ABA signaling (Sun *et al.*, 2017). In plants, mitochondrial NADPH and NADP come from transport into the mitochondria (Bykova and Møller, 2001) followed by the action of transhydrogenase activities which interconvert NADH and $NADP^+$ to NAD^+ and NADPH (Bykova *et al.*, 1999). It is thus possible that, as in man, NADPH levels are controlled by the coordinated action of NADK and NADP producing NADPH dehydrogenases (Pollak *et al.*, 2007b).

Given that an increase in the cytosolic Ca^{2+} content is a common factor in the response of plant cells to a variety of stresses, such as cold, salt, or application of abscisic acid (Sanders *et al.*, 2002). It is conceivable that the CaM-dependent NADK could be an early actor in stress-induced calcium signaling (Hunt *et al.*, 2004). In *A. thaliana*, NADK2 plays a leading role in the production of folial NADP(H) (Chai *et al.*, 2005; Hashida *et al.*, 2009). It is also possible that NADPH production in the perivascular sheaths is performed directly from NADH (Turner *et al.*, 2004) via the action of the CaM-independent NADK3 in response either to stress, developmental signaling. or ABA induction following strong light (Fryer *et al.*, 2003; Chai *et al.*, 2006, Galvez-Valdivieso *et al.*, 2009). Dependent on its subcellular location, it is likely to allow sensitive responses to changes in cytosolic calcium levels (Dieter and Marmé, 1984).

Given the importance of NADPH production in the control of ROS levels required for certain physiological responses, such as ABA-dependent stomatal closure or pathogen defenses, it follows that modulation of NAD(H) kinases activities are potentially involved in these responses (Hunt *et al.*, 2004; Pétriacq *et al.*, 2013). In the light, ferredoxin-NADP reductase (FNR, EC 1.18.1.2) is, however, responsible for the majority of NADPH production in chloroplasts and by extension within the whole cell (Noctor, 2006). However, others enzymes generating NADPH in plants may be involved in ROS and reducing power management. For example, the enzymes glucose-6-phosphate (G6PDH, EC 1.1.1.49) and 6-phosphogluconate dehydrogenase (6PGDH, EC 1.1.1.44) which successively convert glucose 6-phosphate + NADP to 6-phosphogluconate + NADPH then 6-phosphogluconate + NADP to ribulose 5-phosphate + CO_2 + NADPH (Pugin *et al.*, 1997) in the cytosolic and plastid localized pentose phosphate pathway (Dennis *et al.*, 1997) and the non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase (NP-GAPDH, EC 1.2.1.9) of glycolysis converting D-glyceraldehyde 3-phosphate and $NADP^+$ and H_2O to 3-phospho-D-glycerate and NADPH and H^+ (Rius *et al.*, 2008; Piattoni *et al.*, 2013). In addition, the TCA cycle enzymes isocitrate dehydrogenase NADP in the mitochondria (ICDH, EC 1.1.1.42, converting isocitrate and NADP to α-ketoglutarate and CO_2 and NADPH) (Galvez-Valdivieso *et al.*, 1999), malate dehydrogenase NADP in plastids (MDH, EC 1.1.1.82, converting malate and NADP into NADPH and oxaloacetate Heyno *et al.*, 2014), and malic enzyme in the cytosol (ME, EC 1.1.1.40, converting malate and NADP to pyruvate and CO_2 and NADPH; Doubnerová and Ryšlavá, 2011) also function in the regulation of NADP(H) content. Furthermore, the aldehyde dehydrogenases (ALDH, EC 1.2.1.3) present in the plastids, mitochondria and cytosol (Sunkar *et al.*, 2003; Hou and Bartels, 2014) and the bifunctional enzyme methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase (MTHD/MTHCH, EC 1.5.1.5, converting 5,10-methylene-tetrahydrofolate and NADP into 10-formyl tetrahydrofolate and NADPH), located in the cytosol and the mitochondria (Cossins *et al.*, 1993;. Kirk *et al*, 1995), also contribute considerably to the NADP(H) balance.

2. NADP phosphatase (NADPPase)

NADP may also be converted to NAD^+ by a phosphatase activity. The NADPPase activity (EC 3.1.3.-) was initially detected in rat liver mitochondria (Richter, 1987) and subsequently in bacteria (Reidl *et al.*, 2000; Kawai *et al.*, 2004). It has been shown that its activity is correlated to the circadian rhythm in Euglena (Laval-Martin *et al.*, 1990) and seed dormancy in oat, however, to date the protein is only partially purified (Gallais *et al.*, 2000).

In *Avena sativa*, two proteins were extracted from caryopses embryos, one 37 kDa, and the other 160 kDa. The former displaying an activity that is four times lower than the latter but a very high substrate specificity for $NADP^+$ (Gallais *et al.*, 2000). More recently, an inverse correlation between NADK and NADPPase activities in *A. thaliana* was associated with a difference of dormancy between the studied ecotypes (Hunt and Gray, 2009). That said, in the absence of known protein sequence and cloning of the gene encoding this protein, very less information is currently available on the NADPPase. However, in archaea, it is suggested that this activity could be produced by a bifunctional protein exhibiting NADPPase/NADK activities with the activity of NADPPase probably being carried by an inositol monophosphatase/fructose bisphosphatase type domain (Kawai and Murata, 2008). However, as yet, no enzyme classification (EC) number has been provided for such an enzyme according to the Brenda database (http://www.brenda-enzymes.org/) of the University of Braunschweig (Schomburg *et al.*, 2014).

D. The metabolism of NAD^+

Beyond its role in redox mechanism, NAD^+ is catabolized by enzymes involved in cellular signaling processes (Hunt *et al.*, 2004; Noctor *et al.*, 2006). These processes involve cleavage of ribose linked nicotinamide which either occurs at the diphosphate bridge that joins the two nucleotides or at the *β-N*-glycosidic bridge linking ADP-ribose and nicotinamide. Both processes release a large amount of energy. Several enzymes are able to break the glycosidic bond of the NAD^+ molecule nicotinamide alternatively releasing cyclic ADP-ribose (cADPR), the free ADP-ribose or ADP-ribose conjugated to proteins.

1. Utilization of NAD and NADH by adenosine-5′-diphosphateribosyl-cyclase (ADPR cyclase)

Production of cADPR has been extensively studied in *Aplysia californica*, a marine gastropod, in which nerve transmission mechanisms and signaling are well characterized. cADPR is one of three molecules, alongside inositol 1,4,5 tris-phosphate (IP3) and nicotinic acid adenine dinucleotide phosphate (NAADP), capable of inducing an intracellular calcium release (Allen *et al.*, 1995). cADPR is a second messenger

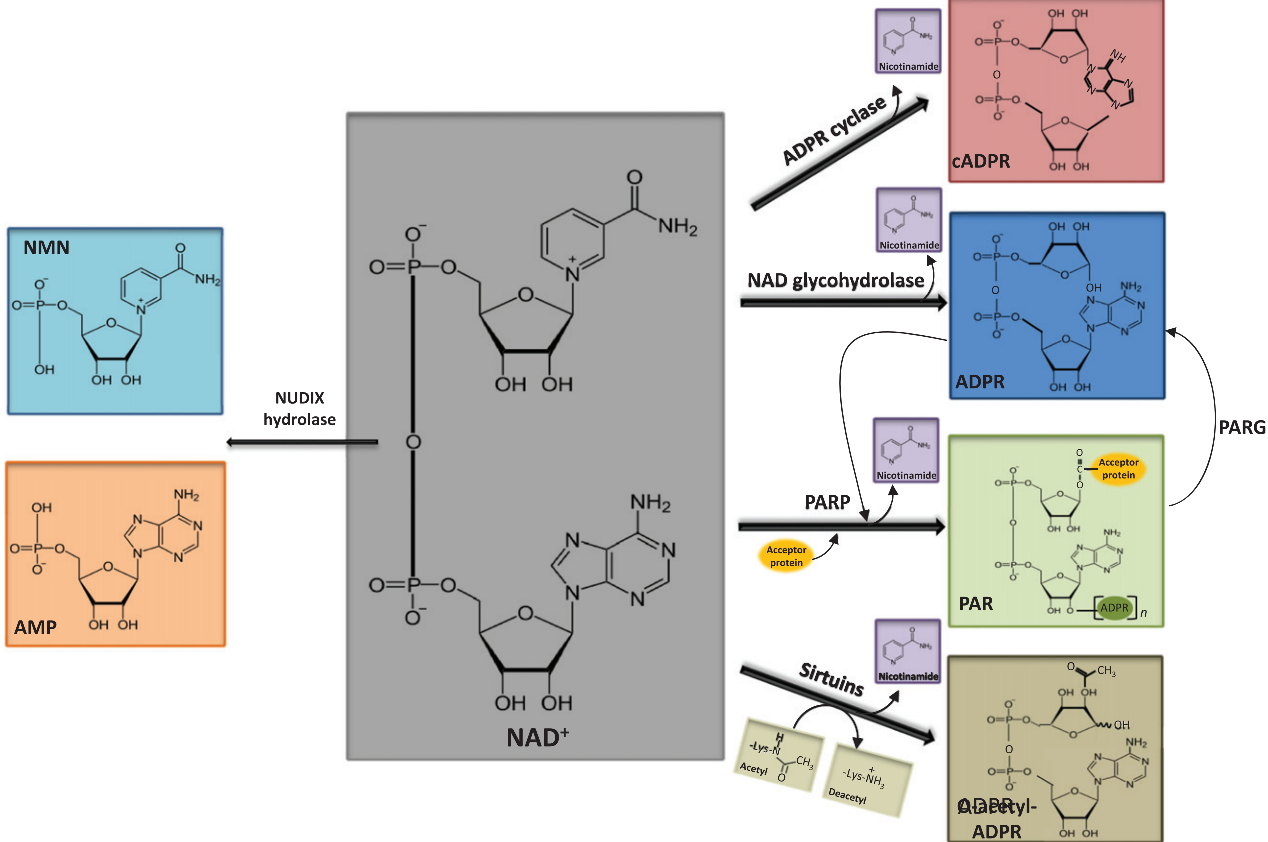

Figure 4. The metabolism of NAD^+. ADPR: adenosine diphosphate ribose cyclic; AMP: adenosine monophosphate; cADPR: cyclic ADPR; NAD^+: nicotinamide adenine dinucleotide; NMN: nicotinamide mononucleotide; PAR: poly-ADPribose; PARG: poly-ADP-ribose glycohydrolases; PARP: poly-ADPribose polymerases.

whose primary function appears to be in the physiological depolarization of neurons in Aplysia. ADPR cyclase (EC 3.2.2.6) catalyzes the cleavage of NAD^+ and binds the remaining two ends of the molecule to produce the cADPR (Figure 4; Lee and Aarhus, 1991).

In *A. thaliana*, cADPR synthesis activity was detected in protein extracts of seedlings treated with ABA. On the supply of radioactive NAD^+ radiolabeled cADPR protein was detected (Sánchez *et al.*, 2004). In plants, cADPR involvement in stomatal closure was demonstrated using the pharmacological approach with drugs blocking cADPR synthesis or its agonists reducing ABA-triggered stomatal closure. In addition, microinjection of cADPR mimics the ABA effect (Wu *et al.*, 1997; Leckie *et al.*, 1998), whilst calcium release was also demonstrated by patch-clamp experiments using sugar beet vacuoles (Allen *et al.*, 1995), following the injection of cADPR. Therefore, cADPR can be considered as an actor of signaling cascades in plants. cADPR is also involved in the cytokinin signaling pathway in *A. thaliana* (Hwang and Sheen, 2001; Sánchez *et al.*, 2004). In addition, a human ADPR cyclase (CD38, Lee, 2012) was expressed in the apoplast of *A. thaliana* to degrade apoplastic NAD^+ suggesting that only NAD^+, not cADPR or NaADP was involved in mechanisms of plant defense (Zhang *et al.*, 2012, Pétriacq *et al.*, 2013). However, more recent work has shown that the dose-dependent fluctuation of the cytosolic calcium pool following NAD treatment could be caused by a cADPR production under pathogen attack (Pétriacq *et al.*, 2016a, 2016b).

The nicotinate adenine dinucleotide phosphate (NaADP), produced by ADPR cyclase (EC 3.2.2.5) by deamination of NADP, is also involved in calcium signaling in many organisms including plants (Navazio *et al.*, 2000; Navazio *et al.*, 2001; Guse and Lee, 2008). As yet the synthesis of NAADP is not fully understood, however, it appears to also be a product of ADPR cyclase, on a reaction base exchange of NADP with nicotinic acid (Figure 4; Chini *et al.*, 2002). In mammals, the ADPR cyclase is also involved in the production of ADPR via the activities cADPR hydrolase (EC 3.2.2.6, linearization cADPR; Genazzani *et al.*, 1996; Zielinska *et al.*, 2004) and NADase (or NAD^+ glycohydrolase; EC 3.2.2.5) which allow it to cleave NAD^+ to nicotinamide and ADPR (Liu *et al.*, 2009a). In plants, these activities are also presumed to

be present given the existence of the metabolites produced by these enzyme activities within plant tissues (Hunt *et al.*, 2004).

2. Utilization of NAD^+ by mono- and poly-ADPribose polymerases (PARP)

Another major non-redox utilizer of NAD^+ is the reaction catalyzed by the various isoforms of poly-ADPribose polymerase (PARP; EC 2.4.2.30). These proteins transfer one or more ADP-ribose groups to proteins using NAD^+ as an acceptor (Hunt *et al.*, 2007). PARP is involved in a large number of fundamental processes such as DNA repair, modifications, and decompaction of chromatin by regulating the methylation patterns of DNA, gene transcription, cellular apoptosis, and telomere length (Caiafa *et al.*, 2009; Bürkle, 2001; Briggs and Bent, 2011; Lamb *et al*, 2012; Swindall *et al.*, 2013).

The best characterized member of the PARP protein family is the human PARP1 (Swindall *et al.*, 2013), which consists of three domains: (i) an N-terminal domain which acts as a detector of broken DNA, (ii) a central automodification domain which is involved in the recruitment of enzymes associated with the repair mechanism via the excision of bases, and (iii) the C-terminal catalytic domain which carries the ADP-ribosylation activity (De Murcia and Ménissier de Murcia 1994). *A. thaliana* encodes three isoforms of PARP: (i) PARP2 (Counterpart of human encoded PARP1 by *At2g31320*), (ii) the PARP3 (counterpart human encoded PARP2 At5g22470) lacking the N-terminal domain canonical detector zinc finger breaks in DNA, and (iii) PARP1 (homolog of the male encoded PARP3 *At4g02390*), lacks the canonical N-terminal domain and but contains a central SAP domain binding to DNA (Briggs and Bent, 2011; Lamb and *et al*, 2012; Bianchi and De Maio, 2014). Plants also contain PARP-like proteins, called ORS (for "one RCD similar") which contain the PARP catalytic domain. There are two types of ORS, one present in all plants and another group named RCD (for "Radical Cell Death"; Ahlfors *et al.*, 2004) that are only present in Eudicots (Lamb *et al.*, 2012). This protein group lacks the ability to poly(ADP)-ribosylate targets but rather ubiquitously catalyzes mono-ADP-ribosylation (Briggs and Bent, 2011).

When a PARP protein binds to a broken DNA strand, its catalytic activity is activated. NAD^+ is then used for the poly(ADP)ribosylation of the PARPs themselves as well as transcription factors present at the fracture site. These changes in transcription factors prevent their association with their DNA binding site, blocking the formation of the complex which initiates transcription and thereby preventing a transcription of the broken DNA. The self-modifications of PARP furthermore dissociates PARP from the DNA, releasing the access of DNA repair proteins (Oei *et al.*, 1998; Oei and Ziegler, 2000).

PARPs are involved in responses to various stresses in many organisms including plants (Doucet-Chabeaud *et al.*, 2001; De Block *et al.*, 2005; Ying *et al.*, 2003; Pellny *et al.*, 2009; Vigani and Zocchi, 2009; Adams-Phillips *et al.*, 2010), whereas ORS is involved solely in the maintenance of redox homeostasis (Ahlfors *et al.*, 2004; Liu *et al*, 2014a). As described above, the poly(ADP)-ribosylation (parpylation) is a posttranslational modification of proteins which adds ADP-ribose groups to protein acceptors. These changes are reversible on the action of poly-ADP-ribose glycohydrolases (PARG), which hydrolyze the ADP-ribose protein polymers. The ADP-ribose released by PARG does not accumulate but is rather subsequently hydrolyzed by Nucleoside Diphosphate linked to X (NUDIX) hydrolases (Figure 4).

3. Poly-ADP-ribose glycohydrolases (PARG)

As mentioned above protein modification by PARylation can be reversed by poly-ADP-ribose glycohydrolases (PARG; EC 3.2.1.143), which catalyze the hydrolysis of the glycosidic linkage of ADP-ribose polymers to liberate free ADP-ribose. These enzymes have both endo- and exoglycosidase activity (Davidovic *et al.*, 2001). The *A. thaliana* genome contains two adjacent PARG genes (*At2g31870* and *At2g31865*), derived from a duplication event (Bowers *et al.*, 2003). Generally, plants contain several PARG genes, whereas animals have only one member which encodes several isoforms (Briggs and Bent, 2011). In plants, PARGs are localized in the nucleus, cytosol, and mitochondria (Bonicalzi *et al.*, 2005) and appear to be involved in cell death and pathogen defense (Adams-Phillips *et al.*, 2008; Adams-Phillips *et al.*, 2010).

4. Utilization of NAD^+ and its derivatives by Nudix hydrolases

The Nudix hydrolases (EC 3.6.1.13) are enzymes that cleave the pyrophosphate bridge of molecules derived from nucleoside diphosphates including di- and nucleoside triphosphate and their oxidized forms, dinucleoside polyphosphates, nucleotide sugars, NADH, NADPH, coenzyme A, and rotator unmethylated DNA (Kraszewska, 2008; Song *et al.*, 2013). They were originally discovered in *E. coli* as

suppressor mutations linked to the oxidation of 8-oxo-dGTP (Bessman *et al.*, 1996) yet are a large enzyme family present in all organisms catalyzing the hydrolysis of a highly variable range of substrates including many derivatives of nucleoside diphosphates (Kraszewska, 2008). They, thus play an important role in allowing the control of the cellular concentration of their substrates. In plants, Nudix hydrolases which cleave NAD(P)H produce nicotinamide and the AGP (or ADP in the case of NADPH) (AtNUDT 1, 2, 6, 7,10, 19) (Dobrzanska *et al.*, 2002; Klaus *et al.*, 2005; Ogawa *et al.*, 2005, 2008; Olejnik and Kraszewska, 2005; Jambunathan and Mahalingam, 2006; Ge and Xia, 2008; Ishikawa *et al.*, 2010a; Jambunathan *et al.*, 2010; Yoshimura *et al.*, 2014), whereas those that metabolize ADP-ribose produce free AMP and ribose-5 phosphate (AtNUDT2, 6, 7, 10, 14; Ogawa *et al.*, 2005; Olejnik and Kraszewska, 2005; Jambunathan and Mahalingam, 2006; Muñoz *et al.*, 2006; Ogawa *et al.*, 2008; Jambunathan *et al.*, 2010). Other Nudix hydrolases use either Coenzyme A (AtNUDT11, 15 and potentially 22; Ogawa *et al.*, 2005; Kraszewska, 2008; Ogawa *et al.*, 2008; Kupke *et al.*, 2009), FAD (AtNUDT23; Ogawa *et al.*, 2008), adenosine phosphate (AtNUDT4, 12, 13, 16, 17,18, 21, 25, 28, 29, Olejnik and Kraszewska, 2005; Kraszewska, 2008; Ogawa *et al.*, 2008; Szurmak *et al.*, 2008) or dNTPs (AtNUDT1, 27;. Dobrzanska *et al.*, 2002; Klaus *et al.*, 2005; Ogawa *et al.*, 2005; Yoshimura *et al.*, 2007; Gunawardana *et al.* 2008), as substrate.

The physiological functions of these reactions in the metabolism of NAD^+ are likely either to prevent the accumulation of NADH and thus inhibit oxidative metabolism or release ADP-ribose which can affect a large number of processes (McLennan, 2006; Briggs and Bent, 2011). ADP-ribose is generated either by (i) the PARG, (ii) the ADPR cyclase, (iii) dephosphorylation of ADP-ribose-1′-phosphate produced during NAD^+-dependent RNA splicing (Shull *et al.*, 2005), or (iv) the deacetylation of *O*-acetyl-ADP-ribose released by the operation of the NAD^+-dependent Sir2 type histone deacetylase (Moser *et al.*, 1983; Pfister *et al.*, 2001).

5. Utilization of NAD^+ by histone deacetylases type SIRT

Gene expression in eukaryotes is, in part, controlled by the level of NAD^+ by a mechanism relying on epigenetic modifications of the genome. PARylation of proteins by PARP regulates the methylation patterns of DNA. NAD^+ is also involved in the process of acetylation/deacetylation of histones through SIRT type histone deacetylase. These Sir2 ("Silent Information Regulator 2") type histone deacetylases also called sirtuins (abbreviated to SIRT in yeast and SRT in plants), are histone deacetylases which use NAD^+ as substrate (Imai *et al.*, 2000). The SRTs differ from other histone deacetylases on the bases of their substrate specificity, their sequences, and their protein structures (Hollender and Liu, 2008; Ma *et al.*, 2013.). Sirtuins (EC 3.5.1.98) catalyze an NAD^+-dependent deacetylation of acetyl-Lys in proteins and thereby produce a deacetylated Lys, as well as the metabolites nicotinamide and 2′-*O*-acetyl-ADP-ribose (Figure 4). In plants, acetylation/deacetylation by $^{\varepsilon}$N lysine residues of histone affects the regulatory mechanisms of the transcription and chromatin functions (Hollender and Liu, 2008). Indeed, histone acetylation has consequences on chromatin structure. The added acetyl group neutralizes the positive charge of histone tails that allowing a relaxation of DNA-histone interactions and inter-nucleosomes. This renders chromatin more flexible and more accessible to transcription factors. In general, histone acetylation causes decondensation of chromatin thus allowing transcriptional activation. By contrast, the deacetylation of histone rather represses transcription because it allows the chromatin to close in on itself. Thus, Sirtuins have recently emerged as regulatory elements of longevity, cell survival, apoptosis, and metabolism in a range of different heterotrophic organisms (Houtkooper *et al.*, 2012). Indeed, it has recently been demonstrated that several proteins involved in primary metabolism in the model plant *A. thaliana* are acetylated, including the large subunit of Rubisco and the plastid and mitochondrial ATP synthases with these post-translational modifications giving rise to a change the biochemical properties of the enzymes (Finkemeier *et al.*, 2011; Wu *et al.*, 2011). In addition, in *A. thaliana*, the histone deacetylase SRT2 has been demonstrated to interact with proteins of the inner membrane, such as ATP synthase and ATP carriers, is involved in the coupling between mitochondrial respiration and ATP synthesis (König *et al.*, 2014).

Based on phylogenetic analyzes, there are five classes of sirtuins (I to V), however, not all of them possess only a $^{\varepsilon}$N deacetylase activity. Some, such as Class III mammalian SRT, also possess additional lysine succinylase and demalonylase activities (Du *et al.*, 2011). The most studied belong to the class I (Houtkooper *et al.*, 2012), those of class II contain an additional ADP ribosyltransferase activity, whilst the mammalian SIRT4 activity regulates mitochondrial glutamate dehydrogenase (GDH, EC 1.4.1.4) activity

(Haigis *et al.*, 2006). The plant genome contains only two genes encoding Sirtuins. One is a homolog of mammalian SIRT6 and the other of mammalian SIRT4 (Huang and Tindall, 2007; Greiss and Gartner, 2009; Hu *et al.*, 2009; Zhong *et al*, 2013; König *et al.*, 2014). The homolog SIRT6, also called SRT1, is localized in the nucleus (Huang *et al.*, 2007; Wang *et al.*, 2010), whereas the counterpart of SIRT4, SRT2, is dual localized to the mitochondria and nucleus (Chung *et al.*, 2009; Hu *et al.*, 2009; König *et al.*, 2014.). In plants, these Sirtuins also have a role in the response to stress, defense against pathogens and the suppression of the movement of transposable elements (Wang *et al.*, 2010; Zhong *et al.*, 2013).

E. The salvage pathway(s) of NAD^+ biosynthesis

All plant species have at least two routes by which they recycle NAD^+: (i) via the nicotinamide mononucleotide which is regenerated to NAD^+ in a single step and (ii) via nicotinamide itself which allows the regeneration of NAD^+ following several enzymatic steps (Figure 2).

1. The direct recycling route via nicotinamide mononucleotide

The nicotinamide mononucleotide (NMN) is generated by breaking the diphosphate link of the NAD^+ molecule via the action of NAD diphosphatases (EC 3.6.1.22), such as the nudix hydrolases. It can be converted to NAD^+ in a single step catalyzed by nicotinamide mononucleotide adenyltransferase (NMNAT, EC 2.7.7.1, Figures 2 and 3). In plants, the activity was first measured in purified mitochondrial fractions of Jerusalem artichoke (*H. tuberosus*; Di Martino and Pallotta, 2011). In this study, the authors failed to detect NMNAT activity in non-mitochondrial fractions. However, the purified NMNAT proteins also exhibited NaMNAT activity albeit with a lower affinity for NaMN. A single gene encoding a NaMNAT/NMNAT (*At5g55810*) appears in *A. thaliana* databases (Hashida *et al.*, 2007), suggesting that a single gene encodes several isoforms addressed to different subcellular compartments. Interestingly, whilst most living organisms harbors a bifunctional protein carrying both NaMNAT and NMNAT activities (Berger *et al.*, 2004). However, thus far no extra-mitochondrial NMNAT activity has been discovered suggesting that NAD^+ recycling occurs by other routes in the other subcellular locations. Furthermore, enzymatic analysis of the plant enzyme by Wagner and coworkers is somewhat contradictory. On the one hand, both NaMN/NMNAT activities were measured suggesting a single enzymatic entity accepted both NaMN and NMN as substrates. However, nicotine induction resulted in preferential induction of NMNAT above NaMNAT indicating that the activities may be carried on independent polypeptides (Wagner and Wagner, 1985; Wagner *et al.*, 1986a; Wagner *et al.*, 1986b).

2. The ADPR cyclase-PARP-sirtuin recycling route of nicotinamide

Nicotinamide, released by the cleavage of NAD^+, is deaminated by nicotinamidase (EC 3.5.1.19, Figure 2), to yield nicotinate (Ryrie and Scott, 1969; Ashihara *et al.*, 2005), which is subsequently converted to NaMN via the action of nicotinate phosphoribosyltransferase (NaPT, EC 6.3.4.21 Figure 2).

Nicotinamidase. The bacterial nicotinamidase contains an Asp-Lys-Cys catalytic triad similar to those found in other amidases and its activity is dependent on the interaction with Zn^{2+} ions (Du *et al.*, 2001). Nicotinamidase activity has been measured in several plant species (Schippers *et al.*, 2008; Katahira and Ashihara, 2009). Three *Arabidopsis* genes encode nicotinamidases *At2g22570*, *At5g23230*, and *At5g23220* called NIC1, NIC2, and NIC3, respectively, which exhibit strong sequence homologies with the isochorismatase (EC 3.2.2.1) enzymes that degrade salicylic acid (Hunt *et al.*, 2004; Wang and Pichersky, 2007; Liu *et al.*, 2014). The NIC1 gene is strongly induced in response to ABA treatment, whilst the NIC2 gene is highly expressed in seeds (Hunt *et al.*, 2004). It is commonly accepted that mammals lack nicotinamidase (Hunt *et al.*, 2004; Chappie *et al.*, 2005; Noctor *et al.*, 2006). The existence of a nicotinamidase activity was reported in rat liver protein extracts (Petrack *et al.* 1963). However, in 1971, it was demonstrated that physiological concentrations of nicotinamide were not converted into nicotinate in this tissue (Keller *et al.*, 1971). By contrast, nicotinamide is converted directly to NaMN by nicotinamide phosphoribosyltransferase (NAMPT, EC 2.4.2.12), which was not detected in plants (Wagner *et al*, 1986a; Wang and Pichersky, 2007; Katahira and Ashihara, 2009).

Nicotinate phosphoribosyltransferase. Nicotinate is converted by the NaMN nicotinate phosphoribosyltransferase (NaPT, EC 6.3.4.21), in bacteria (Sorci *et al.*, 2010). The NaPT transfers nicotinate onto 5-phosphoribosyl-1-pyrophosphate (PRPP) to form NaMN with the chemical reaction catalyzed by this enzyme very similar to that catalyzed by QPT with

the exception of the decarboxylation step. Two genes encode this enzyme in *A. thaliana*: (i) NaPT1 (*At4g36940*) and (ii) NaPT2 (*At2g23420*). The NaPT activity was measured in potato tubers (Katahira and Ashihara, 2009) and also in *Arabidopsis* (Pétriacq, 2011). Increased levels of NAD^+ in response to an exogenous supply of quinolinate correlated with increased levels of nicotinate and NaPT activity in *Arabidopsis* suggesting stimulation of the recycling pathways in response to an increased production of NAD^+ (Pétriacq, 2011). Radiolabel feeding experiments using ^{14}C-nicotinate or ^{14}C-quinolinate highlighted that NaPT and QPT contribute equally to NAD^+ synthesis in barley leaves (Ryrie and Scott, 1969).

Increased NaPT activity is also observed when de novo synthesis is disrupted in response to a mutation that affects the catalytic competence of an enzyme involved in the de novo biosynthesis pathway (Schippers *et al.*, 2008). In this case, activation of NaPT2 compensates for the failure of de novo synthesis (Schippers *et al.*, 2008). In mammals, the NaPT activity contributes significantly to the production of NAD^+ (Hara *et al.*, 2007).

The enzymes common to the de novo synthesis and recycling pathways. Two enzymes are common to the *de novo* NAD^+ biosynthesis pathway and to the recycling of nicotinamide and nicotinate: NaMNAT and NADS, presented in the *de novo* biosynthesis of NAD in plants section above. NaMN thus represents the junction between these two metabolic pathways.

3. Other ways of recycling NAD^+ connected to the pyridine nucleotide cycle

As described above, the pyridine nucleotide cycle coupled with NMNAT activity render it possible to regenerate NAD^+ pools (Figure 2). Other processes using hydrolases also generate derivatives of NAD and NMN which can then be recycled. Furthermore, other biosynthetic pathways using metabolic intermediates of pyridine nucleotide cycle and produce storage forms of these nucleotides as well as pyridine alkaloids (Figure 2).

Recycling NAD via NMN. The Nudix hydrolases cleave NAD^+ into NMN and AMP, and NMN is then recycled to NAD^+ by NMNAT activity. However in plants, thus far the NMNAT activity was only detected in the mitochondrial compartment (Di Martino *et al.*, 2013). Other enzymes than Nudix hydrolase, from the family of nucleotide hydrolases (or nucleotides diphosphatases), are, however, present in all subcellular compartments. They cleave NAD^+ and produce NMN in cells (Medda *et al.*, 2000; Moorhead *et al.*, 2003). The NMN product, which is not converted to NAD by NMNAT, feeds the pyridine nucleotide cycle by conversion to nicotinamide (Figure 2). Radiolabeling experiments with NAD^+ and its precursors have shown that plant species produce nicotinamide both directly and via NMN (Ashihara *et al.*, 2011). In lentil (*Lens esculenta*), a protein with nucleotide diphosphatase activity was purified. This protein was able to use all of the pyridine nucleotide as a substrate but exhibited the strongest affinity for NADH (Medda *et al.*, 2000).

Production of nicotinate from NMN in a single step: Tobacco (*Nicotiana tabacum*), coffee (*Coffea arabica*), tea (*Camellia sinensis*), and cocoa (*Theobroma cacao*) produce nicotinamide in one step from NMN. This step is catalyzed by nucleosidase or NMN glycohydrolase (EC 3.2.2.14; Figure 2) (Tarr and Arditti, 1982; Wagner and Wagner, 1985; Zheng *et al.*, 2004; Ashihara and Deng, 2012).

Production of nicotinate from NMN in two steps via nicotinamide riboside: Tea, Madagascar periwinkle (*Catharanthus roseus*), gymnosperms, potatoes, and Fabaceae produce nicotinamide in two steps from NMN. The first step is catalyzed by a 5′nucleosidase which converts NMN to nicotinamide riboside (EC 3.1.3.5, Figure 2). The second enzyme, nicotinamide nucleoside phosphoribohydrolase (EC number undetermined; Figure 2), catalyzes the conversion of nicotinamide to nicotinamide riboside (Koster *et al.*, 1989; Yin and Ashihara, 2007; Ashihara *et al.*, 2005; Katahira and Ashihara, 2009; Ashihara and Deng, 2012).

Production of nicotinate mononucleotide from NMN in three steps: In potato, it is possible to produce NaMN from NMN in three steps. Following synthesis of nicotinamide riboside, it is deaminated to nicotinate riboside (NaR) by nicotinamide riboside deaminase (EC indeterminate; Figure 2). The NaR is subsequently phosphorylated to NaMN by NaR kinase (EC 2.7.1.173; Figure 2) (Koster *et al.*, 1989; Katahira and Ashihara, 2009).

De novo nicotinate synthesis. Nicotinate is produced in plants in two main ways. One way is via the pyridine nucleotides, described above, involving nicotinamidase after conversion of NAD^+ to nicotinamide. The second route of de novo nicotinate biosynthesis is present in all plant species studied. It consists of the synthesis of nicotinate from NaMN in one or two

steps (Figure 2). This route utilizes the excess NaMN from the de novo synthesis of NAD^+ to synthesize molecules, such as storage nicotinate, NaR, and nicotinate-derived secondary metabolites (Figure 2).

One step de novo nicotinate synthesis: Castor (*Ricinus communis*), tobacco, and the Madagascar periwinkle and gymnosperms can synthesize nicotinate in a single step catalyzed by NaMN nucleosidase (EC 3.2.2.14; Figure 2) (Waller *et al.*, 1966; Mann and Byerrum, 1974; Wagner *et al.*, 1986b; Ashihara *et al.*, 2005).

Two steps de novo nicotinate synthesis: Coffee, tea, potatoes, and the Fabaceae produce nicotinate in two steps from NaMN. The first step is catalyzed by a 5'nucleosidase which converts NaMN in NaR or nicotinate riboside (EC 3.2.2.-, Figure 2). The second step catalyzes the conversion of NaR to nicotinate by the NaR nucleosidase (EC number undetermined) (Koster *et al.*, 1989; Zheng *et al.*, 2004; Zheng *et al.*, 2005; Matsui *et al.*, 2007; Matsui and Ashihara, 2008; Yin *et al.*, 2008; Katahira and Ashihara, 2009; Ashihara and Deng, 2012).

Nicotinate conjugation. Nicotinate accumulation has been demonstrated to be toxic for plant cells (Li *et al.*, 2015). Plants have evolved to deal with nicotinate accumulation by methylation or glucosylation of the molecule (Li *et al.*, 2015, 2017), leading to NA-conjugates trigonelline and nicotinate glucoside, respectively (Figure 2). Trigonelline is a pyridine alkaloid widely distributed in land plants and was first isolated from fenugreek seeds (*Trigonella foenum-graecum*; Jahns, 1885). Its precise regulatory functions have to be established, its production may have facilitated the retention of the Press-Handler recycling pathway in plants (Liu *et al.*, 2017). However, demethylation of trigonelline appears to proceed too slowly to fuel maintenance of the nicotinate pool (Upmeier *et al.*, 1988; Willeke *et al.*, 1979). In Brassicacae, nicotinate glucoside also functions as a mobilizable storage form for NAD^+ and may function to protect plant cells from the toxicity of nicotinate accumulation during seed germination (Li *et al.*, 2015). In addition to their detoxification functions, Na-glucoside recycling may also contribute to plant NAD^+ resynthesis (Upmeier *et al.*, 1988; Schwenen *et al.*, 1986).

F. Regeneration of NAD(P)H from their hydrated forms

Many metabolites are subject to changes that may occur spontaneously or under the mis-action of enzymes (Golubev, 1996; D'Ari and Casadesús, 1998; Tawfik, 2010), and the products of their reactions can be useless and even toxic (Linster *et al.*, 2013). This is particularly the case for coenzymes and cofactors which are inherently chemically reactive compounds and thus require effective repair systems (Linster *et al.*, 2013). NADH and NADPH may undergo spontaneous or enzymatic hydration at the C-6 position to yield hydrates of these compounds, called S and R NADHX and NADPHX which are epimers of one another (that is to say, differing only by the configuration of their asymmetric center) (Rafter *et al.*, 1954; Oppenheimer and Kaplan, 1974; Marbaix *et al.*, 2011). Spontaneous hydration of NAD(P)H is favored at low pH and high temperature (Linster *et al.*, 2013). Enyzmatic hydration is carried out by a secondary reaction of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH; EC 1.2.1.12). NADHX and NADPHX cannot act as electron donors or acceptors and they both inhibit dehydrogenases, which renders them toxic (Yoshida and Dave, 1975). Both hydrates are converted to NADH or NADPH by a specific S-form ATP or ADP-dependent dehydratase (EC4.2.1.136, NNRD for "nicotinamide nucleotide repair dehydratase"; Figure 5). R forms are forms interconverted to S-forms by a nicotinamide nucleotide repair epimerase (EC 5.1.99.6, NNRE for "nicotinamide nucleotide repair epimerase"; Figure 5; Acheson *et al.*, 1988; Colinas *et al.*, 2014; Niehaus *et al.*, 2014). These enzymatic activities are found in all living kingdoms and are carried out by the same polypeptide in archaea and most bacteria. However, in eukaryotes they are performed by two distinct polypeptides. In plants, these two enzymes are localized in the cytosol, mitochondria and plastid (Colinas *et al.*, 2014; Niehaus *et al.*, 2014). Spontaneously, The NAD(P)HX can cyclize and yield cyclic NAD(P)HX which cannot be repaired either by the NAD (P)HX epimerase or the NAD(P)HX dehydratase. However, this cyclized form is less toxic to the cell (Colinas *et al.*, 2014; Niehaus *et al.*, 2014.).

II. Subcellular localization and transport of NAD^+ and derivatives

A. Intracellular distribution of pyridine nucleotides

The distribution of NAD^+ pools among subcellular compartments is a crucial issue in order to precisely understand the functions of NAD^+ but also the regulation of its biosynthesis and renewal. Because of their high importance in cellular metabolism, most studies measuring the levels of pyridine nucleotides have

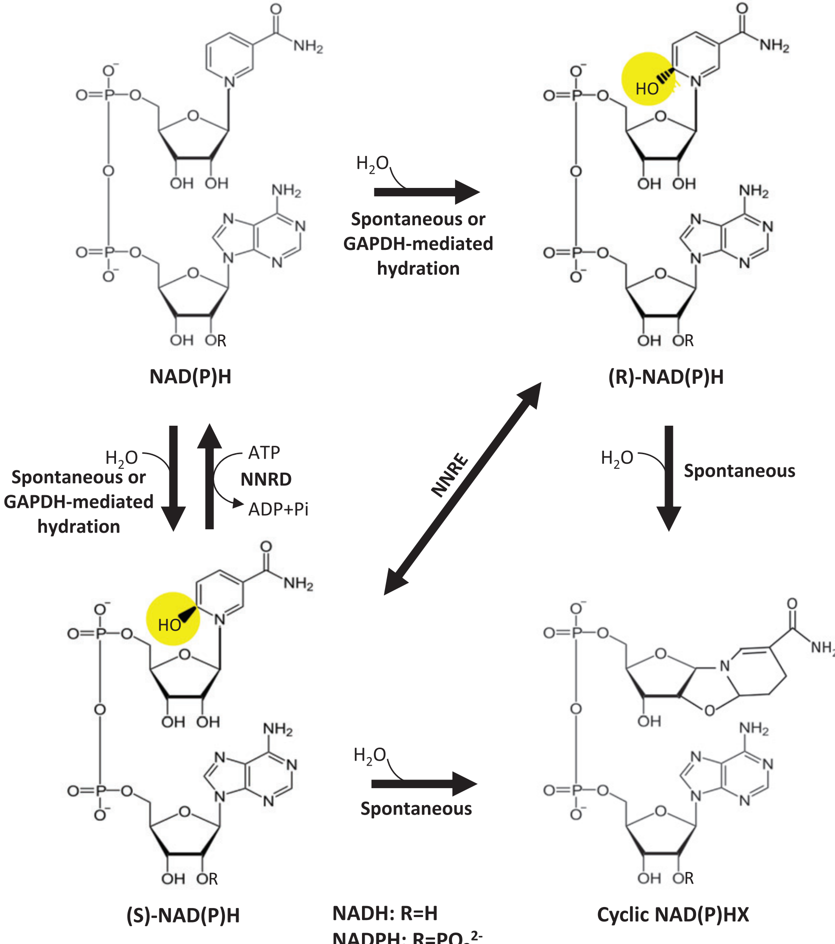

Figure 5. NAD(P)H damage and repair reactions in plants. The spontaneous or GAPDH-mediated hydration of NAD(P)H, and the enzymatic epimerization and dehydratase reactions that reconvert the resulting hydrates, (R)- and (S)-NAD(P)HX, to NAD(P)H. NAD(P)H hydrates can also spontaneously cyclize. GAPDH: glyceraldehyde-3-phosphate dehydrogenase; NAD(P)HX: hydrated forms of NAD(P)H, NNRE: NAD(P)HX epimerase; NNRD: NAD(P)H, NAD(P)HX ehydratase.

focused on NAD^+ and NADP. It is generally accepted that these nucleotides are unlikely to move among cells although their precursors, as well as certain derivatives, can be transported between tissues. Most of the levels reported in the literature required extraction followed by enzymatic measurement methods. A major challenge in this technique is to avoid changes in the state of metabolites during the sample preparation. This problem becomes particularly acute when cell fractionation is required before analysis. Artifacts can arise as a result of exchanges between subcellular compartments during fractionation and changes in the redox state of the molecules because these techniques disrupt cellular integrity and function.

Techniques including non-aqueous fractionation or silicon oil separation of protoplasts under acidic or alkaline buffers were used to overcome these difficulties. Although relatively slow, the first technique prevents leakage and fixes the metabolic state, while the second method is faster, but includes a protoplast preparation step (Stitt *et al.*, 1982; Gardeström, 1987; Heineke *et al.*, 1991). Such fractionation methods have been used for measuring levels of NAD pools in the cytosol, mitochondria, and chloroplast (Figure 6; Heineke *et al.*, 1991; Igamberdiev and Gardeström, 2003; Szal *et al.*, 2008). The levels of NAD^+ and NADP in these compartments were found to vary under light conditions in a range from 0.1 mM to 2 mM, which is similar to intracellular concentrations in yeast (Bogan and Brenner, 2008) and also was similar to what was found in isolated chloroplasts (Takahama *et al.*, 1981). Because of the operation of photosynthesis, the NADP(H) pool is the highest in the chloroplast. The NAD(H) pools are most important in the mitochondria. However, if we look at the contribution of each compartment according to the occupied cell volume (Winter *et al.*, 1994), the pool of cytosolic NAD^+ contributes the bulk of cellular NAD^+.

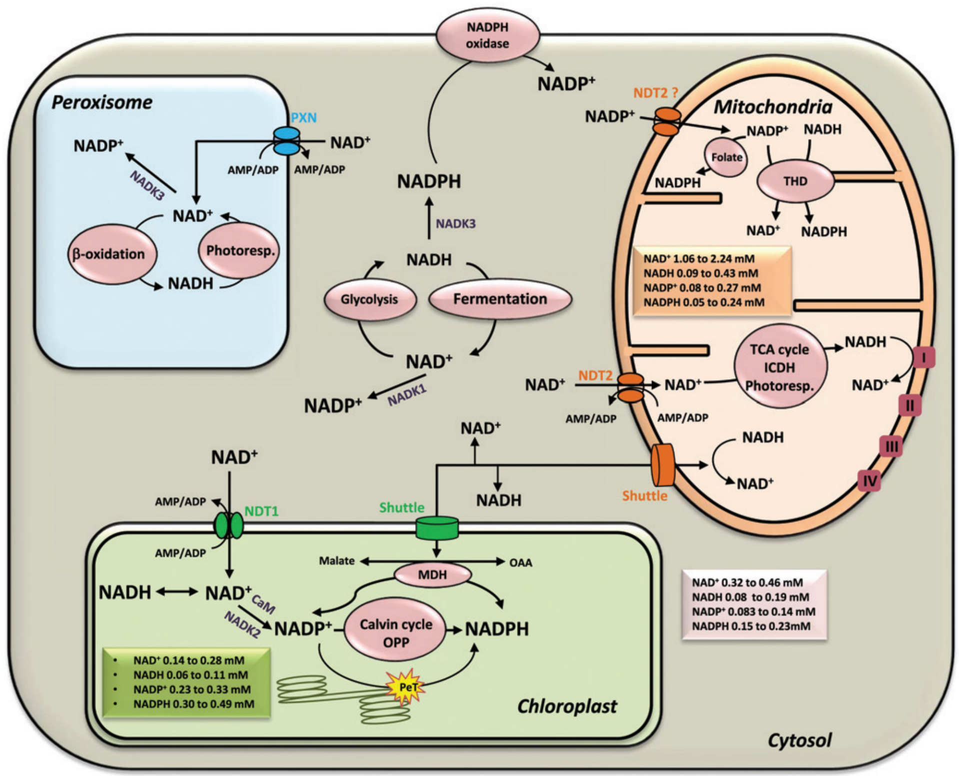

Figure 6. Pyridine nucleotide concentration in the three compartments cytosol, chloroplast and mitochondria in plant cells in light and their regeneration. CaM: calmodulin; ICDH: isocitrate dehydrogenase; MDH: malate dehydrogenase; NADK: NAD kinase; NDT: transporter of nucleotides/nucleosides; OAA: oxaloacetate; OPP: oxidative cycle of pentose phosphates; PXN: peroxisomal nucleotide transporter; pETC: chloroplastic electron transfer chain; Photoresp.: Photorespiration; TCA: tricarboxylic acid ring; THD: transhydrogenase.

The redox state of these pools also varies on a compartmental basis. In the light, pools of NAD and NADP are up to 10 and 6 times more reduced, respectively, in the mitochondria than in the cytosol and chloroplasts (Heineke *et al.*, 1991; Igamberdiev and Gardeström, 2003; Szal *et al.*, 2008). In effect, the contents of $NADP^+$ and NADPH vary considerably during the dark to light transition even temporarily equalizing in the half-hour following illumination (Heber and Santarius, 1965). Very less information is available in the literature concerning (i) the contents of NAD^+ and NADP in the other compartments in plants such as the vacuole, peroxisomes, and nucleus and (ii) the levels of the metabolic intermediates (Guérard *et al.*, 2011; Pétriacq *et al.*, 2012). Techniques are currently under development in several laboratories that aim to measure the levels of NAD^+ and NADP in the nucleus in order to better understand their impact on epigenetic control mechanisms. New techniques are also being developed to quantify in situ the levels of pyridine nucleotides within compartments using microscopy techniques include multi-photon microscopy applied to NAD(P)H (Denk *et al.*, 1990; König, 2000; Maulucci *et al.*, 2014; Morris-Blanco *et al.*, 2014), using a probe of poly (ADP) coupled to ribosylation immunohistochemical detection (Nikiforov *et al.*, 2011) or DUAL-PAM fluorescence detectors to measure plastid NADPH pools (Kauny and Sétif, 2014). The levels usually reported for the pyridine nucleotide do not distinguish between free levels and those bound to proteins, and it is thus possible that the available NAD^+ content is limiting the operation of enzymes. In mammals, it has been estimated that 50% of the NAD^+ pool of erythrocytes is free (Canepa *et al.*, 1991). Work on plant mitochondrial fractions determined that in this compartment 30 to 50% NAD^+ was bound to proteins while only 25% of NADH was in the free state (Hagedorn *et al.*, 2004). These results were confirmed by other studies showing that the free NADH levels were maintained constant regardless of the content of NADH bound to proteins (Kasimova *et al.*, 2006).

B. The passage of redox equivalents (NAD(P)(H)) among compartments

The different compartments have reversible exchange systems for NAD(H) and NADP(H) that indirectly adjust their redox state (Heineke *et al.*, 1991; Shen

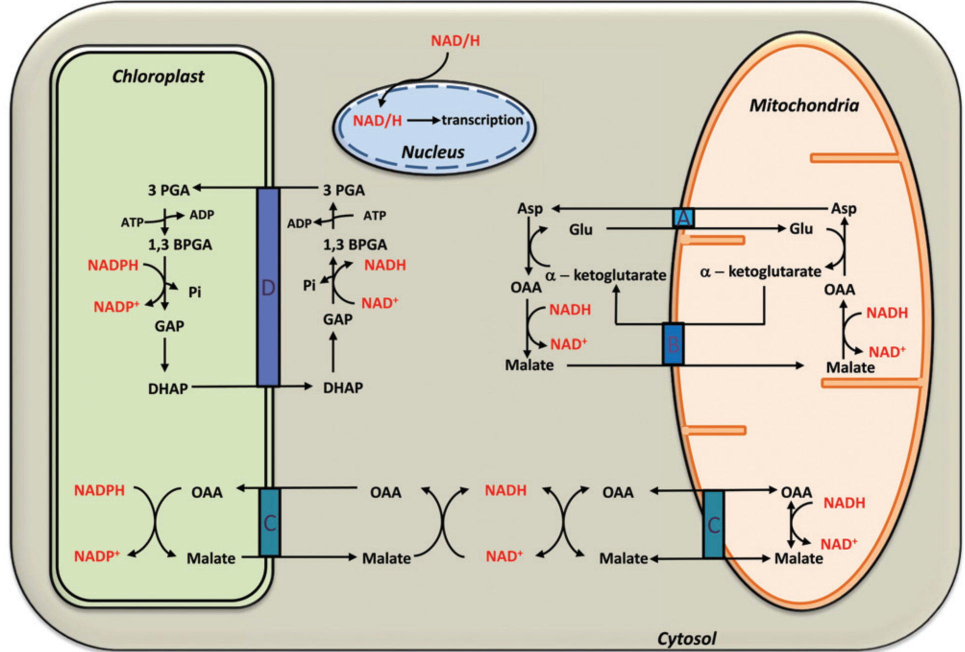

Figure 7. Mitochondrial and chloroplast shuttles. A: Glutamate-aspartate shuttle; B: Malate-a-ketoglutarate shuttle; C: Malate-oxaloacetate shuttle; D: Triose phosphates shuttle; ADP: adenosine diphosphate; Asp: Aspartate; ATP: adenosine triphosphate; 1,3BGPA: 1,3-Ac bisphosphoglyceride; DHAP: dihydroxyacetone phosphate; GAP: 3-phosphoglyceric aldehyde; Glu: Glutamate; OAA: oxaloacetate; 3PGA: 3-phosphoglyceric acid.

et al., 2006). These shuttles maintain a balance between consumption and production of NAD(P)-dependent reducing power and are found throughout living systems (Stein and Imai, 2012; Hummel and Gröger, 2014; Kato and Lin, 2014). Indeed, many metabolite exchange systems are able to transfer redox equivalents through the mitochondrial membrane and chloroplast and thereby link the NAD pools of the different subcellular compartments (Figure 7; Raghavendra and Padmasree 2003; Scheibe *et al.*, 2005; Foyer *et al.*, 2009). These systems include the triose phosphate/3-phosphoglycerate shuttle, the malate/oxaloacetate shuttle and the malate/aspartate shuttle (Day and Wiskich 1981; Journet *et al.*, 1981, Heineke *et al.*, 1991). The glutamate/2-oxoglutarate shuttle, which is essential for nitrogen assimilation and ammonium reassimilation, is also potentially involved in the exchange of redox equivalents (Woo *et al.*, 1987). There are also exchange systems that link the NAD^+ pools of the peroxisome and cytosol (Reumann *et al.*, 1994).

In animals, yeasts and plants, G3PDH localized on the inner membrane of the mitochondrion is believed to take part in the shuttle of redox equivalents between the mitochondria and cytosol (EC 1.2.1.12; Shen *et al.*, 2003; Shen *et al.*, 2006). The catalytic site of the G3PDH is facing the cytosol, which allows it to oxidize cytosolic NADH as the mitochondrial NADH dehydrogenases do (EC 1.6.5.3; Rasmusson *et al.*, 2004; Shen *et al.*, 2006). The mitochondrial G3PDH is, therefore, very important for the oxidation of glycerol to generate energy from lipid reserves in germinating seeds and young seedlings (Shen *et al.*, 2003).

C. The intracellular transport of pyridine nucleotides

Despite the existence of these high-throughput redox exchange systems, available data on the biosynthesis of NAD^+ in cells suggest direct entry of pyridine nucleotides in the organelles. Indeed, as early as 1983, a slow absorption of NAD^+ was observed by purified plant mitochondria (Neuburger and Douce, 1983; Neuburger *et al.*, 1985). Since then, two types of carriers capable of transporting the nucleotides across mitochondrial and plastid membranes were identified, namely NDT1 and NDT2 located at the chloroplast and mitochondria membranes, respectively. NDT1 and NDT2 can exchange NAD^+ for NaMN, NMN, or NaAD, as well as against other nucleotides such as ADP or AMP but cannot exchange for nicotinamide or nicotinate (Palmieri *et al.*, 2009). Indeed, it has been subsequently shown that the NMN and, to a lesser extent, the NaMN could be imported into the mitochondria and converted to NAD^+ in the Jerusalem artichoke (*H. tuberosus*; Di Martino and Pallotta, 2011). In humans, the mitochondrial pyridine

nucleotide carrier preferentially transports NMN, which subsequently serves as the substrate for NMNAT to generate NAD^+ in the mitochondrial compartment (Nikiforov *et al.*, 2011). It was also demonstrated that the $NADP^+$ can be imported into isolated mitochondria, suggesting that there is an $NADP^+$ carrier in the inner membrane of plant mitochondria (Bykova and Møller, 2001). NAD^+ and NADH may also be carried across the peroxisome membrane by a shuttle called PXN. This shuttle transports NAD^+ nucleotides, NADH, ADP, and AMP and can also carry the coenzyme A (CoA), dephospho-CoA, acetyl-CoA, and adenosine 3′, 5′-phosphate (PAP) (Agrimi *et al.*, 2012). PXN is used to supply the peroxisome with the Acetyl CoA and NAD^+ required for optimal degradation of fatty acids as well as the remobilization of lipid reserves, particularly those dependent on β-oxidation (Bernhardt *et al.*, 2012).

It is commonly accepted that the free NAD^+ passes through the nuclear pores to be used by PARP and bind to proteins such as histones like Sirtuin type deacetylase as well as transcription factors regulated by pyridine nucleotides, such as NPAS2 and CtBP (Zhang *et al.*, 2002; Fjeld *et al.*, 2003). The cytosolic redox state of NAD^+/NADH couple could thus link cellular metabolism with gene transcription (Fjeld et *al.*, 2003).

D. The extracellular transport of pyridine nucleotides

In plants, it is commonly accepted that the NAD^+ and NADP work in conjuncture to regulate intracellular signaling process. However, in animals, $NAD(P)^+$ is also present in the extracellular compartment where it can (i) bind to plasma membrane receptors and (ii) be used as an ADP-ribosylate surface receptor triggering a cellular signaling cascade (Zhang and Mou, 2009). There is also a transport of pyridine nucleotides from the extracellular medium inwards to the cells. However, NAD^+ is only transported into the extracellular medium but not from the extracellular medium to the interior of cells. NAD-nucleotide dinucleotide glycohydrolases localized on the external cell surface degrade NAD^+ to NMN, which is in turn converted by an extracellular nucleotidase to the 5'-nicotinamide riboside, which subsequently enters the cell via nucleoside transporters (SLC28 and SLC29; Zhang *et al.*, 2013.) and fuels intracellular synthesis of NAD^+ (Aleo *et al.*, 2001; Nikiforov *et al.*, 2011). $NAD(P)^+$ may also be released into the extracellular space in response to stimulation (Sáez *et al.*, 2003; Smyth *et al.*, 2004; Bruzzone *et al.*, 2006). $NAD(P)^+$ released into the extracellular space in mammals can be metabolized by CD38 (an animal ADPRcyclase) to produce cADPR and NAADP which are both involved in calcium signaling (Billington *et al.*, 2006; Bruzzone *et al*, 2006).

In plants, it has been shown that the hypersensitive reaction causes a leak of pyridine nucleotides which increases their extracellular concentrations to induce expression of pathogenesis-related (PR) genes. Furthermore, these effects appear to be calcium-dependent (Zhang and Mou, 2012; Fu and Dong, 2013). Further experiments revealed that infiltrating protoplasts with NAD^+ and $NADP^+$ did not result in the increased intracellular nucleotides content, suggesting that these molecules are not transported inwardly in plants (Zhang and Mou, 2009). However, on the provision of quinolinate plant cells accumulate NAD^+ (Pétriacq *et al.*, 2012). In yeast, quinolinate, but also nicotinate and nicotinamide riboside, may be imported from and excreted to the extracellular medium, whilst nicotinamide is only imported. In plants, two permease type of carriers have been identified, Nrt1 and TNA1 which allow the incorporation of nicotinamide riboside and quinolinate, respectively (Belenky *et al.*, 2011; Ohashi *et al.*, 2013.). These pyridine nucleotide exchanges allow cells to store these metabolites extracellularly and reuse them at will to maintain appropriate intracellular concentrations of NAD^+ (Ohashi *et al.*, 2013). Intriguingly, in plants, another precursor of NAD^+, NaMN has been demonstrated to stimulate potato seedling growth.

Recent research conducted in bacteria and mammals suggest that in addition to their role in the oxidative metabolism and cell signaling, pyridine nucleotides could regulate the transport of ions. Indeed, it has demonstrated that about a dozen transport systems were regulated by molecules of NAD(P)/(H) and their products, ADPR and cADPR in these organisms. Intriguingly, both the redox state and pyridine nucleotide levels *per se* participate in the control of intra- and extra-cellular potassium, sodium, and calcium (Kilfoil *et al.*, 2014).

III. The functions of NAD^+ in plants

A. Redox functions of NAD^+ and their implications

1. The $NAD(P)^+$/NAD(P)H redox couples

$NAD(P)^+$ is a coenzyme reducing power transducer, i.e., it is capable of transferring electrons to a molecule at a more oxidized state molecule. Thus, there is a reduced NAD(P)H or oxidized $NAD(P)^+$ form and a couple such as the $NAD(P)^+$/NAD(P)H is known as a redox couple. The tendency of couples to accept or donate electrons to another couple is called the

redox potential. This potential can reveal the feasibility and the direction in which the electrons are transferred between components of a biochemical system. All redox potentials are defined according to their ability to receive or donate electrons to a standard hydrogen electron (SHE, a 1-M solution of H^+, pH 0 in which is immersed a platinum electrode), and are expressed in volts. In biology, redox potentials are defined at pH 7 and at 25 °C, which for the reference torque $H_2/2H^+$ has a redox potential of −420mV. These redox potentials are recorded when couples balance reduced/oxidized states at what is known as their equilibrium midpoint (EM) potential. From these potential values, it is possible to determine a difference in redox potential between two redox couples that allows the transfer of electrons ΔEm ($Em_{acceptor} - Em_{donor}$). For example, in the mitochondrion during electron transfer from the donor NADH to the acceptor O_2, the $\Delta Em = 0.82 - (-0.32)$ V, i.e., 1.14 volts allowing one to deduce the free energy change of the reaction, which in this case is exergonic. During the reverse transfer water to $NADP^+$ in photosynthesis, the value will be identical but the sign will be reversed and thus the reaction is endergonic and requires energy supply in the form of light. $NADP^+$ is generally used as reducing agent in biosynthetic pathways (photosynthesis, nitrogen assimilation, and biosynthesis of fatty acids), whereas NAD^+ is largely involved in catabolism where it acts as an oxidant. Plant cells contain many major redox couples which regulate the transfer of electrons within cells as well as regulating flux across chloroplast and mitochondrial membranes and thus determine the overall cellular redox status. These compounds have very different concentrations depending on the physiological state of the cell. Because of their negative redox potential, some couples such $NAD(P)^+$/NADPH tend to act as reductants, while others such as reactive oxygen species are strong oxidizing agents (Foyer and Noctor, 2005).

2. The role of NAD(P)H in maintaining the cellular redox status

Low oxygen levels accompanied the early evolution of life on earth, with the appearance of cyanobacteria and plants subsequently enriching the atmosphere with oxygen to levels close to current levels 550 million years ago (Fournier, 2003). Aerobic cells cope with these oxygen concentrations by maintaining a highly reduced internal environment. This is made possible by the interactions between soluble redox including NAD^+, $NADP^+$, glutathione (GSSG/GSH), and ascorbate (DHA/ASC). In particular, the pyridine nucleotides ($NAD(P)^+$/NAD(P)H) are the major form of soluble redox in cells. Indeed, by contrast to antioxidant compounds such as glutathione and ascorbate which react spontaneously with oxygen, pyridine nucleotides react slowly with oxygen and oxidation is dependent on enzymatic reactions. Within cells, pools of glutathione and ascorbate react, first, spontaneously or under the action of enzymes such as (per) oxidases with oxygen, and, second, are reduced by high capacity reductase which depends upon the reducing power of NAD^+ and $NADP^+$ (Figure 8). Glutathione and ascorbate are the bulwark of a redox buffer system for $NAD(P)^+$-dependent detoxification of reactive oxygen species. Disruption of this maintenance system generates a redox signal which is encountered in many stress related to (a)biotic disturbances and/or developmental processes. In these processes, the $NADP^+$/NADPH couple plays a particularly important role because it is at the junction of metabolism and ROS detoxification (Figure 8).

In chloroplasts, the cofactor concentration of oxidized $NADP^+$ available for its reduction by ferredoxin $NADP^+$ reductase determines the nonlinear flow of electrons to other acceptors, such as molecular oxygen (O_2). In case of over-reduction of the $NADP^+$ to NADPH pool, due to environmental stress which causes either an electron flow in the case of strong light, or unavailability of NADPH to metabolic reactions in the case of disease, nutritional, cold, or drought stress, the electrons are deflected and ROS formation is accelerated (Scheibe *et al.*, 2005). NAD(P)H is also a precursor for cytosolic ROS when used as a substrate by the NAD(P)H oxidases (Foreman *et al.*, 2003; Kwak *et al.*, 2003). NAD(P)H is also involved in the generation of NO via the reactions catalyzed by nitrate reductase (NR) and nitrite reductase (Stöhr *et al.*, 2001; Galeeva *et al.*, 2012). NR can catalyze the transfer of the reducing power of NAD(P)H to O_2 and generation of ROS (Yamasaki and Sakihama, 2000). Moreover, the alternative oxidase of the mitochondrial electron transport chain could be controlled by changes of NADPH/$NADP^+$ ratio that follow alterations in light and CO_2 (Igamberdiev and Gardeström, 2003). ROS management is also largely dependent on NAD(P)H in plant cells. Indeed, among the five major ROS detoxification systems, namely (i) the water-water cycle (Mehler Reaction), (ii) catalases (EC 1.11.1.6), (ii) glutathione cycle peroxidases (EC 1.11.1.9), (iv) the ascorbate-glutathione cycle, and (v) detoxification of reductive peroxides, the last three involve glutathione and/or

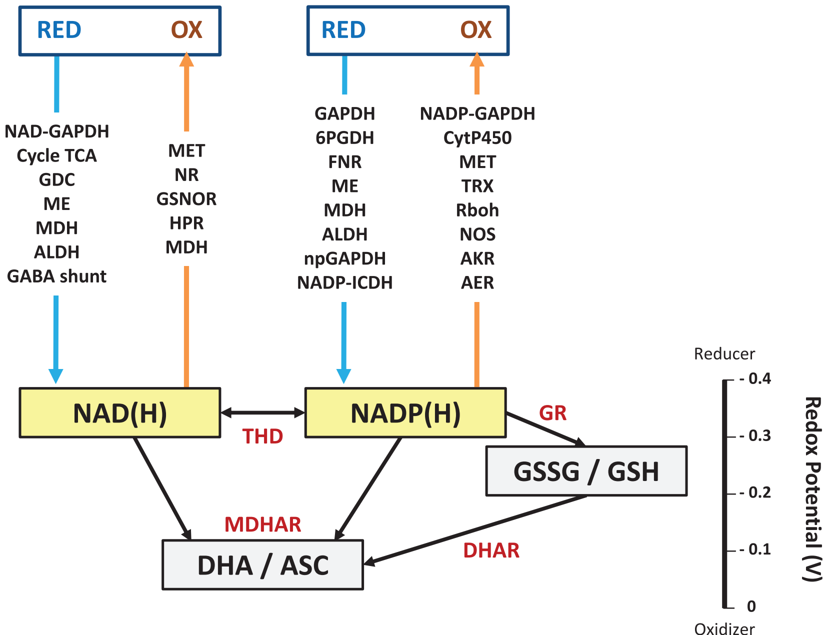

Figure 8. Simplified diagram of the main reactions binding soluble redox couples NAD(P)$^+$/H, ascorbate and glutathione. Importance is given to the main reactions reducing power consumers provided by the pyridine nucleotides. AER: alkenal reductase; ACR: aldo-keto reductase; ALDH: aldehyde dehydrogenase; ASC: ascorbate (reduced); Cyt: cytochrome; FNR: ferredoxin-NADP reductase; GABA shunt: γ-aminobutyrate pathway; (np) GAPDH: glyceraldehyde-3-phosphate dehydrogenase (non-phosphorylating); GDC: glycine decarboxylase; G6PDH: glucose-6-phosphate dehydrogenase; GR: glutathione reductase; GSH reduced glutathione; GSNOR: S-nitrosoglutathione reductase; GSSG: oxidized glutathione; HPR: hydroxypyruvate reductase; ICDH: isocitrate dehydrogenase; MDH: malate dehydrogenase; (M) DHA (R) : (mono) dehydroascorbate (reductase); ME: malic enzyme; MET: mitochondrial electron transport; NOS: nitric oxide synthase; NR: nitrate reductase; OX: oxidation; 6PGDH, 6-phosphogluconate dehydrogenase; Rboh: NADPH oxidases (for "Respiratory burst oxidase counterparts"); RED: reduction; TCA: tricarboxylic acid; THD: transhydrogenase; TRX: thioredoxin.

ascorbate-dependent NAD(P)H (Figure 8) (Sunkar *et al.*, 2003; Apel and Hirt, 2004; Mano *et al.*, 2005; Noctor, 2006). Because of the existence of redox potentials specific to each of the redox active pairs within subcellular compartments, it is difficult to define an overall value for the cellular redox state. In the cytosol and the mitochondria, the NADP and glutathione define a redox state of the order of −250 mV to −300 mV. The redox state of the chloroplast stroma in the light is a little more negative because of ferredoxin leading the reduction reactions, including those of NADP$^+$ (Asada, 1999; Setterdahl *et al.*, 2003; Foyer and Noctor, 2005). NAD(P)$^+$ is converted back into NAD(P)H by enzyme systems as already discussed in the section entitled NAD kinases. The transfer of reducing equivalents among compartments subcellular is provided mainly by shuttles systems described in "*The passage of the redox equivalents among compartments*". Similarly, in response to a need for reducing power, especially in the light as well as stress, plant cells have the ability to stimulate the production of key enzymes which control the synthesis of NAD(P), such as AO, QPT, NaMNAT, and NAD kinases. Transition to light induces NAD kinase production (Tezuka and Yamamoto, 1975), which allows the synthesis of NADPH in the chloroplast, which is essential for the synthesis of chlorophyl and carbon sequestration (Chai *et al.*, 2005).

B. The role of NAD(P)(H) in major metabolic pathways

1. NAD$^+$ control C and N assimilation which underpin plant productivity

Most of the terrestrial organic matter is produced by plants through the assimilation of inorganic carbon and nitrogen from the environment to form organic molecules. The organic matter is produced and regenerated by the molecular processes of photosynthesis and assimilation of nitrogen. Eukaryotic cells compartmentalize these biochemical processes in the various organelles based on the metabolic cycles to transfer reducing equivalents through intracellular membranes. NAD(P)H produced or exchanged among the compartments serves as an electron carrier allowing the maintenance of redox homeostasis and reductive biosynthesis.

2. NADPH production by photosynthesis

The anabolic pathway by which all photosynthetic organisms assimilate CO_2 is known as the Calvin–Benson cycle (Calvin and Benson, 1949). This cycle is divided into three parts: (i) a carboxylation stage which fixes CO_2 in the presence of a sugar acceptor which is the ribulose-1,5-bisphosphate (RuBP) which are then converted to three carbon acids and which is catalyzed by Rubisco (ii) a reductive phase consuming NADPH and ATP produced in the light via the photosynthetic electron transport chain and which converts the three carbons acids to triose phosphates, and finally (iii) a step of regeneration of the triose phosphates in which RuBP consumes ATP. Excess trioses phosphates formed are subsequently exported to other subcellular compartment and serve as a basis for the biosynthesis of all the organic molecules in the plant cell. In the chloroplast, NADPH is formed in the light by the photosynthetic electron transfer chain via ferredoxin NADP reductase (Talts *et al.*, 2007). It can be exchanged with the cytosolic compartment by the malate shuttle (Scheibe and Jacquot, 1983) which includes a malate biosynthesis system and an MDH shuttle (Figure 6) and originates in the dark or in non-green tissues from plastid and/or cytosolic pentose phosphate pathways (Spielbauer *et al.*, 2013). In the chloroplast, the NADPH regulates an NADPH-dependent type C thioredoxin reductase (NTRC, EC 1.8.1.9), which, by reducing ADP-glucose pyrophosphorylase (AGPase, EC 2.7.7.27) is used to activate synthesis in which the degradation of starch (Ekkehard and Stitt, 1989; Sparla *et al.*, 2006; Michalska *et al.*, 2009; Valerio *et al.*, 2011; Bernal-Bayard *et al.*, 2012). Besides its role in the regeneration of the plastids antioxidant pools (König *et al.*, 2002; Pérez-Ruiz *et al.*, 2006), the NADPH-NTRC system also plays an important role in the regulation of the synthesis of chlorophylls (Richter *et al.*, 2013). These regulations operate in concert via the action of plastidial thioredoxin (Geigenberger and Fernie, 2014).

3. NADPH utilization for lipid synthesis

In addition to the synthesis and/or degradation of starch and chlorophyl which are regulated by NADPH, lipid biosynthesis, and more particular fatty acid biosynthesis consume NADPH, ATP, and carbon skeletons. Indeed, it is exclusively in the plastid that *de novo* biosynthesis of fatty acids occurs (Ohlrogge and Browse, 1995). The fatty acid synthase (FAS or fatty-acyl-CoA synthase (EC 2.3.1.86), which is involved in *de novo* biosynthesis of fatty acids, is a multi-enzyme complex that consumes NADPH to drive condensation of malonyl-CoA units of acetyl-CoA until palmitic acid is obtained. Thus, the synthesis of a molecule of palmitic acid is consumed eight molecules of acetyl-CoA, 14 molecules of NADPH and seven molecules of ATP. This explains why the synthesis of fatty acids is closely coordinated with the light reactions of photosynthesis (Geigenberger and Fernie, 2014). Conversely, the catabolism of lipids which leads to the sucrose formation during lipid-resistant seed germination produces NADH in glyoxysomes via β-oxidation of acyl-CoA under the action of the MDH of the glyoxylate cycle. A cytosolic isoform of MDH similarly produces NADH. By this process, germinating oleaginous seeds effectively convert lipids into sugars while providing reduction power in abundance in the form of NADH (Graham, 2008).

4. The utility of NAD(P)(H) in other major pathways of C metabolism

In plant respiration, carbon compounds are degraded to ensure the synthesis of ATP which provides the energy required for cellular processes. Globally, carbohydrates and lipids are transformed into organic acids which the mitochondria use to reduce NAD^+ to NADH. The NADH is then oxidized and the electrons are transferred to the molecular oxygen by the electron transfer chain of the mitochondrial inner membrane. In this process, enzymatic complexes pump protons across the membrane, creating a potential gradient used for ATP synthesis. This catabolic pathway takes place in three main stages: glycolysis, tricarboxylic acid cycle (TCA or Krebs cycle), and the membrane electron transfer. In the first step called glycolysis, the hexose-phosphates are converted into triose-phosphates and then into organic acids, in particular, pyruvate, producing reducing power in the form of NADH under the action of phosphorylating glyceraldehyde-3-phosphate dehydrogenase (G3PDH, EC 1.2.1.9). There is also a non-phosphorylating isoform described above (see the section entitled NAD kinase) which makes it possible to generate NADPH. In plants, enzymes involved in glycolysis are functionally and physically closely associated with mitochondria (Giegé *et al.*, 2003; Graham *et al.*, 2007) and in potatoes, the degree of association of glycolytic enzymes depends on the respiratory intensity (Graham *et al.*, 2007). The pyruvate formed by glycolysis passes directly into the mitochondrial matrix (Lunn, 2007) where it can be converted to acetyl-CoA by pyruvate dehydrogenase, also called pyruvate decarboxylase (EC 1.2.4.1). Note that glycolytic

enzymes such as G3PDH (GAPDH) can be found in the nucleus and generate NADH under stress conditions (Vescovi *et al.*, 2013). It is also possible that hexokinase can be found there, as is the case with other organisms (Kim and Dang, 2005). The second stage, known as the tricarboxylic acid cycle (Krebs, 1937), consists of transforming acetyl-CoA into a range of organic acids transformed via enzymatic reactions that generate reducing power in the form of NADH and of FADH (Rasmusson and Møller, 1990). In plants, the cycle generally does not work cyclically, probably because the TCA cycle works in accordance with the metabolic needs of each organ based on environment conditions (Hanning and Heldt, 1993; Sriram *et al.*, 2004; Alonso *et al.*, 2007; Allen *et al.*, 2009; Tcherkez *et al.*, 2009; Gauthier *et al.*, 2010). Each of the steps that allow the production of NADH would be inhibited by a high $NADH/NAD^+$ ratio, which would balance the oxidation of pyruvate with the oxidative phosphorylation that occurs on the internal mitochondrial membrane (Geigenberger and Fernie, 2014). In a third step, the reducing power, formed by the TCA cycle and glycolysis, transfers its electrons to molecular oxygen via the electron transfer chain of the mitochondrial inner membrane, and an ATP generating proton gradient is created. Plants have, on this electron transfer chain, enzymes unique to the plant kingdom called NAD(P)H dehydrogenase alternates, located on the internal and external faces of the mitochondrial membrane, which allow them to regulate levels of NAD(P)H and optimizing their growth (Rasmusson *et al.*, 2004; Rasmusson and Wallström, 2010; Wallström *et al.*, 2014).

5. Transfering NAD-reductive equivalents between metabolic pathways

One of the major metabolic problems facing the plant is the management of the lack of $NADP^+$ electron acceptor which can be at the origin of a mass production of ROS. Indeed, the photosynthetic electron transfer chain produces more reducing equivalents than required in the chloroplast for the synthesis of sugars (Stitt, 1986). The CO_2 limitation available for the Calvin–Benson cycle and the lack of $NADP^+$ where another photosystem I acceptors lead to the formation of ROS that must be detoxified by various systems. However, there are several mechanisms that compensate for the lack of electron acceptors in the chloroplast. (i) The first of these is called the malate shuttle (Scheibe, 1984). It consists of the synthesis of malate from NADPH-dependent plastid malate dehydrogenase (MDH-NADP), and the malate thus formed is exported to the cytosol via a shuttle (shuttle C, Figure 7) (Taniguchi *et al.*, 2002). The malate shuttle re-balances the NADPH/ATP ration, avoids imbalances that limit the photosynthetic electron flux and redirects the excess reducing power to other compartments where it will be used (Backhausen *et al.*, 1998; Scheibe, 2004). Moreover, MDH-NADP is activated by light. By contrast, it is inhibited by the high $NADP^+/NADPH$ ratios, which makes it an effective system for controlling the redox homeostasis of NADP(H) within the plastid compartment (Scheibe and Jacquot, 1983; Scheibe *et al.*, 2005). The importance of this enzyme is demonstrated by the lethal character of homozygous T-DNA mutants in the *A. thaliana* (Selinski *et al.*, 2014). (ii) A second mechanism is used in plants when the electron acceptor limitation is problematic as well as under conditions of strong light or drought, is that of cyclic electron transfer (Munekage *et al.*, 2004). This system makes it possible to reduce the production of NADPH, to recycle the electrons not used for its synthesis in the absence of acceptor in sufficient quantity, while increasing the production of ATP, and makes it possible to rebalance the ratio ATP/NADPH (Miyake, 2010). Under limiting CO_2 conditions or a continuous lack of $NADP^+$ acceptor, this system avoids mass production of ROS within chloroplasts (Foyer *et al.*, 2012). (iii) The third mechanism involved in chlorophyl containing cells in the light is that of photorespiration. This mechanism constitutes a major sink for reducing equivalents, especially when the demand for NADPH and ATP is problematic, for example at high luminous intensity, high temperature, and when the closed stomata cause an important CO_2 limitation for photosynthesis (Foyer *et al.*, 2009). By re-assimilating the ammonium produced by the decarboxylation of glycine (mainly by glutamine synthetase GS, EC 6.3.1.2, and ferredoxin-dependent glutamate synthase Fd-GOGAT, EC 1.4.7.1, or that dependent on NADH, NADH-GOGAT, EC 1.4.1.14), photorespiration consumes reducing equivalents of ferredoxin, NADH and ATP and regenerates the oxidized equivalents available again for the fixation of electrons in the photosynthetic transfer chain. It also appears that photorespiration stimulates LASPOX activity due to the decarboxylation of glycine, accelerating the oxidation of NADH to NAD^+ and the electron flux of the mitochondrial transfer chain to oxygen (Igamberdiev *et al.*, 1997; Vishwakarma *et al.*, 2014). Photorespiration also releases CO_2 into the mitochondria, which allows the consumption of excess NADPH

and the regeneration of $NADP^+$ in the Calvin–Benson cycle (Busch *et al.*, 2013). It is believed that in normal atmospheric conditions 2-phosphoglycolate (2-PGA) is produced by Rubisco oxygenase activity (Zhu *et al.*, 2008) for every four turns of the Calvin–Benson cycle. Although the impact of a photorespiration inhibitor on photooxidation has been known for a long time (Wu *et al.*, 1991; Kozaki and Takeba, 1996; Osmond and Grace, 1996), it is only recently that the impact of a defective photorespiration on the inhibition of photosystem II has been described (Takahashi *et al.*, 2007). Because of their perivascular sheath, which allows CO_2 to be concentrated, C4 plants have a lower, but non-zero rate of photorespiratory activity due to leakage in the sheaths, which is greater in dicotyledons than in monocotyledons (Dai *et al.*, 1995; Maroco *et al.*, 1997). In *Amaranthus edulis*, photorespiration accounts for 6% of net photosynthesis and photorespiratory mutants are unable to grow in the absence of high CO_2 (Dever *et al.*, 1996; Lacuesta *et al.*, 1997). Evidence of photorespiratory activity in corn is yet older (Chollet, 1976), and low-glycolate oxidase mutants are unable to grow in the air (Zelitch *et al.*, 2009), demonstrating the importance of photorespiratory mechanisms in all plant species (Wingler *et al.*, 2000).

6. N metabolism and its coordination with C metabolism

In addition to light, water, CO_2, and mineral elements are required for plant growth and development. Among mineral elements, nitrogen is probably the most essential because it is used for the synthesis of amino acids which are the building blocks of proteins, nucleotides, chlorophyl, and many other metabolites and cellular components (Taiz and Zeiger, 2008). Nitrogen is, therefore, required in large quantities in order to allow plants to enrich the synthesis of carbon skeletons into more complex molecules essential for the production of biomass. As we document below, pyridine nucleotides play a decisive role in the assimilation of nitrogen by plants and contribute to the close coordination of the carbon and nitrogen metabolisms necessary for the harmonious growth of plants.

In the previous section, we described how photorespiration involves a rather complex carbon recycling and also requires the recycling of ammonium from the decarboxylation of glycine. The latter reaction is catalyzed by glycine decarboxylase or GDC (EC 1.4.4.2, Keys *et al.*, 1978). The ammonium produced by GDC is assimilated to the level of the GS/GOGAT cycle in the chloroplast as glutamate by the use of two enzymes located in both chloroplast and mitochondria: GS (GS2), and GOGAT, mainly the FD-GOGAT (GLU1) and in a minority way the NADH-GOGAT (Hayakawa *et al.*, 1994; Taira *et al.*, 2004; Jamai *et al.*, 2009). The metabolic flux of photorespiration is very high and the mitochondrial conversion of glycine to serine produces considerable amounts of ammonium, up to 10 times more than the primary assimilation of nitrogen (Keys *et al.*, 1978; Rachmilevitch *et al.*, 2004). This process, which is also called the photorespiratory nitrogen cycle (Keys *et al.*, 1978), uses the same isoforms of GS and GOGAT as those involved in the primary assimilation of ammonium (Hirel and Lea 2002). By generating NADH in the mitochondria, this process may contribute to the increase of the pool of NADH in the cytosol under the light.

All plants have the capacity to achieve the primary assimilation of nitrates. This assimilation begins with the reduction of nitrates to nitrites catalyzed by nitrate reductase (NR, EC 1.7.1.1), which requires NADH (Miflin, 1970; Vincentz and Caboche, 1991), yet some isoforms require NADPH (NR-NADPH, EC 1.7.1.3, Savidov *et al.*, 1998). NR is regulated in a very complex manner, enabling controlled reduction, in response to environmental signals, of nitrate reduction in close coordination with the assimilation of carbon. In general, it is coordinated with photosynthesis and is regulated by various factors, such as nitrate content, light, O_2, and CO_2 availability (Campbell *et al.*, 1988; Faure *et al.*, 1991; Vincentz and Caboche, 1991). The ability of chloroplasts and mitochondria to deliver reducing equivalents to the cytosol can influence the rate of nitrate assimilation (Krömer and Heldt, 1991; Hanning and Heldt, 1993). Conversely, low photosynthesis may limit NR activity by decreasing reductant availability (NADH) and by post-translational inactivation of the enzyme (Kaiser *et al.*, 2000; Kaiser *et al.*, 2002). The presence of a nucleotide pyrophosphatase (EC 3.6.1.9) physically associated with NR in *Brassica oleracea* suggests a close control of NADH levels in the vicinity of the enzyme in order to modulate its activity (Moorhead *et al.*, 2003).

As described earlier in this section, the contents and redox state of pyridine nucleotides closely control the activities of the major routes of carbon and nitrogen metabolism. Conversely, metabolic activity modulates NAD(P)(H) levels to acclimate to environmental conditions. One of the main concepts of the integration of nitrogen and carbon metabolism in plants is based on their use of reducing equivalents and ATP. Indeed, it is assumed that the assimilation of nitrate is a strong consumer of reducing power, whereas CO_2 fixation

requires more ATP than reducing power. In this case, ATP is also provided by the other subcellular compartments, in particular, mitochondrial respiration, while the reducing power consumed in the cytosol by nitrate reductase is partly provided by an output of reducing equivalents of plastids and mitochondria. To summarize, carbon fixation consumes three times more ATP than nitrate assimilation and that assimilation of nitrates consumes three times more reducing power than CO_2 fixation in triose phosphates (Woo *et al.*, 1987; Noctor and Foyer, 1998).

Several studies indicate that levels of NAD(H) play a role in the integration of carbon and nitrogen metabolism, particularly those addressing the study of mitochondrial complex I mutants, such as the tobacco CMS II mutant (Dutilleul *et al.*, 2005; Hager *et al.*, 2010; Podgórska *et al.*, 2014). Stopping the oxidation of NADH by complex I resulted in activation of the NAD(P)H dehydrogenases and leads to a nitrogen-rich phenotype of plants rich in nitrogen. These plants displayed a general increase in the contents of organic acids and amino acids, in particular, amines (Dutilleul *et al.*, 2005; Hager *et al.*, 2010). Indeed, a greater assimilation of nitrates was observed in CMS II (Dutilleul *et al.*, 2005; Pellny *et al.*, 2009). Other characteristics typical of N-rich status are found in the mutants of complex I: repression of lateral root growth, altered distribution of biomass between roots and aerial parts in response to nitrogen availability (Pellny *et al.*, 2008). Other examples show that nitrogen nutrition, which constitutes a major sink of reducing power in plants, has a strong influence on carbon metabolism. Thus, when the nitrogen supply relies on ammonium, the NADH content, which is no longer used for the assimilation of nitrates, increases. Plants then increase the activity of their alternate respiratory pathways (NAD(P)H dehydrogenases, LASPOX, and uncoupling proteins) (Escobar *et al.*, 2006), which do not generate ATP, leading to a reduced plant growth.

One of the mechanisms for rebalancing the ATP/NAD(P)H ratios among compartments is based on the operation of organic acid carriers, such as the malate shuttle. When this is absent, it is lethal (Selinski *et al.*, 2014). On the other hand, when the capacity of the malate valve is simply limited, this leads to an increase in the assimilation of nitrogen and glycolysis within the plastidial compartment, by increasing the Fd-GOGAT, NADH-GOGAT, and plastid NAD-GAPDH activities, potentially rebalancing the ATP/NAD(P)H ratios within the chloroplast (Selinski *et al.*, 2014). Thus, the defective malate valve is compensated by an increase in plastidial glycolysis to cover the plastid demand for ATP. Otherwise, there would be too much NADPH in the plastid which would block the electron transfer chain, and therefore the generation of ATP necessary for carbon fixation (Selinski *et al.*, 2014; Selinski and Scheibe, 2014).

C. Importance of NAD(P)(H) in developmental processes

The development of plants is characterized by the appearance of new organs and determines qualitative events, which can be detected over time and supported by metabolic processes. That said metabolic processes involve cofactors like the NAD(P)/H that are essential to them. These features describe why pyrimidine nucleotide levels are highly variable within different organs of the same plant, and thus it is possible to associate the physiological needs of a developmental program with the metabolic activities that underlie them. The levels of these cofactors and their redox state vary not only according to the organs but also according to their age, suggesting a close involvement of pyridine nucleotide levels with organogenesis and organ aging processes (Yamamoto, 1963). Thus, very high levels of NAD^+ are measured in the storage organs such as cotyledons or albumen, whereas NADP (H) levels and NADP/NAD^+ ratio are low. Conversely, in actively growing tissues, the NADP/NAD^+ ratio is high. In the flower organs of *A. thaliana*, there is also a very high accumulation of NAD(P)(H) in pollen, whereas very low levels are measured in petals and pistil (Hashida *et al.*, 2013a). With the age of the plant, a change in the redox status of NADP is observed (Wang and Pichersky, 2007). For example, NADPH/$NADP^+$ ratios decrease with age in cotyledons, hypocotyls, roots, leaves, and flowers (Yamamoto, 1963; Queval and Noctor, 2007; Wang and Pichersky, 2007).

1. NAD in seed germination

Germination is the process by which a seedling is formed from a seed and as such is characterized by the transition from the latent life of the seed to an active life, under the influence of favorable factors. It is a physiological process which begins with seed hydration and ends with the growth of the radicle (Evenari *et al.*, 1966). Thus, a seed germinated when the radicle pierced the seed coat (Come, 1970). Major metabolic events occur during germination, involving pools of free nucleotides.

In fact, radicular breakthrough, which is preceded by high ATP consumption, is characterized by a strong increase in NADP(H) and NAD(H) pool consumption (Brown, 1965). Since the NADP (H)/NAD(H) ratio differs greatly between nondormant and dormant seeds (Gallais *et al.*, 1998), and while NADP levels are difficult to measure for dormant seeds, NAD measurements are sometimes used as an indicator of seed dormancy depth (Hunt and Gray, 2009). In non-dormant seeds of *A. thaliana*, the increase in the NADP(H)/NAD(H) ratio is accompanied by a high elevation of NAD kinases, whereas in dormant seeds NADP phosphatases are very active (Hunt and Gray, 2009). In the dormant oat seeds (*Avena sativa*), there is also a strong NADP phosphatase activity (Gallais *et al.*, 2000).

The decrease in NAD levels observed during germination may also be due to nicotinamidase activities. It is indeed observed in *A. thaliana* T-DNA insertion mutants that the mutation of the *nic2* gene inhibits germination. This inhibition may be due to the accumulation of PARP-inhibiting nicotinamide and the accumulation of NAD^+ in seeds (Hunt *et al.*, 2007). In effect, by treating seeds with the different pyridine nucleotides, it has been shown that the oxidized forms NAD^+ and also $NADP^+$ inhibit seed germination of *A. thaliana* (Hunt *et al.*, 2007).

On the other hand, in germinating seeds, a remobilization of pyridine nucleotides reserves can be observed as it is the case for trigonelline. In fact, trigonelline demethylase activity is induced during germination of coffee beans and mung bean, accompanied by a decrease in trigonelline synthase activity and a concomitant trigonelline stocks decrease in seeds (Shimizu and Mazzafera, 2000; Zheng *et al.*, 2005). It seems that during germination, NAD is remobilized, probably to allow a restart of metabolism and to respond to needs such as the production of ROS which intervenes in signaling processes required at the root emergence, such as ABA signaling, calcium signaling, and redox signaling (Oracz *et al.*, 2009; El-Maarouf-Bouteau *et al.*, 2014). NADPH-dependent ROS production appears to be essential for triggering germination since the absence of NADPH oxidase type B and associated ROS production prevents *A. thaliana* seeds from germinating (Müller *et al.*, 2009).

2. NAD in sexual reproduction

During the floral transition, the apical meristem passes from a vegetative stage to an inflorescence stage. This event is essential for the formation of the reproductive system and requires the intervention of a panel of genes and reactions involving new biosynthesis and redox metabolism.

Indeed, in spinach (*Spinacia oleracea*) grown in long days, the floral transition is accompanied by a depletion of the pyridine nucleotide pools (Bonzon *et al.*, 1983). Similarly, in *A. thaliana*, foliar NAD pools increased sharply during flower transition until flowering initiation. NADP follows the same pattern as NAD but with lower levels compared to NAD (Queval and Noctor, 2007). Once flowering is initiated, NAD contents collapse in rosette leaves (Queval and Noctor, 2007b). In flowering plants, NAD^+ levels of flowers are three times higher than in rosette leaves (Wang and Pichersky, 2007). These data all suggest a remobilization of the foliar NAD^+ pools to provide for the reproductive organs.

The redox state of pyridine nucleotides also appears to play a role in the floral transition. Thus, in *Nicotiana sylvestris*, the increase in the $NADP^+$/NADPH ratio caused by a decrease in the activity of a mitochondrial NADPH dehydrogenase 1 (NDB1) leads to floral induction associated with the expression of genes present in floral meristems (Liu *et al.*, 2009b), and this is probably related to an altered redox metabolism (Kocsy *et al.*, 2013). In *A. thaliana*, a three-fold increase in the NAD^+/NADH ratio compared with that of the rosette leaves was also observed in flowers (Wang and Pichersky, 2007). Although the physiological significance of this observation is not clearly established, it is possible that the redox state of NAD and NADP pool plays a role in the physiology of the reproductive organs. Indeed, NAD^+ levels would contribute to the fate of pollen by negatively regulating germination because plant pollen with 25% fewer NAD germinates prematurely (Hashida *et al.*, 2013a, 2013b). On the other hand, the NAD(P)H levels were greatly increased during pollen grain germination and pollen tube progression (Cárdenas *et al.*, 2006). NAD that accumulates in the pollen grain decreases during germination (Hashida *et al.*, 2013a) and NAD(P)H production is then observed in the subapical region of the growing pollen tube (Cárdenas *et al.*, 2006). This production of NAD(P)H is associated with a high production of ROS in the presence of a high density of mitochondria (Cárdenas *et al.*, 2006). The high levels of NAD in growing pollen tubes are probably the result of accelerated biosynthesis since high NMNAT activity was detected in developing post-meiotic stage microspore in *A. thaliana* (Hashida *et al.*, 2007). Thus, in *nmnat* heterozygous mutants, at 25% decreased NAD levels, the growth of the pollen tube is altered, showing the

importance of NAD biosynthesis for pollen tube growth (Hashida *et al.*, 2007).

As seen previously, the abundant production of NAD(P)H in the subapical regions of growing pollen tubes co-locates with intense ROS production. Transcriptomic data clearly indicate the presence of NADPH oxidases (RbohH and RbohJ) in the male gametophyte (Sagi and Fluhr, 2006). In *Nicotiana tabacum*, NAD(P)H oxidase activity was shown to play an important role in the growth of pollen tubes (Potocký *et al.*, 2007; Marino *et al.*, 2012). The massive production of ROS at the apex of pollen tubes by NAD(P)H oxidases RbohH and RbohJ, activated synergistically by calcium and by phosphorylation, would coordinate cell expansion with exocytosis mechanisms necessary for cell wall synthesis, by limiting growth spurts associated with calcium signaling (Lassig *et al.*, 2014; Kaya *et al.*, 2014).

3. NAD in root development

The elongation of roots and absorbent hairs, which is essential for the absorption of water and soil minerals, is conditioned by NADPH oxidase-dependent ROS production (Foreman *et al.*, 2003; Torres and Dangl, 2005; Cárdenas, 2009; Centeno *et al.*, 2011; Müller *et al.*, 2012; Nestler *et al.*, 2014). As in the case of growing pollen tubes, the production of ROS in the bristles is located at the apex and induces the activation of calcium channels (Foreman *et al.*, 2003; Cárdenas, 2009). As for pollen, growth rate oscillations are synchronized with calcium, pH, and ROS oscillations (Monshausen *et al.*, 2007; Monshausen *et al.*, 2009). NADPH oxidases generate ROS that allows cell wall remodeling in growing cells (Monshausen *et al.*, 2007). NADPH oxidases initiate the production of apoplastic ROS, which is amplified in *Zea mays* by peroxidases that use NADH and hydrogen peroxide as substrate (Liszkay *et al.*, 2004). In *Phaseolus vulgaris*, the activity of NADPH oxidases is necessary for the production of NOS-responsive ROS to induce rapid growth of the absorbent hair (Cárdenas *et al.*, 2008). Finally, lateral root development appears to involve NADPH oxidases in response to auxin-dependent signaling (Gibson *et al.*, 2012; Müller *et al.*, 2012).

D. NAD in the responses to environmental constraints

In a context of climate change, crop yields are more susceptible than ever to significant losses. Crop yield is determined by plant performance and environmental stress resistance which are underpinned by plant energy homeostasis. NAD appears to be a master metabolite in energy homeostasis and plant growth, having a great impact on plant productivity and stress tolerance. Indeed, NAD consuming events are known to play a role in responding to environmental stresses. Traditionally, there are two types of stress that will negatively affect plant growth: (i) biotic stresses, which result from the action of living organisms and harm the plant, such as bacterial and (ii) abiotic stress, which may be of physical origin (extreme temperatures, lack of water, lack of oxygen, excess, or insufficiency of light) or chemical origin (mineral deficiency or excess, soil pH, ozone, toxic chemicals).

1. The key role of NAD in plant immunity

Attacks caused by pathogens, bacteria, fungi, pests, or viruses can cause considerable losses in crop yield. Among the strategies put in place by plants to defend themselves, NAD metabolism plays a central role in controlling cell redox status and signaling functions. Modulations of NAD levels have been observed in plants under attack by pathogens (Pétriacq *et al.*, 2012, 2013, 2016a, 2016b). For example, in barley, infection with *Blumeria graminis* (ex *Erysiphae graminis*) var hordei, the pathogen responsible for powdery mildew in cereals, is accompanied by an increase in NAD^+ levels and a redistribution of $NADP^+$ from plastids to cytosol (Ryrie and Scott, 1968).

ROS involvement is generally associated with higher levels of NAD suggesting the stimulation of NAD biosynthetic pathways in pathogen response (Ryrie and Scott, 1968; Dutilleul *et al.*, 2003b; Pétriacq *et al.*, 2016b). Thus, the overexpression of an NADPH-dependent reductase (NADPH-dependent HC-toxin reductase), involved in the neutralization of a pathogenic toxin in rice, results in a high increase in pyridine nucleotide levels resulting from the increase in NAD synthetase and NAD kinase activities, making the plant less susceptible to attack by the toxin-producing pathogenic bacterium (Hayashi *et al.*, 2005). In *A. thaliana*, NADK1 expression is strongly induced under compatible or incompatible conditions with *Pseudomonas syringae* PV tomato, probably to allow synthesis of NADPH in the cytosolic compartment (Berrin *et al.*, 2005). In tobacco, wounds caused by pests induce NAD-derived nicotine synthesis, which is induced by overproduction of QPT (Baldwin and Ohnmeiss, 1993; Sinclair *et al.*, 2000). An inducible NAD enrichment system by overproducing *E. coli* QPT, NadC, in *A. thaliana*, demonstrated the

implication of an increase in NAD biosynthesis in plant resistance to *Pseudomonas syringae* PV. tomato-AvrRpm1 (*Pst-AvrRpm1*). This NAD-dependent resistance is associated with the induction of SA marker genes such as PR1 and ICS1 and an accumulation of free salicylic acid (Pétriacq *et al.*, 2012, 2013). These results are in agreement with the work of Zhang and Mou who showed that an application of extracellular NAD induces a better resistance of plants to *Pseudomonas* via a salicylic acid-dependent route (Zhang and Mou, 2009, 2012). Pétriacq *et al.* (2016a) further observed that mitochondrial ROS production via NAD signaling in transgenic *nadC* overexpressing plants enhanced resistance against a diverse range of virulent pathogens, including *Pst*-AvrRpt2, *Dickeya dadantii*, and *Botrytis cinerea*. This study also reveals that NAD simultaneously induces different defense hormones and that the NAD-induced metabolic profiles are similar to those of defense-expressing plants after treatment with pathogen-associated molecular patterns. Interestingly, the *Xanthomonas* type II avirulence factor AvrRxo1s, which triggered immunity in *Arabidopsis* (Popov *et al.*, 2016) was recently reported to phosphorylate NAD^+, suggesting that the effector might enhance bacterial virulence on plants through manipulation of primary metabolic pathways to mitigate ROS burst in tobacco (Shidore *et al.*, 2017).

In the study on plants overexpressing *nadC*, a strong induction of LASPO transcripts in response to *Pst* infection was also shown (Pétriacq et al., 2012). These findings are corroborated by the data provided by Genevestigator which show transcriptional regulation of the enzyme in response to various bacterial infections (Zimmermann *et al.*, 2004). LASPO is probably of particular importance in the production of NAD in response to biotic stresses, as this enzyme is found in a cluster of resistance genes in *P. vulgaris* (David *et al.*, 2009). More recently, Cyril Zipfel's laboratory confirmed the involvement of LASPO in plant responses to *Pst* phytopathogenic bacteria. An LASPO T-DNA mutant, called *fin4* (for "flagellin-insensitive 4"), is severely affected in by ROS accumulation in response to the flg22 elicitor in *A. thaliana* (Macho *et al.*, 2012). LASPO is required for NADPH oxidase D-dependent ROS accumulation necessary for stomata closure in response to PAMP (Macho *et al.*, 2012).

The cleavage of NAD also contributes to plant-pathogen interactions. Thus, in a *Sirt2* T-DNA insertion mutant in *A. thaliana*, induced expression of *PR1* genes and genes of the salicylic acid biosynthesis pathway (SA) as *PAD4*, *EDS5*, or *SID2*, makes them more resistant to *Pst* infection (Buck *et al.*, 2004; Wang *et al.*, 2010). On the other hand, Sirt2 overproducing plants show a higher sensitivity to *Pst* correlated with a decrease in SA levels. Sirt2, by consuming NAD, would negatively regulate the basal responses of plants in response to *Pst* phytopathogenic bacteria. Other results suggest a role for poly ADP-ribosylation (PAR) in plant immunity. For example, treatment of seedlings of *A. thaliana* with 3-AB (3-amino benzamide), a PARP inhibitor, would trigger induction of secondary metabolic pathways related to defense reactions as well as ROS production and deposition of callose in response to effectors such as flg2 and efu18 (Adams-Phillips *et al.*, 2010). In addition, *A. thaliana* PARG mutants are more susceptible to infection with gray mold fungus *Botrytis cinerea*, probably because of their limited ability to recycle ADP-ribose to NAD polymers (Adams-Phillips *et al.*, 2010). Several studies show an involvement of the NUDIX hydrolase-encoding AtNUDT7 protein in resistance to biotic stress (Bartsch *et al.*, 2006; Ge *et al.*, 2007; Adams-Phillips *et al.*, 2008). AtNUDT7 is a glycohydrolase with an ADP-ribose pyrophosphatase activity. The mutant *Atnudt7* is more resistant to *Pst* infection (Jambunathan *et al.*, 2010) and to the oomycete *Hyaloperonospora arabidopsis* (Bartsch *et al.*, 2006). This resistance is explained by the fact that *nudt7* mutant has high levels of NAD(P)H and accumulates ROS, which would make it more resistant to pathogens (Jambunathan *et al.*, 2010). Again, these results demonstrate the negative impact of NAD cleavage enzymes on plant resistance to biotic stress.

2. Importance of NAD homeostasis for abiotic stress resistance

Several publications point to the role of NAD concentration and related metabolites in plant resistance to stress such as for tobacco plants deficient in mitochondrial complex I. These plants which breath via alternating dehydrogenases have their growth reduced by their respiration, but their resistance to abiotic stresses is increased (Dutilleul *et al.*, 2003b). This increased resistance is accompanied by an increase in NAD^+ and NADH contents without appreciable changes in the $NADP^+$, NADPH, H_2O_2, ascorbate, or glutathione levels (Dutilleul *et al.*, 2003a, 2003b, 2005). Maintaining a high level of antioxidants also appears to be a factor preventing the occurrence of cold-related lesions in peas or drought-affected wheat plants (Kuraishi *et al.*, 1968; Maciejewska and Kacperska, 1987; Zagdanska and Kozdoj, 1994).

PARP enzymes that are stress-induced are major consumers of NAD because of these enzymes transfer

ADP-ribose units to proteins, releasing nicotinamide and forming long toxic and cell-induced ADP-ribose chains (Andrabi *et al.*, 2006) with simultaneous depletion of ATP (Amor *et al.*, 1998). RNAi lines with decreased PARP activity levels have improved energy use efficiency (EUE) by reducing their mitochondrial respiration and ROS level, which ultimately increases their tolerance to stress abiotic (De Block *et al.*, 2005). The transcripts *PARP1* and *PARP2* accumulate in response to genotoxic stresses, such as gamma rays and ROS (Amor *et al.*, 1998; Babiychuk *et al.*, 2001; Doucet-Chabeaud *et al.*, 2001). It appears that depending on the severity of the damage caused by stress, PARPs can protect or aggravate damage to DNA (Briggs and Bent, 2011). Low activation of PARPs would lead to protection, whereas high activation would lead to cell death (Amor *et al.*, 1998; Ogawa *et al.*, 2009). In addition, inhibition of PARP activities by 3-aminobenzomide (3-AB) increased growth rates of both primary and lateral roots, leading to a more developed root system (Liu *et al.*, 2017). Although the mechanisms remain uncertain, the level of poly(ADP)-ribose synthesized from NAD is proportional to the severity of stress (Leist *et al.*, 1997; Ha and Snyder, 1999). Interestingly, a decrease in PARPs increases stress tolerance, possibly due to a decrease in NAD consumption (De Block *et al.*, 2005). The decrease in NAD consumption could influence the metabolism and transduction of signals, such as those related to ABA (Vanderauwera *et al.*, 2007). Indeed, the synthesis of ABA consumes NADP(H) (Barrero *et al.*, 2005; Gonzalez-Guzman *et al.*, 2012). Other enzymes consuming NAD are also involved in the response to abiotic stress. Thus, rice plants overexpressing *SRT2* from rice, OsSRT1, are made more resistant to oxidative stress, whereas a subexpression of the same gene induces cell death, probably in connection with an activation of the transposable elements (Huang *et al.*, 2007). In *A. thaliana*, GFG1 (for growth factor gene 1) is a Nudix hydrolase carrying the ADP-ribose pyrophosphatase activity. It is essential for responding to abiotic stress, probably because it degrades ADP-ribose polymers formed during stress (Jambunathan and Mahalingam, 2006).

NADPH is an important carrier of reducing power, especially for antioxidant defense systems. In rice, different NAD kinases are variably induced by multiple abiotic stresses, and promoters of NAD kinase genes have domains responding to heat and drought (Li *et al.*, 2014). In *A. thaliana*, cytosolic NADPH is produced by NAD kinase 3 (Chai *et al.*, 2006), and a mutant for this NADK3 makes the plants more sensitive to oxidative stress. Cytosolic NAD kinase 1 and 3 are induced by exposure to abiotic stresses, such as methyl-viologen-induced stress, high salinity, or osmotic shock (Berrin *et al.*, 2005, Chai *et al.*, 2006). In pea, calmodulin (CaM)-dependent NAD kinase activity is known to be induced by cold stress (Ruiz *et al.*, 2002). A higher sensitivity to oxidative stress was observed in NAD kinases (Berrin *et al.*, 2005; Chai *et al.*, 2005, 2006) in response to salinity and drought (Zagdanska, 1990). Because the major ROS generator in plants is NADPH oxidase activity, levels of NADPH may be limiting for ROS generation in some cases (Torres *et al.*, 2002; Kawai and Murata, 2008). One study showed that NADPH oxidases are involved in response to wounds in tomato plants (Sagi and Fluhr, 2006). Another study has shown that NADPH oxidases are necessary for the rapid and systemic generation of injury-induced ROS and that ROS accumulate in the apoplast cells away from the wound site, suggesting that NADPH oxidases are involved in the spread of ROS (Miller *et al.*, 2009). NADPH oxidases are also involved in the signaling cascade induced by mechanical stimulation of the absorbent hairs (Monshausen *et al.*, 2009). It has been shown that ABA induces the expression of NADPH oxidases D and F during an osmotic stress in the guard cells and that these NADPH oxidases were essential for ABA-and brassinosteroid-dependent stomata closure (Kwak *et al.*, 2003; Xia *et al.*, 2009). *NaMNAT* is also strongly expressed in stomatal cells to provide NAD(P)(H) in an amount sufficient to produce ROS via NADPH oxidases. The under-expression of *NaMNAT* results in insufficient levels of NAD and ROS to ensure stomata closure (Hashida *et al.*, 2010). Moreover, the amount of NAD produced under the action of NaMNAT makes it possible to protect the cells from oxidative stress generated by ABA-dependent signaling in the stomata (Hashida *et al.*, 2010). NAD regenerated by NaMNAT participates in ROS production that stimulates ABA production (Kwak *et al.*, 2003) which activates the cleavage of NAD into cADPR. The latter triggered calcium signaling that is essential for the closure of stomata (Leckie *et al.*, 1998; Allen *et al.*, 2001).

3. Importance of NAD-consuming reactions for an optimal plant growth

Coordination between plant metabolism and epigenetic regulation of gene expression is of primary importance for plant facing varying environmental conditions for optimal growth. The central metabolite NAD^+ is a substrate of enzymes called Sirtuins (SIR) that are

involved in $^{\varepsilon}$N-lysine deacetylation of proteins. These modifications target proteins such as histones in the nucleus and metabolic enzymes in mitochondria and chloroplasts and play an important role not only in the epigenetic regulation of gene expression but also in the control of metabolic enzyme activity. As such, NAD levels and its redox state could coordinate metabolic activity with gene expression.

Sirtuins are NAD^+-dependent lysine deacetylases, yielding O-acetyl-ADP-ribose, the deacetylated substrate, and nicotinamide as products. Considerable attention has been paid to the hypothetical role of fluctuating NAD^+ levels as a function of energetic state and the activity of Sirtuins deacetylase enzymes in animal and yeast cells. It becomes apparent that SIR serves as both energy and redox sensor and transcriptional effector by controlling acetylation states of histones. NAD^+ levels may increase upon caloric restriction in yeast and animal cells, thereby offering an alternative means of Sirtuins activation (Kaelin and McKnight, 2013). However, it remains unclear whether Sirtuins activity is operatively linked to the metabolic state *via* fluctuations in the intracellular levels of NAD^+. In addition, Situins proteins do not just deacetylate histones but also transcription factors, thereby controlling their activity (Blander and Guarente, 2004).

Nicotinamide, the product of NAD cleavage, is acting as a feedback inhibitor of Situins and PARP NAD-consuming activities. This mechanism can counteract extensive NAD^+ breakdown in response to stress (Denu 2005; Rankin *et al.*, 1989). Interestingly, Nicotinamide is reported to protect plant cells from oxidative stress, probably due to stimulation of glutathione synthesis, and may exert an epigenetic control of gene expression with a global DNA hypomethylating effect (Berglund *et al.*, 2017). Meanwhile, nicotinamide stimulated acotinase and fumarase activities that have a key role in energy metabolism.

In plant cells, fluctuation of NAD^+ reflects activities of a more complex metabolic network (e.g., respiration/photosynthesis/photorespiration/pentose-phosphate cycle, etc.) and redox states due to both metabolic activities and stress-responses. Whether intracellular levels of NAD^+ are linked to activation of plant SIR and PARP proteins to control gene expression and metabolic activity in plant cells remains to be elucidated.

4. The central role of NAD homeostasis in plant performance

As we have seen above, the metabolism of NAD is of great importance for plant primary metabolism and responses to environmental constraints. The impact of redox and energy metabolism on plant productivity and resistance to stress is well known (Nunes-Nesi *et al.*, 2005; Dobrota, 2006; Hashida *et al.*, 2009). Under stressful conditions, the plant draws on its energy metabolism when energy production is often already affected. Below a certain threshold, growth stops, lesions appear and accumulate, which can lead to plant death. Although photosynthesis is the source of carbon skeletons and conditions plant productivity, cellular respiration converts fixed carbon into energy that is used for plant growth and development. In these energy flows the main redox carrier is NAD. Five molecules of ATP are required for its biosynthesis from aspartate and a maximum of three are required for its recycling (Noctor *et al.*, 2006; Hashida *et al.*, 2009). For normal growth and development, plants closely control their NAD levels (Titok *et al.*, 1995; Wang and Pichersky, 2007). When exposed to environmental conditions leading to oxidative stress, PARPs are induced, consume large amounts of NAD and may even modulate the activity of energy metabolism enzymes (De Block *et al.*, 2005; De Block and Van Lijsebettens, 2011; De Block et al., 2012. Andrabi *et al.*, 2014). The maintenance of plant energy homeostasis is likely to be achieved by monitoring PARP activity, activation of NAD recycling pathways, and modulation of respiratory metabolism (Amor *et al.*, 1998; Dutilleul *et al.*, 2003a; De Block *et al.*, 2005; Hauben *et al.*, 2009). In short, an improvement in energy homeostasis reduces net energy consumption when plants are subject to unfavorable conditions.

IV. Integrated effects of modifying the expression of the constituent enzymes of NAD^+ biosynthesis and metabolism

Phenotypes of plants deficient in the expression of enzymes of NAD metabolism

1. L-Aspartate oxidase (LASPO)

Early attempts to determine the physiological role of enzymes involved in NAD^+ biosynthesis from Aspartate in *Arabidopsis* indicated that *LASPO*, quinolinate synthetase (QS), and quinolinate phosphoribosyltransferase (QPT) are essential for plant growth and development (Katoh *et al.*, 2006). In the initial studies, homozygous T-DNA insertion lines for genes encoding these enzymes were not found, and heterozygous plants self-pollinated resulted in wild-type and heterozygous plants at a 1:2 ratio, without any homozygous plants in the next generation. These results were consistent with the hypothesis that homozygous

null alleles for *LASPO*, QS, and QPT genes have embryo-lethal phenotypes (Katoh *et al.*, 2006).

Recently, viable *Arabidopsis* knockdown mutants for *LASPO* were obtained and characterized (Macho *et al.*, 2012; Hao *et al.*, 2018). LASPO is a plastidial and flavoprotein enzyme, catalyzing the first reaction of *de novo* NAD biosynthesis, oxidizing L-aspartate, and iminoaspartate. In addition, it has been shown that this enzyme is able to catalyze different reactions such as L-aspartate: fumarate oxidoreductase activity (Tedeschi *et al.*, 1996; Hao *et al.*, 2018) and fumarate reductase (Tedeschi *et al.*, 1996). This enzyme is also required for stomatal immunity against the *Pseudomonas syringae*, which suggests a novel specific requirement for *LASPO* activity in pathogen-associated response (Macho *et al.*, 2012). In addition, transgenic lines with low and high expression levels of *LASPO* revealed that NAD^+ levels and *LASPO* activity are strongly correlated, revealing that this enzyme tightly controls NAD^+ biosynthesis in *Arabidopsis* leaves (Hao *et al.*, 2018). Moreover, as mentioned in previous sections, biochemical analysis of *LASPO* protein revealed that its metabolic and biochemical regulations allow a fast and fine-tuning to match pyridine production to changing physiological conditions (Hao *et al.*, 2018).

2. Quinolinate synthetase (QS)

The QS from *Arabidopsis* carries a Cys desulfurase domain which stimulates reconstitution of the oxygen-sensitive Fe-S cluster that is required for QS activity (Murthy *et al.*, 2007). An *Arabidopsis* mutant line, named as an OLD5 mutant, carrying a lesion in this enzyme did not show any change in the activity of QS but a reduced Cys desulfurase activity (Schippers *et al.*, 2008). The characterization of this mutant indicated that QS is involved in an early onset of developmental senescence in *Arabidopsis* plants (Schippers *et al.*, 2008). Furthermore, the OLD5 mutation increased the NAD steady-state levels in parallel with increased activity of NAD salvage pathway enzymes, higher levels of TCA cycle intermediates and several amino acids. The mutant plants also displayed a higher respiration rate concomitant with increased expression of oxidative stress markers. Thus, it was suggested that alteration in the oxidative state might be integrated into a plant developmental program which leads to an early senescence phenotype in the mutant plants.

3. Nicotinate (and/or nicotinamide) mononucleotide adenylyltransferase (NMNAT)

As indicated above QPT is essential for plant growth, and therefore homozygous plants could not be isolated (Katoh *et al.*, 2006). Similarly, homozygous mutant plants could not be isolated for the following enzyme in the de novo pathway, NMNAT, suggesting that the gene encoding NMNAT is also indispensable for NAD biosynthesis in *Arabidospsis* (Hashida *et al.*, 2007). Despite that, promoter activity analyses demonstrated that NMNAT gene is spatio-temporally regulated during microspore development and pollen tube growth. These results suggested that the lack of NMNAT expression in the heterozygous mutant lead to a decrease in NAD content in pollen (Hashida *et al.*, 2007). In addition, cytological analysis of atnmnat mutant was gametophytically impaired in pollen tube growth indicating the essentiality of this enzyme for normal pollen growth and seed production. Further studies with the same enzyme also suggest that NAD^+ accumulation regulates pollen fate and acts as a negative regulator of pollen germination (Hashida *et al.*, 2013a, 2013b).

Interestingly, nmnat heterozygous mutants also displayed abnormal stomatal behavior once it had been exposed to oxidative stress and the ABA-induced oxidative stress caused stomatal cell death in the mutant (Hashida *et al.*, 2010). These results suggest that NAD metabolism plays an important role during stomatal movement and also during drought stress responses. In the agreement, over-expression of NMNAT gene in transgenic *Arabidopsis* plants lead to enhanced stomatal closure and tolerance to drought stress (Hashida *et al.*, 2010). Taken together the results obtained by Hashida and coauthors indicated that NMNAT is associated with tolerance to stressful oxidative signaling in guard cells during stomatal closure.

4. NAD synthase (NADS)

Probably, because its importance for the NAD biosynthesis, as observed for the other enzymes of de novo pathway described above, knockout mutants for genes encoding NADS, which participates in the final step of NAD biosynthesis, have not been described. Recently, however, *Arabidopsis* plants overexpressing NADS gene have been generated and characterized (Hashida *et al.*, 2016). NADS overexpressing plants displayed enhanced activity of NAD biosynthesis without alterations in the levels of NAD^+, NADH, $NADP^+$, or NADPH. Interestingly, in the same plants, the amounts of some intermediates were elevated, suggesting increased NAD metabolism. NADS overexpressing plants also showed shorter longevity in comparison with untransformed plants, with leaves turning yellow immediately after bolting. This study indicated that NAD redox state might be facilitated by

Table 1. *Arabidopsis* NAD metabolism genes and reported mutants.

		Reported mutants		
Protein name	Locus identifier	Mutant name	Mutant Identification code	References
L-aspartate oxidase (AO)	At5g14760	nr	SALK_013920	Katoh *et al.*, 2006
		fin4-1[pubmedMismatch]	nr	Macho *et al.*, 2012
		fin4-2 or *laspo2*	SALK_013920	Macho *et al.*, 2012; Hao *et al.*, 2018
		fin4-3 or laspo1	SAIL_1145_B10	Macho *et al.*, 2012; Hao *et al.*, 2018
Quinolinate synthase (QS)	At5g50210	onset of leaf death5	*QS/OLD5*	Schippers *et al.*, 2008
			SALK_079205	Schippers *et al.*, 2008
			SALK_075260	Katoh *et al.*, 2006
Nicotinate/Nicotinamide mononucleotide adenyltransferase (NMNAT)	At5g55810		atnmnat/+	Hashida *et al.*, 2007, 2010, 2013a
NAD synthetase (NADS)	At1g55090	NADS	Overexpressing lines	Hashida *et al.*, 2016
NAD kinase	At1g21640	NADK2	*SALK_122250*	Chai *et al.*, 2005
	At1g78590	NADK3	SALK_079342	Chai *et al.*, 2006
	At3g21070	NADK1	SAIL_1304_B02	Berrin *et al.*, 2005
Poly(ADP-ribose)polymerase(PARP)	At5g22470	PARP1	SAIL_632_D07	Pham *et al.*, 2015
			SALK_108092	Rissel *et al.*, 2014
	At2g31320	PARP2	SALK_111410	Pham *et al.*, 2015
	At4g02390	PARP3	SAIL_1250_B03	Pham *et al.*, 2015
Nicotinate phosphoribosyltransferase (NPT or NAPRT)	At4g36940	NPT1	nr	
	At2g23420	NPT2	nr	
Quinolinic acid phosphoribosyl transferase (QPT or QPRT?)	At2g01350	QPT	EGT3031643	Katoh *et al.*, 2006
Nicotinamidase (NIC)	At2g22570	NIC1	SALK_131410	Wang and Pichersky, 2007
	At5g23230	NIC2	FLAG_415C12	Hunt *et al.*, 2007
	At5g23220	NIC3	nr	
	At3g16190	NIC4	nr	
Sirtuin-type Lys deacetylases (SIR2)	At5g09230	srt2-1	SALK_131994.45.80	König *et al.*, 2014
		srt2-2	SALK_149295.52.35	König *et al.*, 2014
	At5g55760		nr	
Poly-ADP-ribose glycohydrolases (PARG)	At2g31870	*parg1-1*	SALK_147805	
		parg1-2	SALK_116088	
	At2g31865	*parg2*	GABI-Kat 072B04	
	At5g47650	pqr-216	Activation-tagged mutants	Ogawa *et al.*, 2009
Nudix hydrolases	At4g12720	nudt7-1	SALK_046441	Ge *et al.*, 2007
	At2g04450	*nudx6*	SALK ????	Ishikawa *et al.*, 2010a
	At3g46200	knockout-nudx9	SALK_025038C	
		knockdown-nudx9	SALK_027992	
	At5g45940		nr	
	At1g12880		nr	
	At3g26690		SALK_058284	Ogawa *et al.*, 2008
	At4g11980		SALK_087382	Ogawa *et al.*, 2008
	At1g28960		SAIL_1255_G04	Ogawa *et al.*, 2008
	At3g12600		nr	
	At2g01670		nr	
	At1g14860		nr	
	At5g20070		SALK_115339 and SALK_135053	Ogawa *et al.*, 2008; Maruta *et al.*, 2016; Corpas *et al.*, 2016
	At5g19460		SALK_138802	Ogawa *et al.*, 2008
	At1g73540		SALK_055509	Ogawa *et al.*, 2008
	At2g33980		nr	
	At2g42070		SAIL_539_H02	Ogawa *et al.*, 2008
	At5g19470		nr	
	At3g10620		SALK_040636	Ogawa *et al.*, 2008
	At5g06340		SALK_139887	Ogawa *et al.*, 2008
	At1g30110		SALK_016093	Ogawa *et al.*, 2008
	At1g68760		nr	
	At1g79690		nr	
	At1g18300		nr	
	At2g04430		nr	
	At5g47240		nr	
	At4g25434		nr	
Chloroplast NAD transporter (NDT1)	At2g47490		nr	
Mitochondrial NAD transporter (NDT2)	At1g25380		nr	
Peroxisomal NAD carrier (PXN)	At2g39970	*pxn-1*	GABI_046D01	Bernhardt *et al.*, 2012
		pxn-2	GABI_830A06	Bernhardt *et al.*, 2012
		pxn-3	SAIL_636F12	Bernhardt *et al.*, 2012

nr: not reported.

an imbalance between NAD generation and degradation in response to bolting. Further analysis revealed that the modulation of NAD redox homeostasis enhanced flux though TCA cycle flux, and thus generating reactive oxygen species (Hashida *et al.*, 2016).

5. Nicotinamidase (NIC)

NIC catalyzes the conversion of nicotinamide to nicotinic acid in the NAD salvage pathway. In *Arabidopsis* genome, three genes with homology to nicotinamidase from yeast and bacteria and activity *in vitro* have been identified (Table 1) (Hunt *et al.*, 2007; Wang and Pichersky, 2007). The proteins encoded by At2g22570, At5g23230, and At5g23220 were named NIC1, NIC2, and NIC3, respectively. The homozygous plants for NIC1 allele, nic1-1, exhibited lower levels of NAD^+ and $NADP^+$ under normal growth conditions and under stress conditions, the mutant plants exhibited hypersensitivity to ABA and NaCl treatments. These effects were related to the inability of the mutant plants to increase the cellular levels of NAD(H) under these growth conditions (Wang and Pichersky, 2007). Another study characterized the gene encoding NIC2 protein, which is highly expressed in mature seed (Hunt *et al.*, 2007). In this study, it was shown that seeds from nic2-1 knockout mutant have reduced NIC activity, increased NAD levels, retarded germination, and impaired germination. This phenotype is restored by after-ripening or moist chilling, but the seeds remained hypersensitive to the application of nicotinamide or ABA. Interestingly, the reduced germination potential observed for nic2-1 seeds could be associated with reduced poly(ADP-ribose) polymerase (PARP) activity (Hunt *et al.*, 2007). In this study, it was proposed that NAD metabolism plays an important role during germination and that NIC activity in seed promotes germination either by altering NAD levels, reducing ABA sensitivity, and releasing inhibition of PARP activity.

6. ADP-ribose transferase

As discussed in other sections, NAD is also a substrate for NaM producing enzymes, particularly PARP also known as ADP-ribose transferase. This enzyme is the key enzyme in one of the major NAD^+-consuming process, the poly(-ADP-ribosyl)ation (Belenky *et al.*, 2007). Studies on the expression and localization of the three *Arabidopsis* isoforms of PARP indicated that PARP1 and PARP2 are expressed in shoot apex, young siliques, and closed and open flowers. In addition, these two genes also appear to be expressed in dry seeds, young seedlings, and late seedlings. By contrast, PARP3 seems to be expressed only in dry seeds and seeds of mature siliques (Jia *et al.*, 2013; Rissel *et al.*, 2014; Schulz *et al.*, 2012, 2014). Furthermore, although PARP3 is narrowly expressed in roots and leaves, it is massively expressed in seeds with the other isoforms displaying contrasting expression patterns (Pham *et al.*, 2015). GFP analysis revealed that PARP1 is not restricted only to the nucleus but was also visible in the chloroplasts although PARP2 was found in both chloroplasts and mitochondria (Pham *et al.*, 2015). PARP3 was clearly localized in the nuclei (Rissel *et al.*, 2014; Pham *et al.*, 2015) and a partial localization of PARP3 was also observed in cytosol (Pham *et al.*, 2015). Physiological and biochemical analysis of knockdown mutants for PARP1, PARP2, and PARP3 under non-stressing conditions revealed that the absence of any individual PARP isozymes does not affect photosynthetic machinery and respiration rate (Pham *et al.*, 2015). In the same study, ^{14}C positional labeling experiments indicated a mild increase in the proportion of carbohydrate oxidation performed by the TCA cycle in parp2 and parp3 mutant plants and a stronger increase in parp3 plants. Surprisingly, there was only a tendency of increased NADH content in all analyzed mutant lines, decreased $NADH/NAD^+$ ratio for parp3 mutant, with significant increases in the content of $NADP^+$ and NADPH for parp1 and parp3 plants without alterations in the $NADPH/NADP^+$ ratio.

Metabolite profiling revealed that no clear metabolic changes are displayed by the lack of individual PARP isozymes (Pham *et al.*, 2015). The exception is for in parp3 mutant plants where alterations in intermediates of the photorespiratory pathway, namely glycine and serine, glycerate and glycolate, as well as the stress related amino acids GABA and proline and the TCA cycle intermediates malate and succinate were observed. Taken together, these results indicated that PARP isoforms have non-redundant and also non-nuclear metabolic roles and are highly important in rapidly growing tissues such as the shoot apical meristem, roots, and seeds.

The physiological roles of PARP in plants under biotic and abiotic stress responses have been shown in the last decade (Amor *et al.*, 1998; de Block *et al.*, 2005; Vanderauwera *et al.*, 2007; Pham *et al.*, 2015; Rissel *et al.*, 2014, 2017; Schulz *et al.*, 2012). These studies demonstrated that PARP participates in stress responses, activation of non-homologous end-joining repair mechanism, and seed development. Recently, the functional redundancy of the three PARP isozymes during stress responses have been addressed

(Rissel *et al.*, 2017). In this study, stress responses of single, double, and triple PARP knockout mutant plants under abiotic and biotic stress were evaluated. Unexpectedly, this study revealed that, in contrast to previous reports, plant performance was not altered in any of the studied mutant lines suggesting that the stress-related phenotypes observed for PARP mutant lines are conditional dependent (Rissel *et al.*, 2017).

7. Sirtuins or histone deacetylases

Sirtuins, also known as histone deacetylases, are enzymes that catalyze an NAD^+-dependent deacetylation of acetyl-Lys in proteins and thereby produce a deacetylated Lys, as well as the metabolites nicotinamide and 2′-O-acetyl-ADP-ribose. In *Arabidopsis* genome, two sirtuins from two classes, have been found (Pandey *et al.*, 2002), with Silent Information Regulator1 homolog (SRT1) from class IV and SRT2 from class II (Pandey *et al.*, 2002). Recently, the role of the mitochondrial predicted SRT2 of *Arabidopsis* has been studied (König *et al.*, 2014). This study demonstrated that that SRT2 catalyze a Lys deacetylase. This protein is located at the inner mitochondrial membrane, interacting with protein complexes mainly involved in energy metabolism and metabolite transport. Despite the fact that srt2 mutant plants did not show growth phenotype, a metabolic phenotype with altered levels in sugars, amino acids, and ADP contents was observed. In addition, it was observed a reduction in the coupling of respiration to ATP synthesis in these lines although the mitochondrial ADP uptake was increased. Thus, this study suggests that SRT2 plays an important role in fine-tuning mitochondrial energy metabolism (König *et al.*, 2014). Recently, additional T-DNA insertion plants for SRT1 and 2 have been described (Zhang *et al.*, 2018). It was demonstrated that the expression levels of SRT1 in srt2 mutants and SRT2 in srt1 mutants are all increased suggesting a compensatory effect between the two SRT isoforms. Surprisingly, this study also demonstrated that SRT1 and SRT2 interact with a critical protein for ethylene signaling, the EIN2 nuclear-associated protein1 (ENAP1) and thus indicating that SRT1 and SRT2 are required for negative regulation of certain ethylene-responsive genes (Zhang *et al.*, 2018).

In rice two homologs for SRT2 have been found (Pandey *et al.*, 2002). Characterization of RNA interference transgenic plants for OsSRT1 indicated an increase of histone H3K9 acetylation and a decrease of H3K9 dimethylation, H_2O_2 accumulation, DNA fragmentation, programmed cell death, and mimicking plant lesions and its overexpression enhances the tolerance of redox (Huang *et al.*, 2007). Recently, it was demonstrated that OsSRT1 can regulate carbon metabolic flux through the repression of glycolysis by the deacetylation of both histone and glycolytic glyceraldehyde-3-phosphatedehydrogenase (GAPDH) (Zhang *et al.*, 2017).

8. Nicotinate phosphoribosyltransferase (NaPRTase)

In the NAD salvage pathway, nicotinate is converted to NaMN by NaPRTase (Wang and Pichersky, 2007; Hashida *et al.*, 2009). Despite the fact that plants homologs of NaPRTase have been already found (Katoh and Hashimoto, 2004), our understanding of its physiological roles and regulation of this enzyme in plants is still limited. In rice, a recessive point mutation in the gene encoding nicotinate phosphoribosyltransferase (OsNaPRT1), known as Leaf Tip Senescence 1 (LTS1), has been recently identified (Wu *et al.*, 2016). In this study, a point mutation in OsNaPRT1 showed plant dwarfism, withered leaf tip phenotype and early leaf senescence compared to the wild-type.

9. Nudix (nucleoside diphosphates linked to some moiety X) hydrolases

In *Arabidopsis*, 28 genes encoding Nudix hydrolases (AtNUDXs) have been identified, and the homologs are distributed to the cytosol and organelles, such as chloroplasts and mitochondria (Ogawa *et al.*, 2005, 2008). Studies on molecular, enzymatic properties and physiological roles of these proteins clearly revealed that they play important roles in plant physiology (for review see Yoshimura and Shigeoka 2015). However, because of the high number of substrates that can be used by NUDXs proteins, the function of many of these enzymes remains to be elucidated. Research efforts have been made to identify the physiological importance of these proteins, and therefore *Arabidopsis* mutant lines have been isolated for several genes encoding NUDX enzymes (Table 1). Intriguing, T-DNA insertion mutants for several AtNUDX did not exhibit phenotype under optimal growth conditions (Ogawa *et al.*, 2008). This suggests that several AtNUDXs are either not essential for development under optimal conditions or they play redundant roles in *Arabidopsis* plants. Interestingly, for some of the characterized AtNUDXs proteins, which have NAD(P)H pyrophosphohydrolase activity, silenced lines showed impacts on the pyridine nucleotides status and stress tolerance (Ge *et al.*, 2007; Maruta *et al.*, 2016; Corpas *et al.*, 2016).

Recently, *Arabidopsis* T-DNA insertion lines for AtNUDX19, which has NADPH specific hydrolytic activity *in vitro* (Ogawa *et al.*, 2008), were characterized in details (Maruta *et al.*, 2016; Corpas *et al.*, 2016). These studies revealed that NADPH levels increase in nudx19 mutant lines under both optimal and high light conditions. Under the same conditions, it was observed that $NADP^+$ and NAD^+ levels decreased, which lead to high redox states of NADP(H). Interestingly, despite the observed changes in the cellular redox state, the AtNUDX19 silenced plants displayed high tolerance to photooxidative stresses (Maruta *et al.*, 2016). Additional study demonstrated association between the absence of AtNUDX19 and increase in the activity of all NADP-dehydrogenases under physiological and arsenic-induced stress conditions in roots (Corpas *et al.*, 2016). Together, these studies indicated that AtNUDX19 plays a role as a modulator of cellular levels and redox states of pyridine nucleotides and is involved in oxidative stress responses through changes in photosynthesis, antioxidant system, and possibly hormonal signaling. Similar phenotypes were observed for other AtNUDXs silenced plants.

Based on the amounts of NADH and ADP-ribose as well as the pyrophosphohydrolase activities toward both molecules in the leaves of AtNUDX2 overexpressing and suppressing plants, it was verified *in vivo* that this enzyme hydrolyzes only ADP-ribose, and this may be attributed to a posttranslational protein modification (Ogawa *et al.*, 2009). Thus, these results suggested that AtNUDX2 acts maintaining the levels of NAD^+ and ATP via nucleotide recycling from the free ADP-ribose molecules produced by the degradation of poly(ADP-ribose) polymers in order to prevent excess stimulation by the PAR reaction under oxidative stress conditions (Ogawa *et al.*, 2009).

It has been shown that AtNUDX7 enzyme has ADP-ribose and NADH pyrophosphatase activities (Ogawa *et al.*, 2005). *Arabidopsis* T-DNA insertion mutant plants for AtNUDX7 (also named as AtNUDT7) displayed altered cellular redox homeostasis and a higher level of NADH in pathogen-infected leaves (Ge *et al.*, 2007). These results indicate that by altering the cellular antioxidant status the mutation in AtNUDX7 amplify defense responses, and thus suggesting that NUDT7 modulates the defense response to prevent excessive stimulation. In addition, it was shown that AtNUDX acts at early responses to DNA damage caused by oxidative stress, by modulating the poly(ADP-ribosyl)ation reaction (Ishikawa *et al.*, 2009).

Further evidence for the involvement of NUDX family members in pathogen attack responses in plants have been provided in AtNUDX6. The AtNUDX6 gene encodes an ADP-ribose (Rib)/NADH pyrophosphohydrolase. It was shown that this enzyme catalyzes mainly hydrolysis of NADH as a physiological substrate and hardly contributed to that of ADP-ribose (Ishikawa *et al.*, 2010a). By using a knock out T-DNA insertion line (nudx6) and overexpressing lines, it was demonstrated that AtNUDX6 is a modulator of NADH rather than ADP-Rib metabolism and furthermore it impacts the plant immune response as a positive regulator of Nonexpressor of pathogenesis-related genes1 (NPR1)-dependent Salicylic Acid signaling pathways (Ishikawa *et al.*, 2010a). Together, these studies demonstrated that AtNUDX7 plays a role as a negative regulator to prevent excessive stimulation of the defense response, which is dependent on and independent of NPR1 and SA accumulation (Ge *et al.*, 2007; Ishikawa *et al.*, 2010b). On another hand, AtNUDX6 function as a positive regulator through NPR1-dependent SA signaling pathways (Ishikawa *et al.*, 2010a, 2010b).

10. NAD transporters

As mentioned in the previous sections, NAD^+ has multiple and essential functions and, therefore, its cellular levels should be maintained either through *de novo* synthesis or salvage pathways, which involves recycling of NAD^+ degradation products. Because in eukaryotic cells both pathways take place in the cytosol, NAD has to be distributed to diverse cell compartments. As a consequence, transport proteins are required to shuttle NAD across intracellular membranes. In plants, humans, and fungi, members of the mitochondrial carrier family are involved in the import of NAD^+ into mitochondria, plastids, and peroxisomes (Todisco *et al.*, 2006; Palmieri *et al.*, 2009; Agrimi *et al.*, 2012). These transporters have been characterized by *in vitro* uptake assays using recombinant protein reconstituted into liposomes. Based on these biochemical studies, it has been demonstrated that the NAD^+ transporters function as antiporters, importing NAD^+ in a strict counter-exchange with another molecule (Todisco *et al.*, 2006; Palmieri *et al.*, 2009; Agrimi *et al.*, 2012; Bernhardt *et al.*, 2012).

Despite the fairly detailed molecular and biochemical characterization of NAD^+ transporters, the physiological function of this transport is still poorly understood. In plants, a peroxisomal NAD^+ transporter from *Arabidopsis*, named as PXN, was identified (Agrimi *et al.*, 2012; Bernhardt *et al.*, 2012).

When assayed *in vitro*, PXN transporter is able to catalyze the import of NAD^+ or CoA, the exchange of NAD^+/NADH, and the export of CoA (Agrimi *et al.*, 2012; Bernhardt *et al.*, 2012). However, *in vivo* assays performed in *Saccharomyces cerevisiae*, demonstrated that PXN catalyzed the import of NAD into peroxisomes against AMP in intact yeast cells (Van Roermund *et al.*, 2016). This study also suggested that the counter-exchange substrate for the NAD^+ import is produced via the hydrolysis of NADH to AMP, which is catalyzed by the NADH pyrophophatase AtNUDT19 in *Arabidopsis*. In plant system, the characterization of PXN silenced lines demonstrated that the absence of this transporter in *Arabidopsis* leads to defects in NAD-dependent β-oxidation during seedling establishment (Bernhardt *et al.*, 2012). Furthermore, this study revealed a delay in the breakdown of fatty acid released from seed storage oil. Interestingly, PXN mutant plants were able to grow under ambient CO_2 conditions without showing the typical photorespiratory phenotype. This phenotype is intriguing because photorespiration is a NAD-dependent process in peroxisomes which might be affected by impaired NAD^+ import.

In *Arabidopsis*, others two NAD^+ transporters have been identified (Palmieri *et al.*, 2009). In this study, it was demonstrated that AtNDT1 and AtNDT2 proteins, characterized as a plastid and mitochondrial NAD^+ transporters, respectively (Palmieri *et al.*, 2009). Although the molecular and biochemical characterization of these NAD^+ transporters have been described, the physiological function of these proteins is still unrevealed.

References

Acheson, S. A., Kirkman, H. N., and Wolfenden, R. 1988. Equilibrium of 5,6-hydration of NADH and mechanism of ATP-dependent dehydration. *Biochemistry*. **27**: 7371–7375.

Adams-Phillips, L., Briggs, A. G., and Bent, A. F. 2010. Disruption of poly(ADP-ribosyl)ation mechanisms alters responses of *Arabidopsis* to biotic stress. *Plant Physiol.* **152**: 267–280.

Adams-Phillips, L., Wan, J., Tan, X., Dunning, F. M., Meyers, B. C., Michelmore, R. W., and Bent, A. F. 2008. Discovery of ADP-ribosylation and other plant defense pathway elements through expression profiling of four different *Arabidopsis-Pseudomonas* R-avr interactions. *Mol. Plant Microbe. Interact.* **21:** 646–657.

Agrimi, G., Russo, A., Pierri, C. L., and Palmieri, F. 2012. The peroxisomal NAD^+ carrier of *Arabidopsis thaliana* transports coenzyme A and its derivatives. *J. Bioenerg. Biomembr.* **44:** 333–340.

Ahlfors, R., Lång, S., Overmyer, K., Jaspers, P., Brosché, M., Tauriainen, A., Kollist, H., Tuominen, H., Belles-Boix, E., Piippo, M., Inzé, D., Palva, E. T., and Kangasjärvi, J. 2004. *Arabidopsis* RADICAL-INDUCED CELL DEATH1 belongs to the WWE protein-protein interaction domain protein family and modulates abscisic acid, ethylene, and methyl jasmonate responses. *Plant Cell.* **16:** 1925–1937.

Aleo, M. F., Giudici, M. L., Sestini, S., Danesi, P., Pompucci, G., and Preti, A. 2001. Metabolic fate of extracellular NAD in human skin fibroblasts. *J. Cell Biochem.* **80:** 360–366.

Allan, E. and Trewavas, A. 1985. Quantitative changes in calmodulin and NAD kinase during early cell development in the root apex of *Pisum sativum* L. *Planta.* **165:** 493–501.

Allen, G. J., Chu, S. P., Harrington, C. L., Schumacher, K., Hoffmann, T., Tang, Y. Y., Grill, E., and Schroeder, J. I. 2001. A defined range of guard cell calcium oscillation parameters encodes stomatal movements. *Nature.* **411:** 1053–1057.

Allen, D. K., Libourel, I. G., and Shachar-Hill, Y. 2009. Metabolic flux analysis in plants: coping with complexity. *Plant Cell Environ.* **32:** 1241–1257.

Allen, G. J., Muir, S. R., and Sanders, D. 1995. Release of Ca^{2+} from individual plant vacuoles by both InsP3 and cyclic ADP-ribose. *Science.* **268:** 735–737.

Alonso, A. P., Goffman, F. D., Ohlrogge, J. B., and Shachar-Hill, Y. 2007. Carbon conversion efficiency and central metabolic fluxes in developing sunflower (*Helianthus annuus* L.) embryos. *Plant J.* **52:** 296–308.

Amor, Y., Babiychuk, E., Inzé, D., and Levine, A. 1998. The involvement of poly(ADP-ribose) polymerase in the oxidative stress responses in plants. *FEBS Lett.* **440:** 1–7.

Andrabi, S. A., Kim, N. S., Yu, S. W., Wang, H., Koh, D. W., Sasaki, M., Klaus, J. A., Otsuka, T., Zhang, Z., Koehler, R. C., Hurn, P. D., Poirier, G. G., Dawson, V. L., and Dawsonet, T. M. 2006. Poly(ADP-ribose) (PAR) polymer is a death signal. *Proc. Natl. Acad. Sci. U.S.A.* **103:** 18308–18313.

Andrabi, S. A., Umanah, G. K., Chang, C., Stevens, D. A., Karuppagounder, S. S., Gagné, J. P., Poirier, G. G., Dawson, V. L., Dawson, T. M. 2014. Poly(ADP-ribose) polymerase-dependent energy depletion occurs through inhibition of glycolysis. *Proc. Natl. Acad. Sci. U.S.A.* **111:** 10209–10214.

Apel, K. and Hirt, H. 2004. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. *Annu. Rev. Plant Biol.* **55:** 373–399.

Asada, K. 1999. The water-water cycle in CHLOROPLASTS: scavenging of active oxygens and dissipation of excess photons. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **50:** 601–639.

Ashihara, H. and Deng, W. W. 2012. Pyridine metabolism in tea plants: salvage, conjugate formation and catabolism. *J. Plant Res.* **125:** 781–791.

Ashihara, H., Stasolla, C., Yin, Y., Loukanina, N., and Thorpe, T. A. 2005. De novo and salvage biosynthetic pathways of pyridine nucleotides and nicotinic acid conjugates in cultured plant cells. *Plant Sci.* **169:** 107–114.

Ashihara, H., Yin, Y., Deng, W. W., and Watanabe, S. 2010. Pyridine salvage and nicotinic acid conjugate synthesis in leaves of mangrove species. *Phytochemistry.* **71:** 47–53.

Ashihara, H., Yin, Y., and Watanabe, S. 2011. Nicotinamide metabolism in ferns: formation of nicotinic acid glucoside. *Plant Physiol. Biochem.* **49:** 275–279.

Babiychuk, E., Van Montagu, M., and Kushnir, S. 2001. N-terminal domains of plant poly(ADP-ribose) polymerases define their association with mitotic chromosomes. *Plant J.* **28:** 245–255.

Backhausen, J. E., Emmerlich, A., Holtgrefe, S., Horton, P., Nast, G., Rogers, J. J., Müller-Röber, B., and Scheibe, R. 1998. Transgenic potato plants with altered expression levels of chloroplast NADP-malate dehydrogenase: interactions between photosynthetic electron transport and malate metabolism in leaves and in isolated intact chloroplasts. *Planta.* **207:** 105–114.

Baldwin, I. T. and Ohnmeiss, T. E. 1993. Alkaloidal responses to damage in Nicotiana native to North America. *J. Chem. Ecol.* **19:** 1143–1153.

Barrero, J. M., Piqueras, P., González-Guzmán, M., Serrano, R., Rodríguez, P. L., Ponce, M. R., and Micol, J. L. 2005. A mutational analysis of the ABA1 gene of *Arabidopsis thaliana* highlights the involvement of ABA in vegetative development. *J. Exp. Bot.* **56:** 2071–2083.

Bartsch, M., Gobbato, E., Bednarek, P., Debey, S., Schultze, J. L., Bautor, J., and Parker, J. E. 2006. Salicylic acid-independent ENHANCED DISEASE SUSCEPTIBILITY1 signaling in *Arabidopsis* immunity and cell death is regulated by the monooxygenase FMO1 and the Nudix hydrolase NUDT7. *Plant Cell.* **18:** 1038–1051.

Belenky, P., Bogan, K. L., and Brenner, C. 2007. NAD^+ metabolism in health and disease. *Trends Biochem. Sci.* **32:**12–19.

Belenky, P., Stebbins, R., Bogan, K. L., Evans, C. R., and Brenner, C. 2011. Nrt1 and Tna1-independent export of NAD^+ precursor vitamins promotes NAD^+ homeostasis and allows engineering of vitamin production. *PLoS One.* **6:** e19710.

Berger, F., Lau, C., Dahlmann, M., and Ziegler, M. 2005. Subcellular compartmentation and differential catalytic properties of the three human nicotinamide mononucleotide adenylyl transferase isoforms. *J. Biol. Chem.* **280**: 36334–36341.

Berger, F., Ramírez-Hernández, M. H., and Ziegler, M. 2004. The new life of a centenarian: signalling functions of NAD(P). *Trends Biochem. Sci.* **29:** 111–118.

Berglund, A. K., Navarrete, C., Engqvist, M. K., Hoberg, E., Szilagyi, Z., Taylor, R. W., Gustafsson, C. M., Falkenberg, M., and Clausen, A. R. 2017. Nucleotide pools dictate the identity and frequency of ribonucleotide incorporation in mitochondrial DNA. *PLoS Genetics.* **13:** e1006628.

Bernal-Bayard, P., Hervás, M., Cejudo, F. J., and Navarro, J. A. 2012. Electron transfer pathways and dynamics of chloroplast NADPH-dependent thioredoxin reductase C (NTRC). *J. Biol. Chem.* **287:** 33865–33872.

Bernhardt, K., Wilkinson, S., Weber, A. P., and Linka, N. 2012. A peroxisomal carrier delivers NAD^+ and contributes to optimal fatty acid degradation during storage oil mobilization. *Plant J.* **69:** 1–13.

Berrin, J. G., Pierrugues, O., Brutesco, C., Alonso, B., Montillet, J. L., Roby, D., and Kazmaier, M. 2005. Stress induces the expression of AtNADK-1, a gene encoding a NAD(H) kinase in *Arabidopsis thaliana*. *Mol. Genet. Genomics.* **273:** 10–19.

Bessman, M. J., Frick, D. N., and O'Handley, S. F. 1996. The MutT proteins or "Nudix" hydrolases, a family of versatile, widely distributed, "housecleaning" enzymes. *J. Biol. Chem.* **271:** 25059–25062.

Bhatia, R. and Calvo, K. C. 1996. The sequencing expression, purification, and steady-state kinetic analysis of quinolinate phosphoribosyl transferase from *Escherichia coli*. *Arch. Biochem. Biophys.* **325:** 270–278.

Bianchi, A. R. and De Maio, A. 2014. Synthesis and degradation of poly(ADP-ribose) in plants. *Front. Biosci. (Landmark Ed)* **19**: 1436–1444.

Billington, R. A., Bruzzone, S., De Flora, A., Genazzani, A. A., Koch-nolte, F., Ziegler, M., and Zocchi, E. 2006. Emerging functions of extracellular pyridine nucleotides. *Mol. Med.* **12:** 324–327.

Blander, G. and Guarente, L. 2004. The Sir2 family of protein deacetylases. *Annu. Rev. Biochem.* **73:** 417–435.

Bogan, K. L. and Brenner, C. 2008. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD^+ precursor vitamins in human nutrition. *Annu. Rev. Nutr.* **28:** 115–130.

Bonicalzi, M. E., Haince, J. F., Droit, A., and Poirier, G. G. 2005. Regulation of poly(ADP-ribose) metabolism by poly(ADP-ribose) glycohydrolase: where and when? *Cell Mol. Life Sci.* **62:** 739–750.

Bonzon, M., Simon, P., Greppin, H., and Wagner, E. 1983. Pyridine nucleotides and redox-charge evolution during the induction of flowering in spinach leaves. *Planta.* **159:** 254–260.

Boshoff, H. I., Xu, X., Tahlan, K., Dowd, C. S., Pethe, K., Camacho, L. R., Park, T. H., Yun, C. S., Schnappinger, D., Ehrt, S., Williams, K. J., and Barry, C. E. III 2008. Biosynthesis and recycling of nicotinamide cofactors in *Mycobacterium tuberculosis*. An essential role for NAD in nonreplicating bacilli. *J. Biol. Chem.* **283:** 19329–19341.

Bossi, R. T., Negri, A., Tedeschi, G., and Mattevi, A. 2002. Structure of FAD-bound L-aspartate oxidase: insight into substrate specificity and catalysis. *Biochemistry.* **41:** 3018–3024.

Bowers, J. E., Chapman, B. A., Rong, J., and Paterson, A. H. 2003. Unravelling angiosperm genome evolution by phylogenetic analysis of chromosomal duplication events. *Nature.* **422:** 433–438.

Briggs, A. G. and Bent, A. F. 2011. Poly(ADP-ribosyl)ation in plants. *Trends Plant Sci.* **16:** 372–380.

Brown, E. G. 1965. Changes in the free nucleotide pattern of pea seeds in relation to germination. *Biochem. J.* **95:** 509–514.

Bruzzone, S., Moreschi, I., Guida, L., Usai, C., Zocchi, E., and De Flora, A. 2006. Extracellular NAD^+ regulates intracellular calcium levels and induces activation of human granulocytes. *Biochem. J.* **393:** 697–704.

Buck, S. W., Gallo, C. M., and Smith, J. S. 2004. Diversity in the Sir2 family of protein deacetylases. *J. Leukoc. Biol.* **75:** 939–950.

Bürkle, A. 2001. Poly(APD-ribosyl)ation, a DNA damage-driven protein modification and regulator of genomic instability. *Cancer Lett.* **163:** 1–5.

Busch, F. A., Sage, T. L., Cousins, A. B., and Sage, R. F. 2013. C3 plants enhance rates of photosynthesis by reassimilating photorespired and respired CO2. *Plant Cell Environ.* **36:** 200–212.

Bykova, N. V. and Møller, I. M. 2001. Involvement of matrix NADP turnover in the oxidation of NAD-linked substrates by pea leaf mitochondria. *Physiol. Plant*. **111:** 448–456.

Bykova, N. V, Rasmusson, A. G., Igamberdiev, A. U., Gardeström, P., and Møller, I. M. 1999. Two separate transhydrogenase activities are present in plant mitochondria. *Biochem. Biophys. Res. Commun*. **265:** 106–111.

Caiafa, P., Guastafierro, T., and Zampieri, M. 2009. Epigenetics: poly(ADP-ribosyl)ation of PARP-1 regulates genomic methylation patterns. *FASEB J*. **23:** 672–678.

Calvin M. and Benson, A. A. 1949. The path of carbon in photosynthesis IV: the identity and sequence of the intermediates in sucrose synthesis. *Science*. **109:** 140–142.

Campbell, W. J., Allen, L. H., and Bowes, G. 1988. Effects of CO(2) concentration on rubisco activity, amount, and photosynthesis in soybean leaves. *Plant Physiol*. **88:** 1310–1316.

Canepa, L., Ferraris, A. M., Miglino, M., and Gaetani, G. F. 1991. Bound and unbound pyridine dinucleotides in normal and glucose-6-phosphate dehydrogenase-deficient erythrocytes. *Biochim. Biophys. Acta*. **1074:** 25059–104.

Cárdenas, L. 2009. New findings in the mechanisms regulating polar growth in root hair cells. *Plant Signal. Behav*. **4:** 4–8.

Cárdenas, L., Martínez, A., Sánchez, F., and Quinto, C. 2008. Fast, transient and specific intracellular ROS changes in living root hair cells responding to Nod factors (NFs). *Plant J*. **56:** 802–813.

Cárdenas, L., McKenna, S. T., Kunkel, J. G., and Hepler, P. K. 2006. NAD(P)H oscillates in pollen tubes and is correlated with tip growth. *Plant Physiol*. **142:** 1460–1468.

Centeno, D. C., Osorio, S., Nunes-Nesi, A., Bertolo, A. L., Carneiro, R. T., Araújo, W. L., Steinhauser, M. C., Michalska, J., Rohrmann, J., Geigenberger, P., Oliver, S. N., Stitt, M., Carrari, F., Rose, J. K., and Fernie, A. R. 2011. Malate plays a crucial role in starch metabolism, ripening, and soluble solid content of tomato fruit and affects postharvest softening. *Plant Cell*. **23:** 162–184.

Chai, M. F., Chen, Q. J., An, R., Chen, Y. M., Chen, J., and Wang, X. C. 2005. NADK2, an *Arabidopsis* chloroplastic NAD kinase, plays a vital role in both chlorophyll synthesis and chloroplast protection. *Plant Mol. Biol*. **59:** 553–564.

Chai, M. F., Wei, P. C., Chen, Q. J., An, R., Chen, J., Yang, S., and Wang, X. C. (2006) NADK3, a novel cytoplasmic source of NADPH, is required under conditions of oxidative stress and modulates abscisic acid responses in *Arabidopsis*. *Plant J*. **47**: 665–674.

Chappie, J. S., Cànaves, J. M., Han, G. W., Rife, C. L., Xu, Q., and Stevens, R. C. 2005. The structure of a eukaryotic nicotinic acid phosphoribosyltransferase reveals structural heterogeneity among type II PRTases. *Structure*. **13:** 1385–1396.

Chini, E. N., Chini, C. C. S., Kato, I., Takasawa, S., and Okamoto, H. 2002. CD38 is the major enzyme responsible for synthesis of nicotinic acid-adenine dinucleotide phosphate in mammalian tissues. *Biochem. J*. **362:** 125–130.

Chollet, R. 1976. Effect of glycidate on glycolate formation and photosynthesis in isolated spinach chloroplasts. *Plant Physiol*. **57:** 237–240.

Chung, P. J., Kim, Y. S., Park, S. H., Nahm, B. H., and Kim, J. K. 2009. Subcellular localization of rice histone deacetylases in organelles. *FEBS Lett*. **583:** 2249–2254.

Cicchillo, R. M., Tu, L., Stromberg, J. A., Hoffart, L. M., Krebs, C., and Booker, S. J. 2005. *Escherichia coli* quinolinate synthetase does indeed harbor a [4Fe-4S] cluster. *J. Am. Chem. Soc*. **127:** 7310–7311.

Colinas, M., Shaw, H. V., Loubéry, S., Kaufmann, M., Moulin, M., and Fitzpatrick, T. B. 2014. A Pathway for Repair of NAD(P)H in Plants. *J. Biol. Chem*. **289:** 14692–14706.

Come, D. 1970. *Les obstacles à la germination*. Ed Masson Cie 162 p.

Cormier, M. J., Charbonneau, H., and Jarrett, H. W. 1981. Plant and fungal calmodulin: Ca^{2+}-dependent regulation of plant NAD kinase. *Cell Calcium*. **2:** 313–331.

Corpas, F. J., Aguayo-Trinidad, S., Ogawa, T., Yoshimura, K., and Shigeoka, S. 2016. Activation of NADPH-recycling systems in leaves and roots of *Arabidopsis thaliana* under arsenic-induced stress conditions is accelerated by knock-out of Nudix hydrolase 19 (AtNUDX19) gene. *J. Plant Physiol*. **192:** 81–89.

Cossins, E. A., Kirk, C. D., Imeson, H. C., and Zheng, L. L. 1993. Enzymes for synthesis of 10-formyltetrahydrofolate in plants. Characterization of a monofunctional 10-formyltetrahydrofolate synthetase and copurification of 5,10-methylenetetrahydrofolate dehydrogenase and 5,10-methenyltetrahydrofolate cyclohydrolase activities. *Adv. Exp. Med. Biol*. **338:** 707–710.

D'Ari, R. and Casadesús, J. 1998. Underground metabolism. *Bioessays*. **20:** 181–186.

Dahmen, W., Webb, B., and Preiss, J. 1967. The deamido-diphosphopyridine nucleotide and diphosphopyridine nucleotide pyrophosphorylases of *Escherichia coli* and yeast. *Arch. Biochem. Biophys*. **120:** 440–450.

Dai, Z., Ku, M., and Edwards, G. E. 1995. C4 Photosynthesis (The Effects of Leaf Development on the CO2-Concentrating Mechanism and Photorespiration in Maize). *Plant Physiol*. **107:** 815–825.

David, P., Chen, N. W., Pedrosa-Harand, A., Thareau, V., Sévignac, M., Cannon, S. B., Debouck, D., Langin, T., and Geffroy, V. 2009. A nomadic subtelomeric disease resistance gene cluster in common bean. *Plant Physiol*. **151:** 1048–1065.

Davidovic, L., Vodenicharov, M., Affar, E. B., and Poirier, G. G. (2001) Importance of poly(ADP-ribose) glycohydrolase in the control of poly(ADP-ribose) metabolism. *Exp. Cell Res*. **268:** 7–13.

Day, D. A. and Wiskich, J. T. 1981. Glycine metabolism and oxalacetate transport by pea leaf mitochondria. *Plant Physiol*. **68:** 425–429.

De Block, M. and Van Lijsebettens, M. 2011. Energy efficiency and energy homeostasis as genetic and epigenetic components of plant performance and crop productivity. *Curr. Opin. Plant Biol*. **14:** 275–282.

De Block, M., Verduyn, C., De Brouwer, D., and Cornelissen, M. 2005. Poly(ADP-ribose) polymerase in plants affects energy homeostasis, cell death and stress tolerance. *Plant J*. **41:** 95–106.

De Block, M., Hannah, M., Van der Kelen, K., and Van Breusegem, F. 2012. A gene expression signature for the

selection of high energy use efficient plants. *U.S. Patent Application No. 13/876,365*.

De Ingeniis, J., Kazanov, M. D., Shatalin, K., Gelfand, M. S., Osterman, A. L., and Sorci, L. 2012. Glutamine versus ammonia utilization in the NAD synthetase family. *PLoS One*. **7:** e39115.

De Murcia, G. and Ménissier de Murcia, J. 1994. Poly(ADP-ribose) polymerase: a molecular nick-sensor. *Trends Biochem. Sci.* **19:** 172–176.

Denk, W., Strickler, J. H., and Webb, W. W. 1990. Two-photon laser scanning fluorescence microscopy. *Science*. **248:** 73–76.

Dennis, D. T., Huang, Y., and Negm, F. B. 1997. Glycolysis, the oxidative pentose phosphate pathway and anaerobic respiration. *Plant Metab.* eds *D.T.* ***D***: 105.

Denu, J. M. 2005. The Sir2 family of protein deacetylases. *Curr. Opin. Chem. Biol.* **9:** 431–440.

Dever, L., Bailey, K., Lacuesta, M., Leegood, R., and Lea, P. 1996. The isolation and characterization of mutants of the C-4 plant Amaranthus edulis. *Comptes rendus Acad. Sci. III. La Vie* **319**: 951–959.

Di Martino, M. L., Fioravanti, R., Barbabella, G., Prosseda, G., Colonna, B., and Casalino, M. 2013. Molecular evolution of the nicotinic acid requirement within the Shigella/EIEC pathotype. *Int. J. Med. Microbiol.* **303:** 651–661.

Di Martino, C. and Pallotta, M. L. 2011. Mitochondria-localized NAD biosynthesis by nicotinamide mononucleotide adenylyltransferase in Jerusalem artichoke (*Helianthus tuberosus* L.) heterotrophic tissues. *Planta*. **234:** 657–670.

Dieter, P. and Marmé, D. 1984. A Ca^{2+}, Calmodulin-dependent NAD kinase from corn is located in the outer mitochondrial membrane. *J. Biol. Chem.* **259:** 184–189.

Dobrota, C. 2006. Energy dependent plant stress acclimation. *Rev. Env. Sci. Biotechnol.* **5:** 243–251.

Dobrzanska, M., Szurmak, B., Wyslouch-Cieszynska, A., and Kraszewska, E. 2002. Cloning and characterization of the first member of the Nudix family from *Arabidopsis thaliana*. *J. Biol. Chem.* **277:** 50482–50486.

Doubnerová, V. and Ryšlavá, H. 2011. What can enzymes of C4 photosynthesis do for C3 plants under stress? *Plant Sci.* **180:** 575–583.

Doucet-Chabeaud, G., Godon, C., Brutesco, C., de Murcia, G., and Kazmaier, M. 2001. Ionising radiation induces the expression of PARP-1 and PARP-2 genes in *Arabidopsis*. *Mol. Genet. Genomics*. **265:** 954–963.

Du, W., Ren, S., Suo, Q., Yang, M., He, D., and Liu, J. 2011. Construction of Sirtl shRNA interfering vector and its effects on cell proliferation and apoptosis. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* **28:** 972–975.

Du, X., Wang, W., Kim, R., Yakota, H., Nguyen, H., and Kim, S. H. 2001. Crystal structure and mechanism of catalysis of a pyrazinamidase from Pyrococcus horikoshii. *Biochemistry* **40**: 14166–14172.

Dutilleul, C., Driscoll, S., Cornic, G., De Paepe, R., Foyer, C. H., and Noctor, G. 2003a. Functional mitochondrial complex I is required by tobacco leaves for optimal photosynthetic performance in photorespiratory conditions and during transients. *Plant Physiol.* **131:** 264–275

Dutilleul, C., Garmier, M., Noctor, G., Mathieu, C., Chétrit, P., Foyer, C., and De Paepe, R. 2003b. Leaf mitochondria modulate whole cell redox homeostasis, set antioxidant capacity, and determine stress resistance through altered signaling and diurnal regulation. *Plant Cell.* **15:** 1212–1226.

Dutilleul, C., Lelarge, C., Prioul, J. L., De Paepe, R., Foyer, C. H., and Noctor, G. 2005. Mitochondria-driven changes in leaf NAD status exert a crucial influence on the control of nitrate assimilation and the integration of carbon and nitrogen metabolism. *Plant Physiol.* **139:** 64–78.

Ekkehard, H. and Stitt, M. 1989. Perturbation of photosynthesis in spinach leaf discs by low concentrations of methyl viologen: influence of increased thylakoid energisation on ATP synthesis, electron transport, energy dissipation, light-activation of the Calvin-Benson-cycle enzymes, and contr. *Planta*. **179:** 51–60.

El-Maarouf-Bouteau, H., Sajjad, Y., Bazin, J., Langlade, N., Cristescu, S. M., Balzergue, S., Baudouin, E., and Bailly, C. 2014. Reactive oxygen species, abscisic acid and ethylene interact to regulate sunflower seed germination. *Plant Cell Environ*. **38:** 364–374.

Escobar, M. A., Geisler, D. A., and Rasmusson, A. G. 2006. Reorganization of the alternative pathways of the *Arabidopsis* respiratory chain by nitrogen supply: opposing effects of ammonium and nitrate. *Plant J.* **45:** 775–788.

Evenari, M., Koller, D., and Gutteman, Y. 1966. Effects of the environment of the mother plants on the germination by control of seed-coat permeability to water in Ononis sicula. *Aust. J. Biol. Sci.* **19**: 1007–1016

Faure, J. D., Vincentz, M., Kronenberger, J., and Caboche, M. 1991. Co-regulated expression of nitrate and nitrite reductases. *Plant J.* **1:** 107–113.

Finkemeier, I., Laxa, M., Miguet, L., Howden, A. J., and Sweetlove, L. J. 2011. Proteins of diverse function and subcellular location are lysine acetylated in *Arabidopsis*. *Plant Physiol.* **155:** 1779–1790.

Fjeld, C. C., Birdsong, W. T., and Goodman, R. H. 2003. Differential binding of NAD + and NADH allows the transcriptional corepressor carboxyl-terminal binding protein to serve as a metabolic sensor. *Proc. Natl. Acad. Sci. U.S.A.* **100:** 9202–9207.

Foreman, J., Demidchik, V., Bothwell, J. H., Mylona, P., Miedema, H., Torres, M. A., Linstead, P., Costa, S., Brownlee, C., Jones, J. D., Davies, J. M., and Dolan, L. 2003. Reactive oxygen species produced by NADPH oxidase regulate plant cell growth. *Nature*. **422:** 442–446.

Foster, A. C., Zinkand, W. C., and Schwarcz, R. 1985. Quinolinic acid phosphoribosyltransferase in rat brain. *J. Neurochem.* **44:** 446–454.

Fournier, H. 2003. Chroniques de la vie sur Terre pendant quatre milliards d. Ed Publib 1–124

Foyer, C. H., Bloom, A. J., Queval, G., and Noctor, G. 2009. Photorespiratory metabolism: genes, mutants, energetics, and redox signaling. *Annu. Rev. Plant Biol.* **60:** 455–484.

Foyer, C. H., Neukermans, J., Queval, G., Noctor, G., and Harbinson, J. 2012. Photosynthetic control of electron transport and the regulation of gene expression. *J. Exp. Bot.* **63:** 1637–1661.

Foyer, C. H. and Noctor, G. 2005. Redox homeostasis and antioxidant signaling: a metabolic interface between stress perception and physiological responses. *Plant Cell.* **17:** 1866–1875.

Friedkin, M. and Lehninger, A. L. 1949. Esterification of inorganic phosphate coupled to electron transport between dihydrodiphosphopyridine nucleotide and oxygen. *J. Biol. Chem.* **178:** 611–644.

Frost, G. M., Yang, K. S., and Waller, G. R. 1967. Nicotinamide adenine dinucleotide as a precursor of nicotine in *Nicotiana rustica* L. *J. Biol. Chem.* **242:** 887–888.

Fryer, M. J., Ball, L., Oxborough, K., Karpinski, S., Mullineaux, P. M., and Baker, N. R. 2003. Control of ascorbate peroxidase 2 expression by hydrogen peroxide and leaf water status during excess light stress reveals a functional organisation of *Arabidopsis* leaves. *Plant J.* **33:** 691–705.

Fu, Z. Q. and Dong, X. 2013. Systemic acquired resistance: turning local infection into global defense. *Annu. Rev. Plant Biol.* **64:** 839–863.

Galeeva, E. I., Trifonova, T. V., Ponomareva, A. A., Viktorova, L. V., and Minibayeva, F. V. 2012. Nitrate reductase from Triticum aestivum leaves: regulation of activity and possible role in production of nitric oxide. *Biochem. Biokhimiia.* **77:** 404–410.

Gallais, S., de Crescenzo, M. A., and Laval-Martin, D. L. 2000. Evidence of active NADP(+) phosphatase in dormant seeds of *Avena sativa* L. *J. Exp. Bot.* **51:** 1389–1394.

Gallais, S., Pou De Crescenzo, M. A., and Laval-Martin, D. L. 1998. Pyridine nucleotides and redox charges during germination of non-dormant and dormant caryopses of *Avena sativa* L. *J. Plant Physiol.* **153:** 663–669.

Galvez-Valdivieso, G., Fryer, M. J., Lawson, T., Slattery, K., Truman, W., Smirnoff, N., Asami, T., Davies, W. J., Jones, A. M., Baker, N. R., and Mullineaux, P. M. 2009. The high light response in *Arabidopsis* involves ABA signaling between vascular and bundle sheath cells. *Plant Cell.* **21:** 2143–2162.

Gardeström, P. 1987. Adenylate ratios in the cytosol, chloroplasts and mitochondria of barley leaf protoplasts during photosynthesis at different carbon dioxide concentrations. *FEBS Lett.* **212:** 114–118.

Gauthier, P. P., Bligny, R., Gout, E., Mahé, A., Nogués, S., Hodges, M., and Tcherkez, G. G. 2010. In folio isotopic tracing demonstrates that nitrogen assimilation into glutamate is mostly independent from current CO_2 assimilation in illuminated leaves of *Brassica napus*. *New Phytol.* **185:** 988–999.

Ge, X., Li, G. J., Wang, S. B., Zhu, H., Zhu, T., Wang, X., and Xia, Y. 2007. AtNUDT7, a negative regulator of basal immunity in *Arabidopsis*, modulates two distinct defense response pathways and is involved in maintaining redox homeostasis. *Plant Physiol.* **145:** 204–215.

Ge, X. and Xia, Y. 2008. The role of AtNUDT7, a Nudix hydrolase, in the plant defense response. *Plant Signal Behav.* **3:** 119–120.

Geigenberger, P. 2003. Response of plant metabolism to too little oxygen. *Curr. Opin. Plant Biol.* **6:** 247–256.

Geigenberger, P. and Fernie, A. R. 2014. Metabolic control of redox and redox control of metabolism in plants. *Antioxid. Redox. Signal.* **21:** 1389–1421.

Genazzani, A.A, Bak, J., and Galione, A. 1996. Inhibition of cADPR-hydrolase by ADP-ribose potentiates cADPR synthesis from beta-NAD^+. *Biochem. Biophys. Res. Commun.* **223:** 502–507.

Gerdes, S. Y., Kurnasov, O. V., Shatalin, K., Polanuyer, B., Sloutsky, R., Vonstein, V., Overbeek, R., and Osterman, A. L. 2006. Comparative genomics of NAD biosynthesis in cyanobacteria. *J. Bacteriol.* **188:** 3012–3023.

Gibson, S. W., Conway, A. J., Zheng, Z., Uchacz, T. M., Taylor, J. L., and Todd, C. D. 2012. *Brassica carinata* CIL1 mediates extracellular ROS production during auxin- and ABA-regulated lateral root development. *J. Plant Biol.* **55:** 361–372.

Giegé, P., Heazlewood, J. L., Roessner-Tunali, U., Millar, A. H., Fernie, A. R., Leaver, C. J., and Sweetlove, L. J. 2003. Enzymes of glycolysis are functionally associated with the mitochondrion in *Arabidopsis* cells. *Plant Cell.* **15:** 2140–2151.

Golubev, A. G. 1996. The other side of metabolism. *Biokhimiia (Moscow, Russ).* **61:** 2018–2039.

Gonzalez-Guzman, M., Pizzio, G. A., Antoni, R., Vera-Sirera, F., Merilo, E., Bassel, G. W., Fernández, M. A., Holdsworth, M. J., Perez-Amador, M. A., Kollist, H., and Rodriguez, P. L. 2012. *Arabidopsis* PYR/PYL/RCAR receptors play a major role in quantitative regulation of stomatal aperture and transcriptional response to abscisic acid. *Plant Cell.* **24:** 2483–2496.

Graham, I. A. 2008. Seed storage oil mobilization. *Annu. Rev. Plant Biol.* **59:** 115–142.

Graham, J. W., Williams, T. C., Morgan, M., Fernie, A. R., Ratcliffe, R. G., and Sweetlove, L. J. 2007. Glycolytic enzymes associate dynamically with mitochondria in response to respiratory demand and support substrate channeling. *Plant Cell.* **19:** 3723–3738.

Greiss, S. and Gartner, A. 2009. Sirtuin/Sir2 phylogeny, evolutionary considerations and structural conservation. *Mol. Cell.* **28:** 407–415.

Griffith, G. R., Chandler, J. L., and Gholson, R. 1975. Studies on the de novo Biosynthesis of NAD in *Escherichia coli.* The separation of the nadB gene product frome the nadA product and its purification. *Eur. J. Biochem.* **54:** 239–245.

Guérard, F., Pétriacq, P., Gakière, B., and Tcherkez, G. 2011. Liquid chromatography/time-of-flight mass spectrometry for the analysis of plant samples: a method for simultaneous screening of common cofactors or nucleotides and application to an engineered plant line. *Plant Physiol. Biochem.* **49:** 1117–1125.

Gunawardana, D., Cheng, H. C., and Gayler, K. R. 2008. Identification of functional domains in *Arabidopsis thaliana* mRNA decapping enzyme (AtDcp2). *Nucleic Acids Res.* **36:** 203–216.

Guse, A. H. and Lee, H. C. 2008. NAADP: a universal Ca^{2+} trigger. *Sci. Signal.* **1:** re10.

Ha, H. C. and Snyder, S. H. 1999. Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. *Proc. Natl. Acad. Sci. U.S.A.* **96:** 13978–13982.

Hagedorn, P. H., Flyvbjerg, H., and Møller, I. M. 2004. Modelling NADH turnover in plant mitochondria. *Physiol Plant.* **120:** 370–385.

Hager, J., Pellny, T. K., Mauve, C., Lelarge-Trouverie, C., De Paepe, R., Foyer, C. H., and Noctor, G. 2010. Conditional modulation of NAD levels and metabolite profiles in *Nicotiana sylvestris* by mitochondrial electron transport and carbon/nitrogen supply. *Planta.* **231:** 1145–1157.

Haigis, M. C., Mostoslavsky, R., Haigis, K. M., Fahie, K., Christodoulou, D. C., Murphy, A. J., Valenzuela, D. M., Yancopoulos, G. D., Karow, M., Blander, G., Wolberger, C., Prolla, T. A., Weindruch, R., Alt, F. W., and Guarente, L. 2006. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. *Cell*. **126:** 941–954.

Hanning, I. and Heldt, H. W. 1993. On the function of mitochondrial metabolism during photosynthesis in spinach (*Spinacia oleracea* L.) leaves (partitioning between respiration and export of redox equivalents and precursors for nitrate assimilation products). *Plant Physiol*. **103:** 1147–1154.

Hao, J., Pétriacq, P., de Bont, L., Hodges, M., and Gakière, B. 2018. Characterization of L-aspartate oxidase from *Arabidopsis thaliana*. *Plant Sci*. **271:** 133–142.

Hara, N., Yamada, K., Shibata, T., Osago, H., Hashimoto, T., and Tsuchiya, M. 2007. Elevation of cellular NAD levels by nicotinic acid and involvement of nicotinic acid phosphoribosyltransferase in human cells. *J. Biol. Chem*. **282:** 24574–24582.

Harden, A. D. and Young, W. J. 1906. The alcoholic ferment of yeast-juice Part II. The coferment of yeast-juice. *Proc. R. Soc. London Ser. B, Contain Pap a Biol Character*. **78:** 369–375.

Hashida, S., Itami, T., Takahara, K., Hirabayashi, T., Uchimiya, H., and Kawai-Yamada, M. 2016. Increasedrate of NAD metabolism shortens plant longevity by accelerating developmental senescence in. *Arabidopsis. Plant Cell Physiol*. **57:** 2427–2439.

Hashida, S., Itami, T., Takahashi, H., Takahara, K., Nagano, M., Kawai-Yamada, M., Shoji, K., Goto, F., Yoshihara, T., and Uchimiya, H. 2010. Nicotinate/nicotinamide mononucleotide adenyltransferase-mediated regulation of NAD biosynthesis protects guard cells from reactive oxygen species in ABA-mediated stomatal movement in *Arabidopsis*. *J. Exp. Bot*. **61:** 3813–3825.

Hashida, S., Kawai-Yamada, M., and Uchimiya, H. 2013b. NAD^+ accumulation as a metabolic off switch for orthodox pollen. *Plant Signal Behav*. **8:** 1–3.

Hashida, S., Takahashi, H., Kawai-Yamada, M., and Uchimiya, H. 2007. *Arabidopsis thaliana* nicotinate/nicotinamide mononucleotide adenyltransferase (AtNMNAT) is required for pollen tube growth. *Plant J*. **49:** 694–703.

Hashida, S., Takahashi, H., Takahara, K., Kawai-Yamada, M., Kitazaki, K., Shoji, K., Goto, F., Yoshihara, T., and Uchimiya, H. 2013a. NAD^+ accumulation during pollen maturation in *Arabidopsis* regulating onset of germination. *Mol. Plant*. **6:** 216–225.

Hashida, S., Takahashi, H., and Uchimiya, H. 2009. The role of NAD biosynthesis in plant development and stress responses. *Ann. Bot*. **103:** 819–824.

Hauben, M., Haesendonckx, B., Standaert, E., Van Der Kelen, K., Azmi A, Akpo, H., Van Breusegem, F., Guisez, Y., Bots, M., Lambert, B., Laga, B., and De Block, M. 2009. Energy use efficiency is characterized by an epigenetic component that can be directed through artificial selection to increase yield. *Proc. Natl. Acad. Sci. U.S.A*. **106:** 20109–20114.

Hayakawa, T., Nakamura, T., Hattori, F., Mae, T., Ojima, K., and Yamaya, T. 1994. Cellular localization of NADH-dependent glutamate-synthase protein in vascular bundles of unexpanded leaf blades and young grains of rice plants. *Planta*. **193:** 455–460.

Hayashi, M., Takahashi, H., Tamura, K., Huang, J., Yu, L. H., Kawai-Yamada, M., Tezuka, T., and Uchimiya, H. 2005. Enhanced dihydroflavonol-4-reductase activity and NAD homeostasis leading to cell death tolerance in transgenic rice. *Proc. Natl. Acad. Sci. U.S.A*. **102:** 7020–7025.

Heber, U. W. and Santarius, K. A. 1965. Compartmentation and reduction of pyridine nucleotides in relation to photosynthesis. *Biochim. Biophys. Acta. Biophys. Incl. Photosynth*. **109:** 390–408.

Heineke, D., Riens, B., Grosse, H., Hoferichter, P., Peter, U., Flügge, U. I., and Heldt, H. W. 1991. Redox transfer across the inner chloroplast envelope membrane. *Plant Physiol*. **95:** 1131–1137.

Heyno, E., Innocenti, G., Lemaire, S. D., Issakidis-Bourguet, E., and Krieger-Liszkay, A. 2014. Putative role of the malate valve enzyme NADP-malate dehydrogenase in H_2O_2 signalling in *Arabidopsis*. *Philos. Trans. R. Soc. Lond., B, Biol. Sci*. **369:** 20130228.

Hirel, B. and Lea, P. J. (2002) The biochemistry, molecular biology and genetic manipulation of primary ammonia assimilation. In *Photosynthetic Nitrogen Assimilation and Associated Carbon and Respiratory Metabolism*, C. H. Foyer and, G. Noctor, Eds. Springer Science & Business Media: Netherlands, pp. 71–92.

Hollender, C., and Liu, Z. 2008. Histone deacetylase genes in *Arabidopsis* development. *J. Integr. Plant Biol*. **50:** 875–885.

Hosokawa, Y., Mitchell, E., and Gholson, R. 1983. Higher plants contain L-asparate oxidase, the first enzyme of the *Escherichia coli* quinolinate synthetase system. *Biochem. Biophys. Res. Commun*. **111:** 188–193.

Hou, Q. and Bartels, D. 2014. Comparative study of the aldehyde dehydrogenase (ALDH) gene superfamily in the glycophyte *Arabidopsis thaliana* and Eutrema halophytes. *Ann. Bot*. **115:** 465–479.

Houtkooper, R. H., Pirinen, E., and Auwerx, J. 2012. Sirtuins as regulators of metabolism and healthspan. *Nat. Rev. Mol. Cell Biol*. **13:** 225–238.

Hruz, T., Laule, O., Szabo, G., Wessendorp, F., Bleuler, S., Oertle, L., Widmayer, P., Gruissem, W., and Zimmermann, P. 2008. Genevestigator v3: a reference expression database for the meta-analysis of transcriptomes. *Adv. Bioinformatics*. **2008:** 420747.

Hu, Q., Chen, C., Yan, J., Yang, X., Shi, X., Zhao, J., Lei, J., Yang, L., Wang, K., Chen, L., Huang, H., Han, J., Zhang, J. H., Zhou, C. 2009. Therapeutic application of gene silencing MMP-9 in a middle cerebral artery occlusion-induced focal ischemia rat model. *Exp. Neurol*. **216:** 35–46.

Huang, L., Sun, Q., Qin, F., Li, C., Zhao, Y., Zhou, D.-X. 2007. Down-regulation of a SILENT INFORMATION REGULATOR2-related histone deacetylase gene, OsSRT1, induces DNA fragmentation and cell death in rice. *Plant Physiol*. **144:** 1508–15019.

Huang, H. and Tindall, D. J. 2007. Dynamic FoxO transcription factors. *J. Cell Sci*. **120:** 2479–2487.

Hummel, W. and Gröger, H. 2014. Strategies for regeneration of nicotinamide coenzymes emphasizing self-sufficient closed-loop recycling systems. *J. Biotechnol*. **191:** 22–31.

Hunt, L. and Gray, J. E. 2009. The relationship between pyridine nucleotides and seed dormancy. *New Phytol.* **181:** 62–70.

Hunt, L., Holdsworth, M. J., and Gray, J. E. 2007. Nicotinamidase activity is important for germination. *Plant J.* **51:** 341–351.

Hunt, L., Lerner, F., and Ziegler, M. 2004. NAD – new roles in signalling and gene regulation in plants. *New Phytol.* **163:** 31–44.

Hwang, I., and Sheen, J. 2001. Two-component circuitry in *Arabidopsis* cytokinin signal transduction. *Nature.* **413:** 383–389.

Igamberdiev, A. U., Bykova, N. V., and Gardeström, P. 1997. Involvement of cyanide-resistant and rotenone-insensitive pathways of mitochondrial electron transport during oxidation of glycine in higher plants. *FEBS Lett.* **412:** 265–269.

Igamberdiev, A. U. and Gardeström, P. 2003. Regulation of NAD- and NADP-dependent isocitrate dehydrogenases by reduction levels of pyridine nucleotides in mitochondria and cytosol of pea leaves. *Biochim. Biophys. Acta.* **1606:** 117–125.

Imai, S., Armstrong, C. M., Kaeberlein, M., and Guarente, L. 2000. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature.* **403:** 795–800.

Ishikawa, K., Ogawa, T., Hirosue, E., Nakayama, Y., Harada, K., Fukusaki, E., Yoshimura, K., and Shigeoka, S. 2009. Modulation of the poly(ADP-ribosyl)ation reaction via the *Arabidopsis* ADP-ribose/NADH pyrophosphohydrolase, AtNUDX7, is involved in the response to oxidative stress. *Plant Physiol.* **151:** 741–754.

Ishikawa, K., Yoshimura, K., Harada, K., Fukusaki, E., Ogawa, T., Tamoi, M., and Shigeoka, S. 2010a. AtNUDX6, an ADP-ribose/NADH pyrophosphohydrolase in *Arabidopsis*, positively regulates NPR1-dependent salicylic acid signaling. *Plant Physiol.* **152:** 2000–2012.

Ishikawa, K., Yoshimura, K., Ogawa, T., and Shigeoka, S. 2010b. Distinct regulation of *Arabidopsis* ADP-ribose/NADH pyrophosphohydrolases, AtNUDX6 and 7, in biotic and abiotic stress responses. *Plant Signal Behav.* **5:**839–841.

Jahns, E. 1885. Ueber das Alkaloïd des indischen Hanfs. *Arch. Pharmazie.* **225:** 20130228–483.

Jamai, A., Salomé, P. A., Schilling, S. H., Weber, A. P., and McClung, C. R. 2009. *Arabidopsis* photorespiratory serine hydroxymethyltransferase activity requires the mitochondrial accumulation of ferredoxin-dependent glutamate synthase. *Plant Cell.* **21:** 595–606.

Jambunathan, N., and Mahalingam, R. 2006. Analysis of *Arabidopsis* growth factor gene 1 (GFG1) encoding a nudix hydrolase during oxidative signaling. *Planta.* **224:** 1–11.

Jambunathan, N., Penaganti, A., Tang, Y., and Mahalingam, R. 2010. Modulation of redox homeostasis under suboptimal conditions by *Arabidopsis* nudix hydrolase 7. *BMC Plant Biol.* **10:** 173.

Jia, Q., Dulk-Ras, A., Shen, H., Hooykaas, P. J., and Pater, S. 2013. Poly(ADP-ribose)polymerases are involved in microhomology mediated back-up non-homologous end joining in *Arabidopsis thaliana. Plant Mol. Biol.* **82:** 339–351.

Journet, E. P., Neuburger, M., and Douce, R. 1981. Role of glutamate-oxaloacetate transaminase and malate dehydrogenase in the regeneration of NAD for glycine oxidation by spinach leaf mitochondria. *Plant Physiol.* **67:** 467–469.

Kaelin Jr, W.G., and McKnight, S. L. 2013. Influence of metabolism on epigenetics and disease. *Cell.* **153:** 56–69.

Kaiser, W. M., Kandlbinder, A., Stoimenova, M., and Glaab, J. 2000. Discrepancy between nitrate reduction rates in intact leaves and nitrate reductase activity in leaf extracts: what limits nitrate reduction in situ? *Planta.* **210:** 801–807.

Kaiser, W. M., Stoimenova, M., and Man, H. M. 2002. What limits nitrate reduction in leaves? In *Photosynthetic Nitrogen Assimilation and Associated Carbon and Respiratory Metabolism*, C. H. Foyer and G. Noctor, Eds. Springer Science & Business Media: Netherlands, pp. 63–70.

Kasimova, M. R., Grigiene, J., Krab, K., Hagedorn, P. H., Flyvbjerg, H., Andersen, P. E., and Møller, I.M. 2006. The free NADH concentration is kept constant in plant mitochondria under different metabolic conditions. *Plant Cell.* **18:** 688–698.

Katahira, R. and Ashihara, H. 2009. Profiles of the biosynthesis and metabolism of pyridine nucleotides in potatoes (*Solanum tuberosum* L.). *Planta.* **231:** 35–45.

Kato, M. and Lin, S. J. 2014. Regulation of NAD^+ metabolism, signaling and compartmentalization in the yeast *Saccharomyces cerevisiae. DNA Repair (Amst).* **23:** 49–58.

Katoh, A. and Hashimoto, T. 2004. Molecular biology of pyridine nucleotide and nicotine biosynthesis. *Front Biosci.* **9:** 1577–1586.

Katoh, A., Uenohara, K., Akita, M., and Hashimoto, T. 2006. Early steps in the biosynthesis of NAD in *Arabidopsis* start with aspartate and occur in the plastid 1. *Plant Physiol.* **141:** 851–857.

Kauny, J. and Sétif, P. 2014. NADPH fluorescence in the cyanobacterium Synechocystis sp. PCC 6803: a versatile probe for in vivo measurements of rates, yields and pools. *Biochim. Biophys. Acta.* **1837:** 792–801.

Kawai, S., Mori, S., Mukai, T., and Murata, K. 2004. Cytosolic NADP phosphatases I and II from Arthrobacter sp. strain KM: implication in regulation of $NAD^+/NADP^+$ balance. *J. Basic. Microbiol.* **44:** 185–196.

Kawai, S. and Murata, K. 2008. Structure and function of NAD kinase and NADP phosphatase: key enzymes that regulate the intracellular balance of NAD(H) and NADP(H). *Biosci. Biotechnol. Biochem.* **72:** 919–930.

Kaya, H., Nakajima, R., Iwano, M., Kanaoka, M. M., Kimura, S., Takeda, S., Kawarazaki, T., Senzaki, E., Hamamura, Y., Higashiyama, T., Takayama, S., Abe, M., and Kuchitsu, K. 2014. Ca^{2+}-activated reactive oxygen species production by *Arabidopsis* RbohH and RbohJ is essential for proper pollen tube tip growth. *Plant Cell.* **26:** 1069–1080.

Keller, J., Liersch, M., and Grunicke, H. 1971. Studies on the biosynthesis of NAD from nicotinamide and on the intracellular pyridine nucleotide cycle in isolated perfused rat liver. *Eur. J. Biochem.* **22:** 263–270.

Keys, A. J., Bird, L. F., Cornelius, M. J., Lea, P. J., Wallsgrove, R. M., and Miflin, B. J. 1978. Photorespiratory nitrogen cycle. *Nature.* **275:** 741–743.

Kilfoil, R. L., Shtofmakher, G., Taylor, G., and Botvinick, J. 2014. Acetic acid iontophoresis for the treatment of insertional *Achilles tendonitis*. *BMJ Case Rep*. pii: bcr2014206232.

Kim, J. W. and Dang, C. V. 2005. Multifaceted roles of glycolytic enzymes. *Trends Biochem. Sci*. **30:** 142–150.

Kirk, C. D., Chen, L., Imeson, H. C., and Cossins, E. A. 1995. A 5, 10-methylenetetrahydrofolate dehydrogenase: 5. 10-methenyltetrahydrofolate cyclohydrolase protein from *Pisum sativum*. *Phytochemistry*. **39:** 1309–1314.

Klaus, S. M., Wegkamp, A., Sybesma, W., Hugenholtz, J., Gregory, J. F., and Hanson, A. D. 2005. A nudix enzyme removes pyrophosphate from dihydroneopterin triphosphate in the folate synthesis pathway of bacteria and plants. *J. Biol. Chem*. **280:** 5274–5280.

Kocsy, G., Tari, I., Vanková, R., Zechmann, B., Gulyás, Z., Poór, P., and Galiba, G. 2013. Redox control of plant growth and development. *Plant Sci*. **211:** 77–91.

König, K. 2000. Multiphoton microscopy in life sciences. *J. Microsc*. **200:** 83–104.

König, J., Baier, M., Horling, F., Kahmann, U., Harris, G., Schürmann, P., and Dietz, K. J. 2002. The plant-specific function of 2-Cys peroxiredoxin-mediated detoxification of peroxides in the redox-hierarchy of photosynthetic electron flux. *Proc. Natl. Acad. Sci. U.S.A*. **99:** 5738–5743.

König, A. C., Hartl, M., Pham, P. A., Laxa, M., Boersema, P. J., Orwat, A., Kalitventseva, I., Plöchinger, M., Braun, H. P., Leister, D., Mann, M., Wachter, A., Fernie, A., and Finkemeier, I. 2014. The *Arabidopsis* class II sirtuin is a lysine deacetylase and interacts with mitochondrial energy metabolism. *Plant Physiol*. **164:** 1401–1414.

Kornberg, A. 1948. The participation of inorganic pyrophosphate in the reversible enzymatic synthesis of diphosphopyridine nucleotide. *J. Biol. Chem*. **176:** 1475.

Koster, S., Upmeier, B., Komossa, D., and Barz, W. 1989. Nicotinic-acid conjugation in plants and plant-cell cultures of potato (*Solanum tuberosum*). *Zeitschrift fur Naturforsch C-A J Biosci* **44:** 623–628.

Kozaki, A. and Takeba, G. 1996. Photorespiration protects C3 plants from photooxidation. *Nature*. **384:** 557–560.

Kramer, D. M., Avenson, T. J., and Edwards, G. E. 2004. Dynamic flexibility in the light reactions of photosynthesis governed by both electron and proton transfer reactions. *Trends Plant. Sci*. **9:** 349–357.

Kraszewska, E. 2008. The plant Nudix hydrolase family. *Acta. Biochim. Pol*. **55:** 663–671.

Krebs, H. A. 1937. The role of fumarate in the respiration of Bacterium coli commune. *Biochem. J*. **31:** 2095–2124.

Krömer, S. and Heldt, H. W. 1991. On the role of mitochondrial oxidative phosphorylation in photosynthesis metabolism as studied by the effect of oligomycin on photosynthesis in protoplasts and leaves of barley (*Hordeum vulgare*). *Plant Physiol*. **95:** 1270–1276.

Kupke, T., Caparrós-Martín, J. A., Malquichagua Salazar, K. J., and Culiáñez-Macià, F. A. 2009. Biochemical and physiological characterization of *Arabidopsis thaliana* AtCoAse: a Nudix CoA hydrolyzing protein that improves plant s plant development . *Physiol Plant*. **135:** 365–378.

Kuraishi, S., Arai, N., Ushijima, T., and Tazaki, T. 1968. Oxidized and reduced nicotinamide adenine dinucleotide phosphate levels of plants hardened and unhardened against chilling injury. *Plant Physiol*. **43:** 238–242.

Kwak, J. M., Mori, I. C., Pei, Z. M., Leonhardt, N., Torres, M. A., Dangl, J. L., Bloom, R. E., Bodde, S., Jones, J. D., and Schroeder, J.I. 2003. NADPH oxidase AtrbohD and AtrbohF genes function in ROS-dependent ABA signaling in *Arabidopsis*. *EMBO J*. **22:** 2623–2633.

Lacuesta, M., Dever, L. V., Munoz-Rueda, A., and Lea, P. J. 1997. A study of photorespiratory ammonia production in the C4 plant *Amaranthus edulis*, using mutants with altered photosynthetic capacities. *Physiol Plant*. **99:** 447–455.

Lamb, R. S., Citarelli, M., and Teotia, S. 2012. Functions of the poly(ADP-ribose) polymerase superfamily in plants. *Cell Mol. Life Sci*. **69:** 175–189.

Lassig, R., Gutermuth, T., Bey, T. D., Konrad, K. R., and Romeis, T. 2014. Pollen tube NAD(P)H oxidases act as a speed control to dampen growth rate oscillations during polarized cell growth. *Plant J*. **78:** 94–106.

Lau, C., Dölle, C., Gossmann, T. I., Agledal, L., Niere, M., and Ziegler, M. 2010. Isoform-specific targeting and interaction domains in human nicotinamide mononucleotide adenylyltransferases. *J. Biol. Chem*. **285:** 18868–18876.

Laval-Martin, D. L., Carré, I. A., Barbera, S. J., and Edmunds, L. N. 1990. Rhythmic changes in the activities of NAD kinase and NADP phosphatase in the achlorophyllous ZC mutant of Euglena gracilis Klebs (strain Z). *Arch. Biochem. Biophys*. **276:** 433–441.

Leckie, C. P., McAinsh, M. R., Allen, G. J., Sanders, D., and Hetherington, A. M. 1998. Abscisic acid-induced stomatal closure mediated by cyclic ADP-ribose. *Proc. Natl. Acad. Sci. U.S.A*. **95:** 15837–15842.

Lee, H. C. 2012. Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP) as messengers for calcium mobilization. *J. Biol. Chem*. **287:** 31633–31640.

Lee, H. C. and Aarhus, R. 1991. ADP-ribosyl cyclase: an enzyme that cyclizes NAD^+ into a calcium-mobilizing metabolite. *Cell Regul* **2**: 203–209.

Leist, M., Single, B., Künstle, G., Volbracht, C., Hentze, H., and Nicotera, P. 1997. Apoptosis in the absence of poly-(ADP-ribose) polymerase. *Biochem. Biophys. Res. Commun*. **233:** 518–522.

Li, W. Y., Wang, X., Li, R., Li, W. Q., and Chen, K. M. 2014. Genome-wide analysis of the NADK gene family in plants. *PLoS One*. **9:** 1–15.

Linster, C. L., Van Schaftingen, E., and Hanson, A. D. 2013. Metabolite damage and its repair or pre-emption. *Nat. Chem. Biol*. **9:** 72–80.

Liszkay, A., van der Zalm, E., and Schopfer, P. 2004. Production of reactive oxygen intermediates (O_2^{-}, H_2O_2, and $^{\cdot}OH$) by maize roots and their role in wall loosening and elongation growth. *Plant Physiol*. **136**: 3114–3123.

Liu, Q., Graeff, R., Kriksunov, I. A., Jiang, H., Zhang, B., Oppenheimer, N., Lin, H., Potter, B. V., Lee, H. C., and Hao, Q. 2009a. Structural basis for enzymatic evolution from a dedicated ADP-ribosyl cyclase to a multifunctional NAD hydrolase. *J. Biol. Chem*. **284:** 27637–27645.

Liu, Y. J., Nunes-Nesi, A., Wallström, S. V., Lager, I., Michalecka, A. M., Norberg, F. E., Widell, S., Fredlund, K. M., Fernie, A. R., and Rasmusson, A. G. 2009b. A redox-mediated modulation of stem bolting in transgenic

Nicotiana sylvestris differentially expressing the external mitochondrial NADPH dehydrogenase. *Plant Physiol.* **150:** 1248–1259.

Liu, T., Song, T., Zhang, X., Yuan, H., Su, L., Li, W., Xu, J., Liu, S., Chen, L., Chen, T., Zhang, M., Gu, L., Zhang, B. and Dou, D. 2014. Unconventionally secreted effectors of two filamentous pathogens target plant salicylate biosynthesis. *Nat. Commun.* **5:** 4686.

Liu, C., Wu, Q., Liu, W., Gu, Z., Wang, W., Xu, P., Ma, H., and Ge, X. 2017. Poly(ADP-ribose) polymerases regulate cell division and development in *Arabidopsis* roots. *J. Integr. Plant Biol.* **59:** 459–474.

Li, W., Zhang, F., Chang, Y., Zhao, T., Schranz, M. E., and Wang, G. 2015. Nicotinate O-glucosylation is an evolutionarily metabolic trait important for seed germination under stress conditions in *Arabidopsis thaliana*. *Plant Cell.* **27:** 1907–1924.

Li, W., Zhang, F., Wu, R., Jia, L., Li, G., Guo, Y., Liu, C., and Wang, G. 2017. A novel N-methyltransferase in *Arabidopsis* appears to feed a conserved pathway for nicotinate detoxification among land plants and is associated with lignin biosynthesis. *Plant Physiol.* **174:** 1492–1504.

Lunn, J.E. 2007. Compartmentation in plant metabolism. *J. Exp. Bot.* **58:** 35–47.

Ma, X., Lv, S., Zhang, C., and Yang, C. 2013. Histone deacetylases and their functions in plants. *Plant Cell Rep.* **32:** 465–478.

Macho, A. P., Boutrot, F., Rathjen, J. P., and Zipfel, C. 2012. ASPARTATE OXIDASE plays an important role in *Arabidopsis* stomatal immunity. *Plant Physiol.* **159:** 1845–1856.

Maciejewska, U. and Kacperska, A. 1987. Changes in the level of oxidized and reduced pyridine nucleotides during cold acclimation of winter rape plants. *Physiol. Plant.* **69:** 687–691.

Magni, G., Amici, A., Emanuelli, M., Orsomando, G., Raffaelli, N., and Ruggieri, S. 2004. Structure and function of nicotinamide mononucleotide adenylyltransferase. *Curr. Med. Chem.* **11:** 873–885.

Mann, D. F. and Byerrum, R. U. 1974. Activation of the de novo pathway for pyridine nucleotide biosynthesis prior to ricinine biosynthesis in castor beans. *Plant Physiol.* **53:** 603–609.

Mano, J., Belles-Boix, E., Babiychuk, E., Inzé, D., Torii, Y., Hiraoka, E., Takimoto, K., Slooten, L., Asada, K., and Kushnir, S. 2005. Protection against photooxidative injury of tobacco leaves by 2-alkenal reductase. Detoxication of lipid peroxide-derived reactive carbonyls. *Plant Physiol.* **139:** 1773–1783.

Marbaix, A. Y., Noël, G., Detroux, A. M., Vertommen, D., Van Schaftingen, E., Linster, C. L. 2011. Extremely conserved ATP- or ADP-dependent enzymatic system for nicotinamide nucleotide repair. *J. Biol. Chem.* **286:** 41246–41252.

Marino, D., Dunand, C., Puppo, A., and Pauly, N. 2012. A burst of plant NADPH oxidases. *Trends Plant Sci.* **17:** 9–15.

Maroco, J. P., Ku, M. S., and Edwards, G. E. 1997. Oxygen sensitivity of C4 photosynthesis: evidence from gas exchange and chlorophyll fluorescence analyses with different C4 subtypes. *Plant Cell Environ.* **20:** 1525–1533.

Maruta, T., Ogawa, T., Tsujimura, M., Ikemoto, K., Yoshida, T., Takahashi, H., Yoshimura, K., and Shigeoka, S. 2016. Loss-of-function of an *Arabidopsis* NADPH pyrophosphohydrolase, AtNUDX19, impacts on the pyridine nucleotides status and confers photooxidative stress tolerance. *Sci. Rep.* **6:** 37432.

Matsui, A. and Ashihara, H. 2008. Nicotinate riboside salvage in plants: presence of nicotinate riboside kinase in mungbean seedlings. *Plant Physiol. Biochem.* **46:** 104–108.

Matsui, A., Yin, Y., Yamanaka, K., Iwasaki, M., and Ashihara, H. 2007. Metabolic fate of nicotinamide in higher plants. *Physiol Plant.* **131**: 191–200.

Mattevi, A., Tedeschi, G., Bacchella, L., Coda, A., Negri, A., and Ronchi, S. 1999. Structure of L-aspartate oxidase: implications for the succinate dehydrogenase/fumarate reductase oxidoreductase family. *Structure.* **7:** 745–756.

Maulucci, G., Troiani, D., Eramo, S. L., Paciello, F., Podda, M. V., Paludetti, G., Papi, M., Maiorana, A., Palmieri, V., De Spirito, M., and Fetoni, A. R. 2014. Time evolution of noise induced oxidation in outer hair cells: role of NAD(P)H and plasma membrane fluidity. *Biochim. Biophys. Acta.* **1840:** 2192–2202.

McLennan, A. G. 2006. The Nudix hydrolase superfamily. *Cell. Mol. Life Sci.* **63:** 123–143.

Medda, R., Padiglia, A., Lorrai, A., Murgia, B., Agrò, A. F., Castagnola, M., and Floris, G. 2000. Purification and properties of a nucleotide pyrophosphatase from lentil seedlings. *J. Protein. Chem.* **19:** 209–214.

Michalska, J., Zauber, H., Buchanan, B. B., Cejudo, F. J., and Geigenberger, P. 2009. NTRC links built-in thioredoxin to light and sucrose in regulating starch synthesis in chloroplasts and amyloplasts. *Proc. Natl. Acad. Sci. U.S.A.* **106:** 9908–9913.

Miflin, B. J. 1970. Studies on the sub-cellular location of particulate nitrate and nitrite reductase, glutamic dehydrogenase and other enzymes in barley roots. *Planta.* **93:** 160–170.

Miller, G., Schlauch, K., Tam, R., Cortes, D., Torres, M. A., Shulaev, V., Dangl, J. L., and Mittler, R. 2009. The plant NADPH oxidase RBOHD mediates rapid systemic signaling in response to diverse stimuli. *Sci. Signal.* **2:** ra45.

Miyake, C. 2010. Alternative electron flows (water-water cycle and cyclic electron flow around PSI) in photosynthesis: molecular mechanisms and physiological functions. *Plant Cell Physiol.* **51:** 1951–1963.

Monshausen, G. B., Bibikova, T. N., Messerli, M. A., Shi, C., Gilroy, S. 2007. Oscillations in extracellular pH and reactive oxygen species modulate tip growth of *Arabidopsis* root hairs. *Proc. Natl. Acad. Sci. U.S.A.* **104:** 20996–21001.

Monshausen, G. B., Bibikova, T. N., Weisenseel, M. H., and Gilroy, S. 2009. Ca^{2+} regulates reactive oxygen species production and pH during mechanosensing in *Arabidopsis* roots. *Plant Cell.* **21:** 2341–2356.

Moorhead, G. B., Meek, S. E., Douglas, P., Bridges, D., Smith, C. S., Morrice, N., and MacKintosh, C. 2003. Purification of a plant nucleotide pyrophosphatase as a protein that interferes with nitrate reductase and glutamine synthetase assays. *Eur. J. Biochem.* **270:** 1356–1362.

Morris-Blanco, K. C., Cohan, C. H., Neumann, J. T., Sick, T. J., and Perez-Pinzon, M. A. 2014. Protein kinase C epsilon regulates mitochondrial pools of Nampt and

NAD following resveratrol and ischemic preconditioning in the rat cortex. *J. Cereb. Blood Flow Metab*. **34:** 1024–32.

Mortarino, M., Negri, A., Tedeschi, G., Simonic, T., Duga, S., Gassen, H. G., and Ronchi, S. 1996. L-Aspartate oxidase from *Escherichia coli*. I. Characterization of coenzyme binding and product inhibition. *Eur. J. Biochem*. **239:** 418–426.

Moser, B., Winterhalter, K. H., and Richter, C. 1983. Purification and properties of a mitochondrial NAD + glycohydrolase. *Arch. Biochem. Biophys*. **224:** 358–364.

Müller, K., Carstens, A. C., Linkies, A., Torres, M. A., and Leubner-Metzger, G. 2009. The NADPH-oxidase AtrbohB plays a role in *Arabidopsis* seed after-ripening. *New Phytol*. **184:** 885–897.

Müller, K., Linkies, A., Leubner-Metzger, G., and Kermode, A. R. 2012. Role of a respiratory burst oxidase of Lepidium sativum (cress) seedlings in root development and auxin signalling. *J. Exp. Bot*. **63:** 6325–6334.

Munekage, Y., Hashimoto, M., Miyake, C., Tomizawa, K., Endo, T., Tasaka, M., and Shikanai, T. 2004. Cyclic electron flow around photosystem I is essential for photosynthesis. *Nature*. **429:** 579–582.

Muñoz, F. J., Baroja-Fernández, E., Morán-Zorzano, M. T., Alonso-Casajús, N., and Pozueta-Romero, J. 2006. Cloning, expression and characterization of a Nudix hydrolase that catalyzes the hydrolytic breakdown of ADP-glucose linked to starch biosynthesis in *Arabidopsis thaliana*. *Plant Cell Physiol*. **47**: 926–934.

Murthy, N. M., Ollagnier-de-Choudens, S., Sanakis, Y., Abdel-Ghany, S. E., Rousset, C., Ye, H., Fontecave, M., Pilon-Smits, E. A., and Pilon, M. 2007. Characterization of *Arabidopsis thaliana* SufE2 and SufE3: functions in chloroplast iron-sulfur cluster assembly and NAD synthesis. *J. Biol. Chem*. **282:** 18254–18264.

Nasu, S., Wicks, F., and Gholson, R. 1982. L-Aspartate oxidase, a newly discovered enzyme of *Escherichia coli* is the B protein of Quinolinate Synthetase. *J. Biol. Chem*. **257:** 626–632.

Navazio, L., Bewell, M. A., Siddiqua, A., Dickinson, G. D., Galione, A., and Sanders, D. 2000. Calcium release from the endoplasmic reticulum of higher plants elicited by the NADP metabolite nicotinic acid adenine dinucleotide phosphate. *Proc. Natl. Acad. Sci. U.S.A*. **97:** 8693–8698.

Navazio, L., Mariani, P., and Sanders, D. 2001. Mobilization of Ca^{2+} by cyclic ADP-ribose from the endoplasmic reticulum of cauliflower florets. *Plant Physiol*. **125:** 2129–2138.

Nestler, J., Liu, S., Wen, T. J., Paschold, A., Marcon, C., Tang, H. M., Li, D., Li, L., Meeley, R. B., Sakai, H., Bruce, W., Schnable, P. S., and Hochholdinger, F. 2014. Roothairless5, which functions in maize (*Zea mays* L.) root hair initiation and elongation encodes a monocot-specific NADPH oxidase. *Plant J*. **79:** 729–740.

Neuburger, M., Day, D. A., and Douce, R. 1985. Transport of NAD in percoll-purified potato tuber mitochondria: inhibition of NAD influx and efflux by N-4-azido-2-nitrophenyl-4-aminobutyryl-3'-NAD. *Plant Physiol*. **78:** 405–410.

Neuburger, M. and Douce, R. 1983. Slow passive diffusion of NAD^+ between intact isolated plant mitochondria and suspending medium. *Biochem. J*. **216:** 443–450.

Niehaus, T. D., Richardson, L. G., Gidda, S. K., ElBadawi-Sidhu, M., Meissen, J. K., Mullen, R. T., Fiehn, O., and Hanson, A. D. 2014. Plants utilize a highly conserved system for repair of NADH and NADPH hydrates. *Plant Physiol*. **165:** 52–61.

Nikiforov, A., Dölle, C., Niere, M., and Ziegler, M. 2011. Pathways and subcellular compartmentation of NAD biosynthesis in human cells: from entry of extracellular precursors to mitochondrial NAD generation. *J. Biol. Chem*. **286:** 21767–21778.

Noctor, G. 2006. Metabolic signalling in defence and stress: the central roles of soluble redox couples. *Plant Cell Environ*. **29:** 409–425.

Noctor, G. and Foyer, C. H. 1998. A re-evaluation of the ATP: NADPH budget during C3 photosynthesis: a contribution from nitrate assimilation and its associated respiratory activity? *J. Exp. Bot*. **49:** 1895–1908.

Noctor, G., Queval, G., and Gakière, B. 2006. NAD(P) synthesis and pyridine nucleotide cycling in plants and their potential importance in stress conditions. *J. Exp. Bot*. **57:** 1603–1620.

Nunes-Nesi, A., Carrari F., Lytovchenko, A., and Fernie, A. R. 2005. Enhancing crop yield in Solanaceous species through the genetic manipulation of energy metabolism. *Biochem. Soc. Trans*. **33:** 1430–1434.

Oei, S. L., Griesenbeck, J., Ziegler, M., and Schweiger, M. 1998. A novel function of poly(ADP-ribosyl)ation: silencing of RNA polymerase II-dependent transcription. *Biochemistry*. **37:** 1465–1469.

Oei, S. L. and Ziegler, M. 2000. ATP for the DNA ligation step in base excision repair is generated from poly(ADP-ribose). *J. Biol. Chem*. **275:** 23234–23239.

Ogawa, T., Ishikawa, K., Harada, K., Fukusaki, E., Yoshimura, K., and Shigeoka, S. 2009. Overexpression of an ADP-ribose pyrophosphatase, AtNUDX2, confers enhanced tolerance to oxidative stress in *Arabidopsis* plants. *Plant J*. **57:** 289–301.

Ogawa, T., Ueda, Y., Yoshimura, K., and Shigeoka, S. (2005) Comprehensive analysis of cytosolic Nudix hydrolases in *Arabidopsis thaliana*. *J. Biol. Chem*. **280:** 25277–25283.

Ogawa, T., Yoshimura, K., Miyake, H., Ishikawa, K., Ito, D., Tanabe, N., and Shigeoka, S. 2008. Molecular characterization of organelle-type Nudix hydrolases in *Arabidopsis*. *Plant Physiol*. **148:** 1412–1424.

Ohashi, K., Kawai, S., and Murata, K. 2013. Secretion of quinolinic acid, an intermediate in the kynurenine pathway, for utilization in NAD^+ biosynthesis in the yeast *Saccharomyces cerevisiae*. *Eukaryotic Cell*. **12:** 648–653.

Ohlrogge, J. and Browse, J. 1995. Lipid biosynthesis. *Plant Cell*. **7:** 957–970.

Olejnik, K. and Kraszewska, E. 2005. Cloning and characterization of an *Arabidopsis thaliana* Nudix hydrolase homologous to the mammalian GFG protein. *Biochim. Biophys. Acta*. **1752:** 133–141.

Ollagnier-de Choudens, S., Loiseau L, Sanakis, Y., Barras, F., and Fontecave, M. 2005. Quinolinate synthetase, an iron-sulfur enzyme in NAD biosynthesis. *FEBS Lett*. **579**: 3737–3743.

Oppenheimer, N. J. and Kaplan, N. O. 1974. Glyceraldehyde-3-phosphate dehydrogenase catalyzed hydration of the 5-6 double bond of reduced beta-nicotinamide adenine

dinucleotide (betaNADH). Formation of beta-6-hydroxy-1,4,5,6-tetrahydronicotinamide adenine dinucleotide. *Biochemistry.* **13:** 626–4694.

Oracz, K., El-Maarouf-Bouteau, H., Kranner, I., Bogatek, R., Corbineau, F., and Bailly, C. 2009. The mechanisms involved in seed dormancy alleviation by hydrogen cyanide unravel the role of reactive oxygen species as key factors of cellular signaling during germination. *Plant Physiol.* **150:** 494–505.

Osmond C. and Grace, S. 1996. Perspectives on photoinhibition and photorespiration in the field: quintessential inefficiencies of the light and dark reactions of photosynthesis. *J. Exp. Bot.* **47:** 604–604.

Ozment, C., Barchue, J., DeLucas, L. J., and Chattopadhyay, D. 1999. Structural study of *Escherichia coli* NAD synthetase: overexpression, purification, crystallization, and preliminary crystallographic analysis. *J. Struct. Biol.* **127:** 279–282.

Palmieri, F., Rieder, B., Ventrella, A., Blanco, E., Do, P. T., Nunes-Nesi, A., Trauth, A. U., Fiermonte, G., Tjaden, J., Agrimi, G., Kirchberger, S., Paradies, E., Fernie, A. R., and Neuhaus, H. E. 2009. Molecular identification and functional characterization of *Arabidopsis thaliana* mitochondrial and chloroplastic NAD^+ carrier proteins. *J. Biol. Chem.* **284:** 405–31259.

Pandey, R., Müller, A., Napoli, C. A., Selinger, D. A., Pikaard, C. S., Richards, E. J., Bender, J., Mount, D. W., and Jorgensen, R. A. 2002. Analysis of histone acetyltransferase and histone deacetylase families of *Arabidopsis thaliana* suggests functional diversification of chromatin modification among multicellular eukaryotes. *Nucleic Acids Res.* **30:** 5036–5055.

Pellny, T. K., Locato, V., Vivancos, P. D., Markovic, J., De Gara, L., Pallardó, F. V., and Foyer, C. H. 2009. Pyridine nucleotide cycling and control of intracellular redox state in relation to poly (ADP-ribose) polymerase activity and nuclear localization of glutathione during exponential growth of *Arabidopsis* cells in culture. *Mol. Plant.* **2:** 442–456.

Pellny, T. K., Van Aken, O., Dutilleul, C., Wolff, T., Groten, K., Bor, M., De Paepe, R., Reyss, A., Van Breusegem, F., Noctor, G., and Foyer, C. H. 2008. Mitochondrial respiratory pathways modulate nitrate sensing and nitrogen-dependent regulation of plant architecture in *Nicotiana sylvestris*. *Plant J.* **54:** 976–992.

Penfound, T. and Foster, J. W. 1999. NAD-dependent DNA-binding activity of the bifunctional NadR regulator of Salmonella typhimurium. *J. Bacteriol.* **181:** 648–655.

Pérez-Ruiz, J. M., Spínola, M. C., Kirchsteiger, K., Moreno, J., Sahrawy, M., and Cejudo, F. J. 2006. Rice NTRC is a high-efficiency redox system for chloroplast protection against oxidative damage. *Plant Cell.* **18:** 2356–2368.

Petrack, B., Greengard, P., Craston, A., and Kalinsky, H. J. 1963. Nicotinamide deamidase in rat liver and the biosynthesis of NAD. *Biochem. Biophys. Res. Commun.* **13:** 472–477.

Pétriacq, P., de Bont, L., Hager, J., Didierlaurent, L., Mauve, C., Guérard, F., Noctor, G., Pelletier, S., Renou, J. P., Tcherkez, G., and Gakière, B. 2012. Inducible NAD overproduction in *Arabidopsis* alters metabolic pools and gene expression correlated with increased salicylate content and resistance to Pst-AvrRpm1. *Plant J.* **70:** 650–665.

Pétriacq, P., de Bont, L., Tcherkez, G., and Gakière, B. 2013. NAD Not just a pawn on the board of plant-pathogen interactions. *Plant Signal Behav.* **8:** 1–11.

Pétriacq, P., Stassen, J. H., and Ton, J. 2016a. Spore density determines infection strategy by the plant-pathogenic fungus *Plectosphaerella cucumerina*. *Plant Physiol.* **170:** 2325–2339.

Pétriacq, P., Ton, J., Patrit, O., Tcherkez, G., and Gakière, B. 2016b. NAD acts as an integral regulator of multiple defense layers. *Plant Physiol.* **172:** 1465–1479.

Pétriacq, P. 2011. Étude de la biosynthèse du NAD chez les plantes: Conséquences physiologiques de sa manipulation chez *Arabidopsis thaliana*. Thèse, Orsay, FR.

Pfister, M., Ogilvie, A., da Silva, C. P., Grahnert, A., Guse, A. H., and Hauschildt, S. 2001. NAD degradation and regulation of CD38 expression by human monocytes/macrophages. *Eur. J. Biochem.* **268:** 5601–5608.

Pham, P. A., Wahl, V., Tohge, T., de Souza, L. R., Zhang, Y., Do, P. T., Olas, J. J., Stitt, M., Araújo, W. L., and Fernie, A. R. 2015. Analysis of knockout mutants reveals non-redundant functions of poly(ADP-ribose)polymerase isoforms in *Arabidopsis*. *Plant Mol. Biol.* **89:** 319–338.

Piattoni, C. V., Guerrero, S. A., and Iglesias, A. A. 2013. A differential redox regulation of the pathways metabolizing glyceraldehyde-3-phosphate tunes the production of reducing power in the cytosol of plant cells. *Int. J. Mol. Sci.* **14:** 8073–8092.

Podgórska, A., Ostaszewska, M., Gardeström, P., Rasmusson, A. G., and Szal, B. 2014. In comparison with nitrate nutrition, ammonium nutrition increases growth of the frostbite1 *Arabidopsis* mutant. *Plant Cell Environ.* **38:** 224–237.

Pollak, N., Dölle, C., and Ziegler, M. 2007a. The power to reduce: pyridine nucleotides-small molecules with a multitude of functions. *Biochem J.* **402:** 205–218.

Pollak, N., Niere, M., and Ziegler, M. 2007b. NAD kinase levels control the NADPH concentration in human cells. *J. Biol. Chem.* **282:** 33562–33571.

Popov, G., Fraiture, M., Brunner, F., and Sessa, G. 2016. Multiple *Xanthomonas euvesicatoria* type III effectors inhibit flg22-triggered immunity. *Mol. Plant Microbe. Interact.* **29:** 651–660.

Potocký, M., Jones, M. A., Bezvoda, R., Smirnoff, N., and Zárský, V. 2007. Reactive oxygen species produced by NADPH oxidase are involved in pollen tube growth. *New Phytol.* **174:** 742–751.

Preiss, J. and Handler, P. 1958a. Biosynthesis of diphosphopyridine nucleotide I. Identification of intermediates. *J. Biol. Chem.* **233:** 488–492.

Preiss, J. and Handler, P. 1958b. Biosynthesis of diphosphopyridine nucleotide II. Enzymatic aspects. *J. Biol. Chem.* **233:** 493–500

Pugin, A., Frachisse, J. M., Tavernier, E., Bligny, R., Gout, E., Douce, R., and Guern, J. 1997. Early events induced by the elicitor cryptogein in tobacco cells: involvement of a plasma membrane NADPH oxidase and activation of glycolysis and the pentose phosphate pathway. *Plant Cell.* **9:** 2077–2091.

Queval, G. and Noctor, G. 2007. A plate reader method for the measurement of NAD, NADP, glutathione, and ascorbate in tissue extracts: application to redox profiling

during *Arabidopsis* rosette development. *Anal. Biochem.* **363:** 58–69.

Rachmilevitch, S., Cousins, A. B., and Bloom, A. J. 2004. Nitrate assimilation in plant shoots depends on photorespiration. *Proc. Natl. Acad. Sci. U.S.A.* **101:** 11506–11510.

Rafter, G. W., Chaykin, S., and Krebs, E. G. 1954. The action of glyceraldehyde-3-phosphate dehydrogenase on reduced diphosphopyridine nucleotide. *J. Biol. Chem.* **208:** 799–811.

Raghavendra, A. S. and Padmasree, K. 2003. Beneficial interactions of mitochondrial metabolism with photosynthetic carbon assimilation. *Trends Plant Sci.* **8:** 546–553.

Rankin, P. W., Jacobson, E. L., Benjamin, R. C., Moss, J., and Jacobson, M. K. 1989. Quantitative Studies of Inhibitors of ADP-ribosylation in vitro and in vivo. *J. Biol. Chem.* **264:** 4312–4317.

Rasmusson, A. G. and Møller, I. M. 1990. NADP-utilizing enzymes in the matrix of plant mitochondria. *Plant Physiol.* **94:** 1012–1018.

Rasmusson, A. G., Soole, K. L., and Elthon, T. E. 2004. Alternative NAD(P)H dehydrogenases of plant mitochondria. *Annu. Rev. Plant Biol.* **55:** 23–39.

Rasmusson, A. G. and Wallström, S. V. 2010. Involvement of mitochondria in the control of plant cell NAD(P)H reduction levels. *Biochem. Soc. Trans.* **38:** 661–666.

Rawsthorne, S. 2002. Carbon flux and fatty acid synthesis in plants. *Prog. Lipid Res.* **41:** 182–196.

Reidl, J., Schlör, S., Kraiss, A., Schmidt-Brauns, J., Kemmer, G., and Soleva, E. 2000. NADP and NAD utilization in *Haemophilus influenzae*. *Mol. Microbiol.* **35:** 1573–1581.

Reumann, S., Heupel, R., and Heldt, H. 1994. Compartimentation studies on spinach leaf peroxisomes. 2. Evidence for the transfer of reductant from the cytosol to the peroxisomal compartment via a malate shuttle. *Planta.* **193:** 167–173.

Richter, C. 1987. $NADP^+$ phosphatase: a novel mitochondrial enzyme. *Biochem. Biophys. Res. Commun.* **146:** 253–257.

Richter, A. S., Peter, E., Rothbart, M., Schlicke, H., Toivola, J., Rintamäki, E., and Grimm, B. 2013. Posttranslational influence of NADPH-dependent thioredoxin reductase C on enzymes in tetrapyrrole synthesis. *Plant Physiol.* **162:** 63–73.

Rissel, D., Heym, P. P., Thor, K., Brandt, W., Wessjohann, L. A., and Peiter, E. 2017. No silver bullet – canonical poly(ADP-ribose) polymerases (PARPs) are no universal factors of abiotic and biotic stress resistance of *Arabidopsis thaliana*. *Front. Plant Sci.* **8:** 224.

Rissel, D., Losch, J., and Peiter, E. 2014. The nuclear protein poly(ADP-ribose) polymerase 3 (AtPARP3) is required for seed storability in *Arabidopsis thaliana*. *Plant Biol. (Stuttg).* **16:** 1058–1064.

Rius, S. P., Casati, P., Iglesias, A. A., and Gomez-Casati, D. F. 2008. Characterization of *Arabidopsis* lines deficient in GAPC-1, a cytosolic NAD-dependent glyceraldehyde-3-phosphate dehydrogenase. *Plant Physiol.* **148:** 1655–1667.

Rizzi, M. and Schindelin, H. 2002. Structural biology of enzymes involved in NAD and molybdenum cofactor biosynthesis. *Curr. Opin. Struct. Biol.* **12:** 709–720.

Rousset, C., Fontecave, M., and Ollagnier de Choudens, S. 2008. The [4Fe-4S] cluster of quinolinate synthase from *Escherichia coli*: investigation of cluster ligands. *FEBS Lett.* **582:** 2937–2944.

Ruiz, J. M., Sánchez, E., García, P. C., López-Lefebre, L. R., Rivero, R. M., and Romero, L. 2002. Proline metabolism and NAD kinase activity in greenbean plants subjected to cold-shock. *Phytochemistry.* **59:** 473–478.

Ryan, S. M., Cane, K. A., DeBoer, K. D., Sinclair, S. J., Brimblecombe, R., and Hamill, J. D. 2012. Structure and expression of the quinolinate phosphoribosyltransferase (QPT) gene family in Nicotiana. *Plant Sci.* **188:** 102–110.

Ryrie, I.J, and Scott, K. J. 1968. Metabolic regulation in diseased leaves II. Changes in nicotinamide nucleotide coenzymes in barley leaves infected with powdery mildew. *Plant Physiol.* **43:** 687–692.

Ryrie, I. J. and Scott, K. J. 1969. Nicotinate, quinolinate and nicotinamide as precursors in the biosynthesis of nicotinamide-adenine dinucleotide in barley. *Biochem J.* **115:** 679–685.

Sagi, M. and Fluhr, R. 2006. Production of reactive oxygen species by plant NADPH oxidases. *Plant Physiol.* **141:** 336–340.

Sakuraba, H., Tsuge, H., Yoneda, K., Katunuma, N., and Ohshima, T. 2005. Crystal structure of the NAD biosynthetic enzyme quinolinate synthase. *J. Biol. Chem.* **280:** 26645–26648.

Sánchez J.-P., Duque, P., and Chua N.-H. 2004. ABA activates ADPR cyclase and cADPR induces a subset of ABA-responsive genes in *Arabidopsis*. *Plant J.* **38:** 381–395.

Sanders, D., Pelloux, J., Brownlee, C., and Harper, J. F. 2002. Calcium at the crossroads of signaling. *Plant Cell.* **14:** S401–S417.

Savidov, N. A., Alikulov, Z. A., and Lips, S. H. 1998. Identification of an endogenous NADPH-regenerating system coupled to nitrate reduction in vitro in plant and fungal crude extracts. *Plant Sci.* **133:** 33–45.

Scheibe, R. 1984. Quantitation of the thiol group involved in the reductive activation of NADP-malate dehydrogenase. *Biochim. Biophys. Acta.* **788**: 241–247.

Scheibe, R. 2004 Malate valves to balance cellular energy supply. *Physiol Plant.* **120:** 21–26.

Scheibe, R., Backhausen, J. E., Emmerlich, V., and Holtgrefe, S. 2005. Strategies to maintain redox homeostasis during photosynthesis under changing conditions. *J. Exp. Bot.* **56:** 1481–1489.

Scheibe, R. and Jacquot, J. P. 1983. NADP regulates the light activation of NADP-dependent malate dehydrogenase. *Planta.* **157:** 548–553.

Schomburg, I., Chang, A., and Schomburg, D. 2014. Standardization in enzymology—Data integration in the world's enzyme information system BRENDA. *Perspect. Sci.* **1:** 23–15.

Schippers, J. H. M, Nunes-Nesi, A., Apetrei, R., Hille, J., Fernie, A. R., and Dijkwel, P. P. 2008. The *Arabidopsis* onset of leaf death5 mutation of quinolinate synthase affects nicotinamide adenine dinucleotide biosynthesis and causes early ageing. *Plant Cell.* **20:** 2909–2925.

Schmid, M., Davison, T. S., Henz, S. R., Pape, U. J., Demar, M., Vingron, M., Schölkopf, B., Weigel, D., and Lohmann, J. U. 2005. A gene expression map of *Arabidopsis thaliana* development. *Nat. Genet.* **37:** 501–506.

Schulz, P., Jansseune, K., Degenkolbe, T., Méret, M., Claeys, H., Skirycz, A., Teige, M., Willmitzer, L., and Hannah,

M. A. 2014. Poly(ADP-ribose)polymerase activity controls plant growth by promoting leaf cell number. *PLoS One*. **9:**e90322.

Schulz, P., Neukermans, J., Van der Kelen, K., Mühlenbock, P., Van Breusegem, F., Noctor, G., Teige, M., Metzlaff, M., and Hannah, M. A. 2012. Chemical PARP inhibition enhances growth of *Arabidopsis* and reduces anthocyanin accumulation and the activation of stress protective mechanisms. *PLoS One*. **7:** e37287.

Schwenen, L., Komoßa, D., Barz, W. 1986. Metabolism and degradation of nicotinic acid in parsley (*Petroselinum hortense*) cell suspension cultures and seedlings. *Zeitschrift für Naturforschung C*. **41**: 148–157.

Selinski, J., König, N., Wellmeyer, B., Hanke, G. T., Linke, V., Neuhaus, H. E., and Scheibe, R. 2014. The plastid-localized NAD-dependent malate dehydrogenase is crucial for energy homeostasis in developing *Arabidopsis thaliana* seeds. *Mol. Plant*. **7:** 170–186.

Selinski, J. and Scheibe, R. 2014. Lack of malate valve capacities lead to improved N-assimilation and growth in transgenic *A. thaliana* plants. *Plant Signal. Behav*. **9:** e29057.

Setterdahl, A. T., Chivers, P. T., Hirasawa, M., Lemaire, S. D., Keryer, E., Miginiac-Maslow, M., Kim, S.-K., Mason, J., Jacquot, J.-P., Longbine, C. C., de Lamotte-Guery, F., and Knaff, D. D. 2003. Effect of pH on the oxidation-reduction properties of thioredoxins. *Biochemistry*. **42:** 14877–14884.

Shen, W., Wei, Y., Dauk, M., Tan, Y., Taylor, D. C., Selvaraj, G., and Zou, J. 2006. Involvement of a glycerol-3-phosphate dehydrogenase in modulating the NADH/NAD + ratio provides evidence of a mitochondrial glycerol-3-phosphate shuttle in *Arabidopsis*. *Plant Cell*. **18:** 422–441.

Shen, W., Wei, Y., Dauk, M., Zheng, Z., and Zou, J. 2003. Identification of a mitochondrial glycerol-3-phosphate dehydrogenase from *Arabidopsis thaliana*: evidence for a mitochondrial glycerol-3-phosphate shuttle in plants. *FEBS Lett*. **536:** 92–96.

Shi, Q., Li, C., and Zhang, F. 2006 Nicotine synthesis in *Nicotiana tabacum* L. induced by mechanical wounding is regulated by auxin. *J. Exp. Bot*. **57:** 2899–2907.

Shimizu, M. M. and Mazzafera, P. 2000. A role for trigonelline during imbibition and germination of coffee seeds. *Plant Biol*. **2:** 605–611.

Shull, N. P., Spinelli, S. L., and Phizicky, E. M. 2005. A highly specific phosphatase that acts on ADP-ribose 1''-phosphate, a metabolite of tRNA splicing in *Saccharomyces cerevisiae*. *Nucleic Acids Res*. **33:** 650–660.

Sinclai J., Murphy, K. J., Birch, C. D., and Hamill, J. D. 2000. Molecular characterization of quinolinate phosphoribosyltransferase (QPRtase) in Nicotiana. *Plant Mol. Biol*. **44:** 603–617.

Smyth, L. M., Bobalova, J., Mendoza, M. G., Lew, C., and Mutafova-Yambolieva, V. N. 2004. Release of beta-nicotinamide adenine dinucleotide upon stimulation of postganglionic nerve terminals in blood vessels and urinary bladder. *J. Biol. Chem*. **279:** 48893–48903.

Song, M.-G., Bail, S., and Kiledjian, M. 2013. Multiple Nudix family proteins possess mRNA decapping activity. *RNA*. **19:** 390–399.

Sorci, L., Blaby, I., De Ingeniis, J., Gerdes, S., Raffaelli, N., de Crécy Lagard, V., and Osterman, A. 2010. Genomics-driven reconstruction of acinetobacter NAD metabolism: insights for antibacterial target selection. *J. Biol. Chem*. **285:** 39490–39499.

Soriano, E. V., Zhang, Y., Colabroy, K. L., Sanders, J. M., Settembre, E. C., Dorrestein, P. C., Begley, T. P., and Ealick, S. E. 2013. Active-site models for complexes of quinolinate synthase with substrates and intermediates. *Acta. Crystallogr. D Biol. Crystallogr*. **69:** 1685–1696.

Sparla, F., Costa, A., Lo Schiavo, F., Pupillo, P., and Trost, P. 2006. Redox regulation of a novel plastid-targeted beta-amylase of *Arabidopsis*. *Plant Physiol*. **141:** 840–850.

Spielbauer, G., Li, L., Römisch-Margl, L., Do, P. T., Fouquet, R., Fernie, A. R., Eisenreich, W., Gierl, A., and Settles, A. M. 2013. Chloroplast-localized 6-phosphogluconate dehydrogenase is critical for maize endosperm starch accumulation. *J. Exp. Bot*. **64**: 2231–2242.

Sriram, G., Fulton, D. B., Iyer, V. V., Peterson, J. M., Zhou, R., Westgate, M. E., Spalding, M. H., and Shanks, J.V. 2004. Quantification of compartmented metabolic fluxes in developing soybean embryos by employing biosynthetically directed fractional (13)C labeling, two-dimensional [(13)C, (1)H] nuclear magnetic resonance, and comprehensive isotopomer balancing. *Plant Physiol*. **136:** 3043–3057.

Stein, L. R. and Imai, S. I. 2012. The dynamic regulation of NAD metabolism in mitochondria. *Trends Endocrinol. Metab*. **23:**420–428.

Stitt, M. 1986. Limitation of photosynthesis by carbon metabolism: I. Evidence for excess electron transport capacity in leaves carrying out photosynthesis in saturating light and CO(2) *Plant Physiol*. **81:** 1115–1122.

Stitt, M., Lilley, R. M., and Heldt, H. W. 1982. Adenine nucleotide levels in the cytosol, chloroplasts, and mitochondria of wheat leaf protoplasts. *Plant Physiol*. **70:** 971–977.

Stöhr, C., Strube, F., Marx, G., Ullrich, W. R., and Rockel, P. 2001. A plasma membrane-bound enzyme of tobacco roots catalyses the formation of nitric oxide from nitrite. *Planta*. **212:** 835–841.

Sun, L., Li, Y., Miao, W., Piao, T., Hao, Y., and Hao, F. S. 2017. NADK2 positively modulates abscisic acid-induced stomatal closure by affecting accumulation of H_2O_2, Ca^{2+} and nitric oxide in *Arabidopsis* guard cells. *Plant Sci*. **262:** 81–90.

Sunkar, R., Bartels, D., and Kirch, H. H. 2003. Overexpression of a stress-inducible aldehyde dehydrogenase gene from *Arabidopsis thaliana* in transgenic plants improves stress tolerance. *Plant J*. **35:** 452–464.

Swindall, A. F., Stanley, J. A., and Yang, E. S. 2013. PARP-1: friend or foe of DNA damage and repair in tumorigenesis. *Cancers (Basel)*. **5:** 943–958.

Szal, B., Dabrowska, Z., Malmberg, G., Gardeström, P., and Rychter, A. M. 2008. Changes in energy status of leaf cells as a consequence of mitochondrial genome rearrangement. *Planta*. **227:** 697–706.

Szurmak, B., Wysłouch-Cieszyńska, A., Wszelaka-Rylik, M., Bal, W., and Dobrzańska, M. 2008. A diadenosine diadenosine 5',5''-P1P4 tetraphosphate (Ap4A) hydrolase from *Arabidopsis thaliana* that is activated preferentially by Mn^{2+} ions. *Acta. Biochim. Pol*. **55:** 151–160.

Taira, M., Valtersson, U., Burkhardt, B., and Ludwig, R. A. 2004. *Arabidopsis thaliana* GLN2-encoded glutamine

synthetase is dual targeted to leaf mitochondria and chloroplasts. *Plant Cell*. **16:** 2048–2058.

Taiz, L. and Zeiger, E. 2008. *Plant Physiology*, 5th ed. Sinauer Associates Inc.: Sunderland, p. 782.

Takahama, U., Shimizu-Takahama, M., and Heber, U. 1981. The redox state of the NADP system in illuminated chloroplasts. *Biochim. Biophys. Acta. Bioenerg.* **637:** 530–539.

Takahashi, S., Bauwe, H., and Badger, M. 2007. Impairment of the photorespiratory pathway accelerates photoinhibition of photosystem II by suppression of repair but not acceleration of damage processes in *Arabidopsis*. *Plant Physiol*. **144:** 487–494.

Takahashi, H., Takahara, K., Hashida, S., Hirabayashi, T., Fujimori, T., Kawai-Yamada, M., Yamaya, T., Yanagisawa, S., and Uchimiya, H. 2009. Pleiotropic modulation of carbon and nitrogen metabolism in *Arabidopsis* plants overexpressing the NAD kinase2 gene. *Plant Physiol*. **151:** 100–113.

Takahashi, H., Watanabe, A., Tanaka, A., Hashida, S., Kawai-yamada, M., Sonoike, K., and Uchimiya, H. 2006. Chloroplast NAD kinase is essential for energy transduction through the xanthophyll cycle in photosynthesis. *Plant Cell Physiol*. **47:** 1678–1682.

Talts, E., Oja, V., Rämma, H., Rasulov, B., Anijalg, A., and Laisk, A. 2007. Dark inactivation of ferredoxin-NADP reductase and cyclic electron flow under far-red light in sunflower leaves. *Photosyn. Res*. **94:** 109–120.

Taniguchi, M., Taniguchi, Y., Kawasaki, M., Takeda, S., Kato, T., Sato, S., Tabata, S., Miyake, H., and Sugiyama, T. 2002. Identifying and characterizing plastidic 2-oxoglutarate/malate and dicarboxylate transporters in *Arabidopsis thaliana*. *Plant Cell Physiol*. **43:** 706–717.

Tarr, J. B. and Arditti, J. 1982. Niacin biosynthesis in seedlings of *Zea mays*. *Plant Physiol*. **69:** 553–536.

Tawfik, D. S. 2010. Messy biology and the origins of evolutionary innovations. *Nat. Chem. Biol*. **6:** 692–696.

Tcherkez, G., Mahé, A., Gauthier, P., Mauve, C., Gout, E., Bligny, R., Cornic, G., and Hodges, M. 2009. In folio respiratory fluxomics revealed by 13C isotopic labeling and H/D isotope effects highlight the noncyclic nature of the tricarboxylic acid "cycle" in illuminated leaves. *Plant Physiol*. **151:** 620–630.

Tedeschi, G., Negri, A., Mortarino, M., Ceciliani, F., Simonic, T., Faotto, L., and Ronchi, S. 1996. L aspartate oxidase from *Escherichia coli* II. Interaction with C4 dicarboxylic acids and identification of a novel L-aspartate: fumarate oxidoreductase activity, *Eur. J. Biochein*. **426:** 1115–426.

Tedeschi, G., Negri, A., Ceciliani, F., Mattevi, A., and Ronchi, S. 1999. Structural characterization of L-aspartate oxidase and identification of an interdomain loop by limited proteolysis. *Eur. J. Biochem*. **260**: 896–903.

Tedeschi, G., Ronchi, S., Simonic, T., Treu, C., Mattevi, A., and Negri, A. 2001. Probing the active site of L-aspartate oxidase by site-directed mutagenesis: role of basic residues in fumarate reduction. *Biochemistry*. **40:** 4738–4744.

Tezuka, T. and Yamamoto, Y. 1975. Photoactivation of NAD kinase through phytochrome: phosphate donors and cofactors. *Plant Physiol*. **56:** 728–730.

Titok, V. V., Rusinova, O. V., and Khotyleva, L. V. 1995. Changes of nicotinamide coenzymes and adenylate energy charge in leaves of hybrid and parental tomato forms in anin vitro culture. *Biol. Plant*. **37:** 507–513.

Todisco, S., Agrimi, G., Castegna, A., and Palmieri, F. 2006. Identification of the mitochondrial NAD + transporter in *Saccharomyces cerevisiae*. *J. Biol. Chem*. **281:** 1524–1531.

Torres, M. A. and Dangl, J. L. 2005. Functions of the respiratory burst oxidase in biotic interactions, abiotic stress and development. *Curr. Opin. Plant Biol*. **8:** 397–403.

Torres, M. A., Dangl, J. L., and Jones, J. D. 2002. *Arabidopsis* gp91phox homologues AtrbohD and AtrbohF are required for accumulation of reactive oxygen intermediates in the plant defense response. *Proc. Natl. Acad. Sci. U.S.A*. **99:** 517–522.

Turner, W. L., Waller, J. C., Vanderbeld, B., and Snedden, W. A. 2004. Cloning and characterization of two NAD kinases from *Arabidopsis*. identification of a calmodulin binding isoform. *Plant Physiol*. **135:** 1243–1255.

Upmeier, B., Thomzik, J. E., and Barz, W. 1988. Nicotinic acid-N-glucoside in heterotrophic parsley cell suspension cultures. *Phytochemistry*. **27:** 151–3493.

Valerio, C., Costa, A., Marri, L., Issakidis-Bourguet, E., Pupillo, P., Trost, P., and Sparla, F. 2011. Thioredoxin-regulated beta-amylase (BAM1) triggers diurnal starch degradation in guard cells, and in mesophyll cells under osmotic stress. *J. Exp. Bot*. **62:** 545–655.

Van Linden M. R., Dölle, C., Pettersen, I. K., Kulikova, V. A., Niere, M., Agrimi, G., Dyrstad, S. E., Palmieri, F., Nikiforov, A. A., Tronstad, K. J., and Ziegler, M. 2015. Subcellular distribution of NAD + between cytosol and mitochondria determines the metabolic profile of human cells. *J. Biol. Chem*. **290**: 27644–27659.

Van Roermund, C. W., Schroers, M. G., Wiese, J., Facchinelli, F., Kurz, S., Wilkinson, S., Charton, L., Wanders, R. J., Waterham, H. R., Weber, A. P., and Link, N. 2016. The peroxisomal NAD carrier from *Arabidopsis* imports NAD in exchange with AMP. *Plant Physiol*. **171:** 2127–2139.

Vanderauwera, S., De Block, M., Van de Steene, N., van de Cotte, B., Metzlaff, M., and Van Breusegem, F. 2007. Silencing of poly(ADP-ribose) polymerase in plants alters abiotic stress signal transduction. *Proc. Natl. Acad. Sci. U.S.A*. **104:** 15150–15105.

Vescovi, M., Zaffagnini, M., Festa, M., Trost, P., Lo Schiavo, F., and Costa, A. 2013. Nuclear accumulation of cytosolic glyceraldehyde-3-phosphate dehydrogenase in cadmium-stressed *Arabidopsis* roots. *Plant Physiol*. **162:** 333–346.

Vigani, G. and Zocchi, G. 2009. The fate and the role of mitochondria in Fe-deficient roots of strategy I plants. *Plant Signal. Behav*. **5:** 375–379.

Vincentz, M. and Caboche, M. 1991. Constitutive expression of nitrate reductase allows normal growth and development of Nicotiana plumbaginifolia plants. *EMBO J*. **10:** 1027–1035.

Vishwakarma, A., Bashyam, L., Senthilkumaran, B., Scheibe, R., and Padmasree, K. 2014. Physiological role of AOX1a in photosynthesis and maintenance of cellular redox homeostasis under high light in *Arabidopsis thaliana*. *Plant Physiol. Biochem*. **81:** 44–53.

von Euler, H. 1930. *Fermentation of Sugars and Fermentative Enzymes*. Nobel Lect Nobel Foun: Stockholm, Suède.

Wagner, R., Feth, F., and Wagner, K. G. 1986a. Regulation in tobacco callus of enzyme activities of the nicotine pathway: II. The pyridine-nucleotide cycle. *Planta*. **168:** 408–413.

Wagner, R., Feth, F., and Wagner, K. G. 1986b. The pyridine-nucleotide cycle in tobacco: enzyme activities for the recycling of NAD . *Planta*. **167:** 226–232.

Wagner, R. and Wagner, K. G. 1985. The pyridine-nucleotide cycle in tobacco enzyme activities for the de-novo synthesis of NAD. *Planta*. **165:** 532–537.

Waller, J. C., Dhanoa, P. K., Schumann, U., Mullen, R. T., and Snedden, W. A. 2010. Subcellular and tissue localization of NAD kinases from *Arabidopsis*: compartmentalization of de novo NADP biosynthesis. *Planta*. **231:** 305–317.

Waller, G. R., Yang, K. S., Gholson, R. K., Hadwiger, L. A., and Chaykin, S. 1966. The pyridine nucleotide cycle and its role in the biosynthesis of ricinine by *Ricinus communis L. J. Biol. Chem*. **241:** 4411–4418.

Wallström, S.V., Florez-Sarasa, I., Araújo, W. L., Aidemark, M., Fernández-Fernández, M., Fernie, A. R., Ribas-Carbó, M., and Rasmusson, A. G. 2014. Suppression of the external mitochondrial NADPH dehydrogenase, NDB1, in *Arabidopsis thaliana* affects central metabolism and vegetative growth. *Mol. Plant*. **7:** 356–368.

Wang, C., Gao, F., Wu, J., Dai, J., Wei, C., and Li, Y. 2010. *Arabidopsis* putative deacetylase AtSRT2 regulates basal defense by suppressing PAD4, EDS5 and SID2 expression. *Plant Cell Physiol*. **51:** 1291–1299.

Wang, G. and Pichersky, E. 2007. Nicotinamidase participates in the salvage pathway of NAD biosynthesis in *Arabidopsis*. *Plant J*. **49:** 1020–1029.

Wang, H., Wolosker, H., Pevsner, J., Snyder, S. H., and Selkoe, D. J. 2000. Regulation of rat magnocellular neurosecretory system by D-aspartate: evidence for biological role(s) of a naturally occurring free D-amino acid in mammals. *J. Endocrinol*. **167:** 247–252.

Warburg, O. and Christian, W. 1936. Pyridin, der wasserstoffübertragende Bestandteil von Gärungsfermenten. *Helv. Chim. Acta*. **19:** E79–E88.

Warren, N. G., Body, B. A., and Dalton, H. P. 1983. An improved reagent for mycobacterial nitrate reductase tests. *J. Clin. Microbiol*. **18:** 546–549.

Willeke, U., Heeger, V., Meise, M., Neuhann, H., Schindelmeiser, I., Vordemfelde, K., and Barz, W., 1979. Mutually exclusive occurrence and metabolism of trigonelline and nicotinic acid arabinoside in plant cell cultures. *Phytochemistry*. **181:** 105–110.

Wingler, A., Lea, P. J., Quick, W. P., and Leegood, R. C. 2000. Photorespiration: metabolic pathways and their role in stress protection. *Philos. Trans. R. Soc. Lond., B, Biol. Sci*. **355:** 1517–1529.

Winter, H., Robinson, D. G., and Heldt, H. W. 1994. Subcellular volumes and metabolite concentrations in spinach leaves. *Planta* **193**: 530–535.

Wolosker, H., D'Aniello, A., and Snyder, S. 2000. d-Aspartate disposition in neuronal and endocrine tissues: ontogeny, biosynthesis and release. *Neuroscience*. **100:** 183–189.

Woo, K. C., Boyle, F. A., Flugge, I. U., and Heldt, H. W. 1987. N-ammonia assimilation, 2-oxoglutarate transport, and glutamate export in spinach chloroplasts in the presence of dicarboxylates in the light. *Plant Physiol*. **85:** 621–625.

Wu, Y., Kuzma, J., Maréchal, E., Graeff, R., Lee, H. C., Foster, R., and Chua, N. H. 1997. Abscisic acid signaling through cyclic ADP-ribose in plants. *Science*. **278:** 2126–2130.

Wu, J., Neimanis, S., and Heber, U. 1991. Photorespiration is more effective than the Mehler reaction in protecting the photosynthetic apparatus against photoinhibition. *Bot. Acta*. **104:** 283–291.

Wu, X., Oh, M.-H., Schwarz, E. M., Larue, C. T., Sivaguru, M., Imai, B. S., Yau, P. M., Ort, D. R., and Huber, S. C. 2011. Lysine acetylation is a widespread protein modification for diverse proteins in *Arabidopsis*. *Plant Physiol*. **155:** 1769–1778.

Wu, L. W., Ren, D. Y., Hu, S. K., Li M., Dong, G. J., Jiang, L., Hu, X. M., Ye, W. J., Cui, Y. T., Zhu, L., Hu, J., Zhang, G., Gao, Z., Zeng, D., Qian, Q., and Guo, L. 2016. Down-regulation of a nicotinate phosphoribosyltransferase gene, OsNaPRT1, leads to withered leaf tips. *Plant Physiol*. **171**: 1085–1098.

Xia, X.-J., Wang, Y.-J., Zhou, Y.-H., Tao, Y., Mao, W.-H., Shi, K., Asami, T., Chen, Z., and Yu, J.-Q. 2009. Reactive oxygen species are involved in brassinosteroid-induced stress tolerance in cucumber. *Plant Physiol*. **150:** 801–814.

Yamamoto, Y. 1963. Pyridine nucleotide content in the higher plant. effect of age of tissue. *Plant Physiol*. **38:** 45–54.

Yamasaki, H. and Sakihama, Y. 2000. Simultaneous production of nitric oxide and peroxynitrite by plant nitrate reductase: in vitro evidence for the NR-dependent formation of active nitrogen species. *FEBS Lett*. **468:** 89–92.

Yang, Z., Savchenko, A., Yakunin, A., Zhang, R., Edwards, A., Arrowsmith, C., and Tong, L. 2003. Aspartate dehydrogenase, a novel enzyme identified from structural and functional studies of TM1643. *J. Biol. Chem*. **278:** 8804–8808.

Yin, Y. and Ashihara, H. 2007. Involvement of rapid nucleotide synthesis in recovery from phosphate starvation of Catharanthus roseus cells. *J. Exp. Bot*. **58:** 1025–1033.

Yin, Y., Matsui, A., Sakuta, M., and Ashihara, H. 2008. Changes in pyridine metabolism profile during growth of trigonelline-forming Lotus japonicus cell cultures. *Phytochemistry*. **69:** 2891–2898.

Yin, Y., Shimano, F., and Ashihara, H. 2007. Involvement of rapid nucleotide synthesis in recovery from phosphate starvation of Catharanthus roseus cells. *J. Exp. Bot*. **58:** 1025–1033.

Ying, W., Garnier, P., and Swanson, R. A. 2003. NAD^+ repletion prevents PARP-1-induced glycolytic blockade and cell death in cultured mouse astrocytes. *Biochem. Biophys. Res. Commun*. **308:** 809–813.

Yoshida, A. and Dave, V. 1975. Inhibition of NADP-dependent dehydrogenases by modified products of NADPH. *Arch. Biochem. Biophys*. **169:** 298–303.

Yoshimura, K., Ogawa, T., Tsujimura, M., Ishikawa, K., and Shigeoka, S. 2014. Ectopic Expression of the Human MutT-Type Nudix Hydrolase, hMTH1, Confers Enhanced Tolerance to Oxidative Stress in *Arabidopsis*. *Plant Cell Physiol*. **55:** 1534–1543.

Yoshimura, K., Ogawa, T., Ueda, Y., and Shigeoka, S. 2007 AtNUDX1, an 8-oxo-7,8-dihydro-2'-deoxyguanosine 5'-triphosphate pyrophosphohydrolase, is responsible for eliminating oxidized nucleotides in *Arabidopsis*. *Plant Cell Physiol*. **48:** 1438–1449.

Yoshimura, K. and Shigeoka, S. 2015 Versatile physiological functions of the Nudix hydrolase family in *Arabidopsis*. *Biosci. Biotechnol. Biochem*. **79:** 354–366.

Zagdanska, B. and Kozdoj, J. 1994. Water stress-induced changes in morphology and anatomy of flag leaf of spring wheat. *Acta. Soc. Bot. Pol*. **63:** 61–66.

Zelitch, I., Schultes, N. P., Peterson, R. B., Brown, P., and Brutnell, T. P. 2009. High glycolate oxidase activity is required for survival of maize in normal air. *Plant Physiol*. **149:** 195–204.

Zhai, R. G., Rizzi, M., and Garavaglia, S. 2009. Nicotinamide/nicotinic acid mononucleotide adenylyltransferase, new insights into an ancient enzyme. *Cell Mol. Life Sci*. **66:** 2805–2818.

Zhang, T., Berrocal, J. G., Yao, J., DuMond, M. E., Krishnakumar, R., Ruhl, D. D., Ryu, K. W., Gamble, M. J., and Kraus, W. L. 2012. Regulation of poly(ADP-ribose) polymerase-1-dependent gene expression through promoter-directed recruitment of a nuclear NAD + synthase. *J. Biol. Chem*. **287:** 12405–12416.

Zhang, X.-C., Li, M.-Y., Ruan, M.-B., Xia, Y.-J., Wu, K.-X., and Peng, M. 2013. Isolation of AtNUDT5 gene promoter and characterization of its activity in transgenic *Arabidopsis thaliana*. *Appl. Biochem. Biotechnol*. **169:** 1557–1565.

Zhang, X. and Mou, Z. 2009. Extracellular pyridine nucleotides induce PR gene expression and disease resistance in *Arabidopsis*. *Plant J*. **57:** 302–312.

Zhang, X. and Mou, Z. 2012. Expression of the human NAD(P)-metabolizing ectoenzyme CD38 compromises systemic acquired resistance in *Arabidopsis*. *Mol. Plant Microbe. Interact*. **25:** 1209–1218.

Zhang, Q., Piston, D. W., and Goodman, R. H. 2002. Regulation of corepressor function by nuclear NADH. *Science*. **295:** 1895–1897.

Zhang, F., Wang, L., Ko, E. E., Shao, K., and Qiao, H. 2018. Histone deacetylases SRT1 and SRT2 interact with ENAP1 to mediate ethylene-induced transcriptional repression. *Plant Cell*. **30:** 153–166.

Zhang, H., Zhao, Y., and Zhou, D. X. 2017. Rice NAD^+-dependent histone deacetylase OsSRT1 represses glycolysis and regulates the moonlighting function of GAPDH as a transcriptional activator of glycolytic genes. *Nucleic Acids Res*. **45:** 12241–12255.

Zheng, X.-Q., Hayashibe, E., and Ashihara, H. 2005. Changes in trigonelline (N-methylnicotinic acid) content and nicotinic acid metabolism during germination of mungbean (Phaseolus aureus) seeds. *J. Exp. Bot*. **56:** 1615–1623.

Zheng, X.-Q., Koyama, Y., Nagai, C., and Ashihara, H. 2004. Biosynthesis, accumulation and degradation of theobromine in developing Theobroma cacao fruits. *J .Plant Physiol*. **161:** 363–369.

Zhong, X., Zhang, H., Zhao, Y., Sun, Q., Hu, Y., Peng, H., and Zhou, D.-X. 2013. The rice NAD(+)-dependent histone deacetylase OsSRT1 targets preferentially to stress- and metabolism-related genes and transposable elements. *PLoS One*. **8:** e66807.

Zhu, X.-G., Long, S. P., and Ort, D. R. 2008. What is the maximum efficiency with which photosynthesis can convert solar energy into biomass? *Curr. Opin. Biotechnol*. **19:** 153–159.

Zielinska, W., Barata, H., and Chini, E. N. 2004. Metabolism of cyclic ADP-ribose: zinc is an endogenous modulator of the cyclase/NAD glycohydrolase ratio of a CD38-like enzyme from human seminal fluid. *Life Sci*. **74:** 1781–1790.

Zimmermann, P., Hirsch-Hoffmann, M., Hennig, L., and Gruissem, W. 2004. GENEVESTIGATOR. *Arabidopsis* microarray database and analysis toolbox 1. *Plant Physiol*. **136:** 2621–2632.