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DNA damage response upon environmental contaminants: an exhausting work for genomic integrity

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Abstract :

Following exposure to xenobiotics, cellular mechanisms will take place to prevent damages relative to i) DNA, to maintain genome integrity, ii) proteins, to maintain their activities, iii) lipids, to limit peroxidation. This system of cellular defence and resistance is energetically costly. In this commentary review, we discuss the impact of DNA damage and the DNA damage response (DDR) on energetic metabolism. Conversely, we address the question about how energetic metabolism would influence DDR. These points will be highlighted in the context of cancer, in which genome instability and aerobic glycolysis are cancer hallmarks.

Keywords : DNA damage response; energetic metabolism; contaminants; carcinogenesis

Highlights

- **DNA damage response (DDR) and metabolic checkpoints are fine-tuned:**

  Upon contaminants exposure, the activity of DDR requires energetic supply and metabolic adaptation. It includes the regulation of PARP-1, TIGAR, SCO2, PFKB3 and SIRT1 activities.

- **Microenvironment and metabolic reprogramming modulate DDR:**

  Hypoxia, acidosis and nutrient limitations affect xenobiotic cellular defense and DDR.

- **During environmental carcinogenesis, metabolic disturbances negatively impact DDR:**

  The environmental-induced metabolic reprogramming favors genomic instability and tumoral progression.

DNA damage response: an expensive energetic system

DDR is fined-tuned by energetic metabolism to maintain genomic integrity. For this purpose, metabolic and DNA damage checkpoints are the surveillance molecular mechanisms, which induce the coordination of DNA repair with bioenergetics to limit the survival and proliferation of damaged cells and metabolic collapse. The DNA damage checkpoints, characterized in the 90's, include DNA damage sensors, signalling transducers and effectors [1], in order to stop cell cycle to perform repair. The metabolic checkpoints, initially identified in 1974 have been recently revived. They are multiple and specific of the cell type and the environmental context (like AMPK or p53). They sense nutrient depletion and adapt metabolic reactions to the cellular needs, in relationship with cell cycle. The coupling DDR/metabolism is barely described in toxicology but literature is growing and open new doors for discovery.

The impact of DNA damage and its impact on energy metabolism was firstly evidenced with the DNA damage sensor PARP-1 (poly(ADP-ribose) polymerase 1) [2]. Activated by numerous genotoxic stresses (by physical or chemical agents, upon acute or chronic exposure), PARP-1 triggers ATP and NAD^+ depletions, associated by mitochondrial depolarization, reactive oxygen species (ROS) production and apoptosis. NAD^+ resynthesis after PARP-1 overactivation induces a metabolic collapse. It is important to note that PARP-1 is a major caspase target, in order to promote apoptosis induction, a mechanism that also requires energy. Otherwise, due to energy drop, it induces necrosis [3]. However, recent findings underline that an adaptive metabolism can occur, with a stimulation of AMPK (AMP-activated protein kinase), leading to an increase in fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) following DNA damage and PARP-1 activation [2] (Figure 1). Induced by multiple genotoxic stresses (ultraviolet radiation, crosslink agents and ionizing radiation), it could be interesting to study such effects at low doses with environmental contaminants.

PARP-1 also regulates metabolism by interacting with different metabolic partners: SIRT1 (sirtuin 1), nuclear factors and energy sensors (AMPK) [4], showing the possible dialogues between DNA damage and metabolic checkpoints.

When DNA damage checkpoints regulate metabolic pathways

Genotoxicity and bioenergetics upon exposure to contaminants were separately studies for years. Recently, there is growing evidence supporting that DNA damage and metabolic response are interacting networks. When DNA damage occurs, the checkpoints that regulate cell arrest and cell repair are orchestrated by metabolic checkpoints.

SIRT1

SIRT1 is a member of sirtuin family of NAD^+-dependent histone deacetylase, involved in cell resistance, survival and longevity. It regulates energy sensing and is activated by nutrient depletion

(including reduction in glucose access). SIRT1 was recently described as a switch of metabolic and DNA damage checkpoints. Precisely, SIRT1 regulates the acetylation/deactelyation of DNA topoisomerase II binding protein 1 (TopBP1) [5]. On the one hand, glucose deprivation induces SIRT1 activation, transducing ToBP1 deacetylation and thereby inhibiting DNA replication. In contrast, DNA damage inhibits SIRT activity, resulting in TopBP1 acetylation that constitutes DNA damage checkpoint and promote repair. SIRT1 pathway would deserve attention as a target for environmental contaminants (Figure 1). Furthermore, a downregulation of SIRT 1 may be induced through the activation of AhR, a crucial sensor of xenobiotics. It leads to a downregulation of peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) levels together with an increase of its acetylation (inactive fraction of PGC1α), followed by a decreased expression of the levels of phosphoenolpyruvate carboxykinase (PEPCK-C) and glucose-6-phosphate dehydrogenase (G6Pase) [6]. Altogether, these observations provide evidence of a role of SIRT1 in glucose homeostasis

p53

The transcription factor p53 was firstly characterized as the guardian of genome, and thus, as a major regulator of DNA damage checkpoint. When activated by DNA damage, p53 induces cell arrest and DNA repair or in some cases, autophagy induction. If the damages are abundant, it can directly trigger apoptosis. Others stresses also activate p53 such as hypoxia and oxidative stress. The p53-activated cellular responses play a pivotal role in DNA repair, tumorigenesis, cell death and survival. Knowing the multiple functions of p53 as an integrator/checkpoint regulator of DNA damage and metabolic homeostasis, single mutation can promote tumorigenesis and p53 is a major driver suppressor of tumors [7].

For ten years, many works attribute an important role of p53 in the regulation of cellular metabolism of cancer cells, especially in the regulation of glycolysis and OXPHOS (for review [8]). In cancer cells, cells yield high level of aerobic glycolysis and a drop of OXPHOS. This phenomenon, termed as « Warburg » effect (for review [9, 10]), has been identified as a major hallmark of malignancy. It have been recently described that p53 positively upregulates OXPHOS and respiration through upregulation of SCO2 (synthesis of cytochrome *c* oxidase). Moreover, p53 negatively regulates glycolysis through the induction of TIGAR (tumor protein 53 induced glycolysis regulator). Then, the loss of function of p53 by mutations could contribute to the Warburg effect through a metabolic reprogramming that favor glycolysis.

Beyond its activity as a transcription factor, p53 also regulates mitochondria homeostasis during apoptosis, by interacting with pro- and anti-apoptotic Bcl2 members. Thus, the disturbances of p53 pathway by xenobiotics would trigger extensive and various effects.

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TIGAR and PFKFB3: metabolic accelerator and break for DNA repair and synthesis

TIGAR, which is a target gene of p53, is involved in the negative regulation of cellular glycolysis and apoptosis regulation [11]. TIGAR expression reduces fructose-2-6-bisphosphate levels inducing an inhibition of glycolysis and thus producing a decrease in ROS [11]. TIGAR also induces an increase in NADPH generation, *via* an upregulation of glucose-6-phosphate dehydrogenase and pentose phosphate pathway (PPP), allowing an increase in cellular glutathione (GSH) levels leading to ROS quenching and protection from apoptosis. Moreover, TIGAR would contribute to an increase of DNA repair *via* an increase of NAPDH and ribose-5-phosphate, which are important precursors for DNA repair and synthesis [12].

Following genotoxicity and/or mitochondrial stress, ROS can transcriptionally activate p53, upregulate TIGAR and thereby inhibit glycolysis, increase PPP, quench ROS, and increase DNA repair. Altogether, this feedback loop neutralizes ROS to protect genome against genotoxicity and mitochondrial stress. The regulation of TIGAR by pollutants was not examined yet. However anticancer drugs were assessed and support the hypothesis that TIGAR contributes to limit DNA damage by acting on ATM phosphorylation *via* Cdk5 [13]. For the first time, TIGAR was described to be translocated into the nucleus.

In contrast, SCO-2, which is also p53-regulated, enhances respiration. It is hypothesized that the regulation of TIGAR is time- dependent and vary in function of the intensity of cellular and genotoxic stress: a low stress would induce preferentially TIGAR and cell cycle arrest whereas high stress would stimulate SCO2 [8]. These models have been proposed in cancer cells but it could be of high interest to study SCO2 and TIGAR pathways in normal stage regarding different exposures.

PFKFB3 (PFK2 isoform 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3) [14] has been identified as repressed by p53. p53 inhibits PFKB3 expression and thereby decreases glycolysis and promotes PPP, increasing *de novo* synthesis of nucleotide for DNA repair. The maintenance of nucleotide homeostasis through metabolic regulation involving p53 appears to be of major importance for the Nucleotide excision repair (NER) pathway, which requires a high level of nucleotides to repair DNA damage after UV irradiation. PFKB3 could be considered as an important metabolic link between p53-regulated metabolism and DDR. Future studies would be relevant to investigate p53 regulation of PFKB3 in response to various genotoxic agents that required different DNA repair pathways (Figure 2).

When metabolic microenvironment modulates DNA repair: a rheostat for genome integrity maintenance

The cellular context is an important parameter that conditions cell fate. Thus, nutrient availability, oxygen restriction, H^+ overload in the microenvironment would affect DDR.

Under conditions of glucose deprivation, we previously described that it influences SIRT1 activity and so DDR [5]. In tumour environment in which glucose is elevated, there is no systematic effect on p53-regulated DDR [15].

Hypoxia

Hypoxia is a drop to the partial pressure of oxygen below 5%. It occurs in tumoral microenvironment of solid tumours. The transcription factor HIF-1 (hypoxia-inducible factor 1) is a major factor induced in hypoxic conditions but there is growing evidence that a number non-hypoxic stimuli, such as genetic alterations in cancer cells (that activate oncogenes or inactive tumor suppressor genes) are able to turn on HIF-1 [16]. HIF-1 plays also an important role in the regulation of cancer cell metabolism [17, 18]. HIF-1 takes part in the Warburg effect by transcriptional regulation of glycolytic enzymes such as HK2 (hexokinase), PDK1 (pyruvate dehydrogenase kinase isoform 1) and LDH-A (lactate dehydrogenase) leading to decreased OXPHOS, in order to tackle the issue of low O_2 availability.

Thus p53 activity, by limiting Warburg effect when non-mutated, antagonizes HIF1α activity [19].

The cellular response to chemicals in the context of hypoxia was mainly studied in the case of chemotherapies. However, Schults and colleagues studied the impact of hypoxia on the bioactivation and the detoxification of benzo[a]pyrene (B[a]P) [20]. They demonstrated that hypoxia mainly favored the induction of phase I enzymes (CYP1A1 and 1B1) with a lower expression of phase II enzymes (UGT1A6 and 2B7). Then, it enhanced the mutagenicity of B[a]P. Moreover, when HIF1α is activated, it increased the rate of mutations after B[a]P exposure, associated with a decrease of DNA repair excision [21]. This example illustrates how hypoxia can potentiate the carcinogenicity of a pollutant, underlying the importance to consider the partial pressure of O_2 in the toxicological studies.

Acidosis

The excess of extracellular H^+, namely acidosis, is a consequence of the increased glycolysis leading to an increased release of lactate and H^+ from cancer cells. Moreover, pollutants like B[a]P can also induce H^+ efflux [22] and create acidic microenvironment. The team of Goldschalk examined the

cellular response to B[a]P in function of the extracellular pH (pHe). They showed that under acidic conditions (pHe<6), the biotransformation of B[a]P was slower, with a progressive and cumulative production of toxic metabolites that can form DNA adducts. This could be explained by the delay of the induction of CYP1A1 and 1B1 and of DNA repair. Consequently, DNA damage is enhanced by acidic pHe, which increases the mutagenicity of B[a]P [23].

Contaminants promoting the Warburg effect: what consequences on DDR?

At low concentration, our works demonstrated that B[a]P was able to reprogram energetic metabolism towards a Warburg-like effect, with a decrease of OXPHOS and an increase of glycolysis [24, 25]. This process was associated with survival. Knowing the propensity of B[a]P to generate mutagenic DNA adducts, the consequences of such an energetic reprogramming on DDR will deserve have to be examined.

Perspectives about DDR, energetic metabolism and environmental contaminants

Environmental contaminants can increase the occurrence of cancer by compromising genome integrity and the adaptability of energetic metabolism. We could explicit different ways of exposure that could induce different cellular responses. For a short exposure to a low dose of environmental toxicant, the low DNA damage level and the good adaptability of energetic metabolism leads to an efficient DDR, i.e. an efficient DNA repair and maintenance of cellular integrity. When it is a short exposure to a high dose, DNA damage and/or metabolism are overwhelmed to tackle repair. The damaged cells can enter into senescence or cell death. If mutations accumulate, it triggers genomic instability. For the case of low dose of contaminants during a long period (such as life-long exposure), we have less data to assert a clear model. However, we hypothesize that a low DNA damage might not activate the DNA damage checkpoint. When associated with a persistent energetic change through a sustainable metabolic reprogramming, it can favour a deficient DDR and thus promote mutagenesis and cell cycle progression. Thus, we think that chronic exposure even to a low dose of contaminants might facilitate genomic instability and consequently, carcinogenesis (Figure 3).

At the scale of species evolution, the relative low rate of mutations allows the generation of variability that can represent an increase of fitness when the environment is changing. Nevertheless, the majority of spontaneous mutations are deleterious for the species. Consequently, the occurrence of mutations and the energetic cost of fidelity constitute the driving process for evolution under selection. Some DNA repair systems exhibit more fidelity than others do. In the way, Wang & Agrewal [26] demonstrated in drosophila that the nutrient availability tuned the orientation of DDR

pathway. The homolog recombination with the homolog (HR-h) is a highly conservative process to repair double strand breaks (DSB) slowly (7 hours *in vitro* [27]), whereas the single-strand annealing (SSA) is efficient and rapid, but non-conservative. Finally, the nonhomologous end-joining (NHEJ) that does not require namely homologous sequence, is a rapid (30 minutes *in vitro* [27]) and always effective repair system for DSB, and consequently prone to generate a high rate of errors. The authors manipulated the diet of drosophila larvae and studied the impact of the orientation of DDR. SSA and NHEJ systems decreased with the age, in the advantage of HR-h. When the diet is limited to sugar and yeast, it was the most conservative and energetic costly HR-h that ensure DDR. These results should be interpreted at the light of the rate of replication that is lower in individuals with restricted diet. When the resources are elevated, the cell cycle rate is maximized and less compatible with the time required for HR-h. Then, because DDR could lie on replication, DDR is not only linked to energetic metabolism, but also to the dynamics of cell division. At the molecular level, the role of p53 as a crossroad for metabolism, DNA repair and cell cycle, illustrates these interrelated checkpoints of regulation. That is why further studies pointed on carcinogenicity of environmental contaminants at low dose during a long-term exposure should focus on the relationships between DNA damage response, the level of proliferation and the adaptability of energetic metabolism. The rise of new real-time technologies to follow these three processes in adequate models [28] will surely improve our knowledge about environmental carcinogenesis.

Bibliography

[1]. Bartek, J. and J. Lukas, *DNA damage checkpoints: from initiation to recovery or adaptation.* Curr Opin Cell Biol, 2007. **19**(2): p. 238-45 DOI: 10.1016/j.ceb.2007.02.009.

[2]. Brace, L.E., S.C. Vose, K. Stanya, R.M. Gathungu, V.R. Marur, A. Longchamp, H. Trevino-Villarreal, P. Mejia, D. Vargas, K. Inouye, R.T. Bronson, C.H. Lee, E. Neilan, B.S. Kristal, and J.R. Mitchell, *Increased oxidative phosphorylation in response to acute and chronic DNA damage.* NPJ Aging Mech Dis, 2016. **2**: p. 16022 DOI: 10.1038/npjamd.2016.22.

[3]. Bai, P., *Biology of Poly(ADP-Ribose) Polymerases: The Factotums of Cell Maintenance.* Mol Cell, 2015. **58**(6): p. 947-58 DOI: 10.1016/j.molcel.2015.01.034.

[4]. Vida, A., J. Marton, E. Miko, and P. Bai, *Metabolic roles of poly(ADP-ribose) polymerases.* Semin Cell Dev Biol, 2017. **63**: p. 135-143 DOI: 10.1016/j.semcdb.2016.12.009.

[5]. Liu, T., Y.H. Lin, W. Leng, S.Y. Jung, H. Zhang, M. Deng, D. Evans, Y. Li, K. Luo, B. Qin, J. Qin, J. Yuan, and Z. Lou, *A divergent role of the SIRT1-TopBP1 axis in regulating metabolic checkpoint and DNA damage checkpoint.* Mol Cell, 2014. **56**(5): p. 681-95 DOI: 10.1016/j.molcel.2014.10.007.

[6]. Diani-Moore, S., P. Ram, X. Li, P. Mondal, D.Y. Youn, A.A. Sauve, and A.B. Rifkind, *Identification of the aryl hydrocarbon receptor target gene TiPARP as a mediator of suppression of*

hepatic gluconeogenesis by 2,3,7,8-tetrachlorodibenzo-p-dioxin and of nicotinamide as a corrective agent for this effect. J Biol Chem, 2010. **285**(50): p. 38801-10 DOI: 10.1074/jbc.M110.131573.

[7]. Swanton, C., *Intratumor heterogeneity: evolution through space and time.* Cancer Res, 2012. **72**(19): p. 4875-82 DOI: 10.1158/0008-5472.CAN-12-2217.

[8]. Madan, E., R. Gogna, M. Bhatt, U. Pati, P. Kuppusamy, and A.A. Mahdi, *Regulation of glucose metabolism by p53: emerging new roles for the tumor suppressor.* Oncotarget, 2011. **2**(12): p. 948-57 DOI: 10.18632/oncotarget.389.

[9]. Koppenol, W.H., P.L. Bounds, and C.V. Dang, *Otto Warburg's contributions to current concepts of cancer metabolism.* Nat Rev Cancer, 2011. **11**(5): p. 325-37 DOI: 10.1038/nrc3038.

[10]. Jose, C., N. Bellance, and R. Rossignol, *Choosing between glycolysis and oxidative phosphorylation: a tumor's dilemma?* Biochim Biophys Acta, 2011. **1807**(6): p. 552-61 DOI: 10.1016/j.bbabio.2010.10.012.

[11]. Bensaad, K., A. Tsuruta, M.A. Selak, M.N. Vidal, K. Nakano, R. Bartrons, E. Gottlieb, and K.H. Vousden, *TIGAR, a p53-inducible regulator of glycolysis and apoptosis.* Cell, 2006. **126**(1): p. 107-20 DOI: 10.1016/j.cell.2006.05.036.

[12]. Cosentino, C., D. Grieco, and V. Costanzo, *ATM activates the pentose phosphate pathway promoting anti-oxidant defence and DNA repair.* EMBO J, 2011. **30**(3): p. 546-55 DOI: 10.1038/emboj.2010.330.

[13]. Yu, H.P., J.M. Xie, B. Li, Y.H. Sun, Q.G. Gao, Z.H. Ding, H.R. Wu, and Z.H. Qin, *TIGAR regulates DNA damage and repair through pentosephosphate pathway and Cdk5-ATM pathway.* Sci Rep, 2015. **5**: p. 9853 DOI: 10.1038/srep09853.

[14]. Franklin, D.A., Y. He, P.L. Leslie, A.P. Tikunov, N. Fenger, J.M. Macdonald, and Y. Zhang, *p53 coordinates DNA repair with nucleotide synthesis by suppressing PFKFB3 expression and promoting the pentose phosphate pathway.* Sci Rep, 2016. **6**: p. 38067 DOI: 10.1038/srep38067.

[15]. Mason, E.F., Y. Zhao, P. Goraksha-Hicks, J.L. Coloff, H. Gannon, S.N. Jones, and J.C. Rathmell, *Aerobic glycolysis suppresses p53 activity to provide selective protection from apoptosis upon loss of growth signals or inhibition of BCR-Abl.* Cancer Res, 2010. **70**(20): p. 8066-76 DOI: 10.1158/0008-5472.CAN-10-0608.

[16]. Semenza, G.L., *Evaluation of HIF-1 inhibitors as anticancer agents.* Drug Discov Today, 2007. **12**(19-20): p. 853-9 DOI: 10.1016/j.drudis.2007.08.006.

[17]. Semenza, G.L., *Regulation of cancer cell metabolism by hypoxia-inducible factor 1.* Semin Cancer Biol, 2009. **19**(1): p. 12-6 DOI: 10.1016/j.semcancer.2008.11.009.

[18]. Yeung, S.J., J. Pan, and M.H. Lee, *Roles of p53, MYC and HIF-1 in regulating glycolysis - the seventh hallmark of cancer.* Cell Mol Life Sci, 2008. **65**(24): p. 3981-99 DOI: 10.1007/s00018-008-8224-x.

[19]. Obacz, J., S. Pastorekova, B. Vojtesek, and R. Hrstka, *Cross-talk between HIF and p53 as mediators of molecular responses to physiological and genotoxic stresses.* Mol Cancer, 2013. **12**(1): p. 93 DOI: 10.1186/1476-4598-12-93.

[20]. Schults, M.A., K. Sanen, R.W. Godschalk, J. Theys, F.J. van Schooten, and R.K. Chiu, *Hypoxia diminishes the detoxification of the environmental mutagen benzo[a]pyrene.* Mutagenesis, 2014. **29**(6): p. 481-7 DOI: 10.1093/mutage/geu034.

[21]. Schults, M.A., L. Timmermans, R.W. Godschalk, J. Theys, B.G. Wouters, F.J. van Schooten, and R.K. Chiu, *Diminished carcinogen detoxification is a novel mechanism for hypoxia-inducible factor 1-mediated genetic instability.* J Biol Chem, 2010. **285**(19): p. 14558-64 DOI: 10.1074/jbc.M109.076323.

[22]. Huc, L., L. Sparfel, M. Rissel, M.T. Dimanche-Boitrel, A. Guillouzo, O. Fardel, and D. Lagadic-Gossmann, *Identification of Na+/H+ exchange as a new target for toxic polycyclic aromatic hydrocarbons.* FASEB J, 2004. **18**(2): p. 344-6 DOI: 10.1096/fj.03-0316fje.

[23]. Shi, Q., L. Maas, C. Veith, F.J. Van Schooten, and R.W. Godschalk, *Acidic cellular microenvironment modifies carcinogen-induced DNA damage and repair.* Arch Toxicol, 2017. **91**(6): p. 2425-2441 DOI: 10.1007/s00204-016-1907-4.

[24]. Hardonniere, K., M. Fernier, I. Gallais, B. Mograbi, N. Podechard, E. Le Ferrec, N. Grova, B. Appenzeller, A. Burel, M. Chevanne, O. Sergent, L. Huc, S. Bortoli, and D. Lagadic-Gossmann, *Role for the ATPase inhibitory factor 1 in the environmental carcinogen-induced Warburg phenotype.* Sci Rep, 2017. **7**(1): p. 195 DOI: 10.1038/s41598-017-00269-7.

[25]. Hardonniere, K., L. Huc, O. Sergent, J.A. Holme, and D. Lagadic-Gossmann, *Environmental carcinogenesis and pH homeostasis: Not only a matter of dysregulated metabolism.* Semin Cancer Biol, 2017. **43**: p. 49-65 DOI: 10.1016/j.semcancer.2017.01.001.

[26]. Wang, A.D. and A.F. Agrawal, *DNA repair pathway choice is influenced by the health of Drosophila melanogaster.* Genetics, 2012. **192**(2): p. 361-70 DOI: 10.1534/genetics.112.143321.

[27]. Mao, Z., M. Bozzella, A. Seluanov, and V. Gorbunova, *Comparison of nonhomologous end joining and homologous recombination in human cells.* DNA Repair (Amst), 2008. **7**(10): p. 1765-71 DOI: 10.1016/j.dnarep.2008.06.018.

[28]. Mistrik, M., L. Oplustilova, J. Lukas, and J. Bartek, *Low-dose DNA damage and replication stress responses quantified by optimized automated single-cell image analysis.* Cell Cycle, 2009. **8**(16): p. 2592-9 DOI: 10.4161/cc.8.16.9331.

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Legends

Figure 1 : From genotoxic stress to metabolic adaptation and the feedback regulation including SIRT1 intervention.

After DNA damage, the strong activation of PARP1 depletes cells from NAD^+. This energy stress could activate AMPK and stimulate FAO and OXPHOS to encompass NAD^+ drop. SIRT1 and PARP1 compete for NAD^+. This feedback regulates the activity of TopBP1 by acetylation/deacetylation and the consecutive cell cycle arrest, DNA repair and DNA replication after DNA damage checkpoint or inhibition of DNA replication after metabolic checkpoint following glucose deprivation.

AMPK (AMP-activated protein kinase), FAO (fatty acid oxidation), PARP-1 (poly(ADP-ribose) polymerase 1), OXPHOS (oxidative phosphorylation), SIRT1 (sirtuin 1), TopBP1 (DNA topoisomerase II binding protein 1)

Figure 2 : Multiple roles of p53 as a coordinator of metabolic adaptation in response to genotoxic stress

As a transcription factor activated by DNA damage, p53 regulates the expression of genes involved in cell cycle control, DNA repair, autophagy and also energetic metabolism, to promote the synthesis of nucleotides and NADPH that support DNA damage response.

PFKB3 (PFK2 isoform 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3), TIGAR (tumor protein 53 induced glycolysis regulator)

Figure 3 : Proposed models depicting involvement of DNA damage and metabolic checkpoints in the toxicity of environmental contaminants.

For a short exposure to a low dose of environmental toxicant, the low DNA damage level and the good adaptability of energetic metabolism leads to an efficient DDR, i.e. an efficient DNA repair and maintenance of cellular integrity. When it is a short exposure to a high dose, DNA damage and/or metabolism are overwhelmed to tackle repair. The damaged cells can enter into senescence or cell death. If mutations accumulate, it triggers genomic instability. For the case of low dose of contaminants during a long period (such as life-long exposure), we hypothesize that a low DNA damage might not activate the DNA damage checkpoint. When associated with a persistent energetic change through a sustainable metabolic reprogramming, it can favour a deficient DDR and thus promote mutagenesis and cell cycle progression. Chronic exposure even to a low dose of contaminants might facilitate genomic instability and consequently, carcinogenesis.

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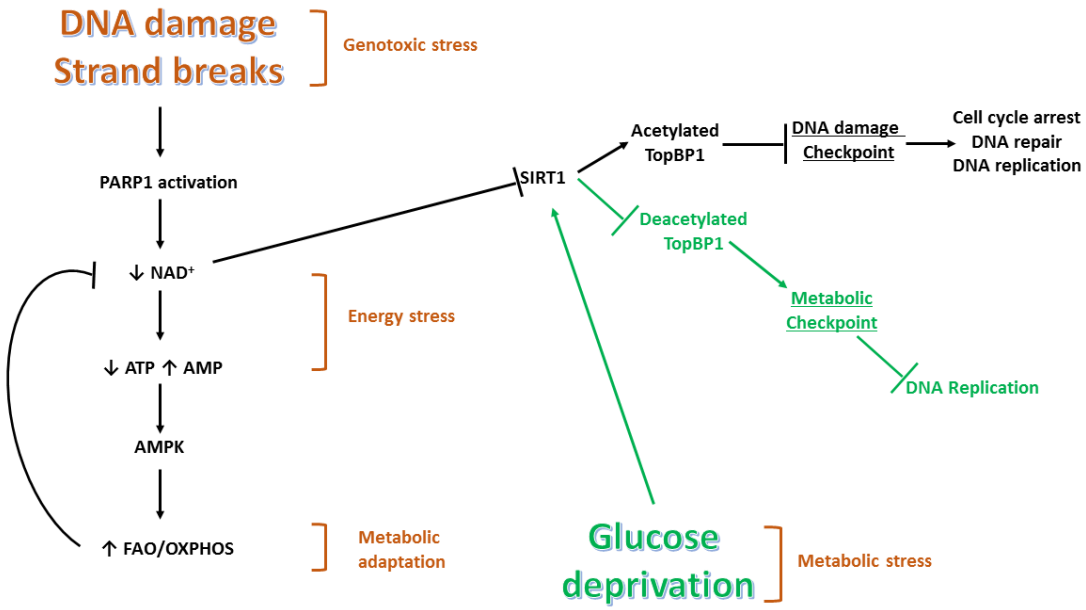

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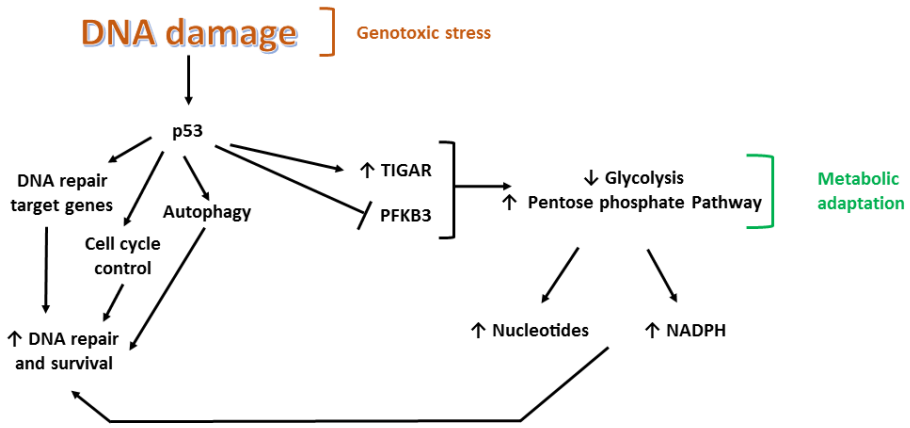

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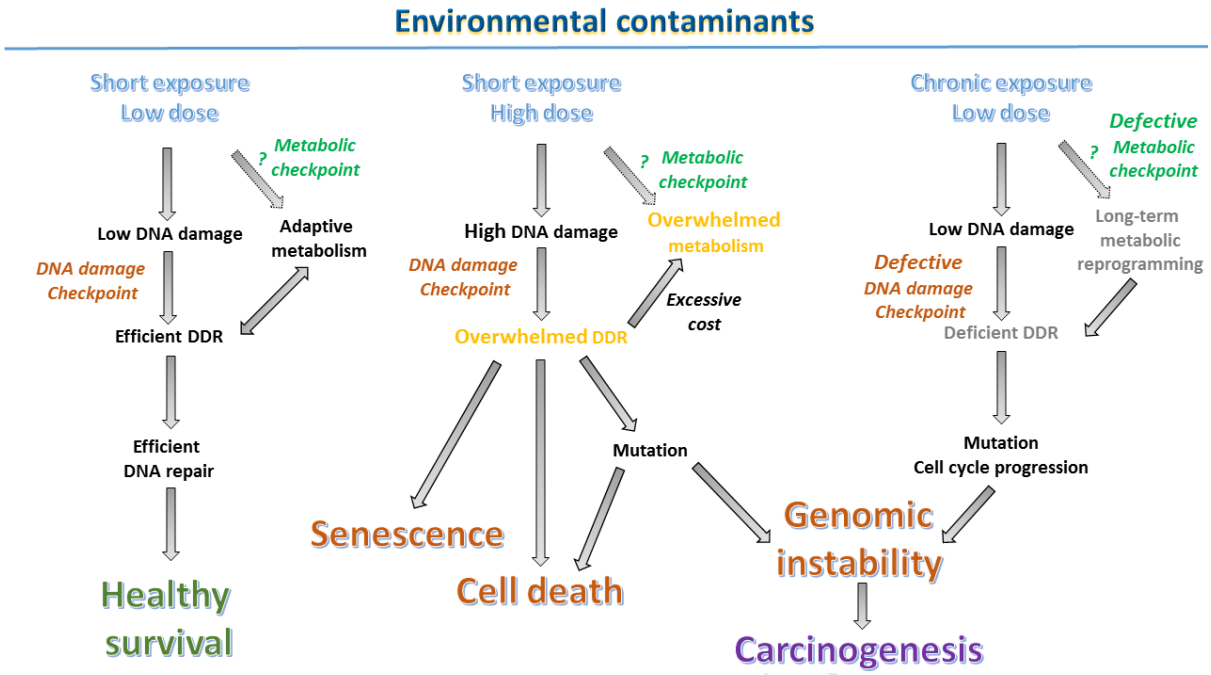

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