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The BAP module: A multi-signal integrator orchestrating growth

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Abstract

Coordination of cell proliferation, cell expansion and differentiation underpins plant growth. To maximise reproductive success, growth needs to be fine-tuned in response to endogenous and environmental cues. This developmental plasticity relies on a cellular machinery that integrates diverse signals and coordinates the downstream responses. In arabidopsis, the BAP regulatory module, which includes the BRASSINAZOLE RESISTANT 1, AUXIN RESPONSE FACTOR 6 and PHYTOCHROME INTERACTING FACTOR 4 transcription factors, has been shown to coordinate growth in response to multiple growth-regulating signals. In this review, we provide an integrative view on the BAP module control of cell expansion and discuss whether its function is conserved or diversified, thus providing new insights into the molecular control of growth.

Coordination of growth: Enter the BAP module

The ability of plants to optimise their genetically-encoded growth by adjusting developmental programs to fluctuating environmental signals define plant phenology and adaptation. In order to grow appropriately, plants must respond accordingly with their developmental stage and their surrounding environment to adjust the growth of their cells. Therefore, the basal cellular processes governing **plant growth** - mainly **cell proliferation** and **cell expansion** (see

Glossary) - must be highly connected to both external and developmental signals. For example, as seeds germinate below ground, they must first develop in the dark prior to reach light and form new organs. To do so, they activate a developmental pathway called **skotomorphogenesis**, where hypocotyl elongation is greatly promoted [1]. Since no division occurs during hypocotyl elongation [2], skotomorphogenesis is mainly driven through cell expansion regulation. Here cell expansion refers to the growth of a differentiated and non-dividing cell that mainly occurs through increase of vacuolar size through water uptake, whereas mitotic growth during cell proliferation depends on cytoplasmic growth and DNA replication [3].

Regulation of cell expansion relies on the coordinated action of growth-promoting transcription factors (TF). BRASSINAZOLE RESISTANT 1 (BZR1) and PHYTOCHROME INTERACTING FACTOR 4 (PIF4)-dependent developmental pathways are independently activated respectively by brassinosteroid (BR) and darkness, whereas BZR1 and PIF4 are able to form a complex which directly targets DNA [4]. In addition, auxin-induced AUXIN RESPONSE FACTOR 6 (ARF6) transcription factor has been shown to interact with both BZR1 and PIF4 [5]. These transcriptional regulators can physically be connected to each other forming a complex system of information **integration** known as the BRZ1/ARF6/PIF4 (BAP) module [4–6]. It has been hypothesized that BZR1, ARF6 and PIF4 could form a trimeric complex able to bind to DNA targets [6] but the presence of such a complex remains to be demonstrated.

In addition to these physical interactions, studies revealed that BZR1, ARF6, and PIF4 share a significant number of targeted genes, supporting a model where the components of the BAP module synergistically promote cell growth [4–6]. In particular, 42% of ARF6-targeted genes are also targeted by both BZR1 and PIF4 [5]. The common targets of the BAP module components controlling cell growth are mainly linked to cell wall modifications and auxin responses including *EXPANSIN*, *SMALL AUXIN UP-REGULATED (SAURs)* and *AUX/IAA* genes [5]. *PACLOBUTRAZOLE RESISTANT 1 (PRE1)* which is an HLH transcription factor that binds and inhibits the growth repressor ILI1 BINDING bHLH PROTEIN1 (IBH1), is also among the common targets of the BAP module thus promoting cell expansion [5,23]. Nevertheless, beyond the shared regulation of common targets, individual signalling pathways also act independently to control specific targets [5]. Altogether, the BAP module components act as key activators of growth during skotomorphogenesis and may provide a general framework for adaptive growth. Indeed, the growing amount of experimental data is drawing

1 the contours of an intricate network of protein interactions and transcriptional regulation
2 underpinning cell expansion making the BAP module a central regulator of growth in various
3 developmental contexts and in different plant species. Beyond its fundamental role in cell
4 expansion regulation, the BAP module forms a precise signal integration system from which
5 the molecular bases are starting to be unravelled.

7 **Integration of hormonal pathways**

8 The BAP module proteins have either individually or collectively been shown to modulate
9 hormonal signalling during growth and development [5]. For example, the transcriptional
10 regulator BZR1 is dynamically regulated by the BRASSINOSTEROID INSENSITIVE 2
11 (BIN2) GSK3-like kinase [9]. Phosphorylated BZR1 inactive form is then unable to trigger
12 BR responses. Besides, BZR1 binds and represses genes involved in BR synthesis, creating a
13 negative feedback loop on BR homeostasis [10]. BZR1 is therefore a central regulator of BR
14 signalling through regulating gene expression that defines wider physiological responses. This
15 involves interaction/coordinated action with other key regulators, including those of the BAP
16 complex. PIF4 was also shown to target key auxin biosynthesis genes to promote hypocotyl
17 elongation [11,12]. Interestingly, it was recently shown that PIFs also directly control BR
18 signalling and responses through regulating key BR synthesis genes such as *DWF4* and
19 *BR6ox2* [13,14]. Additionally, BZR1 directly targets *PIF4* promoter and inhibits its
20 transcription in arabidopsis (*Arabidopsis thaliana*) creating a new regulatory feedback loop
21 [15] (see below). Thus, the BR and auxin signalling pathways are interconnected through the
22 key BAP module components for a coordinated output. In addition to auxin and BR,
23 Gibberellins (GA) are crucial regulators of plant growth as they control both cell division and
24 cell expansion [16]. The DELLA proteins form a family of growth repressors rapidly
25 degraded in presence of GA [17,18]. DELLAs trigger cell growth inhibition by preventing
26 PIF4 and BZR1 binding to their DNA targets [6,17,18]. DELLAs also promote proteasome-
27 mediated degradation of PIF4, providing an additional layer of regulation [19]. Finally,
28 DELLA proteins bind to ARF6 and trigger the inhibition of the auxin-mediated responses [5].
29 Taken together, those results suggest that GA signalling and DELLA proteins could act as
30 major regulators balancing the activity of BAP module.

31 In addition, other input routes have been identified to regulate BAP module activity.
32 JUNGBRUNNEN1 (JUB1), a NAC family transcription factor, regulates GA, BR and light-

mediated signalling, as it directly represses *GA3ox1*, *DWARF4* and *PIF4* genes expression, consequently reducing the synthesis of both GA and BR, as well as decreasing response to changes in light signals [20]. JUB1 directly up-regulates the expression of two DELLAs namely GA INSENSITIVE (GAI) and RGA-LIKE 1 (RGL1) [21]. Finally, PIF4 and BZR1 directly repress JUB1 transcription forming a feedback loop [21]. Consequently, JUB1 stands as a major negative regulator of the BAP module activity.

ETHYLENE RESPONSE FACTOR72 (ERF72), another regulator of the BAP module activity, interacts with BZR1 and ARF6 to inhibit the transcription of BZR1- and ARF6-targeted genes, BEE3 and XTH7 [22]. ERF72 partial inhibition of the BAP module was also shown to be light-modulated, as light triggers nuclear re-localisation of ERF72 [22]. Thus, ethylene signalling pathway also seems to converge towards the BAP module to regulate growth, as ERF72 would inhibit the growth promoting BAP module following a shade-to-light transition. The BAP module network might be even more intricate as ERF72 can also interact with DELLA proteins [23]. In the light of the evidences discussed here, it is immediately apparent that the BAP module plays a critical role in coordinating hormone signalling and responses that govern growth (Fig.1).

Coordination of response to exogenous cues

Responses to light and circadian clock

The ability of plants to reprogram their growth and development in response to exogenous environmental cues underpins adaptation. It has been shown that cell expansion sustaining hypocotyl elongation in the dark is controlled by PIFs [24]. In the light, PIF4 level rapidly decreases through proteasome degradation activated by *phyB* photoreceptor machinery [17,24,25]. Additionally, BIN2 BR-signalling inhibitor can directly mediate PIF4 destabilization [26]. In the dark, DE-ETIOLATED1 (DET1) and CONSTITUTIVE PHOTOMORPHOGENESIS1 (COP1) signalling machinery negatively regulate ELONGATED HYPOCOTYL 5 (HY5), which inhibits PIF4 activity by targets competition [27–29]. Interestingly, HY5 has also been shown to negatively regulate BZR1 at the protein level [30]. Moreover in the dark, COP1 promotes BZR1 phosphorylated forms proteasome degradation counterbalancing BIN2 inhibition [31]. COP1 was also shown to directly bind BIN2 in the dark, adding another level of BR signalling modulation in response to light variations [32]. Finally, under blue light, the photoreceptor CRYPTOCHROME 1 (CRY1)

1 can bind to both PIF4 and BZR1 and prevent their DNA-binding activity [33,34]. CRY1 also
2 interacts with BIN2 to promote BZR1 phosphorylation [34]. Taken together, these features
3 are in line with the increasing role of brassinosteroids in photomorphogenesis and light
4 signalling [35].

5 GA metabolism is dramatically remodelled upon light exposure: the light signalling pathway
6 allows the transcriptional regulation of GA metabolism genes expression to lower GA levels
7 [36]. Light thus triggers the BAP module inhibition and stops hypocotyl elongation through
8 DELLA activation. B-Box transcription factors (BBX) are emerging as key coordinators of
9 hormonal pathways and light regulated developmental processes through the BAP module
10 activity [37]. For instance, the BBX24 transcriptional regulator has been shown to physically
11 interact with DELLA in response to shade, reducing its inhibitory activity toward PIF4 and
12 thus promoting shade avoidance response (SAR) [38].

13 The circadian clock is also an important regulator of the BAP activity controlling notably
14 PIF4 and ARF6 expression [39–41]. The evening complex (EC), composed of EARLY
15 FLOWERING3 (ELF3), ELF4 and LUX ARRHYTHMO (LUX) proteins, binds to the PIF4
16 promoter at the end of the day and reduces its expression [42]. Meanwhile, an EC-
17 independent PIF4 regulation mediated by ELF3 has been demonstrated [43]. Recently, COP1
18 SUPPRESSOR 4 (CSU4) has been shown to coordinate CIRCADIAN CLOCK
19 ASSOCIATED1 (CCA1), the main upstream EC regulator, and PIF4 expression [44].
20 Furthermore, ARF6 has been identified as a direct target of CCA1 [40]. These findings
21 highlight the interplay between circadian clock and BAP-mediated cell expansion.

22 23 *Responses to temperature*

24 Temperature is a key environmental signal resulting in adaptive modulation of growth and
25 development. Exaggerated hypocotyl elongation is a characteristic feature of
26 **thermomorphogenesis**, with PIF4 as the central regulator [45,46]. Indeed, a *pif4* loss-of-
27 function mutant is insensitive to high temperatures [45]. At high temperatures, PIF4
28 repression by ELF3 is released as ELF3 binding to PIF4 promoter is reduced [47]. In addition,
29 *phyB* is less effective in PIF4 light-mediated degradation increasing PIF4 stability [48].
30 Interestingly, increased temperatures promote DET1- and COP1-mediated PIF4 gene
31 expression and protein stabilisation [29]. This is further reinforced by the coordinated
32 competitive regulation of PIF4 function by HY5, which inhibits PIF4-mediated induction of
33 target genes at lower temperatures [29].

Consistent with their cooperative functions in regulating cell elongation, the BAP module proteins play a key role in temperature responsive growth. A positive feed forward loop involving PIF4, auxin, BR and BZR1 that controls temperature responsive growth has been recently identified [15]. PIF4 promotes auxin biosynthesis at elevated temperatures through activating auxin biosynthesis genes [11,12], whereas auxin-dependent cell elongation has been shown to be dependent on BR accumulation and the subsequent activation of BZR1, which in turn promotes PIF4 function through transcriptional activation of *PIF4* [15]. This is further supported by the role of PIF4 in BR biosynthesis directly through activating *DWF4* and *BR6ox2* [13,14]. This, together with the cooperative function of PIF4 and BZR1 in activating common target genes for cell elongation [4,5] further strengthens the argument in favour of the BAP module playing a key role in response to temperature.

Responses to various abiotic and biotic stresses

It is becoming increasingly clear that the BAP module plays a key role in optimising growth in response to exogenous cues. Being one of the central growth control module, the BAP module is targeted during various stress conditions for growth repression through the reduction in GA levels and the consequent activation of DELLA proteins that negatively regulate the BAP module output (Fig.2) [49]. For example, salt-treated plants show low GA concentration and high DELLA levels, similarly to plants raised in a cold environment or under osmotic stress [50–55]. A balanced GA/DELLA response thus integrates various sources of abiotic stresses, triggering or inhibiting cell growth. In the particular case of nutrient starvation such as reduced carbon availability, the down regulation of the BAP module occurs through inhibiting TARGET OF RAPAMYCIN (TOR) kinase activity, which is required for BR responses [56,57]. In response to stress, plants produce reactive oxygen species (ROS) that can damage cells beyond a limit concentration. However, ROS trigger JUB1 activation, which allows a higher tolerance to stress and helps regulating H₂O₂ concentration [20]. In addition, DELLA proteins promote survival by maintaining a low level of ROS in cells [58].

Additionally, PIF4 is a molecular link that coordinates growth and **immunity** in response to seasonal cues [59,60]. In nature, plant adaptation to the prevailing environmental conditions is indeed dependent on the coordination of growth and immunity due to the apparent trade-offs between the two processes. In agreement with its synergistic role in growth control with PIF4, BZR1 also plays an important role in balancing the trade-off between growth and immunity

[61]. While both PIF4 and BZR1 indeed promote hypocotyl elongation, they also act to suppress immunity [29,61].

Thus, the central role of the BAP module in the environmentally modulated growth further exemplifies its significance as a major regulatory hub in plants (Fig. 1).

Modulation of chromatin state

All the components of the BAP module have been shown to be active transcription factors, that can directly control target gene expression. Besides the transcriptional regulation of BAP module components, regulation of their downstream targets provides an additional level of control. For instance, BAF60, which encodes a SWI/SNF chromatin remodeler, competes for some PIF4-regulated targets and acts as an antagonist to hypocotyl growth-promoting genes [62]. Moreover, both the light signalling pathway and the circadian clock regulates BAF60 expression [62], providing an epigenetic framework for the integration of environmental signals. Additionally, BZR1 facilitates BR-responsive chromatin remodelling and antagonizes Polycomb repression through the recruitment of a histone 3 lysine 27 (H3K27) demethylase [63]. BZR1 can also mediate chromatin repression *via* the interaction with the transcriptional co-repressor TOPLESS (TPL) and the subsequent recruitment of histone deacetylases [64]. The possible role of the BAP module in regulating gene expression through chromatin remodelling is further supported by the findings of auxin-mediated transcriptional regulation through differential recruitment of TPL/HDAC co-repressor or SWI/SNF chromatin remodeler [65,66]. These evidences suggest chromatin remodelling as a key route through which the BAP module may be orchestrating a wide array of responses in plants to coordinate growth.

The BAP module in various developmental contexts and across species

With the increasing role of the BAP module in coordinating cell elongation in arabidopsis hypocotyl and young seedlings, it is legitimate to explore a wider role for this module in growth and development, and more generally, in other species. As BR, GA, auxin, temperature and light profoundly affect plant architecture, morphogenesis and senescence, we envisage that the BAP module could constitute a relevant network to drive developmental

processes in the further stages of arabidopsis development and in various environmental conditions as a universal growth-promoting complex.

Several lines of evidences favour this hypothesis. First, some BAP module components control the development of other organs. Stamen elongation depends on cell expansion rather than cell proliferation in the epidermis [67]. The double *arf6 arf8* loss-of-function mutant for auxin responses TFs displays delayed stamen elongation and affects fertilization [68]. ARF8 emerges as an important regulator of stamen filament elongation as one tissue-specific splice variant is able to trigger IAA19 expression allowing late stamen development [69]. Due to its partial redundancy with ARF6 to regulate organ elongation, ARF8 might be an additional member of the BAP module although its molecular interactions with the BAP module TFs remain to be investigated. Functional redundancies have also been shown within the PIF family [70]. These functional redundancies may enhance developmental **robustness** [71]. Additionally, the dynamic regulation of PIF activity by the spectral quality of light through the photoreceptors underpins SAR and neighbour-detection [72] implying that PIF triggered growth responses are conserved in various developmental contexts.

Second, the BAP module control of cell expansion and its regulatory interactions are also conserved in other species. For instance, down-regulation of *SlARF6* and *SlARF8* leads to reduced vegetative growth suggesting that their function is conserved in tomato [73]. *SlPIF4* expression is regulated by light similarly to *AtPIF4* highlighting evolutionarily conserved function of the PIF4 clade [74]. Furthermore, tomato plant over-expressing *AtJUB1* display BR- and GA-deficiency morphological phenotypes [75]. Thus JUB1 is a negative regulator of BR, GA and PIF4 in both arabidopsis and tomato. Taken together, these observations highlight the conservation of cell expansion molecular regulators across phylogenetically distant species like tomato and arabidopsis, that diverged approximatively 112 Mya ago [76]. More generally, in maize, ZmPIF4 physically interacts with the arabidopsis DELLA protein RGA [77]. In rice, OsBZR1 is able to promote the expression of *INCREASED LEAF INCLINATION1 (IL1)*, the *PRE1* homolog gene, which in turns targets and inhibits OsIBH1 [78]. Therefore, the components of the BAP module and their downstream effectors seem to also be conserved in monocotyledonous species. This conservation level highlights the fact that the BAP module constitutes a central growth regulator with ancestral functions predating the split between monocotyledonous and dicotyledonous species.

1 **Concluding remarks**

2 The apparent conservation and pleiotropy of the BAP module suggests that it plays a crucial
3 role during plant evolution allowing **developmental plasticity**. Major signalling pathways
4 promoting growth through cell expansion regulation converge to the BAP module. The
5 different interactions between its components enable the integration of different
6 environmental and hormonal pathways to provide a coordinated growth output. Ultimately,
7 the functioning of this molecular regulatory hub allows adaptive growth (Fig. 3).

8 The BAP module activity could impinge upon the development of several arabidopsis organs.
9 However, it is difficult to assess whether these pleiotropic roles of the BAP module members
10 involve cell expansion *per se* (*i.e.* growth of an already differentiating and non-dividing cell).
11 Cell proliferation in meristems heavily depends on the coupling between mitotic growth and
12 cell division. By controlling the expression of cell wall loosening enzymes as well as auxin
13 production, members of the BAP module may also play a key role during proliferative
14 development but experimental evidences supporting this idea are still lacking. In addition to
15 their role on growth promotion, BAP members could also have more specific effects
16 depending on where they are expressed. For instance, upon exposure to high temperature,
17 PIF4 accumulates in the future stomatal cells to negatively regulates SPEECHLESS thus
18 preventing stomata differentiation [79].

19 Phytohormones signalling pathways and environmental responses are conserved within
20 angiosperms. Thus, we suggest that the presence of the BAP module as a central regulatory
21 hub for development control might be shared by a large amount of plant species, involving
22 similar TFs and connecting the same signalling pathways. As a similar molecular framework
23 is involved in different plant organs or within species, we think that the BAP module
24 constitutes a potential lead for crop improvements. Understanding the BAP module pleiotropy
25 within organs could help deciphering the regulation of growth and the genetic basis of
26 pleiotropy (whether it is a *cis*-regulatory element or a specific amino-acid residue critical for
27 protein-protein interactions) will provide potential targets for new genome editing tools to
28 improve crop performance.

29 Finally, it is important to notice that cell behaviour is integrated at higher level within
30 organismal growth. Because plant development depends on the coordination of both cell
31 expansion and cell division, there are regulatory connections that link these two processes.
32 Therefore, the BAP module must be seen in a more global picture integrated within a cell that

grows and divides, and that is embedded within a tissue in an organ. This implies additional layers of regulation as one can easily imagine that cell expansion has to be coordinated at higher level notably with mechanical stresses [80]. Mechanical stresses emerge as important drivers for growth and development since they connect to core gene regulatory networks. For instance, *SHOOTMERISTEMLESS* (*STM*) expression is modulated through both an auxin-dependent pathway and an auxin-independent mechanotransduction pathway which provide a synergistic framework for the regulation of meristem identity [81]. This is providing future directions to understand how BAP-mediated growth is integrated at the organ level. Therefore it is a challenging time for plant biologists that calls for the development of quantitative tools and multi-scale analysis to allow an integrative view of biological processes ([82] and Outstanding Questions). A detailed understanding of molecular networks will indeed provide invaluable data. Nevertheless, integrating those networks into interconnected networks and at higher scales will be the only way to understand how growth is continuously optimized to respond to environment.

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Figure Legends

Figure 1. The BAP module is a molecular hub. BZR1, ARF6 and PIF4 interact to allow decisive signalling pathways convergence. The BAP module integrates both environmental

1 and hormonal pathways to provide a coordinated growth output. Various key regulators
2 provide additional levels of complexity to control this gene regulatory network.

3
4 Figure 2. Various stresses differentially affect the BAP module activity. Plants use an
5 avoidance strategy in response to starvation, flood or shade events through an activation of the
6 BAP module, as the GA/DELLA balance favors the BAP module activity. In response to salt
7 stress, osmotic stress, cold, the GA/DELLA balance shifts to inactivate the BAP module,
8 promoting stress tolerance. Pathogens lead to BZR1 and PIF4 inhibition. Oxidative stress
9 promotes JUB1 activation. There is an apparent trade-off between BAP-mediated growth
10 promotion and stress tolerance.

11
12 Figure 3. Information integration within the BAP module. This integration system senses
13 various signals, process them and provide an integrative output. Due to the complex
14 regulation of its components, the BAP module can receive and process multi-signal
15 informations from both internal (hormonal concentrations, circadian clock) and external (light,
16 temperature, stresses...) cues to provide an adapted growth response.

19 Glossary

20 **Cell expansion:** Biological process allowing organismal growth whereby a cell increases its
21 volume. This process occurs within non-proliferating tissues and relies mainly on an increase
22 of the cell vacuole volume. Cell elongation, as preferential cell growth in one direction,
23 represents a particular case of cell expansion.

24 **Cell proliferation:** Biological process allowing organismal growth whereby cells increase in
25 numbers. This process requires the coordination of mitotic cell growth driven by cytoplasmic
26 growth and DNA replication and cell division to give rise to two daughter cells.

27 **Developmental Plasticity:** Growth adjustment of an organism that does not require genetic
28 changes.

29 **Integration:** Mechanism whereby multiple-inputs (often from different natures) are
30 coordinated to give rise to a single optimized output.

- 1 **Plant growth:** Set of biological processes required for a tissue or an organ to increase in size.
2 As no cell migration and little cell death occurs in plants, plant growth is mainly driven by
3 cell proliferation and cell expansion.
- 4 **Plant immunity:** Set of biological processes allowing the plant to defend itself against
5 pathogens.
- 6 **Robustness:** Biological property of a system to provide an invariable output in response to
7 variable inputs.
- 8 **Skotomorphogenesis:** Developmental program in which a plant adjusts its growth to a dark
9 environment. Seedlings form apical hooks and elongated hypocotyls, chlorophyll synthesis is
10 inhibited.
- 11 **Thermomorphogenesis:** Developmental program in which a plant adjusts its growth to
12 increased temperature. Seedlings display elongated hypocotyls and petioles.
- 13

Signal reception
Information integration
Response