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Turning on gibberellin and abscisic acid signaling

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The phytohormones gibberellin (GA) and abscisic acid (ABA) play essential and often antagonistic roles in regulating plant growth, development and stress responses. The long-awaited identification of receptors for both GA and ABA has shed light upon the initial events that surround the perception of these two phytohormones. The discovery of these receptors also challenges conventional views of plant hormone signaling and raises intriguing questions regarding the nature of GA and ABA perception and the initiation of their signaling pathways. Moreover, recent advances in understanding GA and ABA signaling point to the existence of multiple, non-linear cell- and compartment-specific pathways that regulate genomic and non-genomic responses to these phytohormones.

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Introduction

The plant hormones gibberellin (GA) and abscisic acid (ABA) exert profound effects on fundamental processes of plant growth and development [1,2]. GA is widely regarded as a growth-promoting compound that positively regulates processes such as seed germination, stem elongation, leaf expansion, pollen-tube growth, flower and fruit development and floral transition [1]. ABA, by comparison, has historically and possibly unduly been considered to function as a growth inhibitor [2]. ABA regulates processes such as embryo maturation, seed development and germination, cell division and elongation, stomatal opening, root development, floral transition and tolerance to abiotic and biotic stress [2]. In several of the above-mentioned processes, including seed germination, floral transition and fruit development, GA and ABA have antagonistic effects, normally with GA promoting and ABA inhibiting these specific processes [3,4••,5].

Over the past two decades, significant progress has been made in understanding the action of these hormones and identifying key enzymes that are involved in their biosynthesis [6,7]. In addition, genetic screens and biochemical analyses have identified intermediates that modulate GA and ABA responses, but none of these intermediates have been shown to affect the entire suite of responses ascribed to each hormone [2]. Earlier attempts at isolating GA and ABA receptors were largely unsuccessful and, consequently, an intimate understanding of the molecular events that surround hormone perception remained elusive [2]. However, the recent discoveries of hormone receptors for GA [8••] and ABA [9••] provide the first steps in these processes. The properties of these receptors, alongside those of the recently identified auxin receptor [10,11], invoke a novel mechanism of hormone action not previously considered. As a consequence, several issues pertaining to the cellular localization, the mechanism(s) of hormone perception and the transduction of signals from GA and ABA receptors must be considered within the context of their individual and confluent signal transduction pathways. The action and downstream signaling components of GA and ABA have been addressed in recent reviews [1,2,6,12,13]. As a result, we limit this review to describe the early events of GA and ABA perception and the initiation of their signal transduction.

Where are GA and ABA perceived?

An essential requirement for an understanding of hormone action is knowledge of the site of perception. Previous studies on barley aleurone protoplasts, utilizing microinjected and cell-impermeable GA or ABA, consistently pointed to the existence of a plasma-membrane receptor for GA and ABA, with the possible existence of an additional cytosolic receptor for ABA [13]. Cumulative evidence of the nuclear location of the rice GA receptor GIBBERELLIN INSENSITIVE DWARF1 (GID1) [8••], the *Arabidopsis* ABA receptor FLOWERING TIME CONTROL LOCUS A (FCA) [9••] and the nuclear-located auxin receptor [10,11] confirm the presence of plant hormone receptors within the cell nucleus.

GID1, a homolog of the hormone-sensitive lipases of animals, localizes predominantly to the nucleus, although lower GID1 levels are detectable in the cytosol [8••]. *gid1* mutants are completely insensitive to GA, and hence it has been proposed that GID1 is the sole receptor for GA [8••]. Analysis of *gid1* mutants for both classical (e.g. seed germination and stem elongation) and novel (e.g. pollen tube growth and meristem development) GA responses should be performed to affirm this observation [1].

Much of the physiological data on the location of GA receptors have been obtained using aleurone cells [13].

It is possible that these specialized terminal endosperm cells employ distinct tissue-specific GA or ABA receptors that act independently of nuclear or cytosolic receptors. On the other hand, it is also worth noting that GA and ABA molecules are capable of traversing membranes in an uncharged state, precluding the need for an extracellular mechanism of hormone perception.

As with GID1, the identification of FCA as an ABA receptor provides strong evidence that nuclear perception is a key facet of the signal transduction pathways for these phytohormones. FCA, a plant-specific RNA-binding protein, possesses two RNA-recognition motifs (RRM) in addition to a tryptophan-tryptophan (WW) protein-interaction domain [14]. Although FCA is predominantly localized to the nucleus, it is important to consider that FCA was purported to be an ABA receptor because it shares sequence homology at the C-terminus with ABAP1, an ABA-binding protein that is associated with the plasma membranes of barley aleurone cells [15]. Hence, a function for FCA in the cytosol or plasma membrane should not be excluded.

GA and ABA signaling pathways: the long and short of it

In a conventional hormone signaling pathway, binding of a ligand by its receptor triggers a cascade of intermediates and secondary messengers that ultimately leads to cellular response. The GA and ABA signal transduction pathways similarly recruit a plethora of intermediates and secondary messengers (e.g. Ca^{2+}, protein phosphorylases, G-proteins, kinases, phosphatases, phospholipases and farnesylation) to achieve temporally distinct genomic and non-genomic response(s) [2,12,16•,17•]. Unlike the previously characterized receptors for the phytohormones ethylene, brassinosteroids, and cytokinin, however, the GID1 [8••], FCA [9••] and TRANSPORT INHIBITOR RESPONSE1 (TIR1) [10,11] receptors reveal a novel signaling mechanism that appears to be short, to be independent of relay intermediates, and to involve only protein–protein interactions that are affected by receptor-hormone binding.

In contrast to other hormone receptors, such as the ethylene receptor ETR1 [18], GID1 and FCA do not possess histidine kinase and receiver domains. GID1 interacts with the rice DELLA protein SLENDER RICE1 (SLR1) in a GA-dependent manner [8••]. DELLA proteins are a family of negative regulators of GA responses that are present in cereals and *Arabidopsis*. They appear to modulate several aspects of light and hormone signaling responses, particularly those related to seed germination. The loss of DELLA protein function leads to altered responses to GA (e.g. in seed germination) that appear to vary among plant species [19,20,21•]. These responses are indicative of the fundamental roles played by DELLA proteins in GA signaling. GA promotes the rapid degradation of DELLA proteins by the 26S proteasome pathway. For example, the binding of GA to GID1 promotes GID1's interaction with SLR1, leading to the destruction of SLR1 in a process that does not appear to require intermediates such as kinases [8••]. Similarly, FCA interacts, through its WW domain, with the proline-rich consensus domain of the polyadenylation factor FLOWERING LOCUS Y (FY) [22], promoting flowering by downregulation of the flowering suppressor *FLOWERING LOCUS C* (*FLC*). This interaction is inhibited by ABA in a concentration-dependent manner [9••] and has no apparent requirement for phosphorylation.

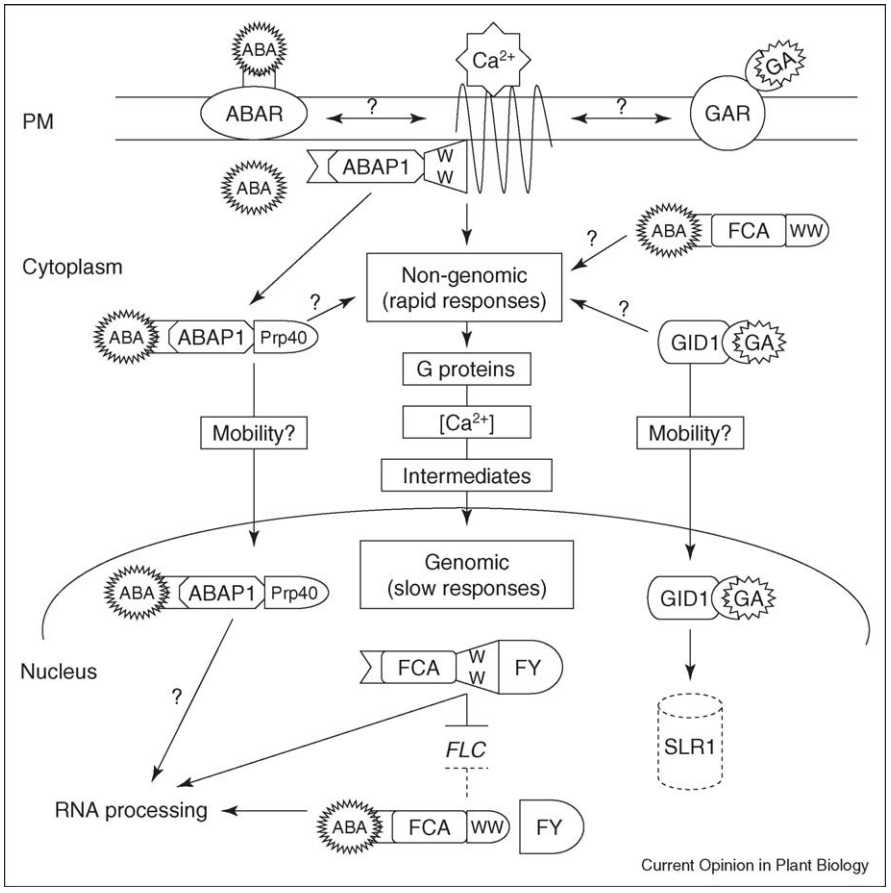
Both GID1–SLR1 and FCA–FY interactions might, however, be restricted to specific cellular compartments (e.g. the nucleus) and potentially encompass only one functional mechanism of hormone perception associated with genomic responses to GA or ABA. Future efforts aimed at further elucidating the function of GID1, FCA, and membrane-associated ABAP1 might reveal that these previously characterized or putative receptors participate in protein interactions that have direct implications for non-genomic responses.

Signaling pathways: how complex are they?

The unique nature of hormone perception and relay displayed by GID1 and FCA also raises intriguing questions about the complexity and confluence of existing signal transduction pathways that have been proposed to cover both genomic (slow) and non-genomic (rapid) responses to GA and ABA (Figure 1). At present, the available evidence suggests that there are either different receptors for genomic and non-genomic responses (i.e. parallel pathways) or a single receptor triggering responses in both groups (i.e. branched pathways). The situation becomes complicated further when one considers the possibility of compartment-specific receptors triggering compartment-specific responses.

Evidence for multiple, parallel pathways is supported by genetic screens and biochemical experiments [2]. Mutants that have altered sensitivity to a hormone do not necessarily display phenotypes for all of the responses ascribed to that hormone. For example, *aba-insensitive* (*abi*) mutants, such as *abi1* and *abi2* show reduced sensitivity to ABA in stomatal aperture and seed germination [2], but do not overcome the ABA-mediated inhibition of lateral root formation [23]. In addition, the inability of *fca-1* mutations to alter stomatal aperture or seed germination, while they modify floral transition and root development, furthers the argument for the existence of multiple, cell-specific perception and/or signaling pathways [9••]. Similarly, when microinjected into *Xenopus* oocytes, cell-specific *Vicia faba* mRNA pools reveal that stomatal guard cells perceive ABA through mechanisms that are distinct from those of mesophyll cells [24].

Figure 1



A schematic model for GA and ABA genomic and non-genomic responses. GA and ABA are perceived by GID1 [8••], FCA [9••], ABAP1 [15] and other putative receptors. Putative plasma membrane (PM) receptors for GA (GAR) and ABA (ABAR) are probably structurally similar to GID1 and FCA/ABAP1 receptors. Receptors in the PM and/or cytoplasm trigger rapid non-genomic responses to GA and ABA that result in events such as changes in Ca^{2+} levels, alterations in G-protein levels and modification of other signaling intermediates [13]. Binding of GA–GID1 is likely to trigger conformational change and nucleo-cytoplasmic shuttling, resulting in the destruction of SLR1. ABA–ABAP1 binding causes conformational change in the WW interaction domain, resulting in the dissociation of ABAP1 from a PM Ca^{2+}-binding protein and its movement to the nucleus. In the nucleus, ABAP1 interacts, through its Prp40 splicing factor, with targets that are involved in RNA processing, whereas FCA interacts with FY to downregulate *FLC* and to auto-regulate the pre-mRNA processing of FCA [14,22]. Like the interaction between ABAP1 and the PM Ca^{2+}-binding protein, the FCA–FY interaction dissociates following ABA binding, resulting in a conformational change that affects FCA's protein interactions.

A heterotrimeric G-protein complex, a G-protein-coupled receptor (GPCR) and Ca^{2+}-dependent events have also been implicated in GA and ABA signaling [2,6,12,13,16•,17•]. GID1 mediation of SLR1 degradation is either downstream or independent of Ca^{2+}-dependent events. Taking into account the differences in response time between the fast changes in cytosolic Ca^{2+} and the slower SLR1 degradation, it is clear that DELLA proteins do not mediate the increase in Ca^{2+} levels [6,13]. Furthermore, metabolites and analogs that share structural similarities with the physiologically active hormone, such as (−)- and trans-ABA, do not trigger seed germination responses that are identical to those induced by the hormone [2], indicating several receptors that have different structural requirements might exist.

The argument that non-linear GA and ABA signaling pathways branch from a single GA-binding and a single ABA-binding site is supported by the recent identification of their hormone receptors [8••,9••]. As most observed classical GA responses are affected in *gid1* mutants [8••], it is most likely that GID1 triggers an additional non-genomic pathway in the cytosol, which is different from that involving the interaction with SLR1 in the nucleus. This pathway might include several rapid events, such as control of Ca^{2+} ion channels. Similarly, the ABA-binding sites in ABAP1 [15] and FCA [9••] are apparently identical and reside at the C-terminal end of both receptors, where ABA binding occurs [9••,15]. A likely site for ABA binding is a hydrophobic region flanked by a hydrophilic platform, which consists mainly of Gln-rich regions in

close proximity to a WW protein-interaction domain. ABAP1 affects ABA signaling intermediates, such as protein kinase PKABA1 [5], which is involved in barley seed germination (A El-Kereamy *et al.* unpublished). In this regard, ABA signaling pathways might have branched from a common ABA-binding site to modulate different ABA responses, such as floral transition and root development (e.g. mediated by FCA) and seed germination (e.g. mediated by ABAP1) [9••,15]. Furthermore, sequence information on the putative 42-kDa ABA-binding protein from the guard cells of bean leaves [25] will determine if this protein also has an identical ABA-binding site.

Similarly, the putative plasma membrane GA receptor in barley aleurones [13] might share a common GA binding site with GID1. The *gid1* deletion and substitution mutants do not show affinity for GA and it is possible that two or more of these mutations share a common GA-binding site [8••]. Homolog identification and/or structural analyses of the GA- and ABA-binding sites of GID1 and FCA/ABAP1, respectively, will provide the tools to narrow down this search.

GA and ABA receptors might fit the ensemble model for steroid receptors

Rapid non-genomic responses, such as ion-channel activation, are characteristic of both GA and ABA signaling. Hence, it is likely that cytosolic and/or membrane-bound receptors participate in the activation of relay intermediates. Nuclear-localized receptors, on the other hand, are more likely to be directed towards the regulation of genomic responses during GA and ABA signaling. For GA signaling, the implications of GA–GID1 binding in the cytosol are currently enigmatic although non-genomic responses (e.g. the activation of Ca^{2+} channels) or nucleo-cytoplasmic shuttling can be envisaged. Moreover, unpublished data from our laboratory suggest that ABA–ABAP1 binding results in changes in ABAP1 protein conformation, the subsequent dissociation from an interacting protein in the plasma membrane, and the appearance of ABAP1 in cytosolic and nuclear compartments. In either instance, if the proteins that interact with characterized (GID1, FCA) or putative (ABAP1) receptors are restricted in their subcellular localization, then the mobility of GA or ABA hormone receptors might have particular relevance for covering the entire suite of non-genomic and genomic responses encompassed by both GA and ABA. The mobility of hormone receptors is not a novel phenomenon: mammalian glutocorticoid receptors have been reported to become extremely dynamic following ligand binding [26]. In this respect, the mechanism for GA and ABA perception and relay appears to be somewhat analogous to the conformational ensemble proposed for a general class of steroids, including brassinosteroid and retinoic acid [27•]. The nuclear and possible plasma-membrane and cytosolic localization of GID1, FCA and ABAP1 receptors support compartment-specific signaling pathways and a possible mechanism that involves receptor mobility between plasma membrane, cytosol and nucleus (Figure 1).

FCA is the only receptor known to affect RNA metabolism by binding directly to RNA [22]. Although ABAP1 does not possess the common RRM to bind RNA, it does possess a WW interaction domain that harbors residues homologous to the Prp40 splicing factor [28]. Several of the WW-containing proteins, such as the FORMIN BINDING PROTEIN 11 (FBP11), are Prp40 orthologs and there is substantial evidence to link nuclear WW-containing proteins to both transcription and RNA splicing [29]. For example, Yes-associated protein (YAP), a WW-containing protein, interacts with POLYOMA ENHANCER-BINDING PROTEIN 2 (PEBP2) transcription factor; whereas Nedd4 (for Neuronal precursor cell expressed developmentally downregulated4), a ubiquitin ligase with a WW domain, interacts with RNA polymerase II and hence affects RNA processing.

Recent studies linked hormone signaling with the post-transcriptional regulation of mRNA [30], but these observations only indirectly linked hormones to RNA processing. There was no evidence that any of the RNA-binding proteins were hormone receptors. The discovery of the RNA-binding protein FCA as a hormone receptor [9••], therefore, provides evidence that some RNA-binding proteins might serve either as hormone receptors or as upstream intermediates in hormone signaling, affecting the transcript levels of genes that mediate cellular responses. As most of the characterized plant RNA-binding proteins have been implicated in ABA signaling, it is possible that ABA signaling is deployed more towards post-transcriptional regulation or that RNA processing connected to other plant hormone signaling pathways remains to be uncovered.

Conclusions

The identification of GID1 [8••] and FCA [9••] as the first receptors for GA and ABA, respectively, marks an important turning point for studies in plant biology. With at least one receptor identified for all the major phytohormones, plant biologists are now faced with the challenging task of identifying the entire gamut of plant hormone receptors and establishing the relationship between the receptors and their downstream components.

For GA and ABA signal transduction pathways in particular, a number of exciting avenues have been presented. These include the search for additional receptors that complement GID1 and FCA to regulate the entire suite of GA and ABA responses. Obvious targets are homologs of GID1 and FCA/ABAP1 receptors. A second area for future research will be detailed exploration of the novel mechanism(s) through which GA and ABA receptors

employ protein–protein interactions and RNA processing to regulate and relay GA and ABA signaling at both the genomic and non-genomic levels. Finally, future research should unravel the dynamic nature of both characterized and putative GA and ABA receptors, and the extent to which their respective pathways mimic or diverge from the steroid conformational ensemble model [27•].

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