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Abscisic Acid Synthesis and Response

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ABSTRACT

Abscisic acid (ABA) is one of the "classical" plant hormones, i.e. discovered at least 50 years ago, that regulates many aspects of plant growth and development. This chapter reviews our current understanding of ABA synthesis, metabolism, transport, and signal transduction, emphasizing knowledge gained from studies of Arabidopsis. A combination of genetic, molecular and biochemical studies has identified nearly all of the enzymes involved in ABA metabolism, almost 200 loci regulating ABA response, and thousands of genes regulated by ABA in various contexts. Some of these regulators are implicated in cross-talk with other developmental, environmental or hormonal signals. Specific details of the ABA signaling mechanisms vary among tissues or developmental stages; these are discussed in the context of ABA effects on seed maturation, germination, seedling growth, vegetative stress responses, stomatal regulation, pathogen response, flowering, and senescence.

INTRODUCTION

Abscisic acid (ABA) is a 15-C weak acid that was first identified in the early 1960s as a growth inhibitor accumulating in abscising cotton fruit ("abscisin II") and leaves of sycamore trees photoperiodically induced to become dormant ("dormin") (reviewed in Nambara and Marion-Poll, 2005; Wasilewska et al., 2008; Cutler et al., 2010). ABA has since been shown to regulate many aspects of plant growth and development including embryo maturation, seed dormancy, germination, cell division and elongation, floral induction, and responses to environmental stresses such as drought, salinity, cold, pathogen attack and UV radiation. However, despite the name, ABA does not appear to control abscission directly; the presence of ABA in abscising organs reflects its role in promoting senescence and/or stress responses, processes which precede abscission. Although ABA has historically been thought of as a growth inhibitor, young tissues have high ABA levels, and ABA-deficient mutant plants are severely stunted (Figure 1) in part because their ability to reduce transpiration and establish turgor is impaired, but also due to excessive ethylene production (reviewed in Sharp, 2002). Exogenous ABA treatment of mutants restores normal cell expansion and growth.

ABA is ubiquitous in plants. It is also produced by some phytopathogenic fungi, bacteria and metazoans ranging from sea

Figure 1. Growth of Ler-0 "wild-type" and ABA-deficient plants (*aba1-1,* ZEP-deficient), without or with ABA treatment.

For ABA treatment, plants were sprayed weekly with 5 mM ABA, starting at the rosette stage and continuing until the siliques started to brown. Photograph courtesy of the Arabidopsis Biological Resources Center.

sponges to humans (reviewed in Nambara and Marion-Poll, 2005; Wasilewska et al., 2008). Although some aspects of signaling appear conserved across kingdoms, there are at least two biosynthetic pathways: fungi produce ABA directly from farnesyl pyrophosphate, whereas plants synthesize it indirectly from carotenoids. As a weak acid (pKa=4.8), ABA is mostly uncharged when present in the relatively acidic apoplastic compartment of plants and can easily enter cells across the plasma membrane. Consequently, control of ABA distribution among plant cell compartments was thought to primarily follow the "anion trap" concept: the dissociated (anion) form of this weak acid accumulates in alkaline compartments (e.g. illuminated chloroplasts) and will redistribute according to the steepness of the pH gradients across membranes. However, multiple plasma membrane-localized transporters have been recently identified. Two ATP-binding cassette (ABC) transporters were identified as an importer (AtABCG40: At1g15520) and exporter (AtABCG25: At1g71960) for ABA, and genetic analyses demonstrated their importance for ABA responses including stomatal regulation, gene regulation, germination inhibition and stress tolerance (Kang et al., 2010; Kuromori et al., 2010). In addition, several members of the NRT/PTR nitrate transporter family appear to function as ABA importers (Kanno et al., 2012). ABA can also be rapidly released from cellular stores of a conjugated glucosyl ester form by glucanases activated or stabilized by dehydrating stresses (Lee et al., 2006; Xu et al., 2012).

A combination of molecular, biochemical, and forward and reverse genetic studies have identified over 200 loci involved in ABA metabolism and response (Tables 1 and 2) and analyzed their functional roles in ABA physiology. During the first 40 years following the identification of ABA, a variety of studies provided evidence for multiple receptor types differing in stereospecificity and subcellular localization, but none were definitively identified. Within the last 6 years, at least three classes of likely ABA receptors have been identified: plasma membrane-associated GTPases with homology to G-protein coupled receptors (GTGs), a chloroplast-localized Mg^{2+} Chelatase subunit, and the soluble PYR/PYL/RCARs (reviewed in Cutler et al., 2010). Although the signaling mechanisms for the first two classes are not well understood, the soluble class is the initial step in what is now known as the "core signaling pathway" for ABA, linking together many of the previously identified signaling elements.

Within the last decade, high throughput "-omics" technologies have permitted the identification and functional analysis of thousands of ABA-regulated genes. We have learned much about the molecular genetics of ABA metabolism and signaling, and this knowledge is already leading to practical applications with agronomic importance such as improved drought resistance.

ABA STRUCTURE, BIOSYNTHESIS, AND METABOLISM

ABA is a sesquiterpenoid ($C_{15}H_{20}O_4$) with one asymmetric, optically active carbon atom at C-1′ (Figure 2). The naturally occurring form is *S*-(+)-ABA; the side chain of ABA is 2-*cis*,-4-*trans*. *Trans, trans*-ABA is biologically inactive, but *R*-(−)-ABA (a possible product of racemization via the catabolite ABA-*trans*-diol) is active in some assays (reviewed in Cutler et al., 2010). A variety

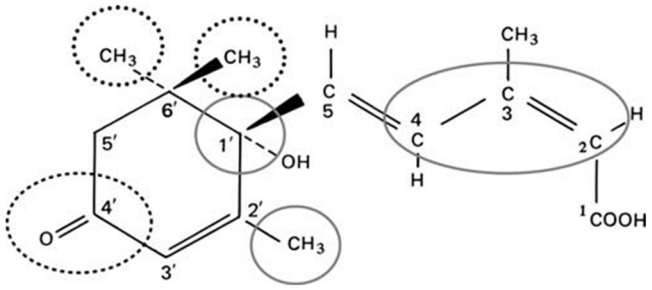


Figure 2. Structure of ABA.

Potentially interacting portions identified by structure-function studies are circled. Critical regions indicated with solid lines and less critical regions with dotted lines. From Plant Cell 18:786-791.

of structure function studies with ABA enantiomers, metabolites and analogs identified the 2-cis, 4-trans side chain configuration, the stereochemistry at C-1', the presence of the 7' methyl group, and the C4' ketone as important for many ABA-like activities. Although interpretation of these studies is complicated by differential stability of the ABA-like molecules and their effects on metabolism of *S*-(+)-ABA, recent crystallization studies with members of the PYR/PYL/RCAR receptor class have demonstrated the basis of the structural requirements (reviewed in Cutler et al., 2010; Miyakawa et al., 2013). These receptors bind ABA through a combination of hydrophobic interactions with residues forming a stereo-selective pocket around the ring and side chain, a water-mediated hydrogen bond network surrounding the side chain, and a charge interaction between a conserved lysine in the receptors and the carboxyl group of the ABA side chain. It remains to be seen how many of these features will be critical for interactions with other classes of ABA receptors.

As for most plant hormones, local active ABA levels reflect a balance of ABA biosynthesis and inactivation by turnover or conjugation, further modified by compartmentation and transport. Early biochemical studies of ABA synthesis, using radioactive or density-labeled precursors, led to a proposed pathway but did not identify any of the responsible enzymes (reviewed in Zeevaart and Creelman, 1988). Subsequent genetic analyses of physiological processes related to ABA activity (seed germination, dormancy, osmotic stress, transpiration, gene expression) resulted in isolation of ABA-deficient mutants in Arabidopsis and other plant species, providing the means to confirm or modify the proposed ABA biosynthetic pathway(s) and identify the enzymes catalyzing each step. In contrast, no ABA catabolism mutants were uncovered, suggesting redundancy of the necessary enzymes. Subsequent bioinformatic and reverse genetic studies have shown that some of the key regulatory steps are actually catalyzed by differentially expressed gene families conserved among plants, while others are controlled by single enzymes.

Many ABA response mutants have altered hormone levels, suggesting that ABA metabolism is subject to feedback regulation. Consistent with this hypothesis, some genes regulating ABA metabolism are regulated by ABA. In addition, several ABA metabolic enzymes are regulated by environmental signals such as

drought, salinity, temperature, and light, as well as by other hormones, intrinsic developmental programs, and circadian rhythms. Presumably, diurnal fluctuations in ABA content and signaling allow plants to anticipate similarly timed fluctuations in light, temperature and water status (reviewed in Seung et al., 2012).

Early, Shared Steps In ABA Biosynthesis

Plant isoprenoids are derived from either a cytoplasmic acetate/mevalonate pathway shared with animals and fungi or a plastidic MEP pathway, named for the first committed molecule (2C-methyl-D-erythritol-4-phosphate) (reviewed in Kirby and Keasling, 2009; Ruiz-Sola and Rodriguez-Concepcion, 2012). The early steps of ABA biosynthesis take place in plastids and begin with the MEP pathway. An Arabidopsis albino mutant, *chloroplasts altered-1* (*cla1:* AT4G15560), is defective in 1-deoxy-D-xylulose-5-phosphate synthase (DXS), the first enzyme of the MEP pathway. Characterization of *cla1* mutants and transgenic Arabidopsis plants with altered *CLA1* expression showed that DXS was rate-limiting for isopentenyl diphosphate production and that ABA and other isoprenoid metabolites including GA were affected.

The next major phase of ABA biosynthesis is production of carotenoids (reviewed in Ruiz-Sola and Rodriguez-Concepcion, 2012). Sequential condensation reactions catalyzed by geranyl geranyl diphosphate synthase (GGPPS: AT4G36810) add one isoprene unit at a time to successively generate C10, C15 and C20 molecules (geranyl diphosphate, farnesyl diphosphate, and geranyl geranyl diphosphate (GGPP), respectively). Subsequent head to head condensation of two GGPPs by phytoene synthase (AT5G17230) produces the C40 skeleton that will become phytoene, the first committed carotenoid. Phytoene is subjected to four consecutive desaturation (dehydrogenation) reactions that lead to the formation of lycopene. These reactions are catalyzed by two homologous enzymes: phytoene desaturase (AT4G14210) and ξ-carotene desaturase (AT3G04870). Mutations affecting phytoene desaturase, as in the maize *viviparous* (*vp*)*5* mutant, result in carotenoid- and ABA-deficiency, and consequently failure to inhibit precocious germination, as well as seedling lethality due to photobleaching. Carotenoid desaturation in plants requires a third enzyme, carotenoid isomerase (CRTISO: AT1G06820), but photoisomerization can supply this function in tissues with adequate light penetration. Mutations affecting this enzyme have been identified in Arabidopsis and tomato. The Arabidopsis *carotenoid and chloroplast regulation-2* (*ccr2*) mutant was identified by the partial inhibition of lutein synthesis in light and the accumulation of poly-cis-carotene precursors in dark-grown tissue. *CCR2* is orthologous to the *tangerine* gene of tomato; both encode CRTISO. Lycopene represents a branch point in that it is cyclized to either α- or β-carotene, by lycopene ϵ-cyclase (AT5G57030) or lycopene β-cyclase (AT3G10230), respectively. Only β-carotene is further metabolized to ABA via zeaxanthin; the α-carotene branch leads to lutein synthesis. However, β-carotene pool sizes in photosynthetic tissues are tightly regulated such that only a small proportion is metabolized to zeaxanthin. Production of zeaxanthin, the first oxygenated carotenoid, is catalyzed by β-carotene hydroxylases encoded by two homologous genes (*BCH1* and *BCH2*: AT4G25700 and AT5G52570) in Arabidopsis and many other species.

All Arabidopsis mutants isolated on the basis of ABA-deficiency affect steps downstream of zeaxanthin synthesis (Figure 3). The first-described ABA-deficient mutant of Arabidopsis, *aba1*, was selected as a suppressor of the non-germinating gibberellin-deficient *ga1* mutant (Koornneef et al., 1982). In addition to producing non-dormant seeds, *aba1* mutants are wilty. Characterizaton of *aba1* mutant alleles showed that the severity of the phenotype and ABA deficiency was correlated with increased zeaxanthin and decreased violaxanthin and neoxanthin (Rock and Zeevaart, 1991), implying that the *ABA1* (AT5G67030) locus of Arabidopsis encodes zeaxanthin epoxidase (ZEP), the enzyme that converts zeaxanthin to violaxanthin via the intermediate antheraxanthin. Mutants with ZEP defects have also been isolated in tobacco and rice; an insertional mutant in the tobacco gene (*N. plumbaginifolia ABA2*) was used to clone the first member of this family (Marin et al. 1996). ZEP is a chloroplast-imported protein sharing similarities with mono-oxygenases and oxidases of bacterial origin. There is a single *ZEP* gene in Arabidopsis, but even the most severe mutants do not completely lack ABA, suggesting the existence of an alternate minor pathway for ABA biosynthesis (Barrero et al. 2005). The reactions catalyzed by ZEP can be reversed by violaxanthin de-epoxidase (VDE: AT1G08550) to produce more photoprotective zeaxanthin in response to a sudden increase in light intensity; this process is known as the xanthophyll cycle. Mutations affecting either ZEP or VDE can result in decreased zeaxanthin accumulation and therefore altered nonphotochemical quenching, as in the *npq* mutants (Niyogi et al. 1998).

ZEP regulation varies among species and tissues: the transcripts are drought-induced in roots but not in leaves of Arabidopsis, *N. plumbaginifolia* and tomato (Audran et al., 1998; Thompson et al., 2000); they are not drought responsive at all in cowpea (Iuchi et al. 2000). In Arabidopsis, tobacco and tomato leaves, *ZEP* transcripts, but not protein levels, fluctuate diurnally (Audran et al., 1998; Thompson et al., 2000; North et al., 2005), possibly because epoxycarotenoids protect the photosynthetic apparatus from photo-oxidatative damage via the xanthophyll cycle. ZEP transcript levels correlate with ABA accumulation in seeds, suggesting a regulatory role in this structure. Overexpression of ZEP in transgenic plants conferred greater tolerance to salt and drought stress, indicating that this enzyme may be limiting for some stress responses (Park et al., 2008). Stress-induced *ZEP* expression is reduced in mutants with defects in ABA biosynthesis and in the *abi1-1* signaling mutant, consistent with positive feedback regulation of ABA synthesis (Xiong and Zhu, 2003).

Late, Specific Steps In ABA Biosynthesis

The final plastid-localized steps in ABA synthesis are conversion to another C40 compound, trans-neoxanthin, isomerization of either (trans)-violaxanthin and trans-neoxanthin to their 9-cis-isomers, and cleavage by 9-*cis*-epoxycarotenoid dioxygenase (NCED) to release the 15C compound xanthoxin, also known as xanthoxal. Neoxanthin synthesis was recently found to depend on the product of the *ABA4* locus (AT1G67080), a highly conserved unique plastid membrane-localized protein (North et al., 2007). The initial *aba4* mutant was isolated on the basis of germination in the presence of the GA biosynthesis inhibitor paclobutrazol, es-

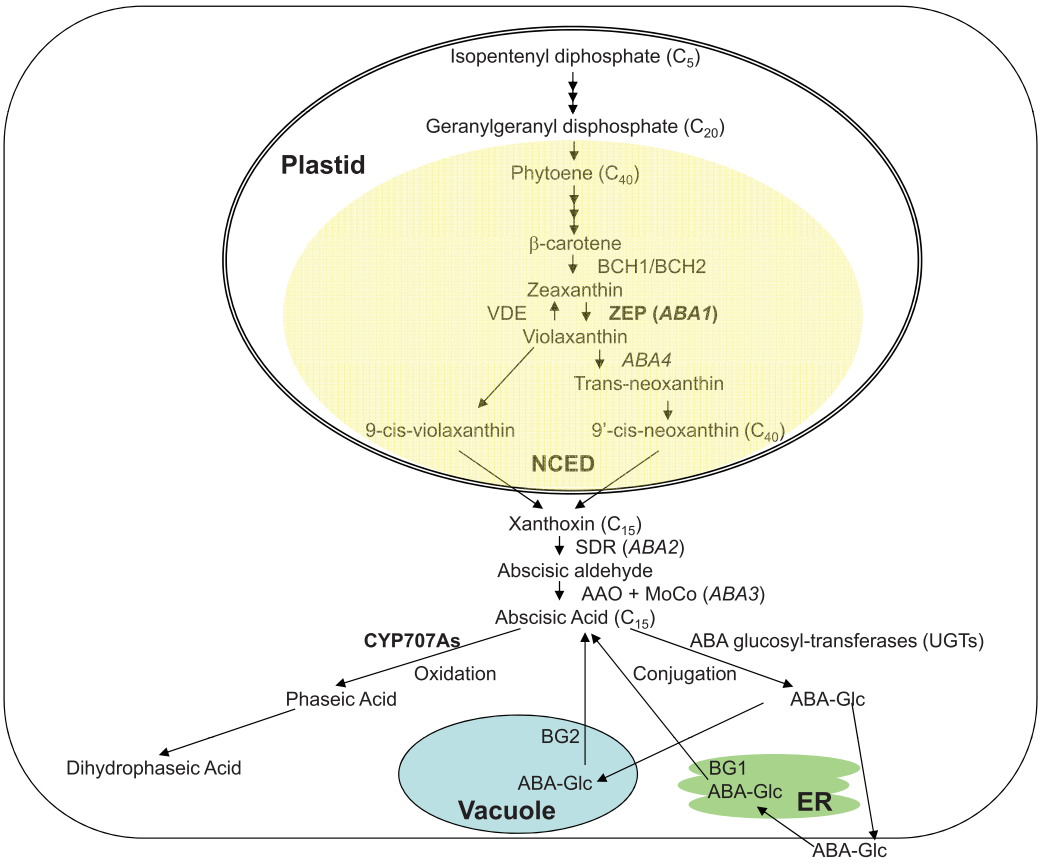


Figure 3. ABA metabolic pathways.

ABA biosynthesis, degradation and conjugation pathways are shown in relation to the cellular compartments where these events occur. Carotenoid intermediates are highlighted in yellow. Enzymes regulating key regulatory steps are shown in bold. Individual loci identified based on ABA deficiency are shown in italics.

sentially a chemical simulation of the original screen for suppressors of GA-deficient mutants. *ABA4* is expressed constitutively and the basal expression levels appear sufficient for ABA synthesis under stress conditions, indicating that transcript levels are not rate-limiting. Furthermore, even *aba4* knockout mutants have relatively mild phenotypes, implying an alternative pathway toward xanthoxin production. This observation supported the previous suggestion, based on *in vitro* studies (Schwartz et al., 1997), that NCED could use either cis-neoxanthin or cis-violaxanthin as substrates. However, the fact that stress-induced ABA was significantly reduced in the *aba4* mutant implied that cis-neoxanthin is the primary intermediate in stressed tissue. In addition, the accumulation of cis-violaxanthin in the *aba4* mutants showed that the ABA4 protein did not provide the predicted isomerase activity; that enzyme has not yet been identified.

Xanthophyll cleavage by NCED is the first committed step in ABA biosynthesis, and is rate-limiting (reviewed in Nambara and Marion-Poll, 2005). Consequently, NCED expression is tightly regulated in response to stress or developmental signals, as well as diurnally. NCEDs are encoded by multigene families in all species analyzed, with differential expression of specific family members contributing to ABA synthesis in different contexts. There is enough redundant function within this family that only a single locus was identified by forward genetic analysis in several species, including Arabidopsis. Although similarly sized families are present in different species, orthologies are not obvious. The first *NCED* gene cloned was maize *VP14*. Since then, the *notabilis* mutant of tomato was shown to be an *NCED* mutant, and bioinformatics studies identified 9 potential *NCED* genes in Arabidopsis, 5 of which actually function as *NCEDs* (Tan et al., 2003). Although all 5 isoforms are plastid-localized, they differ in their binding to the thylakoid membranes: AtNCED5 (AT1G30100) is membrane-bound, whereas AtNCED2 (AT4G18350), AtNCED3 (AT3G14440), and AtNCED6 (AT3G24220) are found in both thylakoids and stroma. Although AtNCED9 (AT1G78390) was initially described as exclusively in the stroma, a recent study suggests that this may have reflected an annotation error (Frey et al. 2012). The functional significance of these differences is not clear, but differential localization might affect access to components affecting enzyme activity or the efficiency of releasing xanthoxin to the cytoplasm for the final steps of ABA synthesis.

Xanthoxin is converted to ABA by a series of oxidative steps via the intermediate abscisic aldehyde. Several additional loci contribute to these last two steps. *ABA2* (AT1G52340) encodes a short chain dehydrogenase/reductase-like (SDR1) enzyme catalyzing production of abscisic aldehyde. The final step creating the carboxyl group at the end of the side chain is catalyzed by abscisic aldehyde oxidase (AAO). Although there are three family members in Arabidopsis, AAO3 (AT2G27150) appears to be the major enzyme involved because only *aao3* mutants show significant decreases in ABA levels and were identified in a screen for wilty mutants, yet had normal seed dormancy (Seo et al., 2000). However, *AAO1* (AT5G20960) and *AAO4* (AT1G04580) are the most highly expressed family members in seeds, and double mutants combining loss of function for either of these loci with *aao3* mutations further depresses ABA accumulation. All of the AAOs require a molybdenum cofactor (MoCo) for activity and *AtABA3* (AT1G16540) encodes the sulfurase that produces a functional cofactor. Consequently, *aba3* mutants are disrupted in all possible AAO activities.

Having identified nearly all the enzymes involved in ABA biosynthesis, it is possible to determine whether any aspects of synthesis are tissue-specific or require transport of intermediates. ABA responses are regulated environmentally in response to stress and developmentally, as in developing seeds and anthers. Although there is substantial basal *ZEP* and *MoCoSu/ABA3* expression in all tissues, SDR1/ABA2 and AAO3 are limited to vascular parenchyma, which is the major site of stress-induced NCED3 expression (Endo et al., 2008). In addition, *NCED3* promoter activity and weak *AAO3* expression is seen in guard cells, suggesting that this "target" tissue could synthesize ABA directly if the SDR1 enzyme catalyzing the intermediate step, encoded by *ABA2*, was available. Although *ABA2* expression is not abundant in mesophyll and guard cells, even this low amount of the ABA2/SDR1 protein appears to be sufficient in guard cells where ABA can be produced cell-autonomously in response to reduced atmospheric humidity (Bauer et al., 2013). These studies are consistent with the early observation that isolated guard cells of *V. faba* could produce ABA in response to osmotic stress (Cornish and Zeevaart 1986).

Genetic analyses of the source of ABA in seeds have shown that the peak in mid-development is primarily derived from maternal tissue, whereas the dormancy-inducing peak during the desiccation phase is produced by the embryo (Karssen et al., 1983 ; Kanno et al., 2010). Similar results were obtained using mutants in either ZEP (*aba1*) or SDR1 (*aba2*), but studies with the latter showed that maternal ABA could be transported into ABA-deficient embryos. Comparison of expression patterns for the rate limiting NCED family suggest that ABA synthesis primarily depends on the action of NCED6 in endosperm, NCED9 in both embryos and endosperm, and NCED2 and NCED3 in the surrounding maternal tissue. Initial reports did not detect ABA2/SDR1 expression in embryos, but microarray studies have shown substantial expression in developing embryos and endosperm (Le et al., 2010). Although AAO1 and AAO4 are more highly expressed in seeds than AAO3, seed ABA levels are more tightly correlated with AAO3 activity, again consistent with a combination of embryonic synthesis and transport from maternal tissues.

As described above, ABA is primarily synthesized in vascular tissues and transported to target tissues. This transport occurs in both xylem and phloem, permitting transport in both directions between roots and shoots. Under drought conditions, apoplastic pH increases, resulting in greater apoplastic retention of ABA which then functions as a root-to-shoot signal leading to reduced transpiration in leaves (reviewed in Davies and Zhang, 1991). In addition to this long distance chemical signaling, studies with ABA-regulated reporters have shown that hydraulic signals reflecting changes in water potential due to soil and root drying can induce local production of ABA in leaves before transport from roots is observed (Christmann et al., 2005; Christmann et al., 2007). However, continued signaling may be mediated by transport of ABA, or its precursors or conjugates.

ABA Catabolism

In addition to ABA synthesis, catabolism is a major mechanism for regulating ABA levels. Arabidopsis utilizes the two major pathways of ABA catabolism: (i) hydroxylation of ABA at the 8′ position by P-450 type monoxygenases to give an unstable intermediate (8′-OH-ABA) that is isomerized to phaseic acid (PA), and (ii) esterification of ABA to ABA-glucose ester (ABA-GE).

The ABA-8′-hydroxylases are encoded by the CYP707A family and were identified by a reverse genetics approach: candidate P450s were identified bioinformatically based on their phylogenic distribution and expression patterns, then functionally tested in yeast for ABA-8′-hydroxylase activity (Kushiro et al., 2004; Saito et al., 2004). The 4 members of this family show different spatial and temporal patterns of expression such that each member plays a slightly different physiological or developmental role. CYP707A1 (AT4G19230) and, to a lesser extent, CYP707A3 (AT5G45340) are most important for ABA catabolism in mid-seed development, but CYP707A2 (AT2G29090) assumes this role towards the end of seed development and during germination (Okamoto et al., 2006). In contrast, all of the CYP707As are induced by both a variety of dehydrating stresses and subsequent rehydration. These expression patterns indicate that ABA levels are regulated through continuous balancing of synthesis and catabolism, including feedback induction of catabolism. In fact, catabolism plays such an important role that CYP707A mutants accumulate far more ABA than lines overexpressing ABA biosynthetic enzymes. Although 8' hydroxylation is the major pathway of catabolism, ABA can also be hydroxylated at the 7' or 9' positions. Initially thought to require a different enzyme, 9'-hydroxylation was recently shown to be a minor side reaction catalyzed by the CYP707As (Okamoto et al., 2011).

ABA or its metabolites can also be inactivated by conjugation to another molecule; the most common conjugate is the glucosyl ester (ABA-GE). There are 8 glucosyltransferases in Arabidopsis capable of catalyzing this reaction (Lim et al., 2005). Although initially considered a permanent inactivation, more recent studies indicate that ABA-GE is a storage or transport form of ABA. ABA-GE accumulates in vacuoles and the apoplast, but is relocalized to the endoplasmic reticulum in response to dehydration. At this site it may be cleaved by β-glucosidases (BG1: AT1G52400) that are rapidly activated by dehydration-induced polymerization (Lee et al., 2006). In addition, a second β-glucosidase isoform (BG2/BGLU33: At2g32860) is present in vacuoles, and appears to be protected from degradation under dehydration stress conditions (Xu et al., 2012).

IDENTIFICATION OF SIGNALING INTERMEDIATES

Four major approaches have been used to identify regulatory factors controlling ABA response: genetics, biochemistry, pharmacology/cell biology, and bioinformatics. Genetic studies have screened for aberrant responses to ABA, based on either a physiological phenotype or aberrant expression of a reporter gene. Biochemical studies have identified cis-acting regulatory regions required for "correct" expression of ABA-inducible genes, then used ligand-binding assays or yeast one-hybrid screens to isolate genes encoding proteins that specifically recognize these DNA sequences. In addition, a variety of ABA-activated or -induced kinases, phosphatases, phospholipases, and transcription factors have been analyzed to determine whether the correlations with ABA-induced gene expression or protein activation reflect any functional significance. Cell biological studies have tested the roles of candidate secondary messengers and signaling intermediates in regulating cellular responses such as stomatal closure or ABA-inducible gene expression. Factors identified through biochemical, cell biological or bioinformatics screens are frequently further analyzed by reverse genetics to identify the physiological role of any potential regulator. Over half of the genes in Arabidopsis belong to multi-gene families, often resulting in functional redundancy that masks the effects of loss of function alleles isolated by traditional forward genetic strategies. However, higher order mutants, gain of function alleles or transgenes, and/or chemical genetic strategies have been used successfully to overcome this redundancy.

Studies of ABA biosynthesis and response mutants have been used to address three fundamental questions: 1) what is the biological role of ABA or any given locus in regulating specific growth responses, 2) what are the products of these loci, and 3) how do they interact to regulate hormone response? The genetic screens and selections that have been used to date include production of non-dormant seeds (Koornneef et al., 1982); loss or gain of sensitivity to ABA or ABA analogs at germination (Koornneef et al., 1984; Finkelstein, 1994; Cutler et al., 1996; Nambara et al., 2002; Park et al., 2009), seedling growth (Lopez-Molina and Chua, 2000), root growth (Himmelbach et al., 1998; Wang et al., 2011), stomatal regulation (Merlot et al., 2002), mis-expression of reporter genes (Ishitani et al., 1997; Foster and Chua, 1999; Bensmihen et al., 2002), and screens for suppressors or enhancers of GA-deficient non-germinating lines or *ABA-INSENSITIVE* (*ABI*) lines (Steber et al., 1998; Beaudoin et al., 2000; Ghassemian et al., 2000). Additional mutants have been isolated with defects in responses to multiple signals, including ABA, via non-ABA-based screens such as salt-resistant germination (Quesada et al., 2000), sugar-resistant seedling growth or gene expression (Arenas-Huertero et al., 2000; Huijser et al., 2000; Laby et al., 2000; Rook et al., 2001), or defects in auxin, brassinosteroid, or ethylene response (Wilson et al., 1990; Alonso et al., 1999; Ephritikhine et al., 1999; Li et al., 2001) or cytokinin production (Nishiyama et al., 2011). Cloning of these genes has identified several major classes of ABA response regulators including transcription factors, protein kinases and phosphatases, RNA processing enzymes, and proteins that metabolize or respond to secondary messengers. The fact that mutations in only some of the hormone response genes appear to affect multiple signaling pathways suggests that interactions among these pathways are relatively specific. Possible mechanisms of cross-talk are discussed in many reviews (Santner and Estelle, 2009; Jaillais and Chory, 2010; Depuydt and Hardtke, 2011). The following sections describe classes of signaling intermediates that were initially identified genetically.

Protein phosphatases

The first Arabidopsis ABA response loci identified by mutations, *ABI1* (*ABA-insensitive 1*: AT4G26080) and *ABI2* (AT5G57050) (Koornneef et al., 1984), were subsequently found to encode highly homologous members of the PP2C family of ser/thr protein phosphatases (Leung et al., 1994; Meyer et al., 1994; Leung et al., 1997; Rodriguez et al., 1998). The initial alleles, *abi1-1* and *abi2-1,* have identical amino acid substitutions in their catalytic domains, resulting in decreased phosphatase activity and an incompletely dominant negative pleiotropic decrease in ABA sensitivity (Koornneef et al., 1984; Finkelstein, 1994; Leung et al., 1997). Additional members of this clade of PP2Cs have since been shown to participate in ABA and/or stress signaling. Most of the loss of function mutants are either hypersensitive to ABA, leading to the name *ABA hypersensitive at germination* (e.g. *AHG1*: AT5G51760 and *AHG3*: AT3G11410), or have no phenotype due to redundancy (Gosti et al., 1999; Kuhn et al., 2006; Yoshida et al., 2006; Nishimura et al., 2007). In combination with studies of higher order mutants and over-expression in protoplasts these results indicate that the majority of these PP2Cs act as negative regulators of ABA response (Sheen, 1998; Rubio et al., 2009). Initial genetic characterization of the *highly ABA induced* (*HAI1:* AT5G59220*, HAI2:* AT1G07430, and *HAI3:* AT2G29380) loci suggested that they encode redundant positive regulators of ABA response at germination, but negative regulators of post-germination drought response (Bhaskara et al., 2012; Lim et al., 2012). However, a more recent report demonstrated that *HAI2* (renamed *HONSU*, a Korean term for "abnormal drowsiness") also negatively regulates ABA response at germination, resulting in a mutant phenotype of deep dormancy (Kim et al. 2013).

Transcriptional regulators

The next three *ABA insensitive* loci identified genetically, *ABI3* (AT3G24650), *ABI4* (AT2G40220), and *ABI5* (AT2G36270), encode transcription factors of the B3-, APETALA2- (AP2), and basic leucine zipper- (bZIP) domain families, respectively (Koornneef et al., 1984; Giraudat et al., 1992; Finkelstein, 1994; Finkelstein et al., 1998; Finkelstein and Lynch, 2000). Although initially thought to be seed-specific because they are most abundantly expressed in seeds and regulate numerous seed-specific genes, all have since been found to affect numerous processes after germination. Transcriptome analyses have reinforced the view that these factors co-regulate many genes and all can act as either activators or repressors, depending on the target gene (Suzuki et al., 2003; Nakabayashi et al., 2005; Koussevitzky et al., 2007; Nakashima et al., 2009 ; Kerchev et al., 2011; Monke et al., 2012).

Similarities in sequence and mutant phenotype, combined with cross-species complementation showed that *ABI3* and the

maize *VIVIPAROUS1* (*VP1*) are orthologs (Suzuki et al., 2001). Of the 43 B3-domain family members encoded in Arabidopsis, 14 are within the *ABI3/VP1*-related subfamily (Riechmann et al., 2000). In addition to *ABI3*, this subfamily includes a family of *VP1/ABI3-like (VAL)* factors (*VAL1*: AT2G30470, *VAL2*: AT4G32010, *VAL3*: AT4G21550) (Suzuki et al., 2007) and two members of the *leafy cotyledon* class of regulators that control embryo maturation: *FUS3* (AT3G26790) and *LEC2* (AT1G28300) (Luerssen et al., 1998; Stone et al., 2001). The *VAL* factors regulate many of the same genes as *ABI3*, but have an opposite effect on their expression possibly via effects on chromatin structure (Suzuki et al., 2007). Although the *leafy cotyledon* class mutants (*lec1:* AT1G21970, *lec2* and *fus3*) are not ABA resistant as single mutants, *lec1* combined with *abi3, abi4 or abi5* mutations and *fus3* combined with the *abi-1, abi2-1* or *abi3* mutations greatly enhance seed ABA resistance (Keith et al., 1994; Parcy et al., 1997; Brocard-Gifford et al., 2003). Unlike the other *leafy cotyledon* mutants, *LEC1* encodes a member of the HAP3 subunit of CCAAT-binding factor family (Lotan et al., 1998).

Within the AP2-domain family, ABI4 is most closely related to the Drought Response Element Binding (DREB) subfamily, but the similarity is limited to the AP2 domain. Although the DREBs mediate abiotic stress-induced expression of many of the same genes as regulated by the ABIs, DREB activity is mostly ABA-independent (reviewed in Lata and Prasad, 2011). Additional AP2-domain family factors participating in ABA response have recently been identified on the basis of binding to a “coupling element” (CE1) present in many ABA-regulated promoters; most of these are most closely related to the ethylene response factor (ERF) subfamily (Lee et al., 2010).

In contrast, ABI5 is a member of a clade of 13 bZIP factors that share at least 3 conserved domains in addition to the bZIP domain (reviewed in Jakoby et al., 2002; Fujita et al., 2013). Although none except ABI5 were identified by forward genetic screens most of the related bZIPs are regulated by and/or mediate ABA- or stress-regulated gene expression. Accordingly, five of these are known as ABA response element (ABRE) binding factors, abbreviated as either ABFs or AREBs (Choi et al., 2000; Uno et al., 2000). Studies of higher order mutants have shown substantial functional overlap among these bZIPs, and some cross-regulation of family members (Finkelstein et al., 2005; Yoshida et al., 2010).

Consistent with co-regulation of the ABI-regulated genes, the G-box type motifs bound by bZIP factors and known as ABREs are highly enriched in the upstream regulatory regions of most of these genes. Strong binding sites for ABI3 and ABI4 are the RY/Sph (Ezcurra et al., 2000; Suzuki et al., 2005) and CE1-like elements (Niu et al., 2002), respectively. Surprisingly, these elements are not present in all of the apparent target genes for these factors, suggesting that formation of a regulatory complex with other factors such as the bZIPs might tether them to regulatory regions lacking their consensus binding sites (Reeves et al., 2011) or that they may enhance binding of the bZIPs (Hill et al., 1996). The bZIP factors function as dimers and family members can form homo- or heterodimers in specific combinations, some of which have been demonstrated by EMSA, yeast two-hybrid, and bimolecular fluorescence complementation (BiFC, e.g. split YFP) assays (Bensmihen et al., 2002; Kim et al., 2002; Yoshida et al., 2010; Lynch et al., 2012). Additional yeast two hybrid studies have shown that numerous members of the ABI5/ABF/AREB class can interact directly with ABI3 (Finkelstein et al., 2005) or DREBs (Lee et al., 2010). Indirect interactions of ABI3 might also be mediated via a 14-3-3 protein, as described for connections among the maize proteins EmBP1, Vp1 and GF14 (Schultz et al., 1998). Such interactions may trigger chromatin remodeling to permit ABA-mediated gene activation (Li et al., 1999; Ng et al., 2006) .

Additional transcription factors involved in ABA- or stress-induced gene expression have been identified as ABA- or stress-regulated genes themselves. For example, some members of the MYB and MYC (bHLH) classes (Urao et al., 1993; Abe et al., 1997), the No Apical Meristem/Cup-Shaped Cotyledon (NAC), homeodomain-leucine zipper (HD-Zip), and WRKY factor families (Rushton et al., 2011) have also been shown to be induced by ABA or abiotic stress or to regulate stress responses. Biological roles have been identified for approximately half of the 190 MYB class transcription factors in Arabidopsis; 14 of these are involved in ABA or stress signaling (Dubos et al., 2010). Of the 133 predicted bHLH factors, only 2 family members have been implicated in ABA or stress signaling to date (MYC2: AT1G32640 and AtAIB: AT2G46510) (Abe et al., 1997; Li et al., 2007), but many members are not yet functionally characterized. However, MYC2 is also involved in mediating cross-talk with jasmonate, ethylene, gibberellin, and light signaling, so is hardly specific for ABA response (Hong et al., 2012). The NACs are another large family, of which at least 31 members are strongly induced by ABA and/or abiotic stress; four of these (ANAC019: AT1G52890, ANAC055: AT3G15500, ANAC072: AT4G27410, and VNI2/ANAC083: AT5G13180) have been shown to be positive regulators of ABA response (Tran et al., 2004 ; Jensen et al., 2010; Yang et al., 2011). At least 3 class I HD-ZIPs (ATHB6: AT2G22430, ATHB7: AT2G46680, and ATHB12: AT3G61890) have been implicated in ABA signaling as part of a negative feedback loop with the ABI-clade PP2Cs and ABA receptors (Himmelbach et al., 2002; Elhiti and Stasolla, 2009; Valdes et al., 2012). Although the WRKY factor family is best known for its role in pathogen response, many family members have recently been shown to either promote or inhibit ABA response, depending on the family member and response (reviewed in Rushton et al., 2011). These WRKYs act at multiple levels including interactions with the chloroplast-localized receptor, and direct regulation both upstream and downstream of some of the bZIP, AP2-domain, MYB, and B3 domain family members described above.

In addition to the many transcription factors that participate in ABA response, numerous regulators of epigenetic effects on ABA- or stress-regulated gene expression have been identified (reviewed in Chinnusamy et al., 2008). These include histone modifying enzymes such as histone deacetylases (HDAs), polycomb group proteins and histone chaperones, modifiers of DNA methylation, and SWI/SNF-class regulators of nucleosome position or structure. Activity of these factors directs major shifts in gene expression through a combination of effects on regulatory gene expression and direct effects on their downstream targets. For example, the SWI/SNF regulator BRAHMA (AT2G46020) directly binds and represses promoters of ABI5, ABI3, and a variety of seed-specific genes such that mutants appear hypersensitive to some aspects of ABA response and ectopically express seed genes in leaves (Tang et al., 2008 ; Han et al., 2012). In contrast,

SWI3B (AT2G33610) is a positive regulator of some ABA-induced gene expression, such that mutants appear ABA resistant (Saez et al., 2008). The ABI-clade PP2C HAB1 (AT1G72770) interacts directly with SWI3B, potentially inhibiting ABA response by regulating SWI/SNF-mediated chromatin remodeling. Studies of histone acetylation have also produced conflicting results: loss of HDA6 (AT4G38130) and HDA19 (AT5G63110) functions result in hypersensitivity to ABA for inhibition of germination and growth, but reduced ABA-induction of several ABA-responsive genes (Chen and Wu, 2010). While clearly important regulators of ABA response, the ABA-induced epigenetic changes have not been globally characterized, and it is not yet clear how HDAs are targeted to histones in specific genomic regions (Kim et al., 2012).

Protein kinases

A screen for defects in stomatal closure identified *open stomata (ost)* mutants by using infrared thermography to detect leaves with cooler temperatures (Merlot et al., 2002). In addition to ABA biosynthetic mutants, this screen identified OST1 (AT4G33950), a SNF1-related protein kinase (SnRK) (Mustilli et al., 2002), and OST2 (AT2G18960), the major plasma membrane H^+-ATPase (Merlot et al., 2007). OST1 is homologous to ABA-activated protein kinases previously identified in wheat seeds (Gomez-Cadenas et al., 1999) and broad bean guard cells (Li and Assmann, 1996). Reverse genetic studies in Arabidopsis have demonstrated overlapping functions in ABA and stress response among the 10 members of this SnRK2 subfamily (Fujita et al., 2009; Nakashima et al., 2009; Fujii et al., 2011). High throughput *in vitro* screens have identified 40-60 potential substrates for several of these kinases, including transcription factors, dehydrins, transporters, and additional kinases, but have also missed some known ion channel substrates (Vlad et al., 2008; Sirichandra et al., 2010). More recently, two phosphoproteomic studies each identified 50-60 potential SnRK2 substrates *in vivo*, but with surprisingly little overlap between these datasets (Umezawa et al., 2013; Wang et al., 2013).

Several additional classes of kinases implicated in ABA and stress response have been identified through reverse genetics: calcium-dependent protein kinases (CPKs/CDPKs/CDKs) (Choi et al., 2005; Mori et al., 2006; Zhu et al., 2007), calcineurin B-like interacting protein kinases (CIPKs), and the three tiers of mitogen-activated protein kinase cascades (MAPKs, MAPKKs, and MAPKKKs). Expression of some of these is induced by stress or ABA, whereas others are activated post-translationally. Several MAPKs and MAPKKs have been shown to be regulated by ABA by both increased expression and activation (reviewed in Liu, 2012). Negative regulation of MAPK signaling is accomplished by MAPK phosphatases (MKPs) and PP2Cs from both the A and B clades. As for the SnRK2s, high throughput screening is identifying hundreds of potential substrates for the CPKs (Curran et al., 2011) and MAPKs (Popescu et al., 2009), including many regulated by multiple kinases. In contrast, very few substrates are known for the CIPKs, but these substrates include their calcium-binding regulatory partners, the CBLs, a K^+ transporter (AKT1) and a Na^+/H^+ antiporter involved in salt tolerance (SOS1) (Qiu et al., 2002; Hashimoto et al., 2012).

Receptors

Despite the abundance of loci identified through standard screens for altered ABA response, no ABA receptors were found by these approaches. However, a screen for resistance to pyrabactin, a small chemical with physiological effects similar to those of ABA, led to identification of the *PYRABACTIN RESISTANT1*(*PYR1:* AT4G17870) gene (Park et al., 2009). Sequence comparisons identified 13 related genes, designated *PYR-like* (*PYLs*) with overlapping expression patterns and varying affinities for ABA and other signaling components (Park et al., 2009; Szostkiewicz et al., 2010; Dupeux et al., 2011; Hao et al., 2011; Zhang et al., 2012; Zhang et al., 2013). The high level of redundancy in this family prevented isolation of mutants by an ABA-based screen, but the interaction between PYR1 and pyrabactin was sufficiently specific to detect resistance in a mutant lacking just this one family member. Several research groups identified the same family of proteins on the basis of their interactions with members of the ABI-clade of PP2Cs (Ma et al., 2009; Nishimura et al., 2010), resulting in the alternate name Regulatory Component of ABA Receptors (RCARs).

Diverse regulators with pleiotropic effects

Negative regulators of ABA signaling identified in forward genetic screens include the *enhanced response to ABA* (*ERA*), *ABA hypersensitive at germination* (*AHG* and *ABH1*)*, supersensitive to A*BA, *drought* and NaCl (*SAD1*), and *hot ABA-deficiency suppressor* (*HAS*) (Plessis et al., 2011) loci. In contrast to the PP2C-encoding *AHG1* and *AHG3*, *AHG2* (AT1G55870), *AHG11* (AT2G44880), *ABH1* (AT2G13540), and *SAD1* (AT5G48870) all encode enzymes involved in RNA processing or degradation (Hugouvieux et al., 2001; Xiong et al., 2001; Nishimura et al., 2005; Murayama et al., 2012) that could affect RNA accumulation at a post-transcriptional step.

ERA1 (AT5G40280) encodes the β subunit of farnesyl transferase, and affects meristem organization as well as ABA signaling (Andrews et al., 2010). Over 100 potential substrates for farnesylation include transcription factors, GTP-binding proteins, cell cycle regulators, cell wall modifiers, and proteins implicated in cytokinin synthesis or auxin response, providing possible mechanisms for pleiotropy, but very few have been confirmed (Galichet and Gruissem, 2003; Galichet et al., 2008). Proteins may be prenylated by addition of either farnesyl or geranylgeranyl isoprenoids (15- and 20-C, respectively), and mutations affecting either of these modifications or their subsequent methylation may result in altered response to ABA (Lan et al., 2010, and references therein).

ERA3 (AT5G03280) is allelic to *EIN2* (Ghassemian et al., 2000), which encodes a membrane-bound putative divalent cation sensor that appears to represent a point of cross-talk between ethylene, ABA, auxin, jasmonic acid, and stress signaling (Alonso et al., 1999). Another highly pleiotropic mutant is *hyl1*, whose physiological defects include stunted growth, *hyponastic leaves* (upward curling of leaf blade), and late flowering (Lu and Fedoroff, 2000). This phenotype may reflect defects in hormonal signaling including reduced response to auxin and cytokinins

and hypersensitivity to ABA. *HYL1* (AT1G09700) expression is repressed by ABA, consistent with a role as a negative regulator of ABA response, and it encodes a dsRNA binding protein (Han et al. 2004) that forms a complex with Dicer-Like1 (DCL1: AT1G01040) to process a subset of miRNA precursors (Kurihara et al. 2006). Additional mutants with pleiotropic defects in response to multiple hormones include two independent jasmonic acid (JA) resistant mutants, *jar1* (AT2G46370) and *jin4*, that also display hypersensitivity to ABA in seed germination assays (Staswick et al., 1992; Berger et al., 1996). Mutants with defects in response to multiple hormones include *axr2-1* (AT3G23050), a dominant negative mutant resistant to auxin, ethylene, and ABA (Wilson et al., 1990); *sax1* (hypersensitive to ABA and auxin, rescuable by exogenous brassinosteroids (BR) (Ephritikhine et al., 1999)); *bri1* (AT4G39400) and *bin2* (AT4G18710) (BR insensitive, ABA-hypersensitive root growth (Clouse et al., 1996; Li et al., 2001)); *prl1* (AT4G15900) (increased sensitivity to sugar, ethylene, ABA, auxin, cytokinin, and cold stress (Nemeth et al., 1998)); and *ctr1* (AT5G03730)(constitutive ethylene signaling, enhanced resistance to ABA inhibition of germination (Kieber et al., 1993; Beaudoin et al., 2000)).

Many loci have been identified using screens based on aberrant reporter gene expression in the presence or absence of ABA, osmotic, sugar or cold stress (Ishitani et al., 1997; Foster and Chua, 1999; Rook et al., 2001; Xiong et al., 2002). Depending on the nature of the defective expression, most of these have been designated *hos* (*high osmotic stress* response), *los* (*low osmotic stress* response), *cos* (*constitutive osmotic stress* response), *fry* (*fiery*, for strong constitutive activation) or *isi* (*impaired sucrose induction of ADP glucose pyrophosphorylase promoter*). Some of those isolated on the basis of defective osmotic stress response have been shown to display aberrant response to ABA as well as to some or all of the environmental or nutritional stresses listed above. Fewer than a tenth of these loci have been cloned; those cloned to date have been found to encode a mix of ABA biosynthetic enzymes (*LOS5/ABA3*: AT1G16540, *LOS6/ABA1*: AT5G67030, *ISI4/ABA2*: AT1G52340) (Rook et al., 2001; Xiong et al., 2001; Xiong et al., 2002), transcriptional regulators (*HOS9/WOX6*: AT2G01500, *HOS15*: AT5G67320, *ISI3/ABI4*, *FRY2/CPL1*: AT4G21670) (Rook et al., 2001; Xiong et al., 2002; Zhu et al., 2004; Zhu et al., 2008), RNA metabolism enzymes (*LOS4*: AT3G53110 and *SICKLE*: AT4G24500) (Gong et al., 2005; Zhan et al., 2012), an ubiquitin E3 ligase (*HOS1*: AT2G39810) (Lee et al., 2001), and a glycolytic enzyme (*LOS2*: AT2G36530) (Lee et al., 2002), as well as proteins of unknown function. *FRY1* (AT5G63980) encodes a bifunctional enzyme with both inositol polyphosphate 1-phosphatase and 3′,(2′),5′-bisphosphate nucleotide phosphatase activities (Xiong et al., 2001; Hirsch et al., 2011). The latter appears to be the significant role *in vivo*, resulting in both increased levels of Pi and reduced levels of 3′-polyadenosine 5′-phosphate (PAP), thereby derepressing several RNA silencing-suppressors.

ABA PERCEPTION

Prior to the identification of specific receptors, numerous studies provided indirect evidence for multiple receptor types (reviewed in Cutler et al., 2010). Induction of ABA response following delivery of ABA to the cytoplasm by microinjection or via a patch-clamp electrode suggested at least some intracellular perception (Allan et al., 1994; Schwartz et al., 1994). Evidence for extracellular perception came from studies using ABA-protein conjugates that could not enter the cell, yet were biologically active, to induce ion channel activity and gene expression (Jeannette et al., 1999). Additional studies showed that ABA could stimulate PLD activity in plasma membrane-enriched fractions from barley aleurone protoplasts in a GTP-dependent manner, suggesting the existence of an ABA receptor system at the plasma membrane linked to PLD activation via G proteins (Ritchie and Gilroy, 2000). Consistent with this, reverse genetic studies have demonstrated roles in ABA signaling for PLDs (Zhang et al., 2009), monomeric G-proteins (Li et al., 2012, and references therein), subunits of heterotrimeric G-proteins (Pandey et al., 2006), and proteins with similarities to G-protein-coupled receptors (Pandey et al., 2009). However, despite the existence of only a sole alpha subunit for Arabidopsis heterotrimeric G-proteins (GPA1: AT2G26300), *gpa1* mutants display reduced sensitivity to ABA in guard cell functions (Wang et al., 2001), yet increased sensitivity to ABA for inhibition of germination or root growth (Pandey et al., 2006), suggesting different roles for G-proteins in distinct responses to ABA.

In addition to the apparent variety in sites of action, assays with various analogs and metabolites indicated that there were different structural requirements for activity in different response pathways (reviewed in Cutler et al., 2010). Given the likely redundancy among numerous receptor types, it is hardly surprising that traditional forward genetic approaches to identifying an ABA receptor were unsuccessful. Although several receptor-like kinases affecting ABA response have been identified (RPK1: AT1G69270, ARCK1: AT4G11890, CRK36: AT4G04490), there is no evidence that any of them bind ABA (Osakabe et al., 2005; Osakabe et al., 2010; Tanaka et al., 2012). However, since 2006 a combination of biochemical and chemical genetic approaches has identified at least three classes of plausible ABA receptors, localized to distinct compartments: the plasma membrane, chloroplasts, and soluble in cytoplasm and nucleus. Monogenic mutants affecting any of these have weak or indiscernible effects on ABA response.

The best-characterized ABA receptors are a family of soluble proteins known as PYR (pyrabactin resistant), PYLs (PYR-like) or RCARs (regulatory component of ABA receptor), which constitute the beginning of the “core ABA signaling pathway” (reviewed in Cutler et al., 2010; Miyakawa et al., 2013). Thirteen members of this family, PYR1 and PYL1-PYL12, have been shown to function as ABA receptors (Fujii et al. 2009). The generalized view of this pathway is that ABA binds to a PYR/PYL/RCAR protein, resulting in a conformational change that enhances stability of a complex with one of the clade A protein phosphatase 2Cs (PP2Cs), thereby inactivating the PP2C and relieving inhibition of SNF1-related kinases (SnRKs) required to activate transcription factors, ion channels and numerous other mediators of ABA response (Figure 4). The PP2Cs may also dephosphorylate other classes of kinases, e.g. the CPKs, and some of the kinase-regulated proteins such as the transcription factors or ion channels, thereby providing a mechanism to restore homeostasis as well as inhibiting activation of ABA response (Brandt et al., 2012; Lynch et al., 2012; Antoni et al., 2012). Additional protein phosphatases from other families have also been shown to inhibit ABA response by

dephosphorylating some of these factors (Dai et al., 2013). Each of these steps involves multiple family members with overlapping functions, explaining why very few components were identified by standard genetic screens for altered response. However, this pathway ties together many of the components that had been identified previously.

Structural studies of the interactions between the PP2Cs and either the PYR/PYL/RCAR or SnRK2 proteins have shown that the same domain of the PP2C is involved in either the "gate-lock-latch" interaction with the receptor or the kinase, such that these interactions are mutually exclusive for any given PP2C molecule (Soon et al., 2012). In addition, different receptor family members may be either monomeric or dimeric in the absence of ABA (Dupeux et al., 2011; Hao et al., 2011; Zhang et al., 2012). The dimeric receptors (PYR1, PYL1, PYL2 and PYL3) dissociate upon ABA binding, thereby exposing the surfaces which interact with PP2Cs, but their intrinsic affinities for ABA are 50-100 fold lower than the monomeric forms. One of the dimeric receptors (PYL3) has the unusual property of changing from a cis-dimer to a trans-dimer before dissociating (Zhang et al., 2012). The monomeric members (PYL4-6 and PYL8-10) can interact weakly with some PP2Cs in the absence of ABA, but the affinity of both classes of receptors for ABA and the PP2Cs increases when present in an ABA-receptor-PP2C complex, leading to the description of the PP2Cs as co-receptors even though they do not make direct contact with the hormone.

Further variations in expression and affinities of the receptor and PP2C family members ultimately permit responses that vary over a wide range of ABA concentrations and cell types. In addition, the ROP11 GTPase (AT5G62880) inhibits ABA response by protecting ABI-clade PP2Cs from inactivation by the PYL9/RCAR1 (AT1G01360) receptor (Li et al., 2012). Although this model emphasizes inhibition of phosphatase activity and increased kinase activity, analysis of rapid ABA-induced changes in overall protein

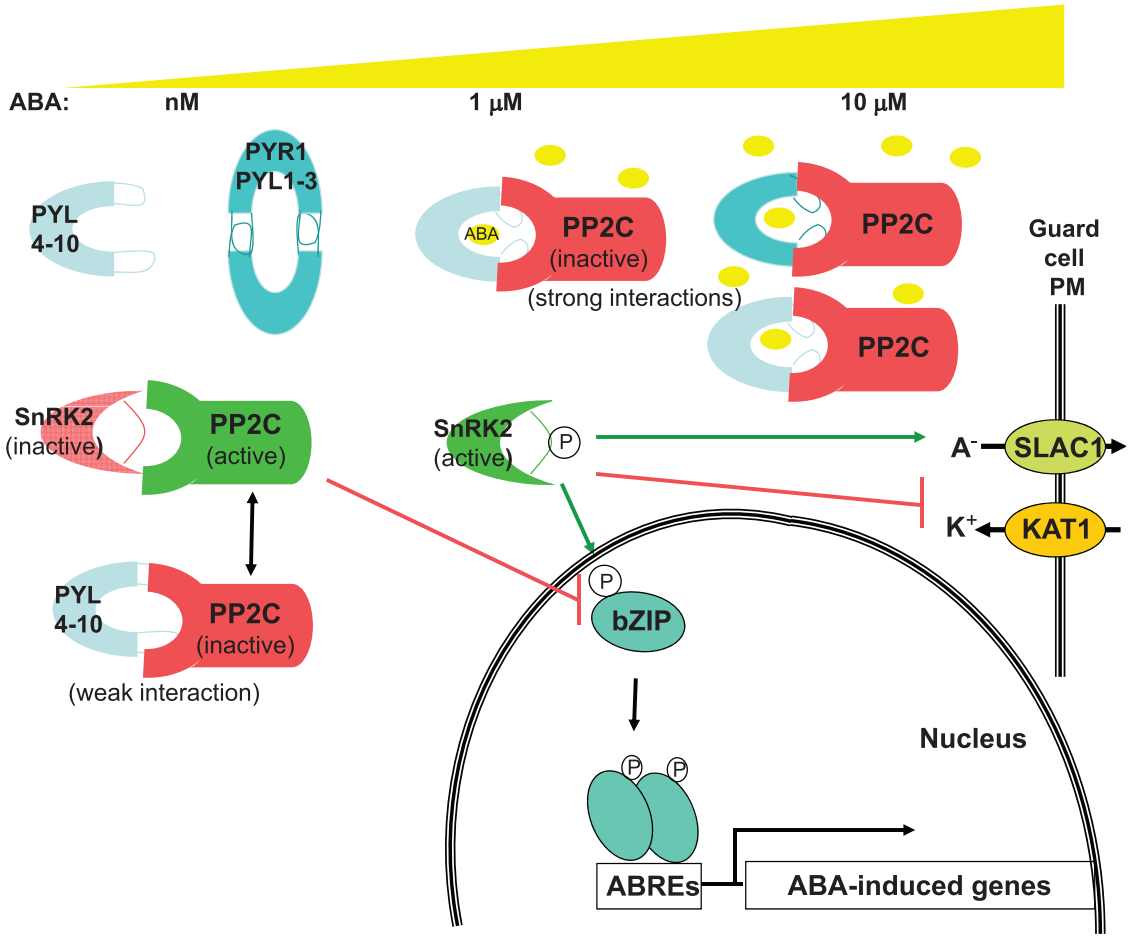


Figure 4. Core ABA signaling pathway interactions across a broad range of ABA concentrations.

Monomeric receptors (PYL4-10) weakly interact with PP2Cs in the absence of ABA and interact strongly at low ABA concentrations when ABA binding alters their conformation. Dimeric receptors (PYR1/PYL1-3) have a lower affinity for ABA, so higher concentrations are needed for them to dissociate and then strongly interact with the PP2Cs. All receptor interactions with PP2Cs result in inactivation of the PP2Cs and derepression of the SnRK2s, which then phosphorylate numerous proteins involved in ABA response. Green arrows indicate activation and red bars indicate repression.

phosphorylation showed similar numbers of proteins increasing or decreasing their phosphorylation state (Kline et al., 2010). Whereas those with increased phosphorylation were mostly SnRK2 kinases and bZIP transcription factors, decreased phosphorylation was seen for aquaporins, several calcium related proteins, and some drought or ABA-responsive proteins. Recently, combined genetic and phosphoproteomic approaches have identified specific substrates of the SnRK2s whose phosphorylation is ABA-dependent (Umezawa et al., 2013; Wang et al., 2013).

The plastid-localized ABA receptor is the H subunit of the Mg Cheletase (CHLH: AT5G13630) required for protoporphyrin synthesis (Shen et al., 2006). Its identity as a receptor is controversial because it was initially identified by homology to a protein that had been affinity-purified from bean leaves via binding to a part of the ABA molecule that is not essential for response, based on structure function studies of analogs. Furthermore, ABA binding to CHLH has not been replicated by other labs or in other species (e.g. barley) (Müller and Hansson, 2009; Tsuzuki et al., 2011), possibly because such experiments are technically challenging for large membrane proteins. However, the Arabidopsis CHLH protein has since been shown to bind ABA in surface plasmon resonance studies and genetic studies have provided functional evidence for a role in ABA signaling (Du et al., 2012). The current view of the signaling pathway initiating with this receptor is that the CHLH is localized in the plastid envelope such that its C-terminus can interact with soluble proteins in the cytosol. In particular, it binds a group of WRKY transcription factors (WRKY40: AT1G80840, WRKY18: AT4G31800, WRKY60: AT2G25000) in the presence of ABA, thereby preventing them from moving to the nucleus where they repress expression of several ABA-response loci, including direct repression of some ABI transcription factors (Shang et al., 2010; Liu et al., 2012) (Figure 5). Consequently, this pathway converges with the "core" pathway by affecting the level of ABI transcription factors. Expression of several PYR/PYL/RCAR receptors, PP2Cs and SnRKs are also altered in the *chlh* and *wrky* mutants, but not always in a manner consistent with their phenotypes, suggesting that there may be complex feedback among these pathways. An additional subunit of the Mg^{2+} Chelatase complex, CHLI (AT4G18480), also contributes to ABA sensitivity although it does not bind ABA itself (Du et al., 2012). This led the authors to suggest that CHLH/CHLI heterodimers function in ABA signaling, while Mg chelatase activity requires association with two additional subunits: CHLD (AT1G08520) and GUN4 (AT3G59400).

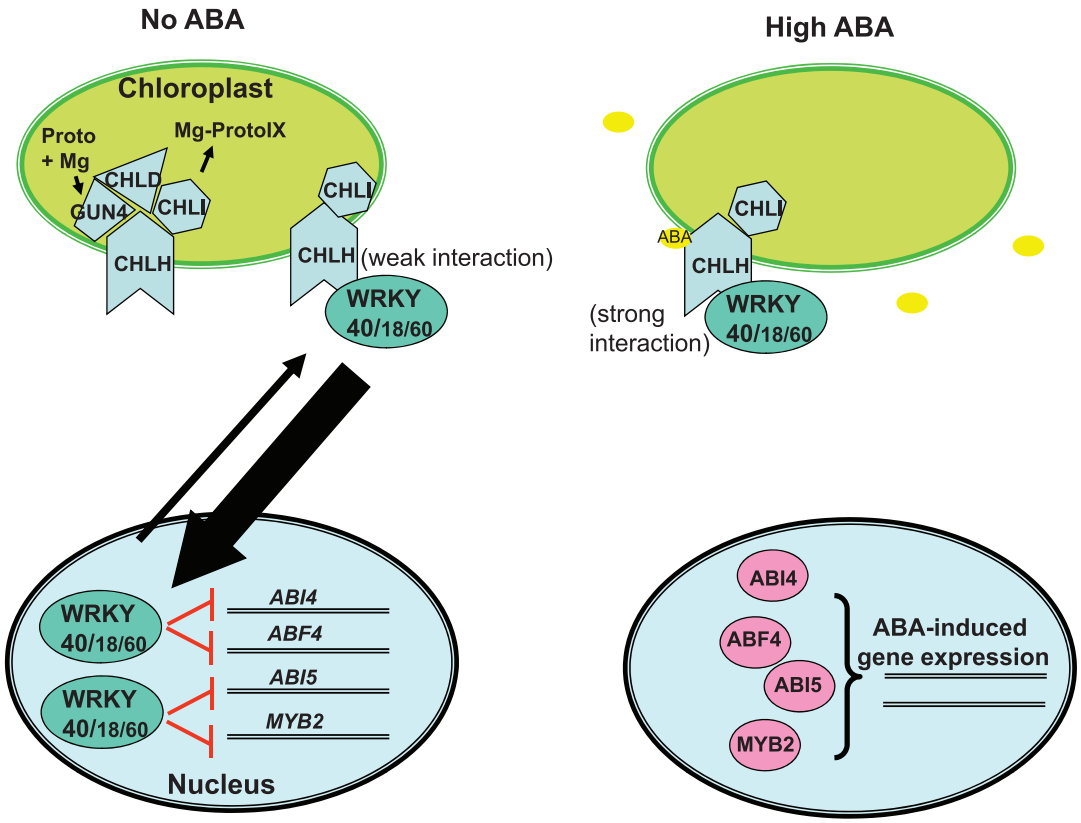


Figure 5. ABA signaling mediated by the plastid-localized CHLH protein.

The H subunit of MgCheletase spans the outer chloroplast membrane. It can associate with 3 other subunits (CHLI, CHLD, and GUN4) to function in synthesis of Mg-ProtophyrinIX (Mg-ProtoIX) within the plastid. Alternatively, in association with CHLI, the C-terminus of CHLH can bind WRKY40 in the cytosol (and, to a lesser extent, WRKY 18 and 60). CHLH/WRKY binding is enhanced by ABA, such that these WRKYs are greatly depleted in nuclei, thereby derepressing several transcription factors that positively regulate ABA-induced gene expression.

Another class of potential receptors was identified through a bioinformatic approach, screening for G-protein coupled receptor(GPCR)-type G-proteins (GTG1: AT3G59400 and GTG2: AT4G27630), then testing their function in ABA binding and response through biochemical and genetic assays (Pandey et al., 2009). ABA binding by the GTGs has also been reported in yeast as well as in vitro (Kharenko et al., 2013). Unlike other GPCRs, the GTGs have both nucleotide-binding and GTPase-activating domains. Although the closest human homolog, GPR89, is actually an anion channel in the Golgi, GPR89 differs from the GTGs in that it lacks GTP binding and GTPase activity. Additional unusual aspects of the GTGs are that ABA binding appears to be stimulated by GDP, and interaction with the G-alpha subunit GPA1 regulates ABA-binding to these receptors, not vice versa. Although transiently expressed GTG:GFP fusions appear localized in the plasma membrane of mesophyll protoplasts (Pandey et al., 2009), transiently expressed GTG:GFP fusions in tobacco leaves were seen mostly in Golgi and ER as well as near the cell periphery, and *GTG1*$_{pro}$:*GTG1-GFP* fusions localized primarily to the Golgi in stable transformants (Jaffé et al., 2012). Furthermore, although double mutants combining the initial mutant alleles appeared hyposensitive to ABA (Pandey et al., 2009), analyses of new mutant *gtg* alleles found major growth defects but no change in ABA response (Jaffé et al., 2012), leaving their role as ABA receptors controversial.

Early steps in ABA signal transduction

Although neither the signaling pathway initiating with the PYR/PYL/RCARs nor that for the CHLH receptors currently explains a dependence on secondary messengers for effects on gene expression, numerous studies have implicated phospholipid-derived signals, Ca^{2+}, nitric oxide (NO), cyclic ADP-ribose, cyclic GMP, and reactive oxygen species (ROS) in ABA signaling. Several of these messengers lead to changes in cytosolic Ca^{2+} by inducing either release of Ca^{2+} from intracellular compartments or influx through plasma membrane channels. The plasma membrane channels are activated by ROS species such as H_2O_2, which is produced by NADPH oxidases. Release from intracellular stores can be induced by phosphoinositides, sphingosine-1-phosphate, cADPR or even Ca^{2+} itself.

Plant polyphosphoinositide metabolism is very complex and it appears that the IP_3 signaling paradigm from animal systems may not apply to plants (reviewed in Munnik and Vermeer, 2010). Although produced by phospholipase C (PLC) activity as in animals, IP_3 is rapidly converted to the more highly phosphorylated inositide $IP_{6,}$ which contributes to ABA-inhibition of stomatal opening by promoting Ca^{2+} release leading to inhibition of K^+ influx channels. Diacylglycerol (DAG), the other product of PLC activity, can be phosphorylated to produce phosphatidic acid (PA). PA is also produced by phospholipase D (PLD) activity. In addition to the multiple metabolic pathways interconnecting these potential signals, most of the enzymes are encoded by gene families. For example, Arabidopsis encodes 7 active PLCs and 11 PLD genes. Structural differences among the PLDs result in different requirements for Ca^{2+} or phospholipids as cofactors, as well as different substrate preferences (reviewed in Guo and Wang, 2012). Many of the PLDs are induced by a variety of stresses (Wang et al., 2000) , but only PLDα1 (AT3G15730) and PLDδ (At4g35790) expression and activity are increased by ABA (Uraji et al., 2012). Consistent with roles for these family members in ABA signaling, mutations in these genes impair ABA effects on stomatal closure and germination inhibition. Furthermore, PA was shown to mediate ABA-induced production of both ROS and NO, leading to stomatal closure through effects on ion channels (Jacob et al., 1999; Zhang et al., 2009). PA also binds to the PP2C ABI1, tethering it to the plasma membrane and interfering with its ability to inhibit ABA response. Several stresses leading to stomatal closure result in ROS production (Lee et al., 1999), and it has been suggested that the ROS-dependent pathway of response is shared by multiple stresses (reviewed in Miller et al., 2009; Suzuki et al., 2011). Consistent with this, enhanced tolerance of abiotic stresses results from constitutive activation of a ROS-activated MAPK cascade (Kovtun et al., 2000).

While ABA signaling can result in sustained $[Ca^{2+}]_{cyt}$ elevations, continuous monitoring of $[Ca^{2+}]_{cyt}$ has demonstrated that various signals affecting stomatal aperture induce $[Ca^{2+}]_{cyt}$ oscillations with distinct periodicity, and that imposing the correct periodicity with exchanges of external buffer solutions can restore normal response to mutants (Allen et al., 2000; Allen et al., 2001). ABA can also induce stomatal closure in guard cells that show no increase in cytosolic calcium, leading to proposals that some ABA signaling is either calcium-independent or due to enhanced sensitivity of Ca^{2+} signaling (Siegel et al., 2009). The observations that sensitivity to Ca^{2+} can change or that distinct oscillation patterns (i.e. a "Ca^{2+} signature") can be recognized as different implies interactions with distinct Ca^{2+} binding proteins leading to different cellular responses. There are multiple families of such proteins including calmodulins (CaM), calcium dependent protein kinases (CDPK/CPKs), and calcineurin B-like proteins (CBLs) and their interacting protein kinases (CIPKs) (reviewed in Luan, 2009; Weinl and Kudla, 2009).

ABA-induced stomatal closing also partly depends on cytosolic alkalization, which precedes production of both ROS and NO, and appears to promote increased NO levels (Irving et al., 1992; Gonugunta et al., 2009). This process requires function of OST1, one of the SnRK2s acting in the core signaling pathway, and is also both induced by increased $[Ca^{2+}]_{cyt}$ and regulates oscillations in $[Ca^{2+}]_{cyt}$ (Islam et al., 2010). Alkalization imposed in isolated membrane patches reveals that it appears to function by increasing the number of K^+_{out} channels available for activation (Miedema and Assmann, 1996). Furthermore, increased external pH decreases K^+_{in} channel activity (Hedrich et al., 1995 Ilan et al, 1996) and increases activation of a guard cell localized K^+_{out} channel (Ilan et al., 1994; Ache et al., 2000). Increasing pH may also be a feedback mechanism for ABA desensitization via activation of ABI1, a negative regulator of ABA response (Leube et al., 1998). Alkalization is also necessary, but not sufficient, for ABA-induced changes in gene expression (van der Veen et al., 1992).

INTERACTIONS WITH DEVELOPMENTAL, STRESS, AND OTHER HORMONE SIGNALING PATHWAYS

The "core signaling pathway" described above functions in many tissues and developmental stages, but the specific receptor, phosphatase, kinase, transcription factor, etc. family mem-

bers and the induced cellular responses vary with the context. Comparison of expression patterns and mutant phenotypes for these regulators has demonstrated that none of the known loci act completely stage-specifically, and many function redundantly. Furthermore, some "ABA response regulators" appear to also function in networks regulating response to sugars, salt, and most known hormones. Although initially selected on the basis of increased or decreased ABA response, not all mutants show consistent hyper- or hyposensitivity for all ABA-regulated responses. Thus it is most useful to consider genetic interactions in the context of specific cell types, since the participants and outcomes of ABA signaling vary. For example, comparison of ABA-regulated transcriptomes identify 1-10% of the genome as ABA-regulated in any given experiment, for a total of nearly 6000 ABA-induced and a similar number of ABA-repressed genes, but very few of the induced genes were common to nearly all conditions (Choudhury and Lahiri, 2010; Wang et al., 2011) (Table 3). Over half of this core set are either signaling factors (ABI-clade PP2Cs, transcription factors, kinases, lipid binding or assorted transporters) or desiccation protectants of the dehydrin or late embryogenesis abundant classes. Despite their apparent central nature in ABA signaling, loss of function for these individual genes has little to no effect on ABA response, presumably due to redundancy with other factors. Interestingly, the core set of repressed genes includes multiple members of the PYR/PYL/RCAR receptor family, providing a mechanism to desensitize ABA response and restore homeostasis. In the following sections, we will consider the ABA signaling networks in maturing seeds, germination, seedlings, vegetative stress responses, stomatal regulation, pathogen response, flowering, and senescence.

Maturing Seeds

Developing embryos enter maturation phase when they undergo a transition from growth by cell division to growth by cell enlargement and begin to accumulate storage reserves. This growth phase transition is correlated with an increase in seed ABA content that appears to be required for cell cycle arrest at the G1/S transition (Levi et al., 1993; Liu et al., 1994). During seed maturation, there are two peaks of ABA accumulation (Figure 6). As discussed earlier, genetic studies indicated that maternal ABA was sufficient to provide the early peak and the later peak was mostly embryonic, but also showed that maternal ABA could still be transported into ABA-deficient embryos at the later stage (Karssen et al., 1983; Kanno et al., 2010).

The early peak, along with *FUS3* and *LEC* gene function, are required to prevent premature germination at the end of the cell division phase of embryogenesis (Raz et al., 2001). Although this ABA peak is reduced three-fold in *fus3* mutants, reflecting the fact that FUS3 promotes ABA synthesis which in turn stabilizes the FUS3 protein (Gazzarrini et al., 2004), only double mutants combining *fus3* with ABA deficiency or ABA insensitivity are viviparous (Keith et al., 1994; Nambara et al., 2000; Brocard-Gifford et al., 2003). Further analyses of these double mutants demonstrated synergistic effects of these transcription factors in promoting embryonic gene expression and suppressing germination-specific genes. The later ABA peak is essential for induction of dormancy (Karssen et al., 1983). PYL5 (At5g05440) is the most highly expressed receptor at this stage (Schmid et al. 2005; Winter et al., 2007), suggesting that it may play a major role in ABA response during seed maturation.

Reserve accumulation and late embryogenesis-abundant (*LEA*) gene expression during maturation are largely controlled by the combinatorial action of transcription factors. Extensive analyses of promoter sequences for storage protein and *LEA* genes have demonstrated the presence of elements required for hormone responsiveness, stage- and tissue-specificity. Many of the major regulators are members of two families of transcription factors: B3 and bZIP domain proteins. In addition, the AP2 domain protein ABI4 and the CCAAT-box binding factor subunit LEC1 regulate many of these genes. The B3 domain family is comprised of two antagonistically acting groups: the AFL (ABI3/FUS3/LEC2) clade proteins promote embryo maturation, while the VAL (VP1/ABI3-Like) clade proteins repress embryonic processes to permit the phase transition to germination, in part through association with chromatin remodeling factors (Suzuki and McCarty, 2008). The bZIP domain proteins also include antagonistically acting factors: ABI5 promotes expression of some *LEAs*, whereas EEL (AT2G41070) inhibits it (Bensmihen et al., 2002). Several embryonically expressed homologs of ABI5 were identified by homology to sunflower proteins identified in one-hybrid screens with the Dc3 promoter and were designated AtDPBFs (Arabidopsis thaliana Dc3 Promoter Binding Factor) (Kim et al., 2002). Although these bZIP factors have similar binding sites and can form heterodimers in specific combinations, a triple knockdown of AtDPBF2/AtbZIP67 (AT3G44460), AtDPBF4/EEL/AtbZIP12, and AtDPBF3/AREB3/AtbZIP66 (AT3G56850) has no obvious maturation or ABA response defects, suggesting either minimal or conflicting functions of these factors, or some redundancy with other regulators (Bensmihen et al., 2005).

The LEC1/AFL and ABI transcription factors are all expressed in embryos, but their spatial and temporal expression patterns differ and there is substantial cross-regulation among them. LEC1 promotes expression of LEC2 and FUS3, which primarily promote embryonic growth, including expression of factors such as ABI3, ABI4, and ABI5 that regulate ABA response (reviewed in Suzuki and McCarty, 2008; Junker et al., 2010). FUS3 and these ABI factors are also auto-regulatory, thereby maintaining their expression when LEC levels decline during seed maturation. Although individual *lec* and *fus3* mutations have little or no effect on ABA sensitivity, double mutants combining them with mutations in ABA response (e.g. *abi1-1*, *abi3*, *abi4*, or *abi5*) are at least 10-fold less sensitive to ABA than their monogenic *abi* parents (reviewed in Finkelstein et al., 2002). Furthermore, these plants produce highly pigmented seeds that fail to accumulate storage reserves or attain desiccation tolerance and may also be viviparous (Keith et al., 1994; Meinke et al., 1994; Parcy et al., 1997; Nambara et al., 2000; Brocard-Gifford et al., 2003).Thus, *ABI*-dependent ABA sensitivity is potentiated by the FUS3 and LEC gene products, reflecting the regulatory hierarchy described above. Additional factors, such as the RING protein DESPIERTO (DEP: AT1G70910), have also been shown to regulate ABA sensitivity and dormancy by effects on ABI expression (Barrero et al., 2010).

Physiological studies have shown that the *ABI3*, *ABI4*, and *ABI5* loci have similar qualitative effects on seed development and ABA sensitivity, but that null mutations in *ABI3* are more se-

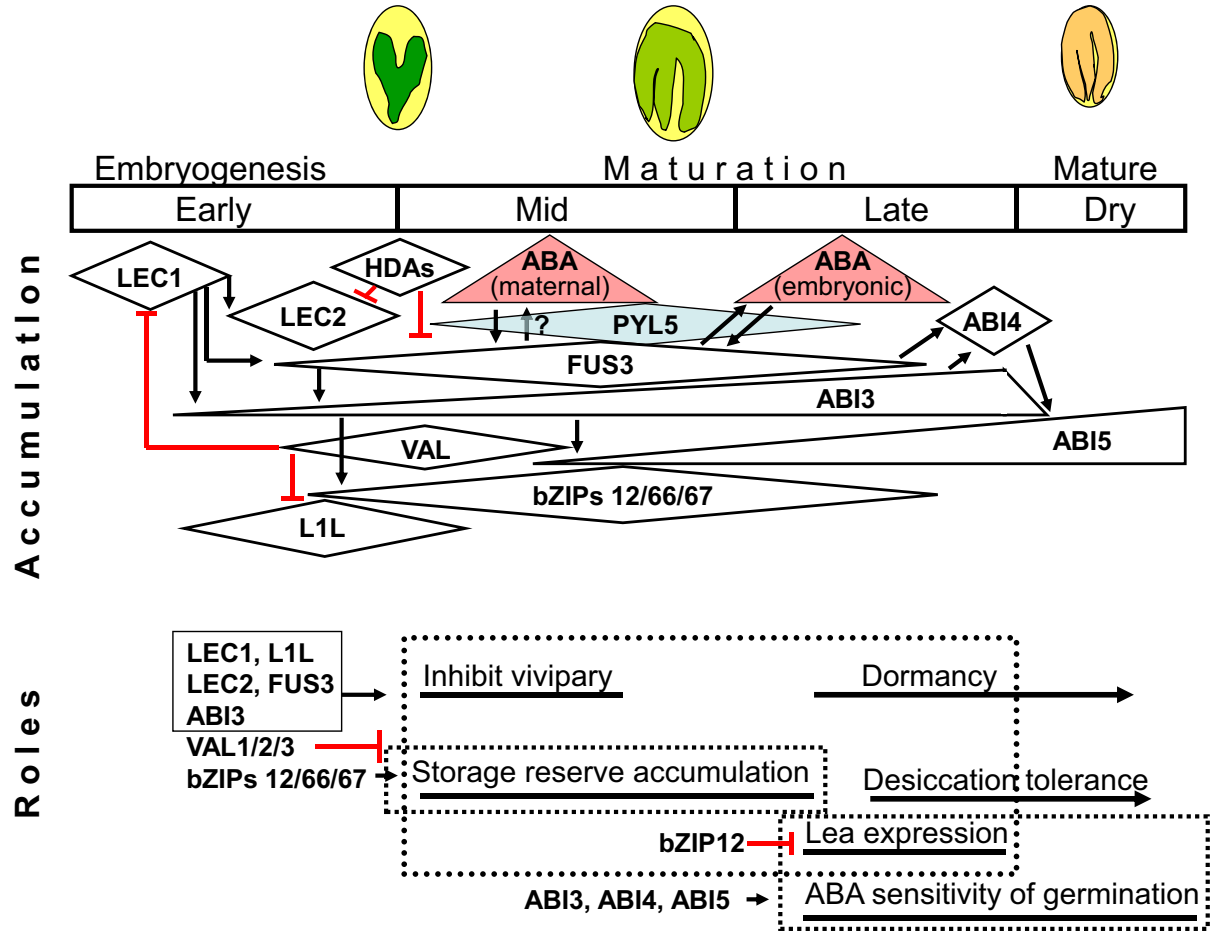


Figure 6. Interactions among some of the hormonal and developmental signals and regulatory elements controlling seed maturation.

In the upper portion ("Accumulation"), factors regulating gene expression during the progression through seed development are shown in boxes representing the relative timing and abundance of their expression. ABA accumulation is depicted in pale red triangles. PYL5 is the ABA receptor that is most highly expressed in mid-seed development, and therefore likely to mediate ABA signaling during this stage. To simplify the diagram, intermediates in this signaling pathway are not shown (see Fig.4 for details). In the lower portion ("Roles"), the events regulated by specific factors are shown. In both parts, arrows represent positive regulation and red bars indicate repression.

vere than those in *ABI4* or *ABI5* (Parcy et al., 1994; Finkelstein et al., 1998; Finkelstein and Lynch, 2000). Ectopic expression of *ABI3*, *ABI4* or *ABI5* results in ABA hypersensitivity of vegetative tissues, including ABA-inducible vegetative expression of several "seed-specific" genes; the ABI3 and ABI4 effects are partly dependent on increased *ABI5* expression (Parcy et al., 1994; Söderman et al., 2000). Transcriptome comparisons have shown that these factors regulate overlapping sets of genes (Suzuki et al., 2003; Nakabayashi et al., 2005; Reeves et al., 2011). Taken together, these results suggest that seed-specific or ABA-inducible expression might be at least partially controlled by regulatory complexes containing these and related transcription factors. Consistent with this, promoters of genes encoding the most abundant transcripts in mature seeds contain potential binding sites for at least two ABI transcription factors, and the bZIP binding sites known as ABREs are overrepresented in all highly expressed genes at this stage (Nakabayashi et al., 2005). Similarly, chromatin immunoprecipitation studies have identified at least 98 genes that are highly expressed in seeds as direct targets of ABI3; these overlap with the regulons of FUS3, LEC2, bZIPs including ABI5, and members of the MYB, MADS and bHLH transcription factor families (Monke et al., 2012). Furthermore, ABI3 (or its monocot ortholog VIVIPAROUS1) and ABI5 (or its rice homolog TRAB1) display direct and synergistic interactions in two-hybrid analyses in yeast and transient reporter activation assays in rice protoplasts (Hobo et al., 1999; Nakamura et al., 2001), and direct *in vivo* binding of ABI5 to the *lea* gene *AtEm6* (AT2G40170) was demonstrated by chromatin immunoprecipitation (Lopez-Molina et al., 2002). Similarly, the CCAAT-box binding factor subunit LEC1 and its closest homolog form complexes with bZIP67/AtDPBF2 and EEL/bZIP12/

AtDPBF4 to direct binding to ABRE-containing promoters such as that encoding the CRC storage protein (AT4G28520) (Yamamoto et al., 2009). In contrast, although ABI4 can directly bind a variety of regulatory sequences in seed-expressed genes that are co-regulated by ABI3 and ABI5 (Bossi et al., 2009; Reeves et al., 2011), it does not interact directly with either ABI3 or ABI5 in yeast two-hybrid assays (Nakamura et al., 2001). However, it does appear to interact with ABI5 in BiFC assays (Figure 7).

Severe defects in seed maturation are observed in either null alleles of *ABI3* or double mutants combining the weak *abi3-1* allele with ABA deficiency (the *aba-1* mutant); these plants produce seeds that have a high degree of denatured protein, and fail to lose chlorophyll, accumulate storage proteins, or attain desiccation tolerance (Koornneef et al., 1989; Giraudat et al., 1992; Nambara et al., 1992; Wolkers et al., 1998). They differ from the *abi lec* and *abi fus* 3 double mutants in that they are not viviparous and do not accumulate anthocyanins. A similar "green seed" phenotype can be produced by severe reduction of free ABA by seed-specific expression of anti-ABA antibodies (Phillips et al., 1997). The *aba*, *abi3-1* effects on desiccation tolerance and seed protein accumulation can be reversed by application of exogenous ABA (Meurs et al., 1992). These results indicate that *ABI3* regulates processes in seed development that respond to high endogenous ABA.

Events regulating ABA response in seeds are also subject to post-transcriptional control. FUS3 and all of the ABI transcription factors are proteasomally degraded (Lopez-Molina et al., 2001; Zhang et al., 2005; Lu et al., 2010; Finkelstein et al., 2011). In addition, miRNAs regulate progression through embryogenesis by suppressing expression of factors promoting maturation, e.g.FUS3, LEC1-LIKE, LEC2, and several bZIPs and MYBs, and promoting expression of chromatin remodeling factors that inhibit the maturation program (Willmann et al., 2011). Consequently, numerous genes encoding storage proteins and enzymes or structural proteins required for oil bodies are also overexpressed in miRNA biogenesis mutants.

In summary, many of the best-characterized loci regulating stage-specific ABA response in embryos encode transcription factors with complex patterns of cross-regulation and some direct interactions such that ectopic expression of several of these factors can confer "seed-specific" gene expression patterns on another developmental stage or tissue. Further regulation of these factors includes pre-transcriptional effects on chromatin and post-transcriptional effects on mRNA stability, translation and protein stability.

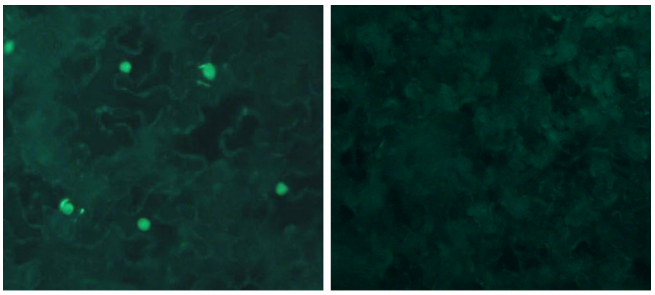


Figure 7. BiFC interaction between ABI4 and ABI5.

N. benthamiana leaf co-infiltrated with *Agrobacterium tumefaciens* carrying plasmids encoding nYFP-ABI4 and either cYFP-ABI5 (left) or cYFP (right), and the P19 protein of tomato bushy stunt virus to enhance transient expression. Fluorescence was scored 3 days later with an Olympus AX70 microscope. (Finkelstein, unpublished)

Germination

The transition from seed maturation and dormancy to germination and seedling growth reflects a change in hormone balance. Genetic evidence for an antagonism between ABA and GA in germination control was initially provided by the isolation of ABA-deficient mutations as suppressors of non-germination due to GA-deficiency (Koornneef et al., 1982), and the GA response mutant *sleepy* (*sly:* AT4G24210) as a suppressor of *abi1-1* (Steber et al., 1998). Dormancy maintenance is correlated with *de novo* synthesis of ABA during imbibition, primarily in the endosperm (Lee et al., 2010), whereas release from dormancy largely reflects increased ABA catabolism in both embryos and endosperm by CYP707A2 (Okamoto et al., 2006) and increased GA synthesis dependent on increased expression of GA3ox1 (AT1G15550) and GA3ox2 (AT1G80340) and decreased expression of the GA inactivating enzyme GA2ox (reviewed in Seo et al., 2009). Changes in the relative levels of ABA and GA are amplified by mutually antagonistic regulation of these hormones' metabolism. For example, GA biosynthetic genes are overexpressed in ABA-deficient mutants and under-expressed in ABA over-accumulators (Seo et al., 2009). Conversely, in the absence of GA, DELLA proteins such as RGL2 (AT3G03450) induce *XERICO* (*XER:* AT2G04240), which encodes a RING-finger protein that promotes ABA synthesis that in turn increases expression of RGL2 and ABA signaling proteins such as ABI5; GA disrupts this loop by promoting degradation of the DELLAs (Piskurewicz et al., 2008).

The ABA/GA balance reflects and thereby mediates environmental regulation of germination. Two of the major dormancy-breaking signals are cold and light (reviewed in Holdsworth et al., 2008). Cold and light both promote GA accumulation by increased GA3ox levels following repression of PHYTOCHROME INTERACTING FACTOR3-LIKE5 (PIL5: AT2G20180) and SPATULA (SPT: AT4G36930), two bHLH factors that inhibit GA3ox expression. PIL5, the light-repressed factor, also promotes expression of ABA biosynthetic enzymes (NCEDs and SDR1) and inhibits CYP707A synthesis via activation of the Zn-finger factor SOMNUS (SOM: AT1G03790), maintaining higher ABA levels in the dark. PIL5 was recently found to interact directly with ABI3 in binding to the SOM promoter (Park et al., 2011). Light exposure also induces the transcription factor ATHB20 (AT3G01220) in the root cap and micropylar endosperm of imbibing seeds, which appears to reduce ABA sensitivity in these growth-limiting tissues (Barrero et al., 2010). Recent field studies have shown that the regulators controlling dormancy vary across seasons: cold soil temperatures correlate with deep dormancy due to increased expression of genes involved in ABA synthesis, GA catabolism, members of the SnRK2 kinase family, and *DELAY OF GERMINATION1* (*DOG1*: AT5G45830), whereas warmer conditions lead to shallow dormancy mediated by PIL5 and DELLAs that can be rapidly repressed by exposure to light (Footitt et al., 2011). Natu-

ral variation in sensitivity to chilling during imbibition may also reflect differences in expression of *FLOWERING LOCUS C* (*FLC:* AT5G10140) during seed maturation; high FLC promotes ABA catabolism and GA synthesis during subsequent cold imbibition (Chiang et al., 2009). In contrast, another flowering regulator (FY: AT5G13480) promotes dormancy, apparently by inhibiting GA synthesis and promoting expression of *ABI5* (Jiang et al., 2012).

Germination is also regulated by nutrient availability, in part through effects on ABA levels. Nitrate supplied either exogenously at germination or via the maternal plant during seed development leads to increased expression of *CYP707A2*, and therefore decreased ABA and dormancy (Matakiadis et al., 2009). In contrast, a wide range of sugar concentrations (5-300 mM) delay germination to a greater extent than a comparable osmotic treatment, and the inhibitory effects of sugar and ABA on subsequent seedling growth are synergistic (Laby et al., 2000; Price et al., 2003; Dekkers et al., 2004) (reviewed in Gibson, 2005). The mechanism of inhibition by sugars is complex, involving both hexokinase-dependent and –independent signaling, some of which is mediated by increased ABA levels due to a combination of increased synthesis and decreased catabolism (Xing et al., 2009; Zhu et al., 2011) as well as increased expression and stability of regulators such as the ABI transcription factors (Arroyo et al., 2003; Bossi et al., 2009; Finkelstein et al., 2011). It has been proposed that the putative glutamate receptor *AtGLR1.1* (AT3G04110) acts as a nitrogen sensor to integrate and regulate the germination response to varying carbon:nitrogen balance (Kang et al., 2004), but this seems more relevant at high C:N ratios than under low C:N (reviewed in Zheng, 2009).

Surprisingly, radicle emergence is observed even in the presence of up to 100 µM ABA when supplemented with low concentrations of sugar (either glucose or sucrose at 30–90 mM) or peptone, but greening and subsequent seedling growth is still blocked (Garciarrubio et al., 1997; Finkelstein and Lynch, 2000). The exogenous sugar might permit germination by overcoming a nutritional deficiency resulting from inhibition of reserve mobilization by exogenous ABA (Garciarrubio et al., 1997). However, reserve mobilization via the glyoxylate cycle is not essential for germination, and post-germinative growth can be supported by either photosynthesis or exogenous sugar in the absence of a functional glyoxylate cycle (Eastmond et al., 2000). The WRINKLED1 (WRI1: AT3G54320) transcription factor, which is induced by sugar and regulates sugar metabolism by increasing expression of glycolytic enzymes, might contribute to this ameliorating effect of sugars (Cernac et al., 2006).Furthermore, ABA inhibits, but does not completely prevent mobilization of seed lipid reserves, which leads to accumulation of sucrose derived from triacylglycerol (Pritchard et al., 2002). Under stress conditions lipid catabolism is limited to the endosperm because the key mediator of ABA-repression is ABI4, which is expressed only in the embryo, thereby leaving the embryo quiescent (reviewed in Penfield et al., 2006). Similarly, induction of ABI5 accumulation by low sucrose and ABA is strongly correlated with maintenance of desiccation tolerance in arrested seedlings (Lopez-Molina et al., 2001). ABA, the induced ABI5, and potentially other interacting factors may prevent the loss of desiccation tolerance by delaying escape from phase two of germination (the post-imbibition period when metabolism increases, but growth pauses) under conditions of low moisture. In contrast to ABI4, ABI5 is expressed in the micropylar region of the endosperm, also known as the endosperm cap, where it can inhibit expression of enzymes required for weakening of the cell layers restricting radicle emergence.

Numerous regulators of ABI5 expression, stability or activity have been identified that contribute to negative feedback loop(s) regulating ABA signaling (reviewed in Fujita et al., 2011). These include multiple E3 ligases (KEG: AT5G13530, DWA1: AT2G19430, DWA2: AT1G76260, SIZ1: AT5G60410) resulting in ubiquitination or sumoylation of ABI5, the phosphatidylethanolamine-binding protein MFT (MOTHER OF FT AND TFL1: AT1G18100) which is induced by DELLAs and ABI5 but represses ABI5 expression (Xi et al., 2010), and a clade of proteins of unknown function (AFPs) that have been proposed to destabilize ABI5 and/or interact with the co-repressor TOPLESS (TPL: AT1G15750) to inhibit expression of ABI5-regulated genes (Lopez-Molina et al., 2003; Garcia et al., 2008; Pauwels et al., 2010). Although KEG is localized in the trans-Golgi network where it would not have access to a nuclear protein such as ABI5 (Gu and Innes, 2012), recent studies have shown that KEG is important for cytoplasmic degradation of ABI5, either prior to nuclear import or following export of ABI5 from nuclei (Liu and Stone, 2013). Hypersensitivity to ABA and sugars is also conferred by mutations in N-end rule loci, but the specific substrates degraded by this pathway have not yet been identified (Holman et al., 2009).

The commitment to germinate is also controlled by interactions between ABA and most other hormones, including brassinosteroids (BR), ethylene, auxin, cytokinins and strigolactones. Some of these interactions modify the ABA/GA balance, while others have different mechanisms of cross-talk.

The interaction with BR was discovered when the GA response mutant *sly* was shown to be rescued by BR (Steber and McCourt, 2001) and BR-deficient and insensitive lines were found to be hypersensitive to ABA (Li et al., 2001; Steber and McCourt, 2001). Since then, ABA and BRs have been found to regulate hundreds of genes in common, with either similar or antagonistic effects, despite their generally antagonistic physiological effects (Nemhauser et al., 2006). At least some of the convergent signaling is mediated by ABA regulation of BR signaling components downstream of BR perception (Zhang et al., 2009).

Interactions with ethylene signaling were implied by the isolation of new alleles of ethylene response genes such as *ETHYLENE INSENSITIVE 2* (*EIN2*) and *CONSTITUTIVE TRIPLE RESPONSE 1* (*CTR1*) in screens for suppressors and enhancers, respectively, of seed sensitivity to ABA (Beaudoin et al., 2000; Ghassemian et al., 2000). The mechanism of this cross-talk is complex such that different combinations of ABA and ethylene signaling mutants appear to act in parallel, intersecting or single pathways, whereas combinations disrupting ethylene signaling and ABA synthesis suggest action in parallel pathways (Cheng et al., 2009). Recent studies of *Lepidium sativum*, a larger-seeded relative of Arabidopsis, have shown that ethylene produced primarily in the radicle induces genes promoting weakening of the micropylar endosperm, thereby antagonizing ABA signaling in these tissues (Linkies et al., 2009). These conflicting effects on signaling are enhanced by ABA-repression of ACC oxidase (Cheng et al., 2009; Linkies et al., 2009). Although ethylene represses an NCED family member and induces a CYP707A family member in seedlings (Cheng et al., 2009), it does not appear to affect these genes during germination (Linkies et al., 2009). However, an ethylene biosynthetic mutant over-accumulates ABA

in response to salt stress, and displays hypersensitivity to exogenous ABA at germination (Dong et al., 2011).

Evidence of cross-talk between auxin and ABA effects on germination is provided by the observations that exogenous auxin enhances the inhibitory effects of ABA, and that the auxin response factor ARF10 (AT2G28350) promotes ABA sensitivity (Liu et al., 2007). ARF10 is subject to post-transcriptional control by miRNA160, and this down-regulation is critical to permit germination.

Cytokinin promotes germination, and this effect is antagonized by ABA inhibition of cytokinin biosynthesis by reducing expression of the main isopentenyl transferase genes expressed in seeds (Wang et al., 2011). Conversely, cytokinins overcome the inhibitory effects of ABA by increasing expression of type A ARR (Arabidopsis Response Regulators) transcription repressors that reduce expression of ABA signaling factors such as ABI5. In addition, the type A ARRs appear to interact directly with ABI5, but it is not clear whether this alters or simply attenuates gene activation by ABI5.

Strigolactones have recently been found to alleviate thermoinhibition of germination by reducing the ABA:GA ratio, in part by reducing expression of ABA biosynthetic enzymes such as NCED9 (Toh et al., 2012).

Interactions among some of the hormonal and environmental signals and regulatory elements controlling germination are summarized schematically in Figure 8. Additional regulators specifically controlling dormancy without altering ABA sensitivity are not included.

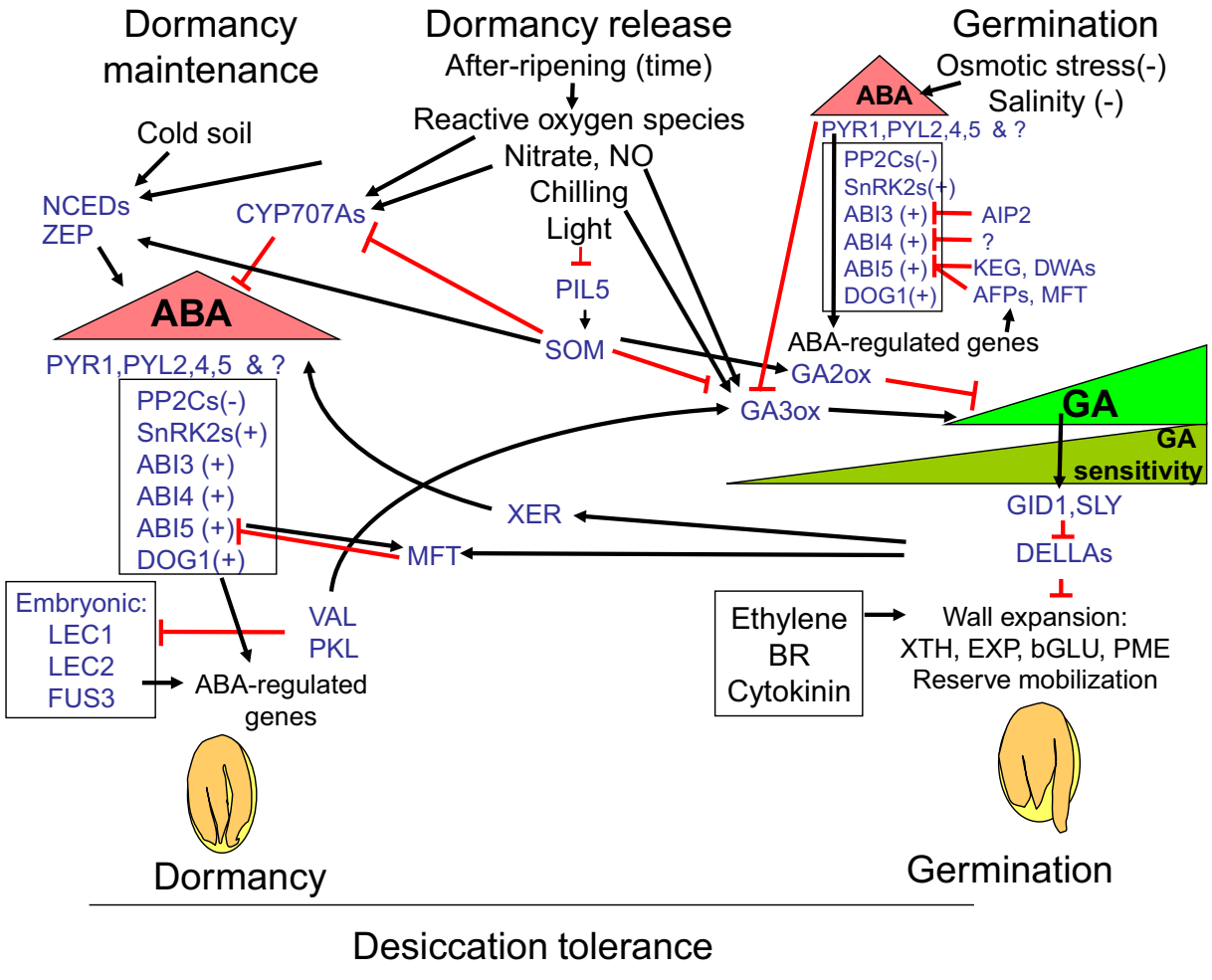


Figure 8. Interactions among some of the hormonal and environmental signals and regulatory elements controlling the transition from dormancy to germination.

ABA receptors listed are those that are most abundantly expressed in dry and imbibing seeds. Red triangles represent ABA accumulation during either dormancy maintenance or in response to dehydrating stresses following dormancy release. Arrows indicate positive regulation and red bars represent repression, illustrating substantial cross-talk controlling ABA/GA balance and feedback within each hormone's signaling network.

Seedling growth

The relative importance of the various family members of the core ABA signaling pathway changes after germination, in part reflecting differences in expression. The receptors that are most highly expressed in most developmental stages are PYR1, PYL1 (AT5G46790), PYL4 (AT2G38310), PYL8 (AT5G53160), PYL5 (AT2G40330), and PYL2 (AT2G26040) (Gonzalez-Guzman et al., 2012). Among these, PYR1 is consistently highly expressed, but the others vary among stages and organs. At the tissue level, further variation is seen. Sextuple mutants knocking out all of these genes are highly resistant to ABA effects on many aspects of growth, but lower order mutants show different degrees of resistance depending on which and how many genes are mutant. The sextuple receptor mutant exhibits greater resistance to ABA than a SnRK2 triple mutant (*snrk2.2/2.3/2.6*, also known as *srk2d/e/i*) for germination and seedling establishment, but growth and fertility of the SnRK2 triple is more impaired. The sextuple receptor mutant also maintains even greater stomatal conductance than ABA deficient or dominant negative PP2C mutants. Comparison of transcriptomes from intact 10-12d old seedlings of the higher order mutants showed that the SnRK2 triple mutant was impaired in ABA-induction of 1800-2400 genes (Fujita et al., 2009; Gonzalez-Guzman et al., 2012), and a similar number were affected in the sextuple receptor mutant; greater than 85% of the genes misregulated in the receptor mutant were misregulated in the SnRK2 mutant. Although these studies did not specify the total number of genes induced by ABA in wild-type plants, previous studies had identified nearly 2000 ABA-induced genes in intact 7d old seedlings (Goda et al., 2008), suggesting that the SnRK2 triple and receptor sextuple mutants disrupted induction of nearly all of these ABA-regulated genes.

Downstream of the SnRK2s, the bZIP transcription factors also change in relative abundance such that seedling growth is controlled more by the ABFs/AREBs than by ABI5 (Finkelstein et al., 2005). These bZIPs have overlapping effects such that higher order mutants are more resistant to ABA. The most severe combination reported, the *areb1/abf2 areb2/abf4 abf3* triple mutants, are extremely ABA-resistant and hypersensitive to drought (Yoshida et al., 2010). At the molecular level, this is reflected in impaired ABA-induction of nearly 30% of the SnRK2 regulated genes (Fujita et al., 2009). Another 25% of the *areb1 areb2 abf3* regulated genes are distinct from those regulated by the SnRK2s, suggesting that some of these bZIPs may be sufficiently activated by other kinases (e.g. CPKs) to induce expression of some ABA-regulated genes (Choi et al., 2005; Zhu et al., 2007; Lynch et al., 2012).

Seedling establishment requires access to adequate nutrients from reserve mobilization and/or environmental sources. As described for germination, high concentrations of exogenous sugars (>300 mM) inhibit seedling development, preventing greening and expansion of true leaves. Induction of developmental arrest is limited to a “window” within the first 2 days after stratification (Gibson et al., 2001), similar to the “checkpoint” for ABA-induced arrest mediated by ABI5 (Lopez-Molina et al., 2001). Numerous ABA response loci participate in this signaling (Dekkers et al., 2008). ABI4 in particular has been shown to directly inhibit expression of photosynthetically active nuclear genes (PhANGs) (Acevedo-Hernández et al., 2005) and to induce a key biosynthetic enzyme for TAG production during nitrogen deficiency in young seedlings (Yang et al., 2011). Possible additional shared mediators of this arrest were identified by a seedling transcriptome comparison in which ~14% of ABA-induced genes were also induced by glucose (Li et al., 2006).

ABA plays another role in nutrient signaling in seedlings by mediating the regulatory effects of nitrate on root branching (Signora et al., 2001). Nitrate effects are also concentration dependent, with localized low nitrate (<1 mM) stimulating lateral root elongation and high nitrate (>10 mM) inhibiting elongation of newly emerged lateral roots throughout the root system; these effects are antagonized by increasing sugar. As initially described for sugar sensing, only ABA-deficient, *abi4* and *abi5* seedlings displayed decreased sensitivity to nitrate inhibition, suggesting that they mediate the inhibitory effect. In contrast, the stimulatory effect of low nitrate also requires ABA, but is enhanced in all of the *abi* mutants tested except *abi5*, consistent with the view that this response involves a different signaling mechanism.

More recently it has become clear that there is substantial cross-talk between nutrient-based and hormonal signaling (reviewed in Krouk et al., 2011). For example, nitrate levels affect auxin transport and signaling, and synthesis of cytokinins and ethylene. Reciprocally, auxin, cytokinins, ethylene and ABA regulate nitrogen uptake and assimilation, creating a cycle in which nutrients control hormone levels and consequently growth and nutrient use. Root branching, which directly affects access to soil nutrients, is regulated by soil nitrogen and phosphate levels, as well as by interactions between auxin, cytokinin and ABA signaling. Both ABI3 and ABI4 have been implicated in the cross-talk with auxin signaling, but with opposite effects. Auxin induces *ABI3* expression in vascular tissue and lateral root primordia, and ABI3 function is required for full auxin-induced lateral root formation (Brady et al., 2003). In contrast, *ABI4* expression in phloem of the upper root is enhanced by ABA and cytokinins, but inhibited by auxin; ABI4 inhibits lateral root formation by reducing polar auxin transport (Shkolnik-Inbar and Bar-Zvi, 2010).

ABA also induces distinct concentration-dependent effects on primary root growth: growth is promoted at nanomolar ABA levels, but inhibited at micromolar levels. Mechanistically, the promotion has been ascribed to decreased cell division in the quiescent center (QC) and suppressed differentiation of stem cells, collectively resulting in meristem maintenance and continued growth (Zhang et al., 2010). The QC regulation depended on action of ABI PP2Cs, ABI3 and ABI5, but not ABI4, whereas stem cell maintenance required ABA-induced expression of WOX5 (AT3G11260) and the auxin-responsive transcription factor MONOPTEROS (MP/ARF5: AT1G19850). More recently, the GRAS-family transcription factor SCARECROW (SCR: AT3G54220) has been shown to directly inhibit QC expression of ABI5 and especially ABI4 in young seedlings, thereby derepressing primary root growth (Cui et al., 2012).

Further hormonal cross-talk affecting primary root growth involving interactions between ABA, auxin, ethylene and brassinosteroid signaling has been discovered through a variety of mutant screens. Many of these interactions appear to affect auxin localization or signaling. For example, ABA treatment led to higher local concentrations of auxin in the QC and surrounding stem cells, correlated with inhibited cell division (Wang et al., 2011). ABA also promotes expression of the auxin response factor ARF2 (AT5G62000), which represses both auxin and ABA signaling,

and further links auxin, ethylene and brassinosteroid response. In addition, ABA has been proposed to potentiate auxin signaling by reducing expression of repressors of auxin response, e.g. the AUX/IAA genes *AXR2/IAA7* and *AXR3/IAA17* (AT1G04250) (Belin et al., 2009).The interactions with ethylene signaling are complex: disruption of ethylene signaling by *ein2/era3* or *etr1* mutations reduced sensitivity of root growth to inhibition by ABA, but ethylene overproducing (*eto*) mutants or constitutive response mutants (*ctr1*) also have decreased ABA sensitivity (Beaudoin et al., 2000; Ghassemian et al., 2000). A possible explanation for this apparent inconsistency is that ABA might inhibit root growth by signaling through the ETR1 response pathway, but only in the absence of ethylene (Ghassemian et al., 2000)

ABA inhibits growth via a combination of limited cell extensibility (Kutschera and Schopfer, 1986) and inhibited cell division due to arrest at the G1 phase of the cell cycle (Levi et al., 1993; Liu et al., 1994)}. The effects of ABA on progression through the cell cycle reflect a combination of direct repression of cell cycle genes, such as *CDKA* (AT3G48750), or DNA replication genes (reviewed in Gutierrez, 2009) and ABA-induced expression of a cyclin-dependent protein kinase inhibitor (KRP1/ICK1: AT2G23430) that interacts with both CDKA and CycD3 and is correlated with decreased Cdc2-like histone H1 kinase activity (Wang et al., 1998).

Most of the studies described above focus on the inhibitory effects of high ABA on growth. However, even well-watered ABA-deficient plants exhibit stunted growth suggesting that the low endogenous ABA levels in unstressed plants promote growth. Studies in maize and tomato indicate that the stunted growth of ABA-deficient plants is due to a failure to inhibit ethylene production, reflecting another antagonistic interaction between ABA and ethylene (Sharp et al., 2000; Spollen et al., 2000).

Stress responses

A critical function of ABA during vegetative growth is to mediate response to environmental stresses such as drought, salinity, and cold (reviewed in Yamaguchi-Shinozaki and Shinozaki, 2006; Qin et al., 2011; Huang et al., 2012). These stresses are similar in that they all impose cellular osmotic and oxidative stress, but they differ in other effects and consequently the appropriate responses are not identical. ABA is also implicated in response to flooding-induced hypoxic stress, which leads to reduced ABA levels in submerged tissues and increased ABA in shoots of flooded plants (Hsu et al., 2011). This might explain the earlier observation that exogenous ABA promoted tolerance of hypoxic stress in roots, but not shoots (Ellis et al., 1999), in that shoots may have already responded by making sufficient ABA to be beneficial.

At the whole plant level, slightly elevated ABA levels (characteristic of mild water stress conditions) promote root growth but inhibit shoot growth, leading to an increased root:shoot ratio. These roots respond to moisture gradients by positive “hydrotropism” (reviewed in Moriwaki et al., 2012). ABA regulates this response via the “core signaling pathway” (Antoni et al., 2013). In contrast, severe water stress inhibits growth of both roots and shoots, but promotes formation of arrested lateral roots, i.e. drought rhizogenesis (Vartanian et al., 1994). Genetic studies have shown that drought rhizogenesis is regulated by ABA, auxin and some gibberellins, and disrupted in the ABA-insensitive mutant *abi1-1*, but not in *abi2-1* or *abi3* mutants.

The flow of water across cell membranes to regulate growth and transpiration is largely controlled by aquaporins present in the tonoplast and plasma membranes. Aquaporin content and activity are regulated by many factors, including effects on transcription, protein stability, subcellular trafficking, and gating by changes in phosphorylation, pH or Ca^{2+} (reviewed in Maurel et al., 2008). Arabidopsis encodes 13 plasma membrane localized isoforms (PIPs) and 10 tonoplast localized aquaporins (TIPs), which display differential organ/tissue/cell-specificities, and different responses to stress or ABA treatment (Jang et al., 2004 ; Alexandersson et al., 2005). Despite their names, some family members transport substrates other than water and may be present in multiple cellular membranes. In principle, TIPs regulate permeability of the tonoplast, which can buffer the cytosol from abrupt turgor and volume changes from water efflux due to dehydrating conditions, whereas PIPs would regulate that efflux. Although there are many conflicting reports, at least partly reflecting differences in experimental conditions, expression of most aquaporins is down-regulated during drought and salt stress, which would limit water loss and potentially create a hydraulic signal to aerial parts that could induce stomatal closure. ABA-induced dephosphorylation of aquaporins is also consistent with reduced water flux (Kline et al., 2010) and decreased activity of aquaporins in bundle sheath cells has been reported as a mechanism for decreased hydraulic conductivity of the leaf vascular system (Shatil-Cohen et al., 2011). However, two Arabidopsis PIPs (*AtPIP1;4*: AT4G00430 and *AtPIP2;5*: AT3G54820) are induced by drought and are highly expressed in guard cells (Alexandersson et al., 2005; Winter et al., 2007; Yang et al., 2008), which could facilitate stomatal closure. Although not compared to unstressed plants, comparison of osmotically stressed maize transgenic lines with different ABA biosynthetic capacity showed that ABA increased expression of several PIPs, especially in roots (Parent et al., 2009). Furthermore, this was correlated with increased hydraulic conductivity that could promote both water uptake by roots and rapid recovery of leaf water potential upon rehydration. Although regulation of aquaporins plays a role in acclimating to water stress, the nuances of this regulation are still not clear.

Within cells, ABA induces accumulation of protectants such as small hydrophilic proteins, sugars, proline, and glycine-betaine, or activates detoxifying mechanisms that confer stress tolerance by regulating redox balance or modifying ion transport to re-establish homeostasis. Extensive studies of stress- and ABA-induced gene expression during vegetative growth reveal two waves of response: an early transient response, peaking at ~3 hrs, and a late sustained response (from ~10 hrs onward). The “early” genes encode regulatory proteins such as transcription factors, protein kinases and phosphatases, and an assortment of *early response to dehydration* (*erd*) genes, many of which encode proteins of unknown function (reviewed in Yamaguchi-Shinozaki and Shinozaki, 2006; Fujita et al., 2011). Many of the “late” genes are named in terms of the stresses that initially identified them, e.g. *responsive to dehydration* (*rd*), *cold-regulated* (*cor*), *low temperature induced* (*lti*) and *cold-induced* (*kin*) gene classes. These are presumed to contribute to the adaptive aspects of induced tolerance since many of them encode proteins that are structurally similar to some of the LEA proteins that accumulate during the

acquisition of desiccation tolerance in seeds, while others encode proteases, presumed chaperonins, enzymes of sugar or other compatible solute metabolism, ion and water-channel proteins, and enzymes that detoxify reactive oxygen species (reviewed in Ingram and Bartels, 1996). In addition to the traditional view that compatible solutes primarily mediate osmotic adjustment, recent studies suggest that they may also contribute to stabilizing redox balance, maintaining protein folding and acting as metabolic signals (reviewed in Szabados et al., 2011). Constitutive expression of stress-induced transcription factors or some of their target genes can increase stress tolerance (reviewed in Thomashow, 1999; Bartels, 2001; Vinocur and Altman, 2005; Peleg et al., 2011; Qin et al., 2011; Sanghera et al., 2011).

As discussed earlier, between 1-10% of the genome has been identified as ABA-regulated in any given experiment, with the variation reflecting both differences in experimental conditions and the stringency of the criteria used to classify genes as ABA-regulated. However, in most of these experiments, similar numbers of genes were identified as ABA-repressed or ABA-induced. The ABA-repressed genes also vary across experiments, but are generally enriched for those encoding proteins required for growth, such as plasma membrane, cell wall and plastid proteins. Surprisingly, the core sets of ABA-repressed genes identified by multiple transcriptome studies are also enriched for stress-induced genes (Choudhury and Lahiri, 2010; Wang et al., 2011).

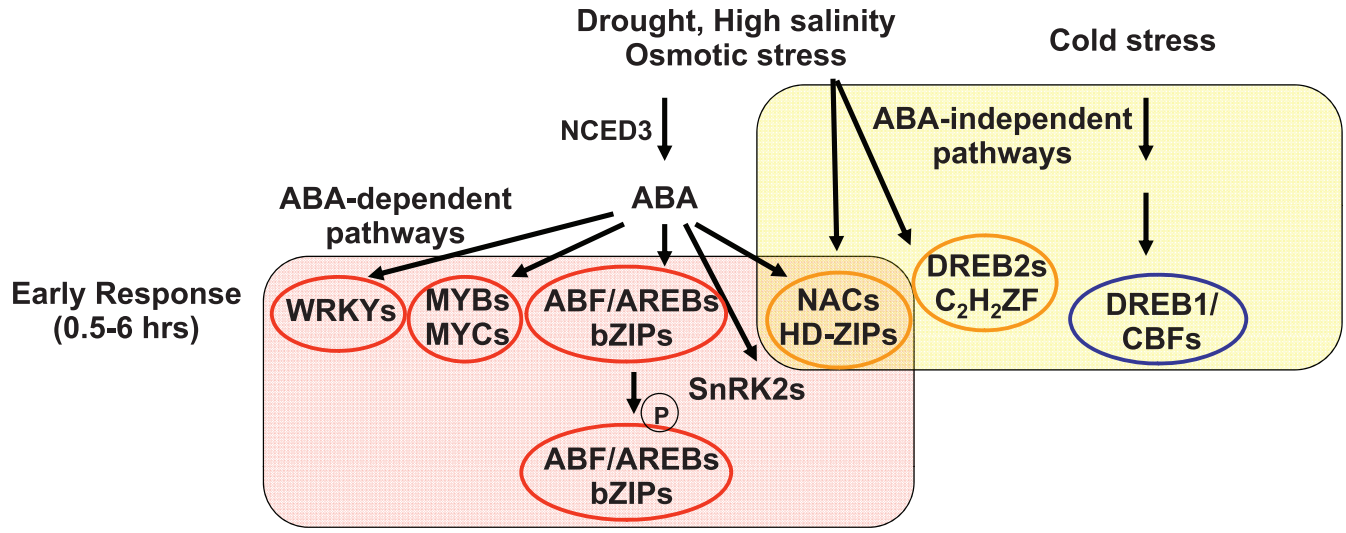
Comparison of stress-induced gene expression in ABA biosynthesis and response mutants has demonstrated that there are both ABA-dependent and –independent signaling pathways producing a complex array of interactions (reviewed in Yamaguchi-Shinozaki and Shinozaki, 2006; Cutler et al., 2010; Huang et al., 2012). While initial studies focused on a relatively small number of marker genes, more recent studies have analyzed entire transcriptomes of different genotypes exposed to various stresses (reviewed in Nakashima et al., 2009). Analyses using tiling arrays have revealed many additional stress-regulated unannotated transcriptional units including antisense transcripts and pseudogenes, and transcription factors not represented on the ATH1 array (Matsui et al., 2008; Zeller et al., 2009). These studies have shown that 25-50% of the genes regulated by ABA are also regulated by drought or salinity, which show even greater overlap with each other (30-70%, depending on the experiment), but that the cold-regulated transcriptome shows less overlap with those induced by other stresses, in part because many fewer genes are cold-regulated. Metabolomic studies also reflect these distinct pathways such that synthesis of branched-chain amino acids, polyamines, proline, and saccharopine is ABA-dependent, whereas production of raffinose family oligosaccharides is ABA-independent (reviewed in Urano et al., 2010).

Consistent with these outputs, at least three distinct transcriptional signaling pathways have been proposed to mediate response to drought stress and an additional pathway mediates cold response (reviewed in Yamaguchi-Shinozaki and Shinozaki, 2006; Nakashima et al., 2009 ; Zhou et al., 2011) (Figure 9). The ABA-dependent pathways are primarily regulated by bZIPs (the "core" signaling pathway), but also by NAC- and MYC/MYB-regulated expression. The ABA-independent pathways depend on expression mediated by drought response element binding (DREB) family members, zinc finger, homeodomain, and NAC proteins. Several of the DREB1 family members are also known as cold response element binding factors (CBFs), reflecting their role in response to cold, while additional members mediate response to salinity. CBF1 (AT4G25490), CBF2 (AT4G25470), and CBF3 (AT4G25480) all increase transiently within 3-12 hrs of exposure to low temperature, but with different kinetics (Kilian et al., 2007). Although the CBFs mediate ABA-independent response, all are weakly induced by 30 minutes of ABA treatment (AtGenExpress data from Shimada lab). CBF4 (AT5G51990), named based on homology to the other CBFs, is expressed at much lower levels than the other CBFs in response to cold, dehydration and ABA. The DREB2 proteins have a slightly different DNA binding specificity than the DREB1s, resulting in regulation of an overlapping subset of genes in response to osmotic and temperature stresses. Surprisingly, the DNA-binding affinity of some CBFs increases at low temperature, providing an additional mechanism for specificity (Xue, 2003). Many stress-induced genes contain binding sites for multiple classes of regulators, e.g. ABREs bound by bZIPs and DRE-like "coupling elements" bound by DREBs, facilitating interaction between ABA-dependent and –independent regulation of these genes (Lee et al., 2010).

Stomatal regulation

In another important response to drought stress, ABA regulates the transpiration rate via effects on stomatal aperture both by promoting closure and inhibiting opening (reviewed in Kwak et al., 2008; Kim et al., 2010; Joshi-Saha et al., 2011). Although both effects result in closed stomata, they are not simple reversals of the same process in that they involve different ion channels regulated by different signaling mechanisms. In addition to this local control of guard cell physiology, recent studies suggest that ABA affects stomatal conductance by reducing hydraulic conductance of leaf vascular tissues, possibly by decreasing bundle sheath aquaporin expression or activity (Pantin et al., 2013). Surprisingly, many mutants that have defects in guard cell response to ABA are still responsive to hydraulic conductance and humidity effects on stomatal conductance (Assmann et al., 2000; Pantin et al., 2013). However, extremely high ABA concentrations (400 µM) were used to provoke stomatal closure in the ABA-insensitive mutants (Pantin et al., 2013), which might account for the discrepancy with the initial observation that 10 µM exogenous ABA intensified withering of stems and siliques of the *abi1-1* and *abi2-1* mutants (Koornneef et al., 1984).

ABA perception in guard cells is mediated by multiple receptors. Several members of the PYR/PYL/RCAR receptor family mediate intracellular perception (Gonzalez-Guzman et al., 2012), whereas the GTG receptors have been implicated in perception at the plasma membrane (Pandey et al., 2009), although their function and localization is controversial. The plastid localized CHLH protein also appears to regulate stomatal response to ABA, but its identity as a receptor is also controversial (Shen et al., 2006; Tsuzuki et al., 2011). Given the potential redundancy of so many receptors, it is somewhat surprising that the redundancy has been characterized only within receptor families: the *gtg* double, but not single, mutants slightly impair ABA-induced stomatal closing (Pandey et al., 2009), and mutations in at least 3 PYR/PYL/RCAR receptors are required to reveal defects in sto-



Extent of overlap among stress-regulated genes:

	1 hr			12 hr		
Stress	**Osmotic**	**Salt**	**Cold**	**Osmotic**	**Salt**	**Cold**
ABA	25.6%	23.5%	4.9%	34.1%	29.1%	10.4%
Osmotic		46.2%	7%		29.8%	15.3%
Salt			9.5%			20.4%

Late response Genes (>10 hrs)

Dehydrins, chaperonins, compatible solute metabolism, ion and water channel proteins, ROS detoxification,…

Figure 9. Stress signaling pathways

Summary of ABA-dependent and ABA-independent pathways mediating response to abiotic stresses. Overlaps among stress-regulated transcriptomes are based on data from ATH1 and tiling arrays presented in (Zeller et al., 2009).

matal conductance, with progressively higher stomatal aperture/conductance in higher order mutants (Gonzalez-Guzman et al., 2012). Combinations of mutations affecting different families of receptors have not yet been tested to determine whether these additive effects would also be observed across families. Interestingly, the PYR/PYL/RCARs have also been found to regulate stomatal response to numerous environmental signals including low humidity, darkness, O_3, and elevated CO_2 (Merilo et al., 2013).

ABA-induced stomatal closure is mediated at least in part by transient increases in $[Ca^{2+}]_{cyt}$ which activate both slow-activating sustained (S-type) and rapid transient (R-type) anion channels. The S-type channels (SLAC1: AT1G12480 and SLAH3: AT5G24030) permit efflux of chloride and nitrate (Negi et al., 2008; Vahisalu et al., 2008; Geiger et al., 2011), whereas a likely R-type channel (AtALMT12: AT4G17970) is permeable to malate and sulfate (Meyer et al., 2010). In addition, phosphate efflux via the PHO1 (AT3G23430) channel was recently shown to contribute specifically to ABA-regulation of stomatal aperture (Zimmerli et al., 2012). The resulting anion efflux depolarizes the plasma membrane, leading to activation of K^+_{out} channels permitting massive K^+ efflux, osmotic water loss and stomatal closure. Much of the K^+ is released from the vacuole by Ca^{2+}-activated K^+ channels in the tonoplast. In addition to these Ca^{2+}-activated events, roughly 30% of ABA-induced stomatal closure appears to be either Ca^{2+}-independent or sensitive to much lower $[Ca^{2+}]_{cyt}$, leading to the hypothesis that ABA "primes" some guard cells such that they become sensitive to resting endogenous Ca^{2+} levels (Siegel et al., 2009; Hubbard et al., 2012).

In contrast to closure, ABA-inhibition of stomatal opening is mediated by inhibition of K^+_{in} channels and the plasma membrane H^+ ATPase, OST2. The decrease in K^+_{in} channel activity is due to a combination of repression by SnRK2.6/OST1-mediated phosphorylation (Sato et al., 2009) and removal from the membrane by endocytosis (Sutter et al., 2007). Reinsertion of these chan-

nels is mediated by the syntaxin SYP121 (AT3G11820). The *ost2* mutants are constitutively active, such that they are not inhibited by ABA and therefore the stomata remain open (Merlot et al., 2007). However, the *ost2* mutants retain some response to two other signals promoting stomatal closure (CO_2 and darkness), indicating that at least part of these signaling pathways are distinct.

Activity of the slow anion channel encoded by SLAC1 is critical for stomatal closing in response to multiple signals including ABA, CO_2, light/dark transitions, Ca^{2+} and ozone (Negi et al., 2008; Vahisalu et al., 2008). The channel is activated by phosphorylation by either SnRK2 or CPK family kinases, such as OST1 or CPK6 (AT2G17290), apparently at distinct sites (Brandt et al., 2012). Consequently, ABA perception results in Ca^{2+}-independent SLAC1 activation by blocking PP2C repression of the SnRK2s and Ca^{2+}-dependent activation of CPKs. Several of the group A PP2Cs that interact directly with the PYR/PYL/RCAR receptors can directly dephosphorylate SLAC1, providing a mechanism to inactivate the channels as well as inhibit their activation.

Ca^{2+} release is regulated by several additional secondary messengers including reactive oxygen species (ROS), nitric oxide (NO), phosphatidic acid (PA), phosphoinositides, and sphingolipids. ROS are produced by AtRbohD/F NADPH oxidases (AT5G47910 and AT1G64060), which are directly activated by the OST1 kinase in the "core signaling pathway". ROS, in turn, promote increased $[Ca^{2+}]_{cyt}$ by activating plasma membrane Ca^{2+} channels and promoting NO and phosphoinositide signaling, which also regulate $[Ca^{2+}]_{cyt}$ by promoting release from internal stores. In addition, ROS and NO activate MAP kinases that promote anion channel activation (reviewed in Neill et al., 2008). ROS production by increased NADPH oxidase activity is also promoted by PA, which also promotes activation of sphingosine kinases (SPHK1 and SPHK2, both encoded by AT4G21540) leading to an increase in the secondary messengers S1P and phyto-S1P; PLD production of PA and SPHK production of phyto-S1P form a feedback loop (reviewed in Guo and Wang, 2012). PA further enhances ABA response by tethering ABI1 to the plasma membrane, thereby inhibiting its ability to inactivate the SnRKs, which in turn results in reduced activity of inward K^+ channels. In contrast to ROS promotion of ABA response, the antioxidant glutathione negatively regulates stomatal response to ABA (Okuma et al., 2011). ROS production and Ca^{2+} signaling are not altered by changes in glutathione levels, leading to the suggestion that glutathione may act by controlling the redox status of downstream signaling components.

Despite the controversy regarding whether canonical G protein coupled receptors exist in plants, numerous studies link heterotrimeric G protein function to aspects of stomatal regulation (reviewed in Zhang, 2011). Null mutants of the G-alpha subunit, *gpa1*, are hyposensitive to ABA for inhibition of light-induced stomatal opening, but still respond to ABA for promotion of stomatal closure. Consistent with these limited effects, detailed electrophysiological studies of the *gpa1* mutants has shown that ABA effects on inward K^+ currents are impaired, but outward, slow anion currents are still activated by ABA. However, activation of the slow anion currents appears to be mediated by two parallel pathways, one involving G-proteins and another that is pH-dependent. Furthermore, G-proteins have recently been found to regulate plasma membrane Ca^{2+} channel activation in response to ABA and the resulting increases in $[Ca^{2+}]_{cyt}$, ROS, and downstream guard cell signaling (Zhang et al., 2011). It is not yet known which of the five guard cell expressed K^+_{in} channels or potential Ca^{2+} channels are regulated by G-proteins.

In addition to response mediated by changes in $[Ca^{2+}]_{cyt}$, extracellular Ca^{2+} ($[Ca^{2+}]_{ext}$) can induce stomatal closure via a pathway that converges with ABA-induced closure. Two potential sensors of $[Ca^{2+}]_{ext}$ are extracellular calmodulin (ExtCaM) and the calcium-sensing receptor (CAS: AT5G23060) localized in thylakoid membranes, both of which cross-talk with ABA signaling by production of H_2O_2 and NO, resulting in transient increases in $[Ca^{2+}]_{cyt}$ (Li et al., 2009; Wang et al., 2012). The ExtCaM-regulated signaling is dependent on GPA1 function to activate H_2O_2 and NO production and signaling, but the connections between ExtCaM and GPA1 are not yet understood. CAS activates H_2O_2 production in chloroplasts, possibly in response to early transient increases in $[Ca^{2+}]_{cyt}$ due to transient activation of plasma membrane Ca^{2+} channels.

The guard cell shape changes that lead to changes in stomatal aperture involve a substantial change in volume, accompanied by up to two-fold changes in membrane surface area and available ion channels accomplished by vesicle secretion and endocytosis (reviewed in Kim et al., 2010). Consistent with this, both v-SNARES (VAMPs) and t-SNARES (syntaxins) have been shown to be important in vesicle trafficking and fusion affecting tonoplast and plasma membranes and stomatal function (Leshem et al., 2010, and references therein). In addition to this structural role, alterations in vesicle trafficking resulted in altered distribution of ROS, which could affect ROS-mediated signaling. Vacuole fusion is also dependent on reorganization of the actin cytoskeleton mediated by the ARP2/3 complex (Jiang et al., 2012). ABA treatment results in rapid disruption of actin filaments which both removes the radial cables that contribute to formation of the stomatal pore and has been shown to enhance activation of stretch-regulated Ca^{2+} channels in *V. faba* guard cell plasma membranes (Zhang et al., 2007). The ABA-induced actin reorganization is inhibited by ABI1 (Eun et al., 2001) and AtRac1, a small GTPase protein that is subject to *ABI1*-dependent inactivation by ABA (Lemichez et al., 2001). In addition, both Ca^{2+} and phosphoinositides have been implicated in regulating ABA effects on actin dynamics in *Commelina* guard cells (Hwang and Lee, 2001 ; Choi et al., 2008).

Although the best-characterized aspects of guard cell response are electrophysiological, secondary messenger signaling and structural changes, ABA has also been shown to modify guard-cell specific gene expression. Recent transcriptome profiling studies have identified over 1000 ABA-regulated genes in guard cells, roughly 300 of which are uniquely ABA-regulated in guard cells (Wang et al., 2011, and references therein). The functional categories most enriched among ABA-induced genes were response to stress, lipid metabolic process, catalytic activity, vacuole and transcription factors. ABA-repressed genes were enriched for plastid, transferase activity, plasma membrane, nucleotide binding functions, and perhaps surprisingly, more stress response genes. Specific ABA-induced genes include those encoding ABA signaling proteins such as multiple members of the ABF transcription factor and group A PP2C families, whereas many of the ABA-repressed genes encoded ABA receptors or ion channels involved in stomatal opening.

Finally, attempts to reassemble the components described above into a coherent system model of guard cell signaling are described in (Li et al., 2006; Hills et al., 2012). These approaches differ in terms of their relative emphasis on signaling factors vs. transport and metabolism of osmolytes, as well as whether the modeling is Boolean or incorporates quantitative kinetics. The more recent modeling platform was used to analyze diurnal changes in various osmolytes and their effects on turgor and stomatal aperture (Chen et al., 2012) and to predict the effects of a SLAC mutation on fluxes through other ion channels (Wang et al., 2012). In both cases, the modeling both corroborated previous experimental data and provided evidence for unexpected new aspects of the network.

Pathogen response

In contrast to its generally protective role in abiotic stress, ABA may promote either susceptibility or resistance to pathogens, depending on the pathogens and their modes of infection (reviewed in Ton et al., 2009; Cao et al., 2011). For example, by promoting stomatal closure ABA blocks a major point of entry for many pathogens. ABA can also enhance resistance to fungal infection by promoting callose deposition in the apoplast that interferes with pathogen entry; both ABI1 and ABI4 promote this response. In contrast, ABA signaling via ABI2 inhibits callose deposition when infected with *P.syringae*. Interpretation of ABA effects is further complicated by cross-talk with other hormones regulating defense responses, e.g salicylic acid, jasmonic acid and ethylene, and the fact that increases in endogenous ABA generally reflect exposure to abiotic stresses, which can compromise plant vitality. In general, ABA promotes early defense responses such as stomatal closure, but is more likely to inhibit late defense responses by suppressing salicylic acid-dependent responses and modulating jasmonic acid- and ethylene-dependent defenses.

Despite the variability in ABA effects on response to different pathogens, some similarities in response to abiotic and biotic stress affecting stomata and callose deposition reflect similarities in underlying signaling mechanisms. For example, cellular redox homeostasis is important in regulating multiple stresses (reviewed in Munné-Bosch et al., 2013), and global comparisons of gene expression (transcriptomes) show that nearly half of the genes regulated by ABA are also regulated by type III virulence factors (de Torres-Zabala et al., 2007). Recent studies have shown that ABI4 integrates redox, sucrose, ABA, and JA signaling (Kerchev et al., 2011), and even promotes resistance to aphid feeding. However, the effects of ABA-deficient and *abi1-1* mutations on resistance to aphids are opposite to those of *abi4* (Kerchev et al., 2013), suggesting that some of the other signals mediated by ABI4 may have a greater effect than ABA on aphid resistance.

Flowering

A variety of ABA synthesis or response loci have been implicated in controlling meristem function or flowering time (reviewed in Rohde et al., 2000)). The *aba1* and *abi1-1* mutants exhibit early flowering under short days (Martinez-Zapater, 1994) and *abi3-4* mutants flower early regardless of daylength (Kurup et al., 2000), while the ABA hypersensitive mutant *hyl1* exhibits delayed flowering (Lu and Fedoroff, 2000), consistent with an inhibitory role of ABA in the floral transition. In contrast, a different class of ABA hypersensitive mutants, *abh1*, flower early due to altered RNA metabolism of flowering time regulators such as *CONSTANS (CO)* and *FLOWERING LOCUS C* (*FLC*) (Kuhn et al., 2007). Genetic interactions with *DET1* and *CONSTANS* , and physical interactions with TIMING OF CAB EXPRESSION (TOC1) and a CONSTANS-related factor suggest that ABI3 affects flowering through cross-talk with light and circadian rhythm controls (Kurup et al., 2000; Rohde et al., 2000). However, these interactions are complex in that the epistatic relationships vary depending on photoperiodic conditions.

Studies of the flowering promoting gene *LEAFY* showed that *LFY* expression is strongly induced by a combination of sucrose and GA, but that ABA fully blocks the GA-induced increase regardless of the GA_3 concentration (Blazquez et al., 1998). Although ABA did not completely eliminate *LFY* promoter activity, the ABA effect appeared “epistatic” to the GA effect. Recent studies of interactions between ABA, GA and BR effects on flowering indicate that the effects of ABA are relatively minor, potentially delaying flowering under unstressed conditions, but promoting it when stressed (Domagalska et al., 2010).

Senescence

The final stage of development for plant organs is senescence, resulting in catabolism of macromolecules and export of the released nutrients to sink tissues in other parts of the plant. Expression of ABA biosynthetic enzymes, and consequently ABA levels, increase during either aging- or stress-induced senescence (reviewed in Lim et al., 2007). Furthermore, exogenous ABA promotes senescence and expression of specific senescence-associated genes (SAGs). Recent studies addressing the mechanism of ABA effects on senescence have identified a receptor kinase, RPK1, that mediates age- and ABA-induced senescence, but only in old leaves (Lee et al., 2011). In addition, an ABA-inducible NAC family transcription factor (AtNAP) has been found to be necessary and sufficient for senescence (Guo and Gan, 2006). One of its direct targets is the *SAG113/HAI1* gene, which encodes a Golgi-localized PP2C that promotes ABA-resistant stomatal opening and water loss leading to dehydration during senescence (Zhang and Gan, 2012). The specific ABA receptor(s) and other upstream effectors leading to these responses are not yet known.

CONCLUSIONS AND PERSPECTIVES

Nearly 5000 studies referencing ABA and Arabidopsis have been published in the past decade, accounting for nearly 8% of all Arabidopsis publications and placing this topic on par with studies of auxin signaling. Major recent breakthroughs include identification of multiple receptor classes, transporters, metabolizing enzymes and numerous regulatory pathways.

Studies of the ABA biosynthesis and response mutants of Arabidopsis have complemented similar studies in other species. A combination of genetic, molecular and biochemical studies has identified enzymes responsible for the many steps of ABA metabolism. The genes or gene families encoding these enzymes have been identified and the roles of specific family members have been elucidated by expression analyses and reverse genetics. As for many other hormones, local ABA levels are controlled by a combination of synthesis, inactivation and transport; the relative contributions of these vary among tissues and developmental stages, and are also subject to environmental and circadian control.

In addition to elucidating pathways of ABA metabolism, mutants with altered ABA levels are useful for studying the role of ABA in physiological and developmental processes. Such studies have confirmed the role of endogenous ABA in dormancy induction, germination inhibition and stomatal regulation, but have also shown that many abiotic stress responses involve complementary or combinatorial responses to endogenous ABA, other hormones, and environmental cues.

Genetic and/or molecular studies have identified nearly 200 loci affecting ABA response, many of whose functions are conserved across species. Within Arabidopsis, ABA signaling is mediated by both redundant and independent mechanisms, some of which also affect response to other signals. In fact, double mutant analyses have revealed cryptic effects of a variety of loci, implicating interactions between ABA signaling and responses to most major classes of hormones, light, abiotic stresses, and nutrient status. Similar to signaling in response to other hormones, ABA response involves interactions between positive and negative regulators. An additional similarity is that some of the negative regulators were initially identified on the basis of reduced response due to dominant negative mutations.

We have learned much about ABA signaling, including the identities of multiple receptors, substrates of the various kinases and phosphatases, which of the known ABA response loci interact directly or indirectly, and the identities of additional signaling elements linking the known elements into complete pathways or networks. Remaining questions include the roles of individual family members in diverse ABA responses, a more complete understanding of the ABA-binding and signaling mechanisms for CHLH and GTG class receptors, and whether any additional receptors have not yet been identified. To fully understand how these pathways are integrated, a systems biology approach will likely be needed. However, practical applications are already possible, creating plants with conditionally altered hormone synthesis or response for improved stress tolerance and reduced crop losses due to preharvest sprouting.

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