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FOCUSED REVIEW

An emerging signaling hub: KAI2 at the nexus of phytohormone networks

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SUMMARY

The KARRIKIN INSENSITIVE 2 (KAI2) receptor, originally characterized for its role in seed germination and light-responsive development, is now recognized as an important signaling component with broad physiological relevance across plant species. While KAI2 is perhaps best known for perceiving exogenous smoked-derived karrikins, recent discoveries have revealed extensive crosstalk between KAI2-mediated signaling and multiple phytohormone pathways. We synthesize the current knowledge of KAI2 crosstalk with core plant hormones like strigolactones, auxin, ethylene, gibberellins, abscisic acid, cytokinins, and salicylic acid. We highlight shared signaling components, transcriptional regulation, and physiological outcomes. We examine how KAI2 signaling modulates hormone signaling and discuss the emerging view of KAI2 as an integrator of environmental and hormonal cues, particularly in stress adaptation and developmental plasticity. Finally, we propose new approaches, including proximity-labeling screens to dissect KAI2's full signaling potential and to explore open questions surrounding the identity and regulation of the endogenous putative KAI2 ligand. These insights position KAI2 as an evolving hub in the plant-signaling network, with implications for both fundamental research and crop improvement.

Keywords: abscisic acid (ABA), auxin, cytokinin, ethylene, gibberallin, hormone perception and signaling, KARRIKIN-INSENSITIVE2 (KAI2), phytohormone crosstalk, salicylic acid (SA), strigolactones (SLs).

BACKGROUND

KARRIKIN INSENSITIVE 2 (KAI2) is a plant α/β-hydrolase receptor first identified in *Arabidopsis thaliana* as HYPOSENSITIVE TO LIGHT (HTL) in a mutant screen (Sun & Ni, 2011). *htl* seedlings show smaller cotyledons, reduced anthocyanin accumulation, elongated hypocotyls, and longer petioles under light conditions. In parallel, KAI2 was shown to be required for the perception of karrikins (KARs), butenolide compounds found in wildfire smoke that promote seed germination (Nelson et al., 2009; Waters et al., 2012). Because KAI2 regulates developmental processes in non-fire-following species, and KARs are not endogenously produced, it is widely proposed that KAI2 perceives an unidentified endogenous ligand, termed KAI2-ligand (KL) (Khosla et al., 2020; Wang et al., 2020; Waters & Nelson, 2023).

KAI2 presumably acts as a dual enzyme-receptor that upon ligand binding and/or hydrolysis, interacts with the F-box protein MORE AXILLARY GROWTH 2 (MAX2 or DWARF3 in rice), a component of the ubiquitin E3 ligase complex SKP1-CULLIN1-F-box (SCF^{MAX2}) (Nelson et al., 2011; Tal et al., 2023). While the precise sequence of events and mode of interaction between MAX2 and KAI2 remains to be fully elucidated, this interaction ultimately leads to ubiquitin-mediated degradation of the downstream repressor proteins SUPPRESSOR OF MAX2 1 (SMAX1) and/or SMAX1-like 2 (SMXL2) (Bennett et al., 2016; Soundappan et al., 2015; Wang et al., 2015). SMAX1 and SMXL2 belong to a clade distantly related to the AAA+ ATPase caseinolytic protease B (ClpB) superfamily (Soundappan et al., 2015). The exact mechanism of transcriptional regulation remains to be resolved.

KAI2 is highly conserved across land plants, with evolutionary origins traced to streptophyte algae nearly 900 million years ago (Wang et al., 2022). It shares close sequence homology with the bacterial butenolide receptor, RsbQ, suggesting possible horizontal gene transfer (Melville et al., 2024; Wang et al., 2022). Nearly all land plants

retain a single copy of KAI2, but some plant lineages have experienced multiple *KAI2* gene duplication events (Bythell-Douglas et al., 2017). These homologs often diverge functionally, show differential tissue expression, and vary in ligand specificity (Carbonnel, Torabi, et al., 2020; Guercio et al., 2022; Stirling et al., 2024; Sun et al., 2020). For example, in pea (*Pisum sativum*), the more conserved *Ps*KAI2A has a selective binding pocket and can rescue Arabidopsis *kai2* phenotypes, whereas *Ps*KAI2B cannot (Guercio et al., 2022). Likewise, in *Lotus japonicus*, *Lj*KAI2a and *LjKAI2b* act redundantly in the root, but only *Lj*KAI2a regulates hypocotyl growth (Carbonnel, Torabi, et al., 2020). *Lj*KAI2a is highly responsive to the KAI2-specific synthetic ligand (−)-GR24, whereas *LjKAI2b* is not. Experiments in *Lotus japonicus*, pea, *Brassica tournefortii*, and rice reveal that just a few amino acid substitutions in the binding pocket can confer specificity to ligands across homologs (Carbonnel, Torabi, et al., 2020; Guercio et al., 2022, 2024; Sun et al., 2020). Notably, Stirling et al. (2024) identified the non-butenolide sesquiterpene (−)-germacrene D as an endogenous ligand for one of the three functional KAI2 homologs in *Petunia hybrida*, *Ph*KAI2ia, supporting diversification of ligand recognition.

KAI2 plays important roles in both plant development as well as stress responses across plant species. In addition to the mutant phenotypes described above, *kai2* and *max2* mutants tend to have deeper primary dormancy and germinate poorly compared to wild-type, even more so when osmotically stressed (Nelson et al., 2009; Wang et al., 2018). These mutants are hypersensitive to drought and temperature stress (Feng et al., 2022; Li et al., 2017, 2020). KAI2-mediated signaling contributes to nutrient-dependent root development and is required for arbuscular mycorrhizal fungal (AMF) colonization (Carbonnel, Das, et al., 2020; Das et al., 2025; Gutjahr et al., 2015; Meng et al., 2022; Song et al., 2016). Taken together, these findings underscore that KAI2 is a central regulatory node in plant development and stress resilience, likely achieved through extensive crosstalk with other phytohormone pathways.

KAI2 AND PHYTOHORMONE CROSSTALK

While KL remains a recalcitrant mystery, the past decade of research has placed KAI2 in the center of significant crosstalk between established hormone pathways. Genetic and physiological studies have revealed that KAI2-mediated signals intersect with those of strigolactones, auxin, ethylene, gibberellins, abscisic acid, cytokinin, and salicylic acid (Figure 1). Below, we review KAI2's multi-faceted interactions with major hormone pathways, highlighting key discoveries in various plant species. We will discuss future perspectives and promising technologies that can untangle the complex signaling networks underlying KAI2's role as a hormone regulatory hub.

Intersections of KAI2 and Strigolactone signaling

Strigolactones (SLs) are a class of carotenoid-derived hormones originally found to trigger AMF hyphae growth (Akiyama et al., 2005). SLs also regulate shoot branching, nutrient-mediated root architecture, and signaling for parasitic plant germination (Barbier et al., 2023; Nelson et al., 2011; Waters et al., 2017). Neofunctionalization of ancestral *KAI2* homologs in flowering plants resulted in the closely related α/β-hydrolase paralog, DWARF14 (D14), the enzyme-receptor for SLs (Bythell-Douglas et al., 2017). Given the evolutionary kinship between KAI2 and D14, it is not surprising that karrikin/KL and SL signaling intersect. Both receptors complex with SCF^{MAX2} after ligand perception and/or hydrolysis. As shown for D14 and MAX2/DWARF3, ligand-induced conformational changes are critical for their interaction, providing the necessary structural plasticity (Liu, Wang, et al., 2023; Shabek et al., 2018; Tal et al., 2023; Yao et al., 2016). The C-terminal region of SCF^{MAX2} plays a key role in regulating D14-SCF^{MAX2} complexing (Shabek et al., 2018; Tal et al., 2023) and SCF^{MAX2} phosphorylation by PHYTOCHROME-ASSOCIATED PROTEIN PHOSPHATASE 5 (PAPP5) may impact the interaction of the KAI2/D14-SCF^{MAX2} (Struk et al., 2021). D14 binding to SCF^{MAX2} recruits SL transcriptional repressors SMXL6/7/8, which like SMAX1/SMXL2, are targeted for ubiquitination and proteasomal degradation (Liu, Wang, et al., 2023; Shabek et al., 2018; Tal et al., 2023; Yao et al., 2016).

There is direct molecular overlap between the D14 and KAI2 signaling pathways. Striking recent evidence shows that the SL-signaling pathway can also target SMAX1 and SMXL2 for degradation under specific conditions (Li et al., 2022; Wang et al., 2020). In Arabidopsis, treating plants with the synthetic SL-specific analog (+)-GR24 leads to D14-dependent proteolysis of SMAX1, and osmotic stress triggers SMAX1 degradation via SL signaling (Li et al., 2022). It is notable that some KAI2 homologs like *Ps*KAI2B, but not *Ps*KAI2A, can weakly bind and hydrolyze D14 ligands (Guercio et al., 2022). A larger and more accessible hydrophobic pocket, similar to D14, gives *Ps*KAI2B the ability to hydrolyze the D14 ligand (+)-GR24 while the more constrained pocket of *Ps*KAI2A cannot (Guercio et al., 2022). Similarly, in the parasitic plant, *Phtheirospermum japonicum*, a divergent clade of KAI2 homologs can perceive D14 ligands and interact with SMAX1, highlighting that SL-signaling can activate KL-pathways in different species (Takei et al., 2024).

There is emerging evidence that KAI2 signaling can also regulate the biosynthesis of strigolactones in some flowering plants (Choi et al., 2020; Mashiguchi et al., 2023). For example, in mycorrhizal angiosperms like rice, the KAI2 paralog D14-like (*Os*D14L) is required for AMF colonization and does so by modulating SL production (Choi et al., 2020; Mashiguchi et al., 2023). Application of a

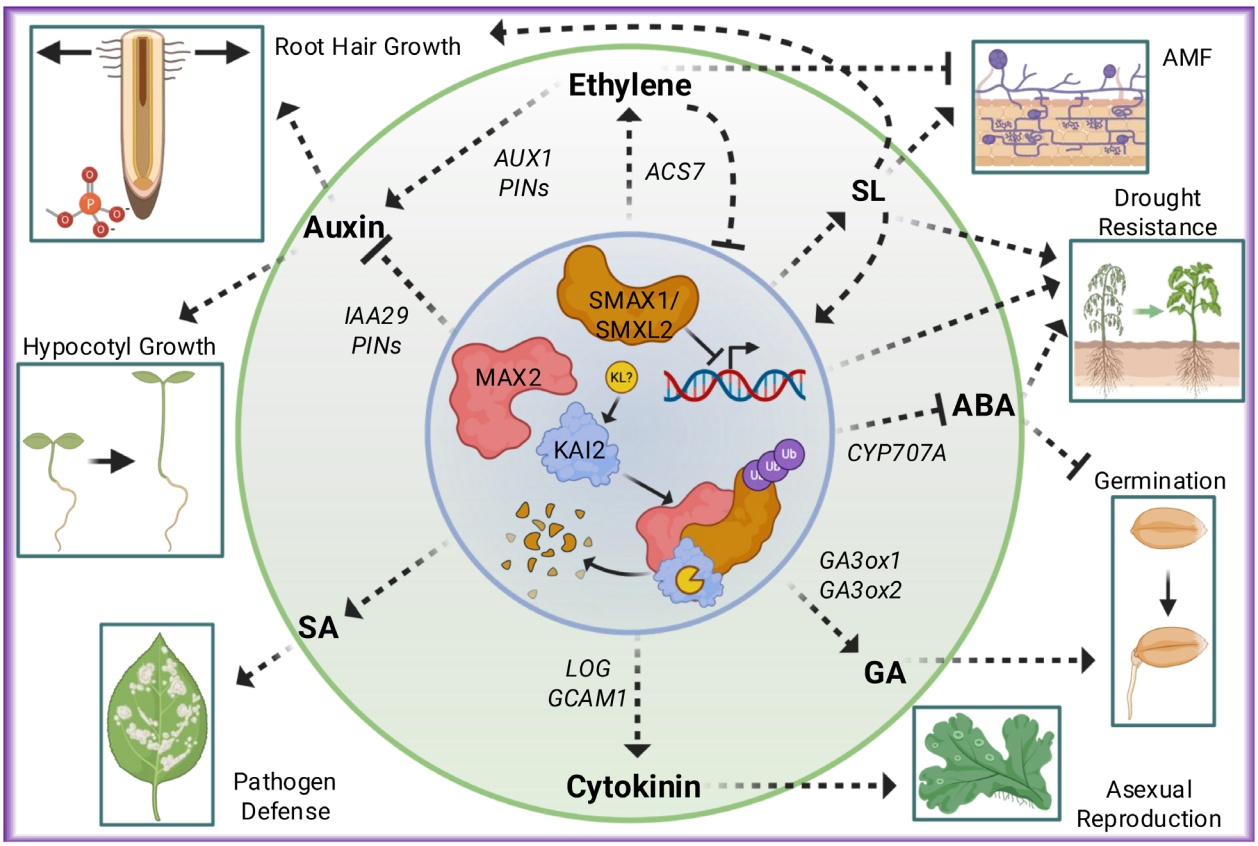

Figure 1. KAI2 as a hub in phytohormone crosstalk.
KAI2 signaling intersects with multiple phytohormone pathways to regulate a wide range of developmental processes and stress responses. The KAI2 signaling pathway is initiated by the perception of an unidentified endogenous ligand (KL, yellow circle). This leads to the presumable binding and/or hydrolysis of KL and the interaction of KAI2 with the F-box protein MAX2, which is part of the SCF E3 ubiquitin ligase complex. This complex targets the SMAX1 and SMXL2 transcriptional repressors for ubiquitination (Ub) and subsequent degradation by the 26S proteasome, activating a range of responses. These include crosstalk with auxin to control hypocotyl growth and root hair development through auxin transporters like AUX1 and PIN proteins or auxin signaling repressors like IAA29. KAI2 signaling causes an increase in ethylene biosynthesis through ACS7 to modulate root hair elongation and arbuscular mycorrhizal fungal (AMF) symbiosis. Interplay between strigolactones (SL) influences AMF symbiosis and drought resistance. KAI2 signaling activates abscisic acid (ABA) catabolic enzymes, CYP707As, stimulating germination, and in parallel KAI2-ABA signaling promotes drought resistance. In coordination with gibberellins (GA), SMAX1 degradation promotes germination through GA3ox1/2. KAI2 controls cytokinin biosynthesis through LOG and GCAM1 and asexual reproduction in bryophytes. and salicylic acid (SA) to bolster pathogen defense. Dashed lines with arrows indicate positive regulation, while lines with blunt ends indicate negative regulation. Figure created using Biorender.com.

specific *Os*D14L-activating synthetic ligand (−)-GR24 was found to significantly boost SL levels in rice roots, an effect absent in *Osd14l* mutant plants (Mashiguchi et al., 2023). SL biosynthetic gene expression and SL content were also elevated by KAI2 activation in other mycorrhizal species like tomato and *Lotus japonicus*, but notably not in non-mycorrhizal Arabidopsis nor in the bryophyte *Marchantia paleacea* (Mashiguchi et al., 2023). Further studies await understanding the intersection of KL/SL signaling pathways that have evolved in mycorrhizal and non-mycorrhizal angiosperms.

Crosstalk between KAI2 and strigolactone pathways positively contributes to Arabidopsis stress resilience. *max2* mutants, deficient in both KL and SL signaling, are highly sensitive to osmotic stress and display thinner cuticles and increased water loss (Bu et al., 2014; Ha et al., 2014). Both *kai2* and *d14* single mutants show impaired drought survival with thinner cuticles as well (Bu et al., 2014; Daszkowska-Golec et al., 2023; Li et al., 2017). *kai2 d14* double mutants display an increased drought sensitivity as compared to single mutants (Li et al., 2020). Transcriptomic comparisons of *kai2* and *d14* mutants under dehydration showed that KAI2 and D14 signaling pathways jointly affected traits like stress-induced glucosinolate production and trehalose metabolism (Li et al., 2020). Mechanistically, both KL/SL signaling increases drought resilience by promoting stomatal closure, enhancing protective metabolites like anthocyanins, and strengthening cell membranes and cuticles (Bu et al., 2014; Daszkowska-Golec et al., 2023; Li et al., 2017, 2020). It

remains unclear if SL or KL is more dominant or upstream in certain drought-response mechanisms. Given the complex interplay, further studies await to dissect the signaling between SL and KAI2 pathways.

KAI2 and auxin Co-regulate plant development

Auxin is a central growth hormone responsible for many plant developmental processes. In particular, auxin is important for both shade avoidance response and thermomorphogenesis, whereby plants typically increase hypocotyl and petiole elongation (Zhao, 2018). Simplified, under normal light conditions, the photoreceptor phytochrome B (phyB) remains in its active form and binds to PHYTOCHROME-INTERACTING FACTOR 4 and 5 (PIF4/5), leading to PIF4/5's degradation (Huq & Quail, 2002; Zhao, 2018). In shade conditions or at high temperatures, phyB becomes inactive, which allows PIF4/5 to accumulate. PIF4/5 then directly activates the transcription of auxin biosynthetic genes, such as *YUCCA8* (*YUC8*), resulting in elevated local auxin production (Sun et al., 2012; Zhao, 2018). This increase in auxin subsequently promotes the elongation of the hypocotyl, resembling *kai2* mutant phenotypes in Arabidopsis or in rice, where knockout of *OsD14L* affects mesocotyl elongation (Choi et al., 2020; Waters et al., 2012; Zheng et al., 2020).

Indeed, *kai2* mutant seedlings have abnormally high auxin levels in the hypocotyl as detected by both fluorescent reporters in planta and mass spectrometry metabolites quantification of seedlings (Hamon-Josse et al., 2022; Xu et al., 2022). *kai2* seedlings treated with auxin biosynthesis or transport inhibitors show partial rescue of the long-hypocotyl phenotype (Hamon-Josse et al., 2022; Xu et al., 2022). Microsurgical decapitation of *kai2* mutant shoot apices restores wild-type hypocotyl phenotypes (Hamon-Josse et al., 2022). These results imply an ectopic accumulation of root-bound auxin through misregulation of auxin efflux carrier PIN-FORMED (PIN) proteins in *kai2* mutants. PIN3 and PIN7 were found to be over accumulated in *kai2* hypocotyls, while PIN1 and PIN2 appear depleted in roots (Hamon-Josse et al., 2022; Villaécija-Aguilar et al., 2022; Xu et al., 2022). Significantly, SL signaling impacts the trafficking and endocytosis of PIN proteins, and karrikins appear to have similar effects on both PIN1 and PIN2 (Zhang et al., 2020) Recent data from Chang et al. (2024) hints at a mechanism of KAI2-auxin crosstalk. They found SMAX1/SMXL2 accumulation stabilizes PIF4/5 by directly interacting with phyB, preventing degradation. PIF4/5 accumulation transcriptionally activates the auxin repressor *INDOLE-3-ACETIC ACID INDUCIBLE 29* (*IAA29*), which, in coordination with SMAX1/SMXL2-dependent expression of *YUC8* results in increased hypocotyl length (Chang et al., 2024).

Loss of KAI2 signaling does not cause increased branching as compared to *d14* mutants, but Arabidopsis *kai2* mutants develop other auxin-dependent phenotypes like flatter rosettes and elongated petioles (Waters et al., 2012). In the monocot *Brachypodium distachyon*, internode length is dependent on *KAI2*, but contrary to Arabidopsis *kai2*, *Bdkai2* mutants show curly leaves (Meng et al., 2022). Additional research is needed for more insight into how KAI2-dependent auxin signaling is regulated in leaf tissues in mature plants.

KAI2-auxin-ethylene signaling crosstalk

Ethylene, a gaseous phytohormone, often acts in concert with auxin to regulate processes like fruit ripening, senescence, skotomorphogenesis, and nutrient growth responses in roots (Bakshi et al., 2015). Under inorganic phosphate (Pi) starvation, plants attempt to increase accessible soil contact by elongating root hairs through a complex KAI2-ethylene-auxin signaling module. In Arabidopsis, low Pi conditions activate KAI2 signaling, as evidenced by transcriptional upregulation of *KAI2* and *MAX2* (Villaécija-Aguilar et al., 2022). KAI2-mediated degradation of SMAX1/SMXL2 transcriptional repressors then in turn promotes expression of the ethylene biosynthesis gene *1-AMINOCYCLOPROPANE-1-CARBOXYLATE synthase 7* (*ACS7*) (Carbonnel, Das, et al., 2020; Villaécija-Aguilar et al., 2022). The resulting rise in ethylene causes the auxin influx carrier, AUXIN TRANSPORTER PROTEIN 1 (AUX1), to accumulate in lateral root cap and epidermal cells. Concurrently, ethylene-induced auxin efflux PIN2 proteins localize to the meristematic zone, and in conjunction with AUX1 drive a shootward transport of auxin promoting root hair growth (Bhosale et al., 2018; Negi et al., 2008; Song et al., 2016; Villaécija-Aguilar et al., 2022). Limited auxin flow in *kai2* mutants means root hair growth is impaired, in contrast to longer root hairs in *smax1 smxl2* mutants. Auxin supplement rescues *kai2* root hair phenotypes, *aux1 smax1 smxl2* triple mutants have short root hairs indicating AUX1 epistasis, and ethylene precursors or inhibitors can rescue the hair phenotypes of *kai2* or *smax1 smxl2*, respectively (Villaécija-Aguilar et al., 2022). These data taken together support the idea that KAI2's main role is upstream of ethylene and auxin transport pathways in nutrient-mediated root architecture. This KAI2-ethylene-auxin module for root hair growth appears conserved in other species; a similar mechanism was observed in *L. japonicus* roots responding to low nutrients (Carbonnel, Das, et al., 2020).

Ethylene plays a key regulatory role in hypocotyl growth (Krahmer & Fankhauser, 2024). Under dark conditions, ethylene inhibits etiolation, but in light conditions, it promotes etiolation, presumably through a PIF-dependent process (Krahmer & Fankhauser, 2024; Zhang et al., 2018). Despite the impact, KAI2-mediated signaling has on hypocotyl phenotypes and convergence on PIFs to regulate downstream auxin, to our knowledge there are no reports

coupling ethylene and KAI2 crosstalk in the aerial portion of seedlings or leaves.

Ethylene and KAI2-mediated signaling intersect to regulate AMF symbiosis. Ethylene has long been known to negatively regulate AMF colonization in roots (Mukherjee & Ané, 2011). As discussed, AMF colonization in rice requires *Os*D14L and is negatively regulated by SMAX1. Degradation of SMAX1 results in increased SL biosynthesis and promotion of AMF colonization (Choi et al., 2020; Das et al., 2025). A new study showed that ethylene strongly promotes SMAX1 accumulation, which then inhibits AMF symbiosis in *L. japonicus* (Das et al., 2025). Mutations in *ETHYLENE INSENSITIVE PROTEIN 2* (*EIN2*), a core ethylene-signaling component, allow greater mycorrhization, and correlate with lower SMAX1 levels. These findings point to a complex feedback mechanism in which ethylene can antagonize KAI2/KL signaling under certain conditions, while at the same time KAI2/KL signaling also regulates ethylene biosynthesis.

KAI2 and gibberellins control germination in tandem

Gibberellins (GAs) are another group of hormones that play central roles particularly in seed germination, seedling development, cell division and elongation (Yamaguchi, 2008). Early studies revealed a dependency on GA biosynthesis for KARs' promotive effect on germination. Specifically, Nelson et al. (2009) found that Arabidopsis seeds mutant for GA biosynthesis, *ga1*, did not germinate in response to KAR treatment, even though the downstream transcriptional responses to karrikin were largely activated. KAR treatment of seeds dramatically induced expression of GA biosynthesis genes of *Gibberellin 3-beta-dioxygenase* (*GA3ox*) *1* and *2* (Nelson et al., 2009). When soybeans are treated with paclobutrazol (PAC), a GA biosynthesis inhibitor, KARs' germination-promoting effects are abolished, indicating GAs are necessary for KAI2-mediated germination (Meng et al., 2016). However, more recent studies have nuanced this relationship and shown that KAI2-mediated signaling can partly bypass the need for GA under certain conditions. A *Striga hermonthica* SL-insensitive KAI2 paralog (*ShHTL7*) heterologously expressed in Arabidopsis can circumvent GA-dependent germination when supplied with the synthetic racemic ligand *rac*GR24 (Bunsick et al., 2020). Arabidopsis *smax1* mutants show resistance to PAC and germinate at high rates, but high PAC concentrations still moderately suppress the hyper-germination phenotype of *smax1 smxl2* double mutants (Bunsick et al., 2020; Xu et al., 2023). *smax1* mutants have remarkably high levels of GA, likely due to constitutive high expression of *GAox1/2* (Xu et al., 2023). In further evidence of crosstalk, SMAX1 can interact with DELLA proteins, GA signaling repressors, to inhibit germination and growth (Xu et al., 2023). This interaction suggests a model where KAI2 and GA signaling pathways both cooperatively alleviate different brakes on growth, while enabling SMAX1 dependent crosstalk.

Complex interplay between KAI2 and abscisic acid regulates osmotic stress response

Whereas GA promotes germination, abscisic acid (ABA) is a key hormone that generally antagonizes germination and promotes stress tolerance, especially in drought and cold responses (van Zelm et al., 2020). There are differing reports of whether *kai2* mutants display hyper- or hyposensitivity to ABA's effects on seed germination. For example, Shah et al. (2021) found *kai2* mutants were hypersensitive to the germination inhibition effects of ABA, and Li et al. (2017) showed ABA inhibition of cotyledon opening was significantly impaired in *kai2* mutants. On the contrary, Wang et al. (2018) showed that *kai2* seeds were much more sensitive to ABA germination inhibition in both Col-0 and Ler Arabidopsis ecotypes. RT-qPCR experiments show that KAR-treated seeds induce transcription of ABA catabolic enzymes, like CYP707A, which is thought to promote release of ABA-mediated dormancy (Brun et al., 2019). Generally, *kai2* mutants do not germinate well under osmotic stress (Lee et al., 2018; Wang et al., 2018). KAR treatment alone stimulates seed germination, but when co-applied with osmotic stress, KARs act to strongly inhibit germination independently of ABA (Wang et al., 2018). Notably, KARs alone do not activate the ABA-signaling pathway but amplify the plant's ABA-dependent downstream response to abiotic stress (Shah et al., 2020).

Apart from germination, *kai2* mutant plants show clear evidence for ABA-hyposensitivity: thinner cuticles, lower anthocyanin accumulation, and failure to close stomata efficiently under drought. (Li et al., 2017). Evidence of *kai2* mutants containing increased intracellular ABA concentration strongly suggests a signaling cross-regulation between KAI2 and ABA levels (Li et al., 2017). Gene expression in *kai2* drought- or salt-stressed plants also indicated a weakened activation of ABA-dependent protective genes (Li et al., 2017, 2020). Meanwhile, *smax1* mutants show enhanced drought tolerance and ABA hypersensitivity phenotypes (Feng et al., 2022). Consistent with KAI2 activation, transgenic Arabidopsis plants overexpressing Chinese tallow tree (*Sapium sebiferum*) *SsKAI2* show hypersensitivity to ABA (Shah et al., 2021). *SsKAI2* overexpression did not significantly change ABA levels but had increased induction of ABA-regulated transcription factors and late response genes (Shah et al., 2021). *SsKAI2* overexpression in Arabidopsis improved cold acclimation in part by amplifying higher levels of ABA-inducible osmoprotectants such as proline and soluble sugars (Shah et al., 2021). Both *smax1* mutants and *KAI2* overexpression result in increased antioxidative capacity and osmoprotection during stress (Feng et al., 2022; Shah et al., 2021).

KAI2 and cytokinin represent an ancestral signaling network

Cytokinins are hormones that typically promote cell division and differentiation, and they play major roles in shoot meristem activity, leaf longevity, and certain developmental switches (Hwang et al., 2012). Intriguingly, recent research has uncovered a direct link between KAI2 signaling and cytokinin biosynthesis in the liverwort *Marchantia polymorpha* (Komatsu et al., 2023, 2025). Liverworts reproduce asexually by producing clonal propagules (gemmae) in specialized structures called gemma cups. Komatsu et al. (2025) showed that when the *Marchantia* KAI2 pathway is activated, one of its downstream effects is the upregulation of a gene called *MpLOG* (*LONELY GUY*). *MpLOG* encodes an enzyme directly involved in cytokinin biosynthesis by converting inactive cytokinin nucleotides into active cytokinin free bases. In either *Mpkai2a* or *Mpmax2* loss-of-function mutants, the expression of *MpLOG* is low, and cytokinin levels in gemma cups are reduced, leading to defects in gemma cup development (Komatsu et al., 2025). Strikingly, *Mplog* knockout mutants phenocopy the KAI2 pathway mutants resulting in compromised gemma cup formation. Moreover, supplying exogenous cytokinin to the *Mpkai2* or *Mplog* mutants can rescue their gemma cup defects, restoring normal asexual reproduction structures (Komatsu et al., 2025). This rescue experiment confirms that cytokinin acts downstream of KAI2 in this developmental context. The study further pinpointed that KAI2 signaling activates *Mp*LOG locally in specific cell types of the gemma cup, and this cell-specific cytokinin production then induces a master regulatory gene called *GCAM1* (*GEMMA CUP-ASSOCIATED MYB 1*) that triggers the formation of gemmae (Komatsu et al., 2023, 2025).

This finding from *Marchantia* provides evolutionary insight suggesting that KL signaling might have coordinated with cytokinin to regulate growth in early land plants (Bythell-Douglas et al., 2017; Komatsu et al., 2025). Outside of *Marchantia*, it would appear that neofunctionalization of KAI2 to D14 has resulted in a shift to strigolactone–cytokinin interaction in angiosperms. Mutation of D14 (but not KAI2) specifically affects cytokinin metabolism gene expression under stress and SL application rapidly upregulates cytokinin catabolic enzymes (Duan et al., 2019; Li et al., 2020). It remains to be seen if KAI2 affects cytokinin levels or signaling in flowering plants during any stage.

KAI2 signaling impacts salicylic acid pathways

Beyond growth and stress hormones, KAI2 signaling has recently been implicated in plant immune responses, particularly those mediated by salicylic acid (SA). Salicylic acid is a key hormone for defense against biotrophic pathogens, orchestrating systemic acquired resistance and local defense gene activation (Peng et al., 2021). *max2* mutants are more susceptible to pathogens like *Pseudomonas syringae*, suggesting these pathways might normally bolster immunity (Zheng et al., 2023). Further dissection revealed that *kai2* mutants had significantly reduced resistance to *P. syringae*, whereas *d14* mutants were as resistant as wild-type (Zheng et al., 2023). This indicates that the KAI2 pathway—not the SL/D14 pathway—impacts SA-mediated immune responses.

Mechanistically, Zheng et al. (2023) provided insight into how KAI2 signaling interfaces with SA signaling. A key finding was that treating plants with KAR enhanced resistance to *P. syringae* in an SA-dependent manner. The authors also observed that in *kai2* or *max2* mutants, the normal SA-triggered defense responses were delayed or weaker and had blunted defense gene expression. Consistently, Zheng et al. showed evidence that *smax1* mutants have elevated resistance, and complementation with a non-degradable SMAX1 made plants more susceptible. Moreover, the triple mutant for *smxl6,7,8* (of the SL pathway) rescued the low immunity of *max2* plants. It is likely that through cross-transcriptional regulation, SMAX1 works together with the SMXL6/7/8 repressors to inhibit SA-mediated defenses, placing KAI2 signaling upstream or at least in parallel with SA signaling. It will be interesting in the future to determine what triggers KL production during biotic stress and whether there is any feedback between SA and KL biosynthesis.

FUTURE PERSPECTIVES AND OPEN QUESTIONS

KAI2 is a versatile signaling hub that interfaces with numerous hormonal pathways, yet many fundamental questions remain. Foremost is the identity of the elusive KL(s). Is it a single compound or a family of related molecules? KL is hypothesized to be a butenolide-type molecule, as evidenced by numerous synthetic butenolide ligands showing strong KAI2 binding and bioactivity (Kushihara et al., 2025; Okabe et al., 2023; Yao et al., 2018; Yao et al., 2021). The existence of diversified KAI2 paralogs hints that a range of KLs or KAR-like signals might exist and may contribute to the specialization of receptors. Intriguingly, some studies hint that KL might also be produced by soil microorganisms or symbionts in certain contexts (Gutjahr et al., 2015). Unraveling KL's identity is a high priority as it would not only solve a decade-old mystery but also enable direct interrogation of KAI2's roles (Boxes 1 and 2).

From a physiological perspective, several key questions remain unresolved. How is KL production regulated by environmental cues? While it is established that KAR derived from fire can activate KAI2, it is unclear whether plants enhance KL synthesis under specific stresses such as drought, altered light quality, or pathogen attack. Given KAI2's documented roles in drought tolerance and

Box 1. Main points

- The KAI2 receptor perceives an unidentified endogenous ligand (KL) to regulate plant development and stress responses by targeting SMAX1/SMXL2 repressors for degradation via the F-box protein MAX2.
- KAI2 controls a wide range of physio-developmental processes in plants through crosstalk with other phytohormones.
- New technologies such as proximity labeling hold the promise of elucidating the highly dynamic and complex interactions between KAI2 signaling components.

Box 2. Open questions

- What is the chemical identity of the primary endogenous KAI2 ligand or family of ligands in plants?
- How do environmental cues such as drought, nutrient levels, light, or pathogen attack regulate the biosynthesis and transport of KL?
- What are transcriptional and post-translational mechanisms responsible for the distinct functions of the multiple, diversified KAI2 paralogs found in many plant species?
- What are the molecular mechanisms by which SMAX1 and SMXL2 repressors integrate signals from the KAI2 pathway with other hormonal cues?

immunity, it is plausible that KL levels or signaling increase during water deficit or pathogen challenge to trigger these responses. Equally important is to decode the tissue-specific sites of KL production and transport—whether KL is synthesized predominantly in seeds, restricted to roots, or broadly distributed across tissues. Finally, the regulatory landscape beyond KL biosynthesis remains largely unknown: what post-translational mechanisms fine-tune KAI2 signaling, and how is KL catabolism itself controlled?

To crack the KL puzzle and further map KAI2's interaction networks, new tools and approaches will be essential (Figure 2). Chemical biology screens using small-molecule libraries have been used successfully to identify receptor targets and inhibitors (Herrmann et al., 2025; Lee et al., 2024; Liu, Li, et al., 2023). A small-molecule screen could survey a large selection of synthetic and natural molecules that may bind KAI2 or trigger the KAI2–MAX2–SMAX1/SMXL2 pathway in bioassays leveraging tools such as fluorescent or luminescent reporters in planta. Synthetic biology approaches using engineered heterologous expression circuits and cell-free reconstituted systems could also be used as discovery platforms. Using recombinantly expressed KAI2 in biochemical assays like differential scanning fluorimetry or high-throughput isothermal titration calorimetry could yield direct insights (Figure 2a). Expanding such screens with diverse plant extracts to include native metabolites might serendipitously hit upon the natural KL(s).

Another promising strategy is proximity-labeling proteomics. Proximity labeling (PL) leverages highly active ligating enzymes fused to bait proteins that when supplied with small-molecule tags, label nearby interacting proteins. Recent advances in PL technology have developed TurboID using a bacterial biotin ligase that can capture transient and dynamic protein interactions. TurboID rapidly labels after biotin application in a 10–20 nm radius, ensuring tight spatiotemporal control over TurboID labeling (Cho et al., 2020). TurboID has been successfully implemented in plants to study immune receptor interactions (Li et al., 2023; Zhang et al., 2024), hormone signaling pathways (Chien et al., 2024; Kim et al., 2023), leaf development (Mair et al., 2019), and the ubiquitin proteasome system (Sun et al., 2024). While other PL techniques exist, for example, peroxidase or pupylation-based PL, TurboID has repeatedly been successfully used in plants.

KAI2 or other KL-signaling components (e.g., SMAX1) fused to TurboID could identify transient KAI2 interactors or larger signaling complexes (Figure 2b). This could potentially uncover enzymes involved in KL biosynthesis or KL/KAI2 catabolism that physically associate with KAI2-signaling machinery whereby a candidate KL-regulating enzyme dynamically colocalizing with KAI2 might be biotinylated in a KAI2 PL experiment. Similarly, PL could reveal if KAI2 participates in larger protein assemblies outside of the canonical SCF^{MAX2} complex. These experiments could also discover new hormone pathways or small-molecule crosstalk. Split-TurboID uses two halves of TurboID fused to two known interacting proteins that reconstitute into a functional biotinylase, limiting non-specific and complex assembly dependent labeling (Cho et al., 2020; Zhang et al., 2024). Known KAI2/KL-pathway downstream components like KAI2 and MAX2 or SMAX1 could be fused to Split-TurboID to reveal interactions that could disentangle the complex KAI2/KL-signaling crosstalk (Figure 2c,d).

Leveraging the structural biology of KAI2 in complex with ligands could yield deeper insight into KL recognition and binding (Guercio et al., 2022, 2024; Kushihara et al., 2025). Crystal structures of ShKAI2iB have shown how karrikins bind in the pocket (Xu et al., 2016). More recently, Kushihara et al. (2025) revealed a crystal structure of KAI2 with a non-hydrolyzable ligand in the active site, but they were unable to activate KAI2 to study ligand-

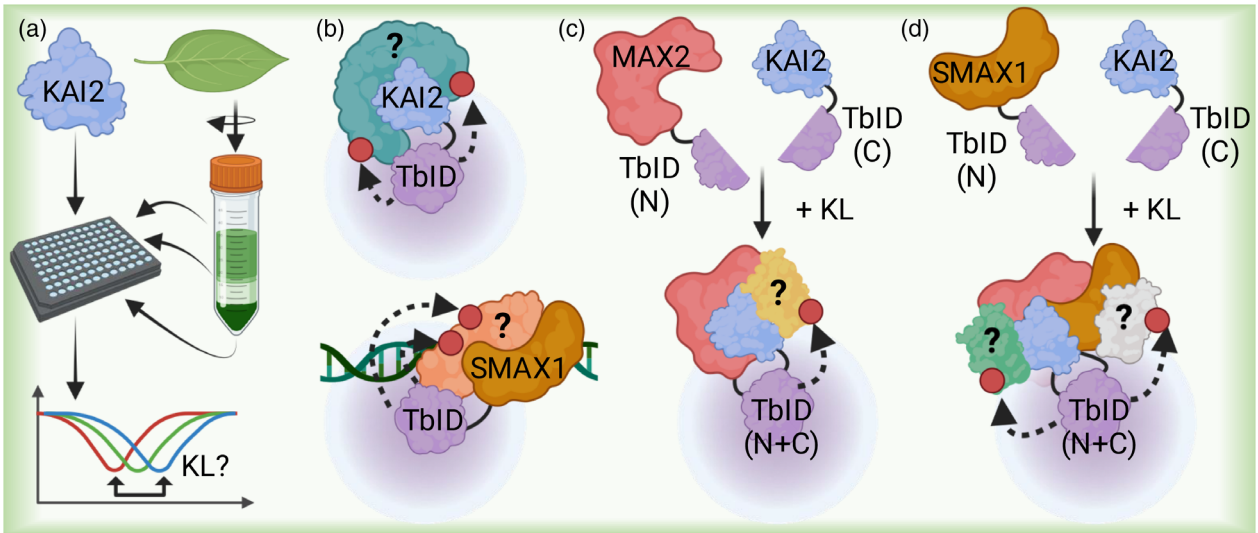

Figure 2. Proposed strategies for uncovering the KAI2 signaling network.
(a) A schematic representation of a potential biochemical approach using high-throughput screening of plant extracts or chemical libraries with recombinant KAI2 protein.
(b) Proximity labeling using TurboID (TbID) fused to KAI2 or SMAX1 can identify dynamic, transient, or low-abundance interacting proteins in vivo by tagging proteins with biotin (small red circle). These unknown interactors ('?') could include proteins involved in KL biosynthesis, KL transport, or novel signaling components.
(c, d) Split-TurboID experiments can map ligand-dependent protein complexes with high specificity. The N-terminal (N-TbID) and C-terminal (C-TbID) halves of TurboID are fused to known interacting partners. Functional TurboID is reconstituted only upon complex formation, which can be triggered by the presence of KL. (c) Split-TurboID fused to KAI2 and MAX2 could identify proteins that regulate or are regulated by the receptor-F-box complex. (d) Split-TurboID fused to KAI2 and SMAX1 could reveal proteins interacting specifically with the receptor-repressor complex. Figure created using Biorender.com.

induced conformational changes. Solving KAI2 structures with a potential intermediate derivative tethered could reveal the chemistry of ligand hydrolysis and help infer a potential KL. A KAI2ia crystal structure with bound (−)-germacrene D or germancrene-derived ligand would be immensely helpful to further understand how KAI2 binds to different classes of KL-like molecules.

In conclusion, the past decade has vastly expanded our understanding of KAI2: from a curious 'smoke sensor' to a broad-spectrum regulator interfacing with many hormone pathways. KAI2-mediated signaling intersects with auxin transport to shape development, with ethylene to adapt to nutrients and AMF, with GA to control germination, with ABA to mitigate environmental stress, with cytokinins to drive organogenesis in bryophytic plants, and with SA to fend off pathogens. This breadth underscores the hypothesis that KAI2's unknown ligand could be an important growth regulator in plants. Solving the mystery of KL and decoding how KAI2 integrates these signals will not only fill a gap in fundamental plant biology but also potentially unlock new strategies for crop improvement under the increasingly challenging growing conditions worldwide. As we deploy innovative tools like proximity labeling, advanced metabolomics, and synthetic biology, we move ever closer to elucidating the full scope of KAI2's role as a hub of hormonal crosstalk in plants.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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