



Molecular basis of strigolactone perception in root-parasitic plants: aiming to control its germination with strigolactone agonists/antagonists

Takuya Miyakawa¹ · Yuqun Xu¹ · Masaru Tanokura¹

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Abstract

The genus *Striga*, also called “witchweed”, is a member of the family Orobanchaceae, which is a major family of root-parasitic plants. *Striga* can lead to the formation of seed stocks in the soil and to explosive expansion with enormous seed production and stability once the crops they parasitize are cultivated. Understanding the molecular mechanism underlying the communication between *Striga* and their host plants through natural seed germination stimulants, “strigolactones (SLs)”, is required to develop the technology for *Striga* control. This review outlines recent findings on the SL perception mechanism, which have been accumulated in *Striga hermonthica* by the similarity of the protein components that regulate SL signaling in nonparasitic model plants, including *Arabidopsis* and rice. HTL/KAI2 homologs were identified as SL receptors in the process of *Striga* seed germination. Recently, this molecular basis has further promoted the development of various types of SL agonists/antagonists as seed germination stimulants or inhibitors. Such chemical compounds are also useful to elucidate the dynamic behavior of SL receptors and the regulation of SL signaling.

Keywords Hydrolase · Karrikin · Parasitic weed · Phytohormone · Shoot branching · Strigolactone analogs · Strigolactone mimics · Ubiquitin–proteasome system

Abbreviations

2-MN	2-Methoxy-1-naphthaldehyde	KAR	Karrikin
5-DS	5-Deoxystrigol	LGS1	LOW GERMINATION STIMULANT 1
ASK1	ARABIDOPSIS SKP-LIKE 1	LRR	Leucine-rich repeat
ATPase	Adenosine triphosphatase	MAX2	MORE AXILLARY GROWTH2
CL	Carlactone	MP	Methyl phenlactonoate
CLA	Carlactonoate	Nij-1	Nijmegen-1
CLIM	Covalently linked intermediate molecule	SCF	SKP1-Cullin-F-box
D14	DWARF14	SL	Strigolactone
DSF	Differential scanning fluorimetry	SLR1	SLENDER RICE1
EAR	Element binding factor-associated amphiphilic repression	SMAX1	SUPPRESSOR OF MAX2 1
GA	Gibberellin	SMXL	SMAX1-Like
HTL	HYPOSENSITIVE TO LIGHT	SOP	Soporidine
ITC	Isothermal titration calorimetry	SPL7	Sphynolactone-7
KAI2	KARRIKIN INSENSITIVE2	TPR	TOPLESS-related protein
		YLG	Yoshimulactone Green
		YLGW	YLG double

✉ Masaru Tanokura
amtanok@mail.ecc.u-tokyo.ac.jp

¹ Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

Introduction

Orobanchaceae is a major family of root-parasitic plants and is divided into 90 genera (one genus is not parasitic) that are composed of more than 2000 species [1]. Each genus

is widely distributed around the world with different host preferences and dependencies. Obligate parasites require parasitism to their host plants for survival, because they lack photosynthesis and/or other physiological functions. In contrast, facultative parasites can grow on their own, whereas they parasitize if host plants are located near them.

The genus *Striga*, also called “witchweed”, is a highly threatening obligate parasite of the family Orobanchaceae; its habitat has expanded over 40 countries in Africa, and some species have reached India and Pakistan beyond the Arabian Peninsula [2, 3]. *Striga* parasitizes major crops, including maize, millet, sorghum, and rice, as host plants, causing a 30–90% reduction in agricultural production [2, 4]. The crop damage caused by *Striga* is estimated to be 111–200 million dollars in rice alone [5] and adversely affect at least 100 million people in sub-Saharan Africa [4]. *Striga* produces over 50,000 very-tiny seeds (approx. 0.2–0.5 mm) [6]. In addition, *Striga* seeds remain viable and dormant in the soil for over 14 years until they perceive germination signals from their host plants [7]. Because of these features, *Striga* can lead to the formation of seed stocks in the soil and to explosive expansion once their crop hosts are cultivated.

The molecular mechanism underlying the interaction between *Striga* and their host plants is required to develop the technology for *Striga* control. Three common strategies have been presented thus far: (1) utilizing host-acquired resistance; (2) suppressing the germination of *Striga* seeds; and (3) depleting the seed stocks in the soil. Based on the host preferences, various crops were screened and analyzed for resistance to *Striga* parasitism. For example, a rice cultivar (Nipponbare) exerts a potent post attachment resistance to *Striga hermonthica* [8]. The parasite penetrates the root cortex but cannot form a connection with the host xylem. Some other hosts induce a hypersensitive reaction at the site of infection to prevent *Striga* parasitism [9]. Regarding the ability to evade the *Striga* germination, some crops secrete modified germination signals that are not capable of inducing effective germination. LOW GERMINATION STIMULANT 1 (LGS1) was identified as a causative gene in sorghum [10]. After germination, the *Striga* radicle invades a host root in close proximity (2–3 mm). In addition, the size of the endosperm is insufficiently large to maintain radicle growth for more than 7 days [6]. Based on the ecological features of *Striga* seeds, “suicidal germination stimulants” have been proposed to eliminate the *Striga* seeds [11]. In the suicidal germination stimulant method, synthetic germination stimulants are applied to the soil before sowing the host crops to induce the germination of *Striga* seeds. Because *Striga* are obligate parasites, they are not capable of surviving without hosts, and thus, the seed stocks could be depleted.

“Strigolactones (SLs)” and their molecular bases in *Striga* germination have been discovered in this past decade and lead to the chemical regulation of the obligate parasite,

which are highlighted from various viewpoints in the recent review articles [12–18]. Here, we outline recent findings on the SL perception mechanism in *Striga* germination and the chemical compounds developed based on the action of SLs.

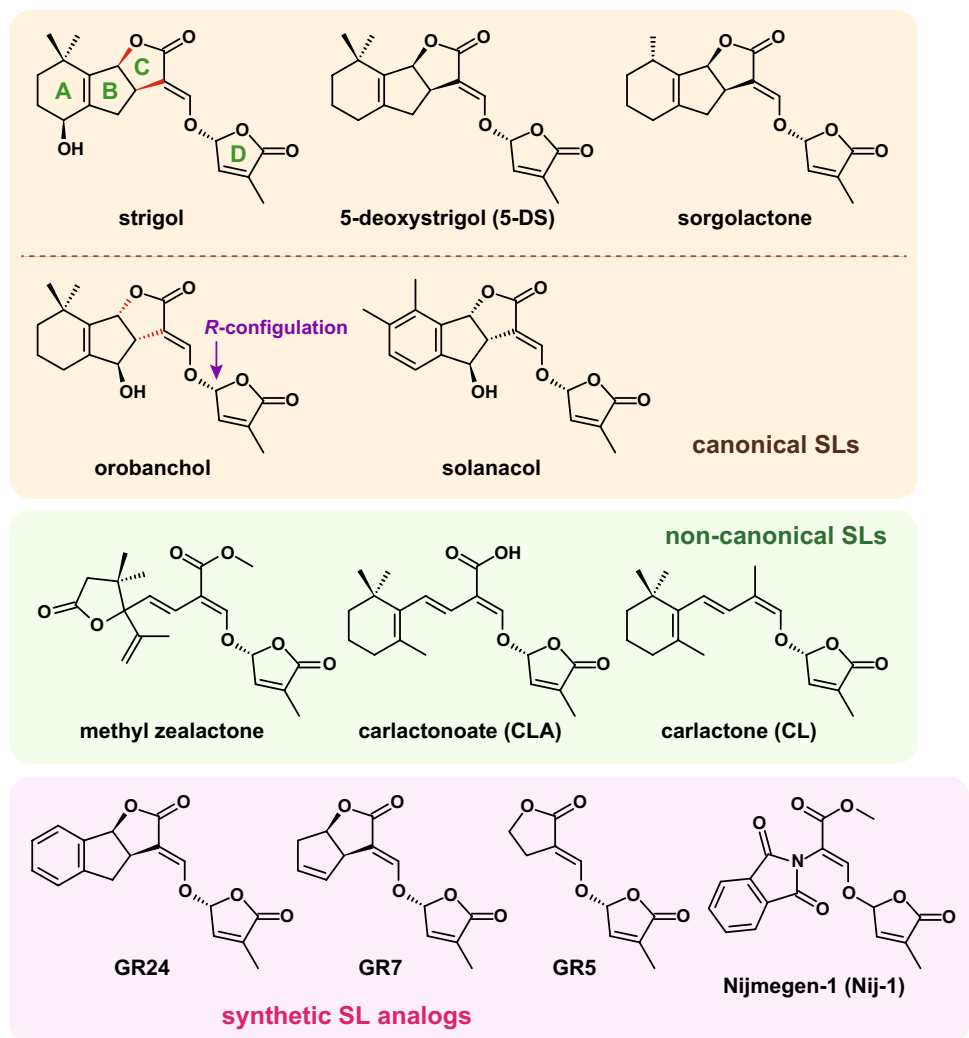
Strigolactones and their roles in the host recognition of root-parasitic plants

After invading a host root, the genus *Striga* initiates the formation of a structure called a haustorium for successful attachment and then grows underground for 4–7 weeks, during which it causes severe damage to the host. Once emerged above ground, it rapidly develops flowers and seeds. *Striga* host sensing is achieved by the perception of SLs, which are exogenous compounds secreted by the host plants. In 1966, strigol was initially isolated as a natural SL from the root exudates of cotton [19] (Fig. 1). The structure of strigol was elucidated in 1972 [20], but its absolute configuration was not reported until 1985 [21]. Later, other germination stimulants were discovered with similar structures to strigol. For example, orobanchol, solanacol, and sorgolactone were identified from the root exudates of red clover [22], tobacco [23], and sorghum [24], respectively. Currently, 17 types of natural SLs have been proven to stimulate the germination of *Striga* and/or other *Orobanche* spp. [25].

Canonical SLs are composed of a tricyclic lactone (ABC-ring) and a butenolide ring (D-ring) that are connected by an enol-ether linkage [11, 26] (Fig. 1). SLs are divided into two classes according to the stereochemistry of the BC junction on the ABC-ring. The SLs belonging to the “strigol class” have the same stereochemistry as strigol. In contrast, the “orobanchol class” is characterized by the opposite stereochemistry of the BC junction to the strigol class [27], which was initially observed in orobanchol [22]. The BC stereochemistry and other modifications of the ABC-ring affect the activity of SLs in *Striga* germination. Studies using different sorghum cultivars showed that the parasitism efficiency of *S. hermonthica* was positively correlated with the amount of 5-deoxystrigol (5-DS) production [28, 29] (Fig. 1). Another stereochemistry, the configuration of the D-ring at C-2', is common to all of the natural SLs in both classes, which is limited to an *R*-configuration. The *R*-configuration is required for greater *S. hermonthica* germination activity compared to the germination promoted by the *S*-configuration.

SLs are instable in water and easily degrade into inactive ABC-rings and D-rings by breakdown of the enol-ether linkage [30], and it is difficult to isolate natural SLs, because only trace amounts are produced in plants [31]. On the other hand, the ABC-ring of natural SLs adopts a variable structure to some extent. This structural information led to the design of synthetic SL analog GR24 (Fig. 1), which has been widely used for research purposes

Fig. 1 Chemical structures of natural (canonical and non-canonical) SLs and synthetic SL analogs. The stereochemistry of the BC junction is different between the strigol and orobanchol classes, indicated by bonds colored in red



because of its high *Striga* germination activity [30, 32]. Compounds lacking the A- or AB-ring of GR24, namely, GR7 or GR5, were also confirmed as retaining the ability to stimulate *Striga* germination. However, only the ABC-ring or D-ring do not show germination activity. These findings suggest that the CD part is bioactive of SLs as germination stimulants [11, 26, 30], which is used as a model for the dedicated design of active SL analogs [33]. Nijmegen-1 (Nij-1) is a first SL analog with the germination activity of root-parasitic plants although it has a carboxy methyl group as an open C-ring. Indeed, Nij-1 showed a considerable reduction of *Striga* seeds as suicidal germination stimulants in the field trials as well as GR24 and GR7, and also worked in tobacco fields infested by *Orobancha ramosa* L. [11, 34]. Recently, new types of natural SLs lacking the A-, B-, or C-ring were isolated from the root exudates of several plants, such as maize and sunflower, as germination stimulants [13] (Fig. 1). These are called non-canonical SLs as which methyl zealactone, an SL biosynthetic precursor carlactone (CL), and

its oxidized metabolite carlactonoate (CLA) are classified. Methyl zealactone has a carboxy methyl group connecting an enol-ether–D-ring moiety similarly to Nij-1, and acts as a germination stimulant for root-parasitic plants [35].

Because the transformation method for *Striga* has not yet been established, a genetic approach is not available to identify the components related to SL-dependent germination using root-parasitic plants. Therefore, recent progress in this field has instead been achieved using chemical tools, including synthetic SL analogs/mimics and model plants that possess a similar pathway of SL signaling.

Similar molecular mechanisms of SL perception and signaling in parasitic and nonparasitic plants

Although SLs are secreted from host plants and used as germination signals in root-parasitic plants, they also have important physiological roles, such as shoot branching

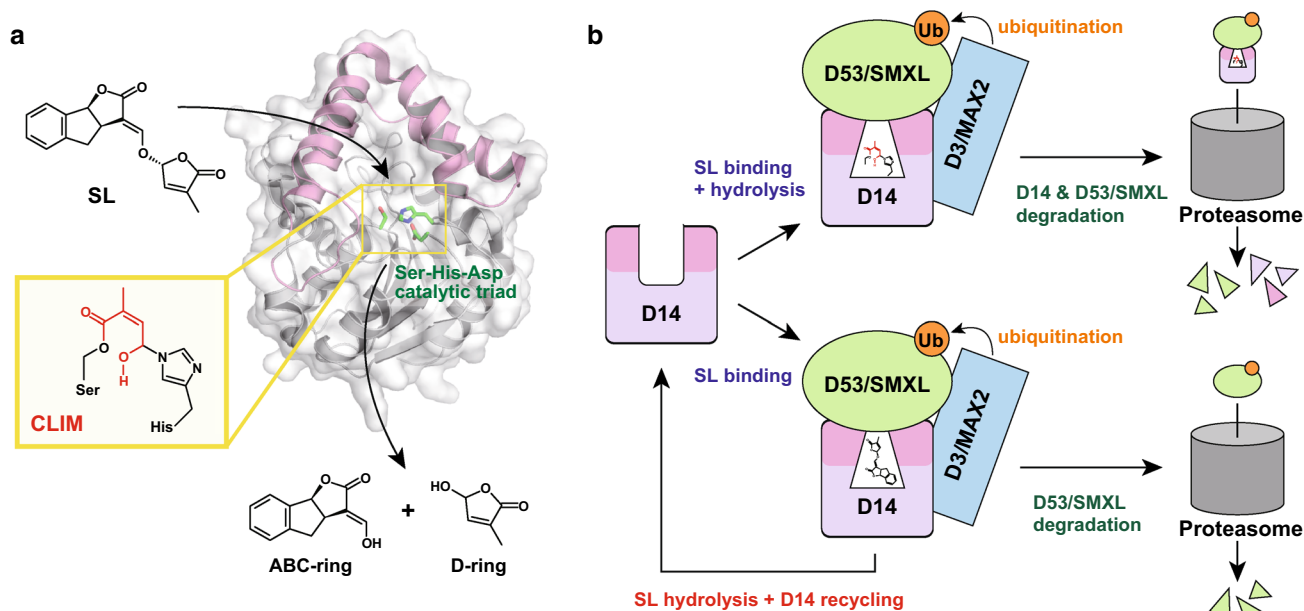


Fig. 2 Molecular function of D14 as an SL receptor. **a** SL hydrolysis in the catalytic pocket of D14. CLIM is an intermediate covalently bound to catalytic residues in the hydrolysis process. The helical cap domain is colored in pink. **b** Schematic diagrams of SL signaling

suppression, root development, and stress responses, as endogenous phytohormones in the host plants [36–38]. The genetic components were initially identified by analyzing the phenotypes of mutants in model plants, including *Arabidopsis* and rice. The core regulatory components for SL signaling are believed to be three types of subcellular proteins: DWARF14 (D14) [39], D3/MORE AXILARY GROWTH2 (MAX2) [40, 41], and D53/SUPPRESSOR OF MAX2 1 (SMAX1)-Like (SMXL) [42, 43].

D14 is the most promising SL receptor and adopts an α/β hydrolase fold that is composed of a core domain with the conserved Ser-His-Asp catalytic triad and a helical cap domain [44–47] (Fig. 2a). Mutational analyses have shown that the catalytic triad is required for SL hydrolysis that breaks the bond between the ABC-ring and the D-ring [44, 47]. The remaining enzymatic activity is unusual in the ligand perception of phytohormone receptors [48]. SLs induce the interaction between D14 and D3/MAX2, which is a key molecular mechanism responsible for the activation of SL signaling (Fig. 2b). D3/MAX2 is a member of the leucine-rich repeat (LRR) family, composed of an N-terminal F-box domain and a C-terminal LRR domain with 19 LRRs in tandem [49, 50]. The F-box domain of MAX2 interacts with ARABIDOPSIS SKP-LIKE 1 (ASK1), which is a component of the SKP1-Cullin-F-box (SCF) ubiquitin ligase complex [51]. Therefore, D3/MAX2 is involved in SL signaling through a ubiquitin–proteasome system. According to this mechanistic insight, D53/

mediated by D14, D3/MAX2, and D53/SMXL. In the upper pathway, SL hydrolysis is required to form ternary complexes of D14, D3/MAX2, and D53/SMXL. The lower pathway shows that SL is hydrolyzed for the deactivation and recycling of D14

SMXL and the DELLA protein SLENDER RICE1 (SLR1) were identified as SL-dependent interaction factors of D14 [42, 43, 46] (Fig. 2b). D53/SMXL is also degraded as a target substrate of D3/MAX2 in SL signaling, and the rice *d53* mutant showed an exaggerated number of tillers compared to wild-type plants and was insensitive to exogenous treatment of 5-DS or GR24 [42, 43]. Although SMAX1 and seven SMXL proteins (SMXL2–8) were identified in *Arabidopsis*, only SMXL6, 7, and 8 were responsible for the SL-dependent regulation of shoot branching [52, 53]. D53/SMXL belongs to the p-loop nucleoside triphosphate hydrolase superfamily, consisting of an N-terminal domain, a D1 ATPase domain, an M domain, and a D2 ATPase domain, similar to the chaperone protein HSP101. The D1 and D2 ATPase domains are responsible for SL-dependent interactions with D14 [43, 54]. In addition, the D2 ATPase domain contains the ethylene response element binding factor-associated amphiphilic repression (EAR) motifs for the interaction with TOPLESS corepressor, which regulates the transcription of many genes for plant development and phytohormone response [42, 55]. In fact, D53 interacts with rice TOPLESS-related proteins (TPRs), especially TPR2 [42]. These results propose that D53/SMXL acts as a repressor of SL signaling through the interaction of TOPLESS and TPRs. One of EAR motifs in D53 binds to the conserved TOPLESS domain (TPD) of TPR2 to mediate TPD tetramer–tetramer interaction, which promotes the assembly of D53–TPR2–nucleosome

complex [55]. On the other hand, SLR1 is a repressor of gibberellin (GA) signaling in rice [56], and GA is a phytohormone that suppresses the shoot branching of plants. Therefore, the interaction between D14 and SLR1 suggests cross-talk between SL and GA signaling in a branching regulation [46].

Recent biochemical and structural analyses proposed the mechanistic basis for the SL-dependent formation of the D14–D3/MAX2 complex that eventually degrades D53/SMXL through its ubiquitination [50, 57]. The interaction with MAX2/D3 in the presence of SLs induced a conformational change in the helical cap domain of *Arabidopsis thaliana* D14 (AtD14), and SL was broken down into the intermediate D-ring molecule (CLIM) at the active site [50] (Fig. 2b). CLIM was proposed to have structures that covalently link with the Ser and His residues of the catalytic triad (Fig. 2a). The covalent linkage of the His residue with the D-ring was also detected by mass spectrometry [57]. These findings concluded that SL hydrolysis was required for the complex formation of D14 with D3/MAX2. However, Seto et al. more recently reported that the AtD14 mutant at the catalytic Asp residue (D218A mutant) was still capable of interacting with MAX2 and SMXL7, complementing the *atd14* mutant phenotype in an SL-dependent manner, although the D218A mutant lacked the hydrolytic activity of SL [58]. Based on these results, an intact SL molecule induces the formation of the D14–D3/MAX2–D53/SMXL complex, and D14 is deactivated after SL hydrolysis (Fig. 2b). Another possible mechanism of SL signaling deactivation involves AtD14 degradation from the MAX2-dependent proteasomal pathway after SL perception [59]. Thus, the accumulated evidence suggests the possibility of multiple SL perception mechanisms and interaction plasticity [46, 54]. According to these mechanisms, the bioactophore of SLs is probably required for their hydrolysis to induce the formation of SL signaling complex and/or to deactivate the signaling.

S. hermonthica has the orthologous genes *D14* (*ShD14*) and *D3/MAX2* (*ShMAX2*), and hence evolutionally conserves a similar SL perception system to host plants. However, no obvious defects in seed germination were observed in the loss-of-function *atd14* mutant. In *Arabidopsis*, HYPOSENSITIVE TO LIGHT/KARRIKIN INSENSITIVE2 (HTL/KAI2) was identified as a seed germination regulator that belongs to the closely related α/β -hydrolase of D14, and its loss-of-function mutant showed a hyperdormant phenotype [60, 61]. These genetic studies elucidated that HTL/KAI2 and MAX2 were necessary for the responses to exogenous SLs and other germination stimulants, including karrikins (KARs) [62–64], which are derived from the smoke of burning vegetation and induce seed germination after forest fires [65–67]. Although HTL/KAI2 is SL-responsive as well as D14, it recognizes different stereoisomers of SL [46, 63,

68]. D14 responses specific to naturally occurring SLs with *R*-configuration at C-2' of the D-ring and HTL/KAI2 exhibit selectivity to non-natural *S*-configuration.

HTL/KAI2 paralogous genes are present in higher copy numbers in seed-parasitic plants than nonparasitic plants. In *S. hermonthica*, 11 HTL/KAI2 paralogs were identified and categorized into three phylogenetic clades: the conserved clade (*ShHTL1/ShKAI2c*), intermediate clade (*ShHTL2* and *ShHTL3/ShKAI2i*), and divergent clade (*ShHTL4/ShKAI2d3* to *ShHTL11/ShKAI2d9*) [69–71] (Fig. 3). All of them possess the conserved Ser-His-Asp catalytic triad and share high sequence similarity. However, ShHTLs belonging to different clades show different responses to SLs and/or KARs in cross-species complementation assays in which *ShHTL* genes were transformed into *Arabidopsis htl/kai2* mutants [69–71]. ShHTL4–9 belong to a parasite-specific clade and recovered seed germination in the loss-of-function mutant by responding to SLs but not KARs. Therefore, ShHTL4–9 from divergent clades are proposed to be SL receptors in root-parasitic plants and are optimized to receive natural exogenous SLs. The SL/KAR responsiveness can be explained by the biochemical properties of ShHTLs among the three phylogenetic clades [72, 73]. The divergent clade (ShHTL4 and ShHTL7) showed hydrolytic activity toward GR24. In contrast, the conserved (ShHTL1) and intermediate (ShHTL3) clades possess KAR-binding properties without hydrolytic activity toward SLs (Fig. 3). According to the isothermal titration calorimetry (ITC) experiments, the binding affinity of ShHTL1 and ShHTL3 toward KAR₁ was slightly higher than that of HTL/KAI2. These SL/KAR selectivities are correlated to the size of catalytic pockets (Fig. 3), which were evaluated by a comparative analysis with the crystal structures of ShHTLs belonging to the three clades [71, 73]. The pocket size is affected by the arrangement of helix α D1 on the helical cap domain and the types of residues located in the pocket [73] (Fig. 3). Among the ShHTLs of the divergent clade, ShHTL7, which has the largest pocket size compared to the remaining ShHTLs, has evolved with unbulky residues. These structural bases may help to develop the chemical compounds that can be used for separately controlling the different clades of ShHTLs to their function in the seed germination of root-parasitic plants.

ShHTL7 and ShHTL4 are capable of binding to ShMAX2 (the D3/MAX2 protein is conserved in *S. hermonthica*) in an SL-dependent manner, whereas this interaction with ShMAX2 is not detected in other clades of ShHTLs (ShHTL1 and ShHTL3) [73, 74]. These observations suggest that the SL-induced seed germination process of *S. hermonthica* shares a similar SL perception mechanism to nonparasitic plants using the divergent clades of ShHTLs instead of D14. However, the role of SL hydrolysis and downstream signaling components are not yet fully understood in seed germination stimulation through the divergent

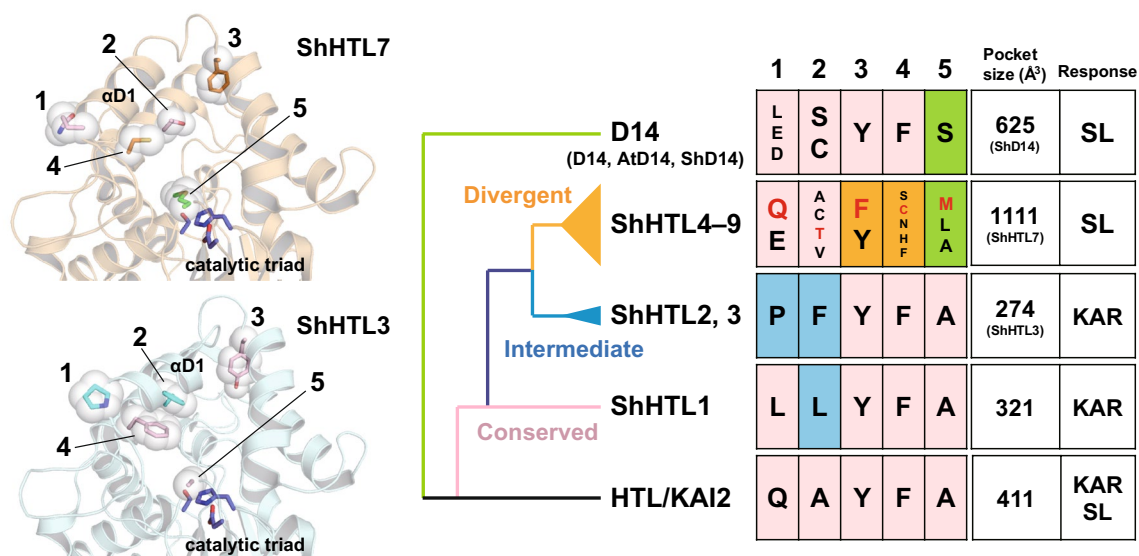


Fig. 3 Structural basis of the molecular evolution of ShHTLs. The catalytic pocket is narrowed by the residues in the blue box (positions 1 and 2 of the intermediate clade and position 1 of the conserved clade) to prevent SL binding. The residue at position 1 affects the arrangement of helix α D1 on the helical cap domain. The residues in the orange box (positions 3 and 4 of divergent clade) contribute to

expanding the catalytic pocket to accept various types of SLs. D14 and ShHTLs of the divergent clade are not capable of binding KAR due to steric hindrance with the residues in the green box (position 5). The residues of ShHTL3 and ShHTL7 (colored in red) are shown on their structure models

clades of ShHTLs, and the target molecules for ShMAX2-dependent proteolysis are likely to be different from shoot branching inhibition through D14.

Development of SL agonists and antagonists

To address the characterization of the parasitic SL receptors with a chemical biology approach because of unavailable genetic approaches, the fluorogenic SL mimic, Yoshimulactone Green (YLG) (Fig. 4), was designed based on the SL hydrolytic activity of the ShHTLs [70]. Competitive binding assays using YLG revealed that ShHTL6 and ShHTL7 exerted high sensitivities to GR24 and strong responses to various SLs [70, 71]. These characteristics are relative to larger pockets than the other ShHTLs, because there is less chance for steric hindrance to occur upon SL binding [73]. A variant of YLG with two D-rings (YLGW) was improved to eliminate background fluorescence and was applied to visualize the dynamic behavior of SL signaling in *S. hermonthica* by utilizing its activity as an SL agonist [70] (Fig. 4). Root elongation occurred after three phases with different fluorescent patterns (initial perception, wake-up wave, and pregermination pause). YLGW fluorescence was strongly detected at the root tip and then gradually spread toward the cotyledon during root elongation. Such a dynamic manner of YLGW fluorescence suggests that the induction of root germination is intricately regulated through SL receptor

activation and degradation, amplification from ethylene production, and cell-to-cell signal spread [16].

SLs play an essential role in the seed germination mechanisms of root-parasitic plants. However, the practical use of natural SLs is limited because of their uneconomical and complicated syntheses and instability; hence, artificial SL analogs, including GR24 and Nij-1, have been developed so far. In addition, synthetic compounds with defective bioactivity of SLs have been explored as SL mimics that can exert a part of SL functions. Debranones (phenoxyfuranone compounds) are the simplest SL mimics and function as shoot branching inhibitors similar to GR24 and modestly induce the seed germination of *Striga* [75, 76] (Fig. 4). Chemical modification improved the stimulation activity of debranones for *Striga* seed germination [77]. The 2-bromo-6-nitrophenyl derivative was the most effective at inducing *Striga* seed germination among all tested debranones. In other synthetic SL analogs/mimics, SL analog with *p*-tolylmalondialdehyde group, and SL mimics with aryloxy or phthalimide groups effectively function as germination stimulants for *Orobanchae*-type parasitic plants [78, 79]. Methyl phenlactonoates (MPs) are SL analogs that are designed by mimicking methyl CLA [80] (Fig. 4). Chemical modification affected the activity of the MPs in *Striga* seed germination and the shoot branching of the nonparasitic model plants. Among the tested MPs, MP1 showed the most efficient activity for *Striga* seed germination but lower activity than MP3 and MP7 for the inhibition of rice tiller outgrowths.

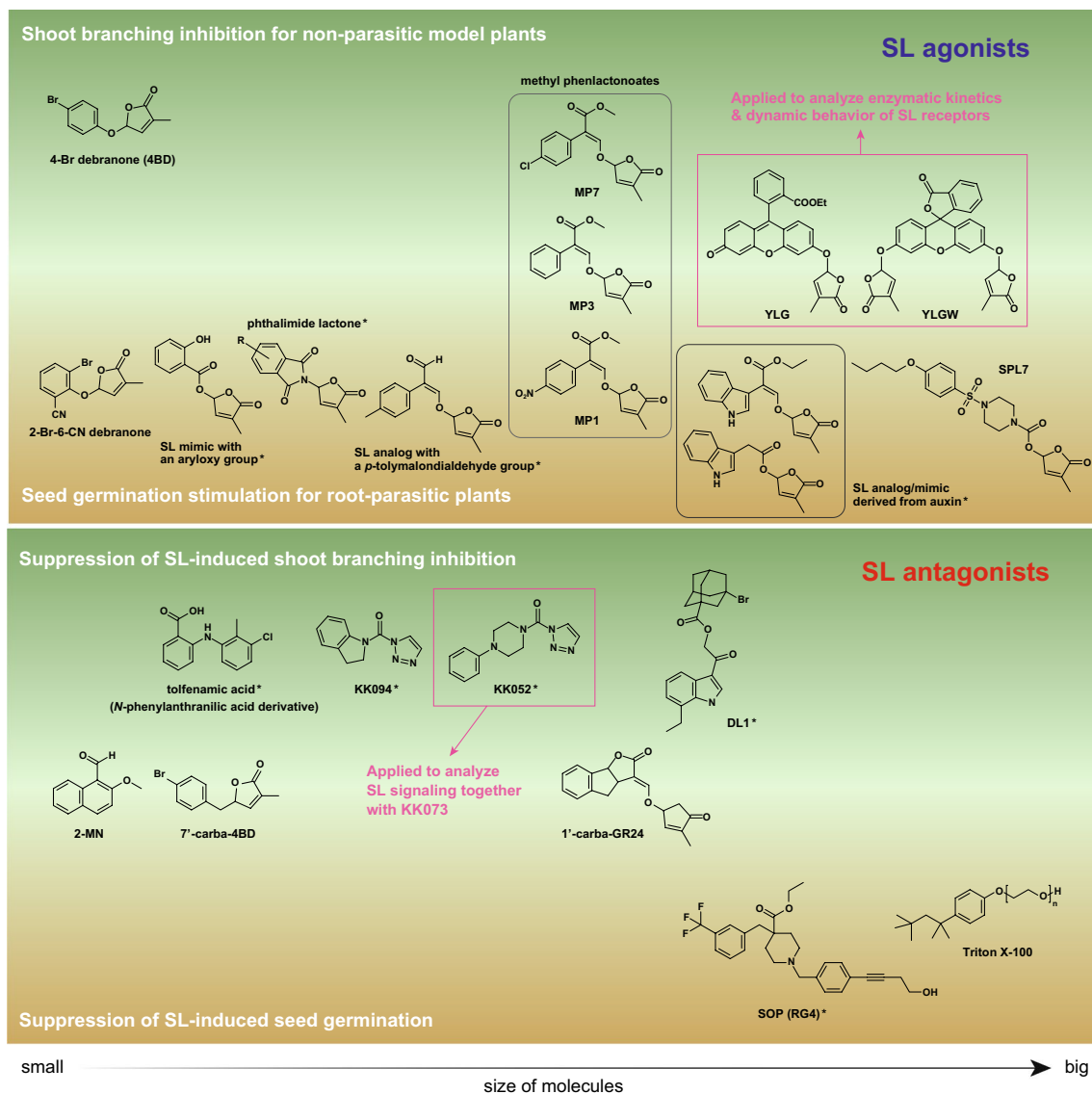


Fig. 4 Synthetic SL agonists and antagonists categorized based on their effects on shoot branching (green field) and seed germination (ocher field). The compounds exhibiting both effects are located

in the middle field. Only one effect was evaluated in the compounds with an asterisk, and the compounds in pink boxes were used to analyze the molecular mechanisms of the SL receptors

Recently, hybrid-type SL analogs/mimics were newly designed by coupling the D-ring with another phytohormone auxin [81, 82] (Fig. 4) and stimulated the seed germination of three types of the parasitic plants, *S. hermonthica*, *Phelipanche ramose*, and *Orobancha minor*. The SL analog derived from auxin, especially, is more effective toward *O. minor* than GR24. The higher activity was observed in the analogs/mimics with a natural monomethylated D-ring than in the derivatives with the di- or trimethylated D-ring.

These SL analogs/mimics can be referred to as SL agonists that are targeted to the D14/HTL-type SL receptors in both parasitic and nonparasitic plants because of their common structural features. Uruguchi et al. designed an SL

mimic, sphynolactone-7 (SPL7), to have a high affinity for ShHTL7 [83] (Fig. 4). In the competitive binding assays using YLG, the IC_{50} value for ShHTL7 was $0.31 \mu\text{M}$, but almost all other ShHTLs and AtD14 showed an IC_{50} value of $> 10 \mu\text{M}$. SPL7 also showed a *Striga*-selective SL agonistic activity in the femtomolar range. These results support that ShHTL7 can play a crucial role in the SL-dependent seed germination of *S. hermonthica*, and is a major target for developing suicidal germination stimulants. Although there is no structural information of SPL7 bound to ShHTL7, it is speculated that sulfonyl piperazine moiety at the ABC-ring portion of SLs contributes to the selectivity to ShHTL7 and the femtomolar-range potency [83]. Practical SL agonists as

suicidal germination stimulants need to fulfill all requirements for *Striga* control in the field. Successful field trial for suicidal germination activity was performed in three SL analogs, Nij-1, MP1, and MP3 [84]. These formulated compounds reduced the number of emerged *Striga* plants to 39–65% in farmer's fields of pearl millet. Formulated MP1 also showed 42% reduction of *Striga* emergence in the sorghum field.

Many types of SL antagonists have also been discovered with in silico and/or chemical library screening to control the second tiller elongation of the host plants and the seed germination of *S. hermonthica* (Fig. 4). 2-Methoxy-1-naphthaldehyde (2-MN) was identified with in silico screening based on the structure of D14 complexed with the D-ring [46, 85]. 2-MN inhibits the D14–D53 and D14–SLR1 interactions to restore the second tiller elongation and suppresses the SL-dependent germination of *Striga* seeds [85]. DL1 and *N*-phenylanthranilic acid derivatives exert the inhibitory activity of the SL receptor and increase the number of shoot branches [86, 87]. These compounds were identified by high-throughput screening using a YLG competition assay or differential scanning fluorimetry (DSF). On the other hand, soporidine (SOP) and Triton X-100 act as SL antagonists that inhibit the germination of *S. hermonthica* in the presence of SLs [88, 89]. Triton X-100 specifically sealed the entrance of the catalytic pocket of ShHTL7.

Carba-SLs are the most simply designed SL antagonists, but their actions are suggestive of the mechanism of SL signaling activation [90]. In these compounds, the ether oxygen of the D-ring or the phenol ether oxygen of the synthetic SL agonists (GR24 and 4-bromodebranone) was replaced with a methylene group (Fig. 4). All carba-SLs are not cleaved by D14 hydrolytic activity; hence, they inhibit the interaction between D14 and D53 and suppress the SL-induced inhibition of rice tiller outgrowths. SL-induced seed germination of *S. hermonthica* is also suppressed by carba-SLs, which are capable of binding to the catalytic pocket of ShHTL7. Recently, Nakamura et al. reported SL agonists/antagonists of triazole urea derivatives (KK compounds) (Fig. 4), which are able to form a covalent bond with the catalytic Ser residue of D14 [91]. Among them, KK094 showed the most potent suppressing effect on the SL-dependent inhibition of second tiller elongation. KK052 also acts as an inhibitor of D14, whereas KK073, with a trifluoromethyl group on the benzene ring of KK052, is capable of inducing the complex formation of D14 with D53 or SLR1. Therefore, the antagonistic and agonistic effects on the SL receptor are switched by the chemical modification of KK compounds, suggesting that these discovered compounds could also be useful to further elucidate the molecular mechanisms of SL signaling.

Summary and future work

In addition to the development of SL analogs based on the bioactophore of SLs, the understanding of D14 and ShHTLs as SL receptors has helped the design of several types of synthetic compounds that exert activity as SL agonists or antagonists. Some of these compounds have the potential to suppress the germination of *Striga* seeds or deplete the seed stocks in the soil as suicidal germination stimulants, because they show better stability compared with the natural SLs and/or selectivity toward root-parasitic plants, including *S. hermonthica*. On the other hand, further mechanistic findings may lead to a new approach to suppress the growth and expansion of root-parasitic plants. Based on the unraveled mechanism of SL-dependent seed germination in *S. hermonthica*, the SL perception system shares similar components between parasitic plants (ShHTLs and ShMAX2) and non-parasitic model plants (D14 and D3/MAX2). However, there are several remaining questions that are yet to be described: for example, the molecular mechanism from SL perception to signal transduction (including the target molecule of the SL receptor complex formed by ShHTLs and ShMAX2), the physiological meaning of the molecular diversity of ShHTLs, and the dynamic behavior of SL signaling in seed germination, which may be characteristic of parasitic plants.

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