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Receptor kinases in plant responses to herbivory

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Plants have the ability to detect and respond to biotic stresses. They contain pattern recognition receptors (PRRs) that specifically recognize conserved molecules from their enemies and activate immune responses. In this review, I discuss recent efforts to discover PRRs for herbivory-associated cues that originate from oral secretions, eggs, damaged plant cells or secondary endogenous signals. Although several potential PRRs have been identified and shown to confer resistance to insects, proof of direct binding to a ligand is scarce and there are still many uncharacterized ligand-receptor pairs. However, several studies suggest that, like for microbial pathogens, plants use similar PRR complexes to detect herbivory.

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Introduction

When exposed to pathogens, plants can recognize so-called pathogen-associated molecular patterns (PAMPs), which are conserved immunogenic molecules, for example, flagellin, chitin. The recognition of these PAMPs is facilitated by plasma membrane-localized pattern recognition receptors (PRRs), also referred to as receptor kinases (RKs). PRRs generally consist of a varying extracellular domain that is connected to a conserved cytoplasmic kinase by a short transmembrane domain, although receptor-like proteins (RLPs) that lack a kinase domain exist [1]. Common extracellular domains consist of leucine-rich repeats (LRRs), which generally bind peptides; lectin (Lec), which binds small metabolites or carbohydrates; and epidermial growth factor (EGF), which binds carbohydrates (Figure 1). Upon ligand perception, PRRs associate with co-receptors and activate a downstream signaling cascade that culminates with the production of defense proteins and metabolites [1,2]. In addition, plants modulate immune responses by secreting peptides that act as secondary endogenous danger signals. These molecules are called phytocytokines and are perceived by PRRs [3].

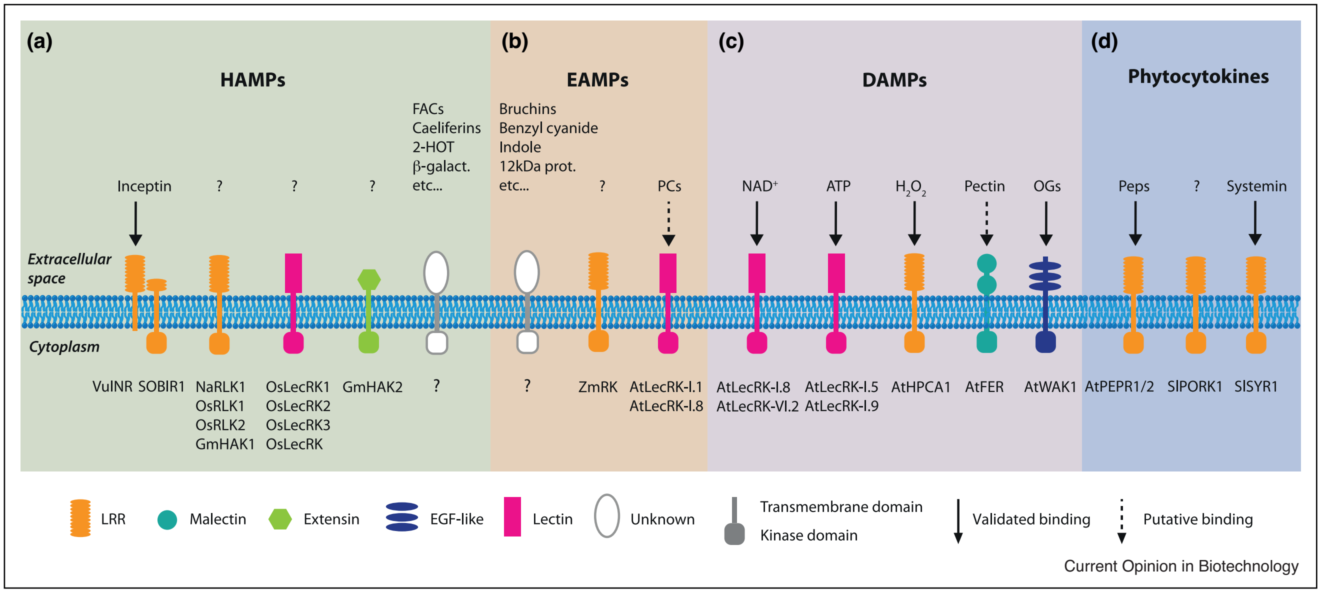
Upon feeding by arthropods, including insects, deployment of a battery of defenses occurs that either directly target herbivores or indirectly attract predators via the emission of volatile compounds [4,5]. These responses follow the perception of the herbivore and activation of a signal transduction cascade, which primarily involves the jasmonate (JA) pathway. By analogy with microbial pathogens, herbivores release herbivore-associated molecular patterns (HAMPs) from the feeding activity of the adult stage or egg-associated molecular patterns (EAMPs) after oviposition, both of which trigger defenses [6–9]. Since larval feeding can damage plant cells, an additional release of immunogenic damage-associated molecular patterns (DAMPs) is caused [3]. In recent years, substantial information has been gathered on the molecular components and signaling steps downstream of herbivory detection [5,10,11]. In sharp contrast, there is still limited information on how HAMPs/EAMPs are recognized. In this review, I present the current knowledge on PRRs for various herbivore-related immunogenic patterns and their role in resistance against herbivory. I also address a potential link between DAMP perception after larval feeding and resistance to pathogens that may enter through wound sites.

HAMP perception

HAMPs are diverse molecules or proteins found in saliva or oral secretions (OS) of herbivores [12] (Table 1). However, very few PRRs for HAMPs have been identified. Fatty acid-amino acid conjugates, including the well known volicitin, are present in OS from different Lepidoptera [13]. These compounds trigger the emission of green leaf volatiles and terpenoids that attract parasitic wasps. Binding of radiolabeled volicitin to a purified plasma membrane preparation from maize leaves suggests the presence of a potential PRR, although this could be due to non-specific binding to a membrane-associated component [14]. Unfortunately, identification of the binding protein has not yet been achieved.

Inceptin (*Vu*-In) is an 11-amino acid cyclic peptide purified from OS of the fall armyworm *Spodoptera frugiperda*. It is generated during digestion of plant chloroplastic ATPase and induces defenses in Fabaceae, including cowpea (*Vigna unguiculata*) [15]. Interestingly, OS of the legume-specialist velvet bean caterpillar *Anticarsia gemmatalis* contain a less bioactive form of *Vu*-In that lacks the C-terminal amino acid (*Vu*-In^{-A}) and

Figure 1



Current Opinion in Biotechnology

Receptor kinases involved in defense against herbivory.

HAMPs **(a)** from arthropod oral secretions or salivary glands, EAMPs **(b)** from eggs and DAMPs **(c)** from damaged cells are perceived by plant plasma-membrane localized pattern recognition receptors (PRRs) that contain various extracellular domains. After ligand binding, these PRRs activate downstream immune responses through their kinase domain. Phytocytokines **(d)** constitute plant secondary danger signals that are secreted in the apoplastic space, are recognized by PRRs, and amplify defense responses. Corresponding PRRs for several HAMPs and EAMPs are still unknown (white). Validated binding between a ligand and its cognate receptor is indicated with a solid arrow, whereas putative binding is indicated by a dotted arrow. Several PRRs have no identified ligand, yet. VuINR/SOBIR1 [17••], NaRLK1 [23], OsRLK1 [20], OsRLK2 [21•], GmHAK1/2 [22•], OsLecRK1/2/3 [18••], OsLecRK [19], ZmRK [31], AtLecRK-I.1 [30], AtLecRK-I.8 [25••,38], AtLecRK-VI.2 [39••], AtLecRK-I.5 [37•], AtLecRK-I.9 [36], AtHPCA1 [41], AtFER [35], AtWAK1 [33], AtPEPR1/2 [44], SlPORK1 [46], SlSYR1 [42••].

antagonizes *Vu*-In activity [16]. Recently, the LRR-RLP VuINR has been identified by QTL mapping and genome-wide association study (GWAS) using variation in the response of cowpea accessions to *Vu*-In^{-A} [17••]. When expressed in *Nicotiana benthamiana*, VuINR is localized to the plasma membrane and confer responsiveness to *Vu*-In by triggering reactive oxygen species and ethylene accumulation, which are typical plant immune responses [17••]. In accordance, *N. benthamiana* transgenic lines expressing VuINR display a significantly enhanced resistance to the beet armyworm *Spodoptera exigua*. Furthermore, immunoprecipitated VuINR-GFP shows retention of acrinidium-labeled *Vu*-In, a binding that is competed by unlabeled *Vu*-In and *Vu*-In^{-A} [17••]. Collectively, these findings strongly suggest that VuINR is a *bona fide* PRR and the first HAMP receptor identified (Figure 1a). Further *in vitro* binding studies with inceptin and the purified VuINR will be required to confirm this important discovery, for example by isothermal titration calorimetry or grating-coupled interferometry.

Various RKs have been implicated in defense against herbivory, the identity of their ligand or HAMPs, however, is still missing and no attempt to test their responsiveness to known HAMPs has been conducted, except for soybean LRR-RK HAKs (see below) (Figure 1a). A locus containing three L-type lectin-receptor kinases (OsLecRK1-3) confers resistance against BPH when introgressed into susceptible rice cultivars [18••]. Silencing another rice OsLecRK reduces defense gene expression and resistance to BPH infestation [19]. Similarly, OsLRR-RLK1 controls the accumulation of JA and the expression of defense genes in rice plants attacked by the striped stem borer (SSB) *Chilo suppressalis*. *OsLRR-RLK1* is induced by SSB herbivory and silenced lines exhibit increased feeding by SSB [20]. In contrast, OsLRR-RLK2 negatively regulates defenses against BPH by modulating the hormonal profile and expression of defense genes, suggesting that binding of this PRR to an OS component may be exploited to the benefit of this insect [21•].

The soybean LRR-RK GmHAK1 and extensin-RK GmHAK2 respond to complex polysaccharides in OS of *Spodoptera litura*. Silenced soybean lines display reduced defense gene induction and enhanced susceptibility to larvae. However, detection of direct binding between GmHAKs and components of the active fraction by isothermal titration calorimetry has not been successful [22•]. Whether these two candidate PRRs act as downstream signaling components or bind other *S. litura* HAMPs remain thus to be explored.

Table 1

HAMPs and EAMPs from arthropods

Name	Origin	Defense response	PRR	Ref.
HAMPs				
2-HOT	*Manduca sexta* OS	Attraction of parasitoids	–	[63]
β-gal.-fur. polysacch.	*Spodoptera littoralis* OS	PM depolarization	–	[64]
β-glucosidase	*Pieris brassicae* OS	Attraction of parasitoids	–	[65]
Caeliferins	*Schistocera americana* OS	Attraction of parasitoids	–	[66]
FAC (volicitin)	*Spodoptera exigua* OS	Attraction of parasitoids	–	[67]
Inceptin	*Spodoptera frugiperda* OS	Defense gene expression	VuINR	[15,17••]
Lipase	*Schistocera gregaria* OS	Release of esterified OPDA	–	[68]
Mp56, Mp57, Mp58	*Myzus persicae* saliva	Reduced aphid fecundity	–	[69]
Mucin-like	*Nilaparvata lugens* saliva	Reduced performance	–	[70]
Nl12, 16, 28, 32, 40, 43	*Nilaparvata lugens* saliva	Defense gene expression	–	[71]
Protein (<10 kDa)	*Myzus persicae* saliva	Defense gene expression	–	[72]
Tetranins	*Tetranychus urticae* saliva	Defense gene expression	–	[73]
EAMPs				
12 kDa protein	*Diprion pini* oviduct	Attraction of parasitoids	–	[74]
Benzyl cyanide	*Pieris brassicae* ARG	Arrest of parasitoids	–	[75]
Bruchin	*Callosobruchus maculatus* ♀	Neoplasm formation	–	[76]
Indole	*Pieris rapae* ARG	Arrest of parasitoids	–	[77]
PCs	*Pieris brassicae* eggs	Defense gene expression	LecRK-I.8?	[25••]
PCs	*Sogatella furcifera* ♀	Ovicidal compound	–	[78]

ARG, accessory reproductive gland secretion; β-gal.-fur. polysacch., β-galactofuranose polysaccharide; EAMP, egg-associated molecular pattern; FAC, fatty acid-amino acid conjugate; HAMP, herbivore-associated molecular pattern; 2-HOT, 2-hydroxy-octadecatrieonic acid; OPDA, 12-oxophytodienoic acid; OS; oral secretions; PCs, phosphatidylcholines; PRR, pattern recognition receptor; ♀, female body; -, unknown.

In *Nicotiana attenuata*, expression of the G-type LecRK *NaLecRK1* is induced by *Manduca sexta* OS. *N. attenuata* lines where *NaLecRK1* expression is silenced accumulate less nicotine and defense proteins and are more susceptible to *M. sexta* herbivory. Since these lines have higher salicylic acid (SA) levels, the hypothesis is that NaLecRK1 inhibits the production of SA to prevent suppression of the JA pathway [23].

Finally, a survey of Arabidopsis transcriptomes after *Pieris rapae* feeding for 3–24 hours indicates that 58 RKs are significantly induced, including 34 LRR-RKs and 11 LecRKs [24], providing an interesting list of potential PRRs.

Currently, it is difficult to speculate on what type of PRR can bind to which orphan HAMP, given the lack structural information for binding sites of complex lipids or carbohydrates, or given the lack of detailed information for which part of defense-inducing proteins is required. Clearly, more efforts should be invested to identify PRRs for these defense-activating compounds. Trying to connect orphan HAMPs (Table 1) with orphan PRRs by testing the responsiveness of knockout lines to purified HAMPs might help in identifying novel HAMP/PRR pairs.

EAMP perception

Plants detect early stages of herbivory by recognizing egg-associated molecular patterns (EAMPs), but knowledge about PRRs is scarce [8,9] (Figure 1b). Phosphatidylcholines (PCs) released from *Pieris brassicae* eggs are EAMPs that trigger immune responses in Arabidopsis [25••]. AtLecRK-I.8 has been identified through a transcriptomic analysis of egg-induced genes and shown to regulate early immune responses [26–28]. Strikingly, a *lecrk-I.8* mutant displays significantly reduced immune responses to PC treatment, suggesting that AtLecRK-I.8 is a PRR involved in PC perception [25••]. However, this hypothesis will need confirmation by *in vitro* binding assays. AtLecRK-I.8 belongs to a clade of eleven L-type LecRKs that are involved in defense [29]. Expression of all these members is induced by *P. brassicae* egg extract treatment and a GWAS has recently revealed that AtLecRK-I.1 controls immune responses against *P. brassicae* eggs [30]. Whether these additional candidate PRRs act as heteromultimers or modulate responses as co-receptors deserves further investigation.

Maize plants respond to SSB oviposition by emitting volatiles that attract egg parasitoids. Several loci associated with this indirect defense have been recently identified through a GWAS, including one containing an LRR-RK potentially involved in egg recognition [31].

Like HAMPs, several EAMPs that induce direct or indirect defenses await discovery of cognate PRRs (Table 1).

DAMP perception

Mechanical damage is an important component of insect feeding. Cell wall debris and cytoplasmic molecules, including ATP, $NAD^+$and H_2O_2, are released in the extracellular space and act as DAMPs that are perceived by PRRs [3] (Figure 1c). The EGF-RK AtWAK1 binds oligogalacturonides, which are fragments of the cell wall-stabilizing polymer pectin, thus potentially playing a role in cell wall integrity [32]. In addition, overexpression of *AtWAK1* in Arabidopsis enhances resistance to the fungal pathogen *Botrytis cinerea* [33]. Similarly, the malectin-RK AtFER senses perturbations of the cell wall integrity after infection with the bacterial pathogen *Pseudomonas syringae* pv. *tomato*, by potentially binding pectin [34,35].

Interestingly, Arabidopsis contains PRRs for extracellular ATP and NAD^+. AtLecRK-I.9 (DORN1) has a high affinity for ATP and its overexpression triggers immune responses that are similar to mechanical wounding, suggesting that AtLecRK-I.9 may detect feeding herbivores via ATP release from damaged cells [36]. AtLecRK-I.5 has even more affinity for ATP and contributes to immunity against bacterial pathogens [37•]. Intriguingly, the L-type lectin domain of AtLecRK-I.8 binds NAD^+ with a Kd in the nanomolar range, although defense gene induction requires millimolar NAD^+ concentration [38]. How and if NAD^+ binding relates to the role of AtLecRK-I.8 in EAMP recognition (see above) is, however, not clear and will deserve further investigation. L-type AtLecRK-VI.2 is another PRR that binds NAD^+/$NADP^+$ and is important for resistance against diverse bacterial pathogens [29,39••,40]. Finally, perception of hydrogen peroxide depends on the Arabidopsis LRR-RK AtHPCA1. Indeed, H_2O_2 activates this PRR by covalent modification of extracellular cysteine residues, which leads to autophosphorylation and downstream immune responses [41].

However, besides a role in resistance to microbial infection, whether PRRs for cell wall components or small cytoplasmic metabolites are implicated in defense against feeding larvae has not been evaluated and is an important question. Indeed, given that open wounds create entry points for opportunistic pathogens and may facilitate infection by virulent strains, DAMP perception may have evolved to specifically respond to these potential infections and not to feeding insects. Further investigation on which pathogens are found in feeding wounds and testing the performance of feeding larvae on mutants of various PRRs for DAMPs may help answer this question.

Phytocytokines and herbivory

Upon herbivory, endogenous peptides are produced by proteolytic cleavage from larger precursor proteins and secreted in the apoplastic space. Perception of these phytocytokines by PRRs amplifies immune responses that are activated by PAMPs or HAMPs [3] (Figure 1d). The 18-aa systemin triggers JA-dependent defenses against herbivores in Solanaceae, it binds to the SlLRR-RK SYR1, and a tomato line that lacks SlSYR1 is more susceptible to *Spodoptera littoralis* [42••]. AtPeps amplify innate immunity in Arabidopsis by triggering JA and salicylic acid (SA) defense pathways [43] and are recognized by two related LRR-RKs (AtPEPR1 and AtPEPR2) [44]. Interestingly, a *pepr1 pepr2* double mutant is more susceptible to *S. littoralis* and infection by *Pseudomonas syringae* pv. *tomato* infection, suggesting a dual role for these PRRs in danger detection [44,45]. In tomato, the LRR-RK SlPORK1 is the closest homolog of AtPEPR1/2 although it regulates responses to systemin [46]. Given that AtPeps only induce defenses in Arabidopsis whereas systemin is specific to Solanaceae, identifying a ligand for SlPORK1 would help understanding its exact role in early signaling steps. Silenced tomato lines are anyhow more susceptible to *M. sexta*, confirming a role for SlPORK1 in response to herbivory [46]. Finally, other phytocytokines have been identified, including for instance RALFs, PIPs, SCOOPs, and CAPE1, but their role in defense against insects is currently unresolved [3,47].

Similar co-receptors are used for HAMP, DAMP and PAMP signaling

Upon PAMP perception, regulatory LRR-RKs including BAK1/SERKs are recruited to form complexes with PRRs. Although not directly binding ligands, these co-receptors are necessary for stabilization of PRR/ligand complexes and for signaling activation [1]. This leads to phosphorylation and dissociation of receptor-like cytoplasmic kinases (RCLKs), which are bound to PRRs at resting state. In turn, RCLKs activate downstream signaling components [1]. Similar co-receptors have been identified in the context of herbivory. For instance, AtBAK1, which is a major co-receptor of FLS2, EFR, PERR1/2 and other PRRs [48], is required for immune responses induced by the aphid *Myzus persicae* and a *bak1* mutant displays reduced immunity to the pea aphid *Acyrthosiphon pisum* [49,50]. Also, AtBAK1 associates with AtLecRK-VI.2, a PRR for the DAMPs NAD^+/$NADP^+$, and is required for downstream responses that are regulated by this PRR [39••]. Similarly, AtSERK1-4 associate with the *Vu*-In PRR VuINR. In addition, since VuINR is a RLP that lacks a signaling kinase domain, it has been shown to interact with the LRR-RK SOBIR1 to potentially form a genuine receptor complex [17••]. The tomato RCLK SlTPK1b is necessary for resistance against *M. sexta* [51]. In contrast, the Arabidopsis RCLK AtBIK1 confers susceptibility to *M. persicae*, indicating that RCLKs may have antagonistic roles depending on the type of herbivore [52].

However, further identification of molecular components of several HAMP/PRR complexes and study of their regulation should help to infer differences and commonalities in PAMP, HAMP and DAMP signaling. While herbivores and necrotrophic microrganisms generally activate the JA pathway whereas biotrophic fungal and microbial pathogens activate the SA pathway [53], another key and unanswered question is how recognition of various immunogenic patterns, which relies on related PRRs and conserved co-receptors, leads to specific downstream signaling steps that activate defenses properly tailored to the herbivore. Signaling-specificity may in part be explained by combinatorial establishment of receptor complexes, structural determinants of PRR activation, protein trafficking, and subcellular localization [54•] but, clearly, more insights on the selectivity of cellular responses to herbivory are needed.

How to identify PRRs for known HAMPs/EAMPs

Given the substantial number of HAMPs/EAMPs with no known PRRs, efforts should be placed in identifying cognate receptors. PRR expression tends to be regulated by biotic stress and this property has been successful for the identification of AtEFR, whose expression is induced after treatment with its bacterial ligand elf18 [55]. The same strategy was used to identify *AtLecRK-I.8*, whose expression was upregulated after oviposition [26,28]. Several Arabidopsis *LecRKs* are induced by different PAMPs and pathogens, but also by whiteflies, suggesting that treatment of plants with specific HAMPs could help find candidate PRRs [56]. Trancriptomic studies in response to various herbivores may thus help in identifying novel PRRs. Alternatively, affinity-labeling of known HAMPs and subsequent purification of plant microsomal membrane fractions may allow identification of novel PRRs, as has been used for the identification of AtPEPR1 [57]. Conversely, a strategy to find ligands for known PRRs may be to immunoprecipitate PRRs from plants exposed to various insects and further analyze bound molecules by mass spectrometry, although there is yet no report on the identification of a ligand using this method.

Whereas a canonical model of innate immunity activation postulates the recognition of HAMPs/EAMPs by cognate PRRs, the possibility of defense activation through a direct interaction with the plasma membrane could be envisaged. OS from several Lepidopteran species contain channel-forming activities when applied to lipid bilayers membranes, and thus could create ion fluxes that are early components of defense activation [58,59]. Phospholipids, including PCs, can be internalized by ATPase flippases and initiate intracellular signaling [60,61].

Conclusion and outlook

Decades of research in plant innate immunity have unveiled a sophisticated surveillance system that detects the presence of microorganisms and arthropods. However, contrary to PAMP perception, only a few PRRs for feeding herbivores have been identified and a *bona fide* HAMP/PRR pair has yet to be discovered. Increased herbivore pressure due to climate warming [62], a reduction of insecticide application in agriculture and evolution of insecticide resistance in insects pose a serious challenge to pest management. Introgression of PRRs into susceptible lines has proven successful to fight BPH and related phloem-sucking herbivores in rice [18••] but whether any PRR can confer robust and durable resistance in diverse crops is still unknown. Pretreatment with HAMPs to induce PRR expression and protect crops from further attacks may constitute another efficient method. As research on PRRs continues to reveal new components of herbivore detection, development of such strategies may reveal efficient and complementary for a more sustainable agriculture. Open questions still remain, for example the contribution of DAMP perception to defense against insects and whether induction of defenses always requires PRRs. With the discovery of more PRRs, scientists in years to come may uncover novel aspects of the fascinating molecular dialogue between plants and herbivores.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Philippe Reymond: Conceptualization, Writing - review & editing.

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