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Plant-arthropod interactions: who is the winner?

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SUMMARY

Herbivorous arthropods have interacted with plants for millions of years. During feeding they release chemical cues that allow plants to detect the attack and mount an efficient defense response. A signaling cascade triggers the expression of hundreds of genes, which encode defensive proteins and enzymes for synthesis of toxic metabolites. This direct defense is often complemented by emission of volatiles that attract beneficial parasitoids. In return, arthropods have evolved strategies to interfere with plant defenses, either by producing effectors to inhibit detection and downstream signaling steps, or by adapting to their detrimental effect. In this review, we address the current knowledge on the molecular and chemical dialogue between plants and herbivores, with an emphasis on coevolutionary aspects.

INTRODUCTION

Plants and herbivorous arthropods have coevolved for millions of years and it is commonly believed that these interactions have generated the large variety of plant and arthropod species that inhabit our planet. Although a large fraction of arthropods provide service to plants in the form of pollination or protection against enemies, they also constitute a threat since they are generally herbivorous. Whether they chew leaf or root material, feed on cell content, mine mesophyll tissue or suck phloem, arthropods from different feeding guilds impose a stress that plants have to resist. Depending on the type of attack, plants have a battery of strategies that include preexisting constitutive defenses complemented by the induction of direct (toxic secondary metabolites and proteins) and indirect (emission of volatiles to attract predators) defenses (Fig. 1). These responses depend on precise perception of the aggressor, followed by a signal transduction cascade that culminates in a transcriptional reprogramming and synthesis of specific defense compounds. Efficient plant resistance imposes a selection pressure on herbivores, which in turn develop ways to interfere with defense mechanisms or adapt to the detrimental effect of toxins. In recent years, a wealth of information has accumulated on molecular components that control this on-going arms race. Several aspects of plant-arthropod interactions have been reviewed elsewhere (Schoonhoven *et al.*, 2005; Zhu-Salzman *et al.*, 2005; Will and van Bel, 2006; Howe and Jander, 2008; Wu and Baldwin, 2010; Hogenhout and Bos, 2011; Farmer, 2014; Jouannet *et al.*, 2014; Hilker and Fatouros, 2015; Schuman and Baldwin, 2016). In this review, we place emphasis on the molecular and chemical dialogue that underlies these interactions. We present the current knowledge on arthropods elicitors and effectors, provide examples of plant defense compounds and adaptations by arthropods, to illustrate a fascinating coevolution between organisms that are generally foes but can also engage in mutualistic relationships.

PERCEPTION OF FEEDING HERBIVORES

Plants have evolved exquisite ways to detect their enemies. When infected by bacterial or fungal pathogens, hosts recognize pathogen-derived molecules from the attacker that have been termed pathogen- or microbe-associated molecular patterns (PAMPs/MAMPs). These PAMPs are highly conserved and are generally associated with a class of attacker. PAMP perception is achieved by plasma membrane-bound pattern recognition receptors (PRRs), which are either receptor-like kinases (RLKs) or receptor-like proteins (RLPs) that lack a cytoplasmic kinase domain (Boller and Felix, 2009; Couto and Zipfel, 2016). Upon ligand binding, PRRs associate with regulatory receptor kinases, including the well-studied BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1) (Couto and Zipfel, 2016). PAMP recognition leads to a transcriptional defense program called pattern-triggered immunity (PTI), which restricts growth of the invading pathogens through local and systemic production of defenses proteins and metabolites (Li *et al.*, 2016). In analogy to plant-pathogen interactions, scientists have identified herbivore-associated molecular patterns (HAMPs) (Mithöfer and Boland, 2008; Bonaventure *et al.*, 2011; Hogenhout and Bos, 2011; Jouannet *et al.*, 2014; Acevedo *et al.* 2015) but knowledge about their corresponding PRRs is scarce.

Arthropod-derived HAMPs

Initially termed "elicitors" because they elicited defense responses from the plant, HAMPs have been found in a variety of sources, including saliva, oral secretions (OS), reproductive glands, whole body or eggs (Table 1). HAMPs (like PAMPs) constitute essential patterns, making it difficult for herbivores to eliminate them and hence avoid recognition.

One of the first and best-known example is volicitin, a fatty acid-amino acid conjugate (FAC) purified from OS of the beet armyworm caterpillar *Spodoptera exigua* (Alborn *et al.*, 1997). When applied to maize leaves, volicitin triggers the emission of a bouquet of volatile terpenoids and indoles that attract parasitic wasps. Volicitin is composed of 17-hydroxylinolenic acid coupled to glutamine. Interestingly, chemical analysis established that linolenic acid originates from the plant and is further hydroxylated and conjugated to glutamine by the insect (Lait *et al.*, 2003; Pare *et al.*, 1998). Volicitin and related FACs (fatty acids of different length and saturation coupled to glutamine or glutamate) were further identified in OS from different Lepidoptera (Pohnert *et al.*, 1999; Halitschke *et al.*, 2001; Mori *et al.*, 2003) and even in other insects (Yoshinaga *et al.*, 2007). The physiological role of FACs is not yet clear but it has been suggested that they are important for nitrogen assimilation in larvae (Yoshinaga *et al.*, 2008). In addition, the amphiphilic nature of these molecules might emulsify the ingested food.

Caeliferins are sulfated hydroxy fatty acids isolated from OS of the grasshopper *Shistocera americana*. In maize, they elicit emission of volatiles similar to those triggered by volicitin, although there is no evidence for natural enemies of grasshoppers (Alborn *et al.*, 2007). 2-hydroxy octadecatrieonic acid (2-HOT) was detected in OS of the tobacco hornworm *Manduca sexta* and triggers the emission of the sesquiterpene trans-α-bergamotene in wild tobacco *Nicotiana attenuata*. In plants, 2-HOT is produced from linolenic acid by the action of α-dioxygenases. Occurrence of 2-HOT in *M. sexta*

OS may allow plants to sense herbivore feeding by the presence of a modified membrane constituent (Gaquerel *et al.*, 2009). Bruchins are fatty acid derived long-chain α,ω-diols, esterified at one or both ends with 3-hydroxypropanoic acid. They were isolated from pea and cowpea weevil oviposition fluid and induce tumor-like growth of undifferentiated cells (neoplasms) on pea pods, like naturally deposited eggs. Neoplasms serve as direct defense by blocking larval entry (Doss *et al.*, 2000). Eggs of the white backed planthopper *Sogatella furcifera* stimulate the production of the ovicidal substance benzyl benzoate in certain rice varieties. Purification of female extracts yielded active phospholipids, including phosphatidylcholine and phosphatidylethanolamine (Yang *et al.*, 2014). Finally, oviposition by the large white *Pieris brassicae* induces defense gene expression, local necrosis and production of reactive oxygen species in Arabidopsis (Little *et al.*, 2007). The inducing activity is found in egg extracts from different insects and is enriched in the lipid fraction (Bruessow *et al.*, 2010).

All the above examples seem to indicate that lipid-derived HAMPs are prevalent in OS from chewing herbivores. However, known HAMPs also include proteins, peptides and small metabolites. A β-glucosidase in *P. brassicae* OS is responsible for volatile emission in cabbage (Mattiacci *et al.*, 1995), a lipase in the grasshopper *Schistocera gregaria* OS induces defense gene expression (Schäfer *et al.*, 2011), and an uncharacterized 12kDa protein from oviduct secretions of the sawfly *Diprion pini* induces volatile emission in pine (Hilker *et al.*, 2005). Inceptin is a peptide that originates from the digestion of plant proteins, illustrating plants' ability to detect feeding-dependent modification of self. This cyclic peptide of eleven amino acids was purified from OS of the fall armyworm *S. frugiperda* and derives from proteolytic cleavage of a plant chloroplastic ATPase in the insect midgut (Schmelz *et al.*, 2006). When applied to cowpea (*Vigna unguiculata*) or maize, inceptin induces the production of defense-related hormones, volatiles and defense compounds. Small metabolites include for example benzyl cyanide and indole from reproductive accessory glands of *P. brassicae* and *Pieris rapae*, respectively. They are associated with eggs and induce indirect plant defense by arresting egg parasitoids at the oviposition site (Fatouros *et al.*, 2008; Fatouros *et al.*, 2009).

The feeding mode and physiology of phloem-sucking aphids have rendered HAMPs isolation difficult. Aphids deliver minute amounts of saliva with their syringe-like stylet when probing and navigating through different cell layers to reach sieve elements. Proteomic and genomic analyses of secreted proteins from the green peach aphid *Myzus persicae* salivary glands have nevertheless identified candidate HAMPs that induced defense gene expression or lowered aphid fecundity when overexpressed in Arabidopsis (Table 1) (de Vos and Jander, 2009; Elzinga *et al.*, 2014). In addition, Thrips and phytophagous mites have different feeding mode than chewing herbivores or aphids. Although they belong to different classes (insects or arachnids), both pierce plant tissues and feed on cell content. The Western flower thrips *Frankliniella occidendalis* and the two-spotted spider mite *Tetranychus urticae* have been used as a model to study Arabidopsis and tomato plant defenses. Whereas transcriptional changes similar to those induced by lepidopteran herbivores were observed, the nature of the eliciting activity is still unknown (de Vos *et al.*, 2005; Abe *et al.*, 2008; Kant *et al.*, 2008; Zhurov *et al.*, 2014).

Interestingly, recognition can be mediated through bacterial PAMPs that are present in OS. A porin-like protein from *Ralstonia* was purified from *S. littoralis* OS and activated early defense responses, including channel formation and calcium fluxes (Guo *et al.*, 2013). The bacterial chaperonin GroEL was identified in saliva of the potato aphid *Macrosiphum euphorbiae*. This protein originated from the endosymbiont *Buchnera aphidicola* and induced PTI responses that depended on BAK1 in Arabidopsis (Chaudhary *et al.*, 2014). These two examples expand the range of potential sources of HAMPs to the gut microbiome.

HAMP recognition by potential PRRs

Strikingly, contrary to the case of bacterial and fungal PAMPs where direct binding to a PRR has been demonstrated (Boller and Felix, 2009; Couto and Zipfel, 2016), there is yet no evidence for a *bona fide* PRR that perceives a HAMP. However, *M. persicae*-derived HAMPs were shown to elicit defenses characteristic of PTI responses in a BAK1-dependent manner (Prince *et al.*, 2014; Vincent *et al.*, 2017). These studies provide evidence for detection of aphid HAMPs by (unknown) PRRs that are distinct from PRRs that detect bacterial and fungal PAMPs (Prince *et al.*, 2014). More than a decade ago, a biochemical study using a radiolabelled form of volicitin reported binding to a plasma-membrane protein from maize leaves (Truitt *et al.*, 2004). However, this protein has not been further characterized and no gene has been cloned. A cluster of three lectin receptor kinase (LecRK) genes conferred resistance to the brown planthopper (BPH) in rice, but whether these LecRK bind to yet unknown HAMPs from BPH or mediate downstream events is unknown (Liu *et al.*, 2015). Arabidopsis LecRK-I.8 is involved in the perception of egg-derived HAMPs. Indeed, a *lecRK-I.8* mutant displayed a significantly reduced expression of the defense gene *PR1* in response to egg extract treatment (Gouhier-Darimont *et al.*, 2013). This interesting observation will however await chemical identification of the lipid-derived HAMP and binding assays.

Recently, a LecRK receptor for extracellular ATP was discovered in Arabidopsis. DORN1 (LecRK-I.9) bound ATP with high affinity and ectopic expression triggered plant responses associated with wounding. It was concluded that DORN1 may mediate perception of feeding herbivores by detecting ATP liberated from cell content after physical damage (Choi *et al.*, 2014). Although ATP is not formerly a HAMP but rather a damage-associated molecular pattern (DAMP), this finding reinforces the hypothesis that LecRKs may be important components of HAMP perception.

Wound responses

It has long been recognized that wounding is an important component of plant responses to chewing herbivores (Green and Ryan, 1972; Howe and Jander; 2008). Early work in Solanaceae identified systemin, a 18-aa polypeptide wound signal that regulates the production of anti-insect proteinase inhibitors (reviewed in Ryan and Pierce, 1998). Although some early responses to herbivory are not or only partially mimicked by mechanical damage (Brichi *et al.*, 2010) and emission of volatiles is specifically triggered by insect-derived cues (Alborn *et al.*, 1997), wounding and feeding activate overlapping sets of genes (Reymond *et al.*, 2000; Major *et al.*, 2006). In addition, jasmonic acid (JA), the main signal controling defenses (see below), rapidly accumulates in response to mechanical damage (Reymond *et al.*, 2000; Glauser *et al.*, 2008). For aphids, turgor changes associated with stylet penetration of the phloem may also contribute to some defense responses, like for instance the rapid plugging of sieve plates by callose or protein aggregates (reviewed in Will and van Bel, 2006).

Since many studies on the role of HAMPs involve exogenous application of OS on wounded leaves, conclusions from such experiments have to be assessed critically. Future experiments aiming at removing HAMPs genetically or physically from the herbivore, as in the case of salivary gland ablation (Musser *et al.*, 2002), will be necessary to demontrate the specific role of these elicitors.

Open questions

In several cases, the defense inducing activity of HAMPs is associated with crude extracts or unknown proteins, but their exact chemical nature is unknown. For most HAMPs, information on their role in arthropod biology is lacking and future work should elucidate why they have been kept since they alert the plant about the attack. In addition, genes responsible for HAMP synthesis need to be identified. Host specificity and distribution in different arthropod taxa should also be addressed. For instance, FACs have a broad-range activity but do not elicit volatile emission in lima bean and cotton (Spiteller *et al.*, 2001; Schmelz *et al.*, 2009). Inceptin action is restricted to Fabaceae while Arabidopsis only responds to caeliferins (Schmelz *et al.*, 2009). Finally, there is a clear lack of knowledge on potential PRRs and efforts should be placed in finding ligand/binding pairs and defining downstream steps to establish if plants use the same molecular machinery to detect HAMPs and PAMPS.

SIGNALING

Upon feeding, early signaling events include membrane depolarization, Ca^{2+} influx, production of reactive oxygen species (ROS), and activation of mitogen-activated protein kinases (MAPK) (Howe and Jander, 2008; Wu and Baldwin, 2010; Vincent *et* *al.*, 2017). These fast responses have been observed in different plant species and thus seem to constitute a general mechanism to transduce HAMP perception. Since Ca^{2+}, ROS, and MAPK are also involved in plant responses to pathogens, how they specifically trigger anti-herbivore defense is currently unknown. For oviposition, there is little information on early signaling steps, however ROS accumulation under eggs has been reported (reviewed in Reymond, 2013; Hilker and Fatouros, 2015). Following early responses to arthropods, alteration in hormonal profile plays a crucial role. JA is the predominant signal that regulates downstream defense steps. Depending on the attacker and on its developmental stage, a role for salicylic acid (SA), ethylene (ET), and other plant hormones as primary signals or modulators has also been reported.

JA pathway

A large body of literature has detailed the importance of the JA pathway in response to necrotrophs and herbivores (Howe and Jander, 2008; Browse, 2009; Acosta and Farmer, 2010; Wu and Baldwin, 2010; Pieterse *et al.*, 2012). In brief, upon damage fatty acids are released from plastidic galactolipids. 13-lipoxygenases ogygenate 18:3 and 16:3 fatty acids to produce hydroperoxides, which are further converted by allene oxide synthase and allene oxide cyclase to 12-oxo-phytodienoic acid (OPDA) and dinor-oxo-phytodienoic acid (dnOPDA), respectively. OPDA and dnOPDA are transferred to peroxisomes where they are reduced by OPDA reductase 3 (OPR3) and subjected to a series of β-oxidation cycles to yield JA (Acosta and Farmer, 2010). Conjugation with Ile by the enzyme JAR1 in the cytosol generates the bioactive (+)-7-iso-JA-Ile (JA-Ile) (Staswick and Tiryaki, 2004; Fonseca *et al.*, 2009). After import in the nucleus, JA-Ile forms a complex with its receptor, the F-box CORONATINE INSENSITIVE 1 (COI1), and a JASMONATE-ZIM DOMAIN PROTEIN (JAZ). This leads to ubiquitination and degradation of the JAZ proteins by the proteasome. JAZs are repressors of transcription factors, including the Arabidopsis bHLH MYC2, MYC3 and MYC4, which control JA-dependent responses additively (Chini *et al.*, 2007; Thines *et al.*, 2007; Browse, 2009; Fernández-Calvo *et al.*, 2011) (Fig. 2). In Arabidopsis, transcriptome analyses revealed that herbivory alters the expression of hundreds of genes and that a majority of these genes are regulated by COI1 and MYC2/3/4 (Reymond *et al.*, 2004; de Vos *et al.*, 2005; Schweizer *et al.*, 2013a; Schweizer *et al.*, 2013b). As a consequence, *coi1-1* and *myc234* mutants were significantly more susceptible to herbivory by the generalist herbivore *S. littoralis* (Fernández-Calvo *et al.*, 2011; Schweizer *et al.*, 2013b). In addition, role of the JAZ1/3/4/9/10-MYC2/3/4 Arabidopsis module in resistance against the generalist *Trichoplusia ni* was recently demonstrated (Major *et al.*, 2017).

That the JA pathway is central to resistance against arthropods in plants was demonstrated using mutants. An original study using the Arabidopsis *fad3–2 fad7–2 fad8* triple mutant deficient in the jasmonate precursor linolenic acid showed that it was highly susceptible to larvae of the saprophagous fungal gnat, *Bradysia impatiens* (McConn *et al.*, 1997). Loss of function of the COI1 homologue in tomato increased susceptibility to the two-spotted spider mite *T. urticae* (Li *et al.*, 2004b), and to the lepidopteran herbivores *M. sexta* (Chen *et al.*, 2005) and *T. ni* (Herde and Howe, 2014). Silencing COI1 in *N. attenuata* improved performance of *M. sexta,* and of the stem weevil *Trichobaris mucorea* (Paschold *et al.*, 2007; Diezel *et al.*, 2011); the silverleaf whitefly *B. tabaci* accelerated nymphal development on Arabidopsis *coi1-1* (Zarate *et al.*, 2007); the isopod crustacean *Porcellio scaber* completely devoured Arabidopsis *aos* whereas wild-type plants remained intact (Farmer and Dubugnon, 2009); silencing LOX and AOC in rice plants increased root herbivory by the generalist cucumber beetle *Diabrotica balteata*, and the specialist rice water weevil *Lissorhoptrus oryzophilus* (Lu *et al.*, 2015); in maize, mutants of *OPR7* and *OPR8*, two close homologues of *OPR3*, were more susceptibile to *S. exigua* (Yan *et al.*, 2012); the tomato jasmonate biosynthesis mutant *def-1* that is impaired in volatile emission did not attract predatory mites when infested with *T. urticae,* indicating that the JA pathway is also essential for indirect defense (Ament *et al.*, 2004). For aphids, Ellis *et al.* (2002) showed that Arabidopsis mutants with constitutive activation of JA-signaling were more resistant to *M. persicae*.

Other hormones

The SA pathway is generally important to fend off biotrophic pathogens and plays a major role in PTI/ETI (Pieterse *et al.*, 2012). SA is a phenolic compound that is mainly synthesized from the precursor chorismate by ISOCHORISMATE SYNTHASE 1 (ICS1/SID2). Activation of the lipase-like protein ENHANCED DISEASE SUSCEPTIBILITY 1 (EDS1) and its related interacting partner PHYTOALEXIN DEFICIENT 4 (PAD4) by biotrophic pathogens trigger SA accumulation (Vlot *et al.*, 2009). Consequently, change in the redox state of the cell redirects the transcriptional coactivator NON EXPRESSOR OF *PR* GENES 1 (NPR1) from the cytosol to the nucleus, where it regulates expression of numerous defense genes, including the SA marker gene *PR-1* (Vlot *et al.*, 2009; Pieterse *et al.*, 2012).

The role of the SA pathway in resistance to arthropods has received some attention. Aphid feeding induced expression of SA-marker genes, but no SA accumulation was observed and studies with SA-pathway mutants in Arabidopsis generated contrasting data on arthropod performance (reviewed in Jaouannet *et al.*, 2014). For example, in one study (Mewis et al., 2005) *npr1* and NahG were less susceptible to the green peach aphid *M. persicae*, whereas this difference was not found by Pegadaraju *et al.* (2005). However, *pad4* showed increased performance to *M. persicae* but this effect was independent on EDS1 (Pegadaraju *et al.*, 2005, 2007). By suppressing *PAD4* expression, *BOTRYTIS*-INDUCED KINASE1 (BIK1) was also shown to confer enhanced susceptibility to *M. persicae*, indicating that this PTI modulator and target of BAK1 acted as a negative regulator of the plant defense to aphids (Lei *et al.*, 2014). Finally, *M. persica*e infestation triggered a transient trehalose accumulation in Arabidopsis, which was shown to enhance PAD4 expression (Singh *et al.*, 2011). PAD4 seems thus to constitute an important component mediating defense against aphids but its connection to the SA pathway remains elusive (Shah and Louis, 2015).

For chewing herbivores, *S. littoralis* larvae were smaller when feeding on *ics1* and *npr1-1*, implying a negative role of SA (Stotz *et al.*, 2002; Bodenhausen and Reymond, 2007). Since the SA pathway is known to antagonize the JA pathway (Pieterse *et al.*, 2012), these findings suggest that the enhanced resistance of the mutants is due to a lack of inhibition of the JA pathway rather than a direct effect of SA (Koornneef and Pieterse, 2008). Spider mite performance was higher on SA-deficient tomato line NahG than on wild type (Villarroel *et al.*, 2016). When the brown planthopper *Nilaparvata lugens* infested a rice line that overexpresses the resistance gene *Bph14,* there was an induced expression of SA-related genes (Du *et al.*, 2009). Finally, SA accumulated in resistant willow genotypes when attacked by the gall midge *Dasineura marginemtorquens* (Ollerstam and Larsson, 2003).

P. brassicae oviposition on Arabidopsis triggered SA accumulation and expression of SA-responsive genes (Little *et al.*, 2007). Follow-up studies using SA-signaling mutants indicated that Arabidopsis responses to egg extract, including defense gene expression, ROS accumulation and local cell death, share similarities with PTI and requires a functional SA pathway (Gouhier-Darimont *et al.*, 2013) (Fig. 2).

ET is a modulator of SA and JA pathways. For instance, the ET pathway has a synergistic effect on the JA pathway to fight necrotrophic pathogens or acts with NPR1 to enable SA antagonistic action on the JA pathway (reviewed in Pieterse *et al.*, 2012). Information on the role of ET against arthropods is however incomplete or inconclusive. The ET-insensitive Arabidopsis mutant *ein2-1* is more resistant to *S. littoralis* feeding (Bodenhausen and Reymond, 2007; Stotz *et al.*, 2000). On the contrary, inhibition of ET perception in maize enhances feeding by *S. frugiperda* (Harfouche *et al.*, 2006). Treatment with HAMPs induced ET production in different plant species (Schmelz *et al.*, 2009). Similarly, FACs elicited ET burst in *N. attenuata* and this prevented SA accumulation, hence reducing a potential inhibitory effect of SA on the JA pathway (Diezel *et al.*, 2009). Whitefly-induced interference of parasitoid attraction triggered by *Plutella xylostella* feeding was abolished in *ein2-1* (Zhang *et al.*, 2013). Finally, inhibition of the JA pathway after *P. brassicae* oviposition-induced SA accumulation in Arabidopsis is dependent on both NPR1 and EIN2 (Schmiesing *et al.*, 2016).

Involvement of abscisic acid (ABA), auxin, gibberellins, brassinosteroids and cytokinins in response to herbivory has been adressed in several studies (reviewed in Erb *et al.*, 2012). The emerging picture is that these hormones primarily act as modulators of the JA pathway and thus do not play a direct role in defense (reviewed in Erb *et al.*, 2012).

Systemic responses

Evidence for a long-distance activation of defenses in response to herbivory has accumulated over years. It requires activation of the JA pathway in local and distal tissues but the nature of the systemic signal (hydraulic, chemical or electrical) has been the subject of controversy (reviewed in Farmer *et al.*, 2014; Huber and Bauerle, 2016). That JA or a precursor is the mobile signal was postulated but not demonstrated (Li *et al.*, 2002a; Stratmann, 2003; Koo *et al.*, 2009). On the other hand, rapid voltage changes in local and distal Arabidopsis leaves in response to *S. littoralis* feeding were recently reported and depended on *GLUTAMATE RECEPTOR-LIKE (GLR)* genes *GLR3.3* and *GLR3.6* (Mousavi *et al.*, 2013; Salvador-Recatalà *et al.*, 2014). Implanting platinum wires in the petiole of a leaf and injecting current triggered JA and JA-Ile accumulation, and defense gene expression in the leaf lamina distal to the treatment site, providing strong evidence for the role of electrical signaling in systemic response to herbivory (Mousavi *et al.*, 2013). Similar electrophysiological changes were further observed in monocotyledonous and dicotyledonous species after challenge with *S. littoralis* and *M. sexta* (Zimmermann *et al.*, 2016). Interestingly, aphid-induced Ca^{2+} accumulation in Arabidopsis was shown to depend on GLR3.3 and GLR3.6, but here a role in long-distance signaling is unlikely (Vincent *et al.*, 2017). In contrast, systemic responses from wounded Arabidopsis cotyledons to roots was shown to be independent of GLRs and electrical signaling but more probably due to JA transport (Gasperini *et al.*, 2015). Similarly, JA but not JA-Ile was identified as a long-distance transmissible signal in *N. attenuata* response to *M. sexta* using stem-to-stem grafted plants (Bozorov *et al.*, 2017). In tomato, application of isotope-labeled precursors in wounded leaves indicated that

JA-Ile may be a mobile signal (Matsuura et al., 2012). It thus appears that a combination of electrical signaling and hormone transport may be responsible for systemic induction of JA-related defenses, but that the contribution of each signal may depend on the organ or plant species considered (Fig. 3).

Oviposition also triggers changes in distal leaves. Egg deposition by the elm leaf beetle *Xanthogaleruca luteola*, the sawfly *D. pini*, and the stemborer moth *Chilo partellus* induced the release of volatiles in local and distal leaves of *Ulmus minor*, *Pinus sylvestris*, and maize respectively (Meiners and Hilker, 2000; Hilker *et al.*, 2002; Tamiru *et al.*, 2011). Recently, *P. brassicae* oviposition on Arabidopsis leaves inhibited infection by the bacterial pathogen *Pseudomonas syringae*, both in local and distal leaves (Hilfiker *et al.*, 2014). This systemic acquired resistance (SAR) depended on the metabolic SAR signal pipecolic acid. Indeed, pipecolic acid accumulated in local and distal leaves after oviposition and mutation in the biosynthesis gene *ALD1* abolished egg-induced SAR (Hilfiker *et al.*, 2014). For all these examples, the nature of the systemic signal is however unknown (Fig. 3).

Open questions

The precise connection between detection of herbivory or egg deposition and the following activation of different signaling pathways is currently unknown. Although the JA pathway is crucial to fend off a majority of herbivores, which downstream defenses genes are critical for resistance is still unresolved in most plant species. The SA pathway may be important in some plant-arthropod interactions, but further experiments should demonstrate SA accumulation and altered performance on SA mutants. Similarly, more work will be necessary to understand the exact molecular contribution of the ET pathway. Modulation of defenses against herbivory by other plant hormones will also have to be better explored (Erb *et al.*, 2012). Finally, a better knowledge on the nature of systemic signals that activate defenses in distal tissues is needed.

DEFENSE COMPOUNDS

Metabolites

The plant multilayered immune system is accompanied by the endogenous production of metabolites with direct antimicrobial or/and insecticidal activity, whereas some metabolites act as signals and contribute to plant immunity by regulatory means (Mithöfer and Boland, 2012). Examples of plant-derived metabolites with a direct insecticidal activity are given in Table 2.

Plants produce non-protein amino acids that function in response to herbivory (reviewed in Huang *et al.*, 2011). One of the best-studied example is L-canavanine, a major nitrogen storage compound in seeds of many species of Leguminosae and a structural analog of L-arginine. L-canavanine is integrated in proteins, which results in the synthesis of dysfunctional proteins and poor larval development (Rosenthal *et al.*, 1976, Rosenthal, 2001). Tobacco and soybean plants respond rapidly to herbivore attack with a production of γ-aminobutyric acid (GABA) (Bown *et al.*, 2002). Larvae of the oblique-banded leafroller *Choristoneura rosaceana* raised on GABA-containing artificial diets showed decreased growth and survival rates, indicating that GABA possess direct insecticidal activity (Bown *et al.*, 2006). This insecticidal activity could result from inhibition of neurotransmission via GABA-regulated fast-acting chloride channels (Hosie *et al.*, 1997, Bown *et al.*, 2006).

Terpenoid-based compounds with insecticidal properties are widely spread in the plant kingdom. Azadirachtin is synthesized by the neem tree *Azadirachta indica* and reduces growth of *Spodoptera littoralis*, *Spodoptera frugiperda*, and *Schistocerca gregaria* by negatively influencing cell division and disruption of the endocrine system (Mordue Luntz *et al.*, 1998). Pyrethrin from *Chrysanthemum cinerariifolium* inactivates sodium channels along nerve cells and thereby harm insects from different orders and families, including Tetranychidae, Pseudococcidae, Auchenorrhyncha, Coleoptera, Caelifera, and Aleyrodidae (Casida *et al.*, 1983). In response to JA, ET, and attack by the European corn borer *Ostrinia nubilalis*, *Zea mays* produces *ent*-kaurane–related diterpenoids, collectively termed kauralexins, which exhibit antifeedant activity on *O. nubilalis* (Schmelz *et al.*, 2011). Moreover, the lactone taraxinic acid β-D-glucopyranosyl ester (TA-G) in latex protects the dandelion *Taraxacum officinale* against its major root herbivore, the cockchafer *Melolontha melolontha*. Silencing of the germacrene A synthase ToGAS1 resulted in decreased levels of TA-G in *T. officinale* and in increased *M. melolontha* feeding (Huber *et al.*, 2016).

Nicotine is one of the best-studied plant-derived alkaloid with insecticidal activity and is produced by native tobacco species, such as *N. attenuata* and *Nicotiana sylvestris*. It is structurally related to acetylcholine and can thereby target acetylcholine receptors in the nervous system of insects (Gepner *et al.*, 1978). Silencing putrescine N-methyltransferase (PMT), which is involved in nicotine biosynthesis, results in decreased constitutive and inducible nicotine levels in *N. attenuata*. Consequently, IR*pmt* plants grown in field experiments were more frequently attacked by the *S. exigua* and *Trimerotropis* spp. grasshoppers (Steppuhn *et al.*, 2004). The medicinal plant *Catharanthus roseus* produces more than a hundred different monoterpene indole alkaloids (MIAs), which are well described as anticancer drugs in chemotherapy. Catharanthine accumulates in leaf wax exudates and exhibits insect toxicity on *Bombyx mori* larvae when included in artificial diet (Roepke *et al.*, 2010). Furthermore, transcriptomic and metabolic analysis showed that *C. roseus* respond to *M. sexta* feeding with the biosynthesis of specific MIAs. Interestingly, *C. roseus* leaf consumption resulted in a rapid death of *M. sexta* larvae, which could be linked to MIA generation and dimerization (Dugé de Bernonville *et al.*, 2017). Other examples of insecticidal alkaloids include caffeine, colchicine, strychnine, and swainsonine (Wink *et al.*, 1998, Mithöfer and Boland, 2012).

Flavonoids, derived from the phenylpropanoid metabolism, are a diverse group of plant secondary metabolites found in all plant species and they display some antiherbivore effects (Ververidis *et al.*, 2007). Rotenone is produced in roots of tropical legumes, such as *Derris eliptica* and *Lonchocarpus*, and is a mitochondrial poison that blocks the electron transport chain and disrupts energy production (Isman *et al.*, 2006). Kaempferol-3,7-dirhamnoside (KRR) accumulates in Arabidopsis in response to *P. brassicae* feeding (Onkokesung *et al.*, 2016). Overexpression of *MYB75*, a transcription factor that activates the anthocyanin pathway, resulted in decreased KRR levels in Arabidopsis plants and increased susceptibility to *P. brassicae*. Furthermore, *P. brassicae* gained less weight when reared on artificial diet containing KRR (Onkokesung *et al.*, 2014).

Aliphatic- and indole-glucosinolates (GS) belong to the best-studied insecticidal metabolites in Brassicaceae, including the model plant Arabidopsis. Aliphatic-GS and indole-GS are derived from methionine and tryptophan, respectively. They are produced in leaves constitutively and act as phytoanticipins in basal immunity against arthropods, but their synthesis can also be induced in response to various pathogen attacks. Thereby, GS biosynthesis relies on a complex regulatory network, controlled by several MYB and MYC transcription factors (Schweizer *et al.*, 2013b; Frerigmann, 2016). Upon plant-tissue disruption, β-thioglucoside glucohydrolase-dependent GS hydrolysis leads to the generation of chemically unstable aglycones, such as toxic nitriles, thiocyanates, and isothiocyanates. These aglycones can react spontaneously with biological nucleophiles and modify proteins and nucleic acids (reviewed Pastorczyk and Bednarek, 2016). Strikingly, GS-deficient Arabidopsis mutants are highly susceptible to arthropod feeding, including chewing larvae, spider mites, and aphids (Mewis *et al.*, 2005; Beekwilder *et al.*, 2008; Schlaeppi *et al.*, 2008; Schweizer *et al.*, 2013b; Zhurov *et al.*, 2014; Madsen *et al.*, 2015). Tryptophan can also serve as a precursor for several indolic alkaloids, which act as defense-related metabolites in Arabidopsis. Camalexin is produced in Arabidopsis upon infestation by the phloem feeding green peach aphid *M. persicae*. Consequently, *M. persicae* grows more successfully on camalexin-deficient *pad3* mutant, indicating that camalexin functions in defense against phloem sap sucking insects (Kettles *et al.*, 2013). Similarly, camalexin accumulated in response to infestation by the cabbage aphid *Brevicoryne brassicae* and aphid performance was augmented on *pad3* (Kusnierczyk *et al.*, 2008).

Many defense compounds are stored in developmental structures, including glandular trichomes, laticifers, resin ducts, and specialized cell types or tissues (Mithöfer and Boland, 2012). Genetic evidence for the role of trichomes as a source of defense against herbivores was provided for tomato (Kang *et al.*, 2010; Bleeker *et al.*, 2012), Arabidopis (Mauricio, 1998), *Arabidopsis lyrata* (Kivimäki et al., 2007) and *Nicotiana attenuata* (Luu *et al.*, 2017). Induction of terpene-containing traumatic resin ducts by JA in Norway spruce provides support for a defensive role of these structures against conifer pests (Martin *et al.*, 2002).

In addition to ingested defense metabolites that target physiological processes in arthropods, plants produce metabolites that harm feeding herbivores physically. In the barrel medic *Medicago truncatula,* calcium oxalate crystals accumulate around secondary veins and act as physical abrasive of *S. exigua* mandibles. Consistent with this, larvae showed a feeding preference for the calcium oxalate-defective mutants *cod5* and *cod6* (Korth *et al.*, 2006). Silica constitutes another important physical defense compound, particularly in grasses (reviewed in Hartley and DeGrabriel, 2016). For example, *Spodoptera exempta* larvae exposed to silica-rich diet displayed mandible wear and reduced growth (Massey and Hartley, 2009).

Proteins and peptides

Besides toxic metabolites, plants produce numerous proteins and peptides with direct insecticidal activity (Table 3). Acrelin-1 is a 60 kDa dimeric glycoprotein found in seeds of the wild kidney bean *Phaseolus vulgaris*. Acrelin-1 is highly resistant to proteolytic degradation and binds to complex glycans, which leads to disruption of the epithelial structure in the midgut of the Mexican bean weevil *Zabrotes subfasciatus* (Fabre *et al.*, 1998). Plant-derived lectins are a heterogenous group of proteins found in many members of Leguminosae. They can bind to specific carbohydrate structures in the insect digestive tract, which leads to harmful effects in the whole insect body. Insecticidal activity of lectins was reported against members of Coleoptera, Lepidoptera, and Homoptera (Vandenborre *et al.*, 2011).

Cyclotides represent a group of small peptides found in Rubiaceae and Violaceae. A cyclic peptide backbone in combination with a cysteine knot confer strong chemical and biological stability. Cyclotides inhibit larval growth and development of the native budworm *Helicoverpa punctigera* and leads to disruption of microvilli and cellular rupture in the gut epithelium of *H. armigera* larvae (Jennings *et al.*, 2001; Barbeta *et al.*, 2008). Canatoxin (CNTX) is an urease found in seeds of the jack bean *Canavalia ensiformis*. Proteolytic activation of CNTX releases a 10 Kda peptide that interferes with serotine-related processes in *Callosobruchus maculatus* and *Rhodnius prolixus* (Stanisçuaski and Carlini, 2012). In tomato, threonine deaminase TD2 has insecticidal properties by depriving herbivores from the essential Thr. Proteolytic activation of TD2 is catalyzed by chymotrypsin in the gut of lepidopteran herbivores, such as *S. exigua*, but not in coleopteran herbivores. Consequently, *S. exigua* larvae performed better on TD2-deficient tomato plants (Gonzales-Vigil *et al.*, 2011).

Arthropod digestion and nutrient acquisition relies on enzymes such as α-amylases, cysteine proteases, and serine proteases. So far, numerous plant protease and amylase inhibitors have been reported that inhibit digestive enzymes and thereby interfere with larval development. For instance, expression of an Arabidopsis cysteine protease inhibitor (*Atcys*) in transgenic white poplar plants is sufficient to inhibit most of the digestive proteinase activity of the leaf beetle *Chrysomela populi* and confers resistance to this insect (Delledonne *et al.*, 2001).

Open questions

Numerous plant-derived insecticides have been identified and some of them are of great interest in agriculture for plant protection. However, activity of most of them has just been studied in artificial diets. We need better knowledge of biosynthetic pathways and generation of knock-out mutants to test their role *in vivo*. Moreover, target sites for many of the known insecticides are poorly characterized.

SUPPRESSION OF DEFENSES

Effective plant PTI exerts as strong selection pressure on aggressors. Bacterial and fungal pathogens have thus evolved numerous effectors to interfere with PTI (Dodds *et al.*, 2009; Deslandes and Rivas, 2012;). These effectors are secreted and transferred or directly injected into plant cells. In return, plants have developed strategies to directly or indirectly detect effectors by intracellular nucleotide-binding, leucine-rich-repeat receptors (NB-LRRs) that trigger an enhanced defense response called effector-triggered immunity (ETI)(Jones and Dangl, 2006). This process illustrates the on-going arms race that has been the driving force for generating a multitude of effectors and defense proteins during plant-pathogen coevolution. Similarly, plant defense suppression by arthropods has been reported in several studies (Table 1).

Arthropod-derived effectors

A seminal discovery by Musser et al. (2002) reported that glucose oxidase (GOX) in *H. zea* salivary glands inhibited nicotine production in tobacco. Elegant experiments using ablation of the secretory apparatus, the spinneret, and ectopic application of active or inactive GOX demonstrated that this enzyme is responsible for a lower accumulation of nicotine upon feeding. Since GOX generates H_2O_2 from D-Glucose, it was further shown that this ROS may interfere with plant defense signaling (Bede *et al.*, 2006; Diezel *et al.*, 2009). An ATP-hydrolyzing apyrase activity was found in *H. zea* saliva.

Tomato plants treated with this enzyme showed reduced defense gene expression (Wu *et al.*, 2012). Since ATP can be perceived as a DAMP by plant PRRs, it is tempting to speculate that some insects have evolved a way to reduce ATP levels in their host. Unknown proteins or peptides from lepidopteran OS inhibited wound-induced defense gene expression in Arabidopsis and tomato, and this was correlated with enhanced insect performance in the case of Arabidopsis (Lawrence *et al.*, 2007; Consales *et al.*, 2012).

Although they act as HAMPs in several insects, FACs may have dual roles. Emission of some volatiles was reduced when *M. sexta* FACs were applied to *N. attenuata* plants. Whether this interfered with parasitoid attraction was however not tested (Gaquerel *et al.*, 2009). Heat-stable components of *M. sexta* OS suppressed wound-induced accumulation of *N. attenuata* transcripts but their chemical nature was not studied (Schittko *et al.*, 2001). Another striking example of a modified HAMP activity is found in the legume-specialist velvetbean caterpillar *Anticarsia gemmatalis*. OS of this insect contain a modified inceptin that does not induce plant defenses and furthermore acts as an antagonist of the normally active inceptin, probably by competing with inceptin-PRR binding (Schmelz *et al.*, 2012).

For spider mites and aphids, examples of effective suppression of defenses exist. In the spider-mite *T. urticae*, two proteins of unknown function suppressed defenses and increased mite performance when expressed in *N. benthamiana* (Villarroel *et al.*, 2016). A salivary component with high homology to human macrophage migration inhibitory factor (MIF) was identified in the pea aphid *Acyrthosiphon pisum* (Naessens *et al.*, 2015). MIFs are important pro-inflammatory cytokines modulating immunity and inflammation in vertebrates. Interestingly, RNAi of *ApMIF1* reduced survival and fecundity of *A. pisum*. In addition, ectopic expression of MIF1 reduced plant defenses in *N. benthamiana* (Naessens *et al.*, 2015). Since MIFs form heterocomplexes and homologues have been recently identified in plant genomes (Panstruga *et al.*, 2015), aphid MIF may interfere with endogenous MIFs to alter plant defenses (Naessens *et al.*, 2015; Reymond and Calandra, 2015). A salivary calcium-binding protein from *Megoura viciae* prevented sieve plate occlusion, a known defense mechanism against phloem-feeding that is triggered by calcium release (Will and van Bel, 2006; Will *et al.*, 2007). *A. pisum,* in which expression of the salivary protein C002 was reduced by RNAi, was impaired in phloem feeding (Mutti *et al.*, 2008). Attempts to identify more aphid effectors have relied on the same proteomic and genomic approaches that sucessfully isolated secreted HAMPs. A series of proteins of unknown function have been tested and were shown to suppress PTI responses and increase aphid performance when expressed *in planta* (Bos *et al.*, 2010; Atamian *et al.*, 2013; Elzinga *et al.*, 2014). For example, the *M. persicae* Mp10 effector suppressed flg22-induced but not chitin-induced ROS production (Bos *et al.*, 2010). Furthermore, Mp10 was shown to act in the BAK1 pathway (Drurey *et al.*, 2017). *M. persicae* Mp1 promoted aphid virulence by targeting a vacuolar sorting protein (VSP52) from its preferred host plants Arabidopis and potato, but not with VSP52 from poor-host barley and *Medicago truncaluta* (Rodriguez *et al.*, 2017). Similarly, a comparative study on aphid effectors revealed that they act in a plant-specific way and that sequences displayed high nonsynonymous substitution rates, indicative of positive selection (Pitino and Hohenhout; 2013).

The Hessian fly *Mayetiola destructor* is an economically important pest of wheat and a well-studied member of the plant parasitic gall midges (Stuart *et al.*, 2012). The Hessian fly genome revealed a large family of secreted proteins (SSGP-71) that resemble ubiquitin E3 ligases in plants (Zhao *et al.*, 2015). They contain a F-box domain and variable leucine-rich repeats (LRR). In plants, the F box interacts with Skp, a component of the SCF-E3-ubiquitin-ligase complex that targets proteins for degradation. Interestingly, two Hessian fly F-box-LRR effectors were shown to directly bind to wheat Skp proteins, suggesting that the role of these effectors is to highjack the plant proteasome in order to block defenses (Zhao *et al.*, 2015). As further evidence that F-box-LRRs are true effectors that can be recognized by NB-LRRs and trigger ETI, mutations in two SSGP-71 genes were associated with regained virulence on wheat cultivars containing the respective *H* resistance genes (Zhao *et al.*, 2015).

As discussed above, JA and SA signaling pathways generally modulate plant defenses against arthropods and pathogens, respectively. These pathways are antagonistic to each other and this property has been highjacked by bacterial effectors to effectively suppress SA-dependent defenses (Pieterse *et al.*, 2012; Zheng *et al.*, 2012; Gimenez-Ibanez *et al.*, 2014). Interestingly, effectors from arthropods also exploit antagonism between SA and JA pathways. In Arabidopsis, defense gene expression and JA levels were lower in response to *S. exigua* larvae with intact salivary glands compared to larvae with ablated spinneret. This effect was lost in a mutant that does not accumulate SA, implying a role for SA in inhibiting JA accumulation (Weech *et al.*, 2008). Silverleaf whitefly induced SA defenses while suppressing JA defenses in Arabidopsis and lima bean (Zarate *et al.*, 2007; Zhang *et al.*, 2009). Similarly, the mealybug *Phenacoccus solenopsis* inhibited JA accumulation and JA-dependent defenses in tomato and this suppression was due to SA accumulation (Zhang *et al.*, 2015). A somewhat twisted example comes from the Colorado potato beetle (CPB) *Leptinotarsa decemlineata* that uses microbe-derived flagellin to trigger SA-dependent inhibition of the JA pathway in tomato. Indeed, bacteria in CPB OS decreased JA-responsive defenses and increased SA and SA-related gene expression. These responses were lost when using antibiotic-treated larvae and a SA-mutant (Chung *et al.*, 2013). The observation that chitinase in larval frass of the fall armyworm *S. frugiperda* suppress maize defenses through induction of the SA-dependent gene expression provides another intriguing evidence of indirect effector-like activity. Finally, *P. brassicae* oviposition or egg extract-treatment triggered SA accumulation, suppressed larval-induced JA-dependent gene expression, and enhanced larval performance in Arabidopsis (Little *et al.*, 2007; Bruessow *et al.*, 2010). This egg-induced inhibition of the JA pathway is achieved through SA-dependent destruction of MYC2, MYC3 and MYC4 transcription factors that control JA defense gene expression (Schmiesing *et al.*, 2016). Intriguingly, *P. brassicae* oviposition also triggers a SAR against bacterial pathogens, a response that may benefit hatching larvae (Hilfiker *et al.*, 2014). This latter phenomenon does not seem to be strictly related to suppression of defenses but illustrates a manipulation of plant signaling pathways by an egg-derived effector, to the potential benefit of the attacker.

Defense suppression by insect-vectored viruses and phytoplasma

Plant pathogens like viruses and phytoplasma are often transmitted by arthropods and thus engage in mutualistic interactions with their vector to ensure dispersal and survival. Improved performance and reproduction of the carrier is thus crucial for the pathogen and consequently compromising plant defenses has obvious advantages. The pathogenesis protein βC1 of *Tomato yellow leaf curl China virus* (TYLCCNV), a begomovirus transmitted by the whitefly *B. tabaci*, binds to the plant transcription factor AS1, triggering a reduced expression of JA-responsive genes (Yang *et al.*, 2008). βC1 interacted with MYC2 and interfered with expression of TPS genes, which are responsible for biosynthesis of defensive terpenoids (Li *et al.*, 2014). Consequently, virus-infected whiteflies displayed a significantly higher survival and reproduction on tobacco plants than non-infected ones (Luan *et al.*, 2013). The C2 protein from the *Tomato yellow leaf curl Sardinia virus* (TYLCSV) and *Tomato yellow leaf curl virus* (TYLCV) was shown to interfere with the activity of COP9 signalosome complex, which subsequently compromised the function of several CUL1-based SCF ubiquitin E3 ligases. Jasmonate responses were altered in Arabidopsis expressing C2 from TYLCSV or TYLCV, suggesting that $\mathrm{SCF}^{\mathrm{COI1}}$ is one target of this virulence factor (Lozano-Durán *et al.* 2011; Rosas-Díaz *et al.*, 2016). The 2b protein of aphid-transmitted *Cucumber mosaic virus* inhibited expression of JA-regulated genes downstream of JA production (Lewsey *et al.*, 2010). *M. persicae* aphid fecundity was enhanced by *Turnip mosaic virus* infection of Arabidopsis, which showed increased callose deposition. This effect depended on ET-signaling and was caused by the Nuclear Inclusion a-Protease domain (Casteel *et al.*, 2015).

Phytoplasma are obligate bacterial pathogens that develop in plant phloem. The Aster Yellows phytoplasma strain Witches' Broom (AY-WB) secretes the SAP11 protein that destabilizes class II CIN-TCP transcription factors, some of which are positive regulators of the JA-biosynthesis enzyme LOX2. As a consequence, Arabidopsis lines expressing SP11 or AY-WB infected plants produced less JA and allowed enhanced performance of the leafhopper vector *Macrosteles quadrilineatus* (Sugio *et al.*, 2011).

Arthropod resistance genes

ETI triggered by pathogen or fungal effectors is driven by NB-LRRs. These resistance proteins usually contain a Toll-Interleukin-1 receptor-Resistance protein (TIR) or a coiled-coil (CC) domain at the amino terminus. They are encoded by numerous resistance (*R*) genes usually clustered in plant genomes, allowing recombination-based diversification to respond to the evolution of pathogen effectors (Jones and Dangl, 2006; McHale *et al.*, 2006). In contrast to *R* genes associated with bacterial and fungal pathogens, only a few arthropod-directed *R* genes have been cloned and characterized (Gururani *et al.*, 2012). *Mi-1.2* from tomato encodes a CC-NB-LRR and confers resistance to the potato aphid, the whitefly *B. tabaci*, the psyllid *Bactericerca cockerelli*, and the root-knot nematode *Meloidogyne incognita*, illustrating the first example of a resistance gene acting against distantly related pests (Milligan *et al.*, 1998; Rossi *et al.*, 1998; Nombela *et al.*, 2003; Casteel *et al.*, 2006). In the presence of potato aphid saliva *Mi-1.2* was shown to interact with *SlSERK1,* a receptor kinase related to Arabidopsis BAK1, and this complex formation is suggested to confer aphid resistance (Peng *et al.*, 2016). *Vat* from melon is also a CC-NB-LRR and, interestingly, provides dual resistance against the aphid *Aphis gossypii* and viruses transmitted by this vector (Dogimont *et al.*, 2014). Resistance to the brown planthopper (BPH) *Nilaparvata lugens,* a sucking insect attacking rice plants, is conferred by two CC-NB-LRR genes, *Bph14* and *Bph16* (Du *et al.*, 2009; Tamura *et al.*, 2014). In lettuce, *Ra* is part of a large CC-NB-LRR gene cluster and provides resistance against the root aphid *Pemphigus bursarius* (Wroblewski *et al.*, 2007). The *AIN* locus in *M. truncatula* is associated with resistance against the bluegreen aphid *Acyrthosiphon kondoi* and resides in a cluster of CC-NB-LRR genes (Klingler *et al.*, 2009). Similarly, *Hdic* is embedded in a family of

NB-LRR *H* resistance genes that are active against the Hessian fly *M. destructor* (Stuart *et al.*, 2012).

Open questions

Chemical identity, mode of action, and molecular target(s) of several effectors are poorly characterized. Whether each type of effector represents an evolutionary response to PTI and appears in only a subset of related arthropod species or biotypes, similar to bacterial or fungal effectors, remains an open question. When effectors inhibit defenses via SA-dependent inhibition of the JA pathway, it is unclear whether activation of the SA pathway by arthropod-derived cues illustrates a strategy evolved by the attacker to indirectly target the JA pathway or whether this is a trade-off, since the SA pathway may be needed for defense.

Strikingly, all examples of cloned resistance genes are CC-NB-LRRs that target phloem-feeding insects. Whether there is a mechanistic reason for such specificity or whether this is explained by a lack of success in cloning resistance genes against members of other feeding guilds will await future experiments. Indeed, many loci providing resistance against different orders of arthropods have been identified in different crop species and need to be characterized (Smith and Clement, 2011; Gururani *et al.*, 2012). Alternatively, other feeding guilds that rapidly consume leaf material may avoid recognition by "eating the evidence". Also, besides F-box-LRR effectors and H resistance proteins in Hessian fly/wheat interaction, information about the nature of effectors interacting with known arthropod NB-LRRs is currently lacking.

PLANT-ARTHROPOD COEVOLUTION

Plants and herbivores are engaged in a continuous battle for survival and rely on different strategies to counteract the evolution of resistance or adaptation to defense compounds. In addition to PTI and ETI immunity responses, which are based on HAMP recognition and inhibition of HAMP-triggered defenses by arthropod effectors (see previous sections), there are numerous examples of behavioral or metabolic responses that overcome plant defenses (Table 4). In a few cases, a successive appearance of defense and counterdefense mechanisms can be observed and nicely illustrates coevolutionary processes that underlie plant-arthropod interactions.

Behavioral adaptations

Capability of arthropods to circumvent plant defenses by specialized feeding behavior has been documented (reviewed in Dussourd, 2017). Cardenolides are toxic cardiac glycosides that inhibit Na/K-ATPase and are stored in latex from several plant families. Larvae of the queen butterfly *Danaus gilippus* cut trenches on leaves of the milkweed *Asclepias syriaca*, releasing a flow of cardenolide-containing latex and thus rendering the plant more palatable (Dussourd and Eisner, 1987). In some *Bursera* species, terpene-containing resin is stored under pressure in leaf canals. Upon feeding, the toxic resin is ejected and solidifies around small herbivores. Adapted members of chrysomelid beetles of the genus *Blepharida* puncture leaf veins to stop the flow before feeding (Becerra, 2003). Leaf vein severing or trench cutting is frequent and found in several arthropod families (Dussourd, 2017).

To avoid defensive trichomes in *Solanum* sp., larvae of the ithomiid butterfly *Mechanitis isthmia* spin a fine silk fabric over spines, allowing them to move and feed safely (Rathcke and Poole, 1975). Another behavioral adaptation is to minimize contact with induced plant defenses. When carefully studying movement of *H. armigera* caterpillars feeding on Arabidopsis, Perkins *et al.* (2013) noticed that larvae moved away from elicited and closely connected leaves, suggesting that they are capable of detecting a signal that triggers this response. The nature of the warning signal is unknown but depends on activation of the JA pathway (Perkins *et al.*, 2013). There are also examples of behaviors that reduce attraction of parasitoids. Larvae of *Heliothis subflexa* have specialized on their host plant *Physalis angulata* by feeding exclusively on fruits, which lack linolenic acid. As a consequence, no volicitin is produced in *H. subflexa* OS and feeding does not trigger volatile emission (De Moraes and Mescher, 2004). Since linolenic acid is required for development of most insect larvae, this physiological adaptation is remarkable and provides both a protection against parasitoids and an exclusive access to a food source. Interestingly, linolenic acid is also a precursor for JA and there is the possibility that *P. angulata* fruits are unable to trigger JA-dependent defenses against herbivores. This hypothesis was however not tested in the study. Recently, the first evidence of insect resistance against an introduced parasitoid wasp was reported (Tomasetto *et al.*, 2017). The Argentine stem weevil *Listronotus bonariensis* was discovered in New Zealand in 1927 and cause intensive damage to pasture grass. Since the introduction of a natural parasitoid of the stem weevil in the 90's there has been a gradual decline in parasitism rate from 80-90% to 10-20%. This sharp reduction is attributed to a host shift from *Lolium multiflorum* to the more widely cultivated *Lolium perenne*, which is potentially impaired in herbivore-induced volatile emission (Tomasetto *et al.*, 2017).

Metabolic resistance

Target modification and metabolism of plant toxins are the main strategies to overcome plant defenses and have been the subject of numerous studies, which in some instances have revealed the molecular mechanism (reviewed in Després *et al.*, 2007; Li *et al.*, 2007; Heidel-Fischer and Vogel, 2015).

Insensitivity of the monarch butterfly *Danaus plexxipus* to cardenolides was attributed to an amino acid substitution in the binding site of a Na/K-ATPase (Holzinger and Wink, 1996). The same substitution was found in four species that span four insect orders and 300 million years of divergence, providing a stunning example of convergent evolution (Dobler *et al.*, 2012). *H. zea* evolved a structural modification in the binding site of a carboxypeptidase to evade inhibition of the potato carboxypeptidase inhibitor (Bayés *et al.*, 2005). Similarly, a single amino acid substitution in chymotrypsin from *Helicoverpa* larvae removes a binding contact to a tobacco proteinase inhibitor (Dunse *et al.*, 2010). As described above, L-canavanine from legumes is a L-Arg analog with insecticidal properties. Larvae of the bruchid beetle *Caryedes brasiliensis* have evolved a discriminating arginyl-tRNA synthetase that does not accept L-canavanine as substrate and thus are protected against the toxic effect of this analog (Rosenthal *et al.*, 1976).

Detoxification of cyanogenic glycosides from *Passiflora* sp. by larvae of the butterfly *Heliconius* is carried out by sequestration and replacement of a nitrile by a thiol group that prevents cyanide release (Engler *et al.*, 2000). However, the enzyme responsible for this reaction has not been identified yet. Another way to avoid cyanide poisoning is to metabolize HCN. Remarkably, the spider mite *T. urticae* has acquired a bacterial gene encoding a β-cyanoalanine synthase (CAS) that can detoxify HCN to β-cyanoalanine (Wybouw *et al.*, 2014). The same activity was found in the lepidopteran herbivore *P. rapae* where CAS genes are also predicted to originate from bacteria through horizontal gene transfer (van Ohlen *et al.*, 2016). Excretion of the alkaloid nicotine by the specialist tobacco hornworm *M. sexta* is thought to be the main method by which this insect can thrive on Solanaceae (Self *et al.*, 1964; Maddrell and Gardiner, 1976). Interestingly, it was recently shown that part of the ingested nicotine is transported from *M. sexta* midgut to the hemolymph, from where it is actively exhaled and used as a defensive signal against the spider predator *Camptocosa parallela* (Kumar *et al.*, 2014).

Arthropod adaptation to the GS-myrosinase system of Brassicaceae has been extensively studied (Winde and Wittstock, 2011). In larvae of *P. rapa*e and *P. brassicae,* midgut nitrile-specifier proteins (NSPs) favor GS hydrolysis to less toxic nitriles, instead of isothiocyanates (ITC) (Wittstock *et al.*, 2004). In contrast, the diamondback moth *P. xylostella* and the desert locust *S. gregaria* detoxify intact GS with a sulfatase, preventing formation of hydrolysis products (Ratzka *et al.*, 2002; Falk and Gershenzon, 2007). Remarkably, the cabbage aphid *B. brassicae* sequesters intact GS from its host plants in the haemolymph and produces a myrosinase in microbodies. Upon attack by predators, aphids use this "mustard-oil bomb" to generate bioactive compounds and defend themselves (Bridges et al., 2002; Kazana et al., 2007). Similarly, the crucifer specialist flea beetle *Phyllotreta striolata* accumulates GS when feeding and has acquired a myrosinase gene (Beran *et al.*, 2014).

Major detoxification gene families from arthropods include cytochrome P450 monooxygenases (CYP450s), glutathione-*S*-transferases (GSTs), UDP-glycosyltransferases (UGTs), carboxyl/cholinesterases (CCEs) and ABC transporters (ABCs) (Li *et al.*, 2007; Heidel-Fischer and Vogel, 2015). These enzymes have relatively broad substrate specificity and are generally important for generalist herbivores that face a variety of plant toxins. Using the polyphagous *T. ni* and defense or signaling mutants, Herde and Howe (2014) were the first to demonstrate transcriptional reprogramming and altered expression of detoxification genes in response to GS in Arabidopsis. Similarly, a comparative transcriptomic analysis of larvae of the generalist *Heliothis virescens* and the specialist *P. brassicae* feeding on Arabidopsis genotypes with contrasting GS levels revealed a significant upregulation of detoxification genes from all the above-mentioned families in the generalist, whereas there was a much-reduced transcriptional activation in the specialist (Schweizer *et al.*, 2017). Furanocoumarins are DNA-interfering agents primarily found in Apiaceae and Rutaceae. Species of the genus *Papilio*, including the black swallowtail *P. polyxenes*, induce the expression of CYP450s from the CYP6B class upon feeding on furanocoumarin-containing plants. CYP6B proteins were shown to metabolize furanocoumarins and were more active in the specialist *P. polyxenes* than in the generalist *H. zea* (Hung *et al.*, 1997; Li *et al.*, 2004a; Li *et al.*, 2007). The fly genus *Scaptomyza* is closely related to the genus *Drosophila* and has acquired the ability to feed on Brassicaceae. A duplication in the GST gene *GstD1* in *S. nigra* is responsible for an enhanced detoxification activity against isothiocyanates, toxic breakdown products of GS, and is postulated to be linked to the evolutionary transition to herbivory in Drosophilidae (Gloss *et al.*, 2014). Gossypol is a major sesquiterpene defensive compound in cotton. Larvae of the generalist Heliothine moth *H. armigera* can develop on cotton plants and are equipped with two UGTs, UGT41B3 and UGT40D1, which are capable of glycosylating gossypol (Krempl *et al.*, 2016).

Although CCEs have been clearly associated with resistance to synthetic insecticides and CCE gene expression is induced after feeding (Li *et al.*, 2007; Teese *et al.*, 2010), there is limited information on their role against plant allelochemicals. In different strains of the gypsy moth *Lymantrya dispar*, larval survival on artificial diet containing phenolic glycosides was positively correlated with CCE activity (Lindroth and Weisbrod, 1991). Similarly, ABC transporters have been associated with insecticide resistance, including *Bacillus thuringiensis* insecticidal toxins (Bt). There is an expansion of ABC genes in the *T. urticae* genome and expression of ABC genes is enhanced upon switching to a different host plant or feeding on artificial diet containing plant secondary metabolites (Grbic *et al.*, 2011; Dermauw *et al.*, 2013a; Dermauw *et al.*, 2013b; Dermauw and Van Leeuwen, 2014; Tay *et al.*, 2015; Bretschneider *et al.*, 2016). However, direct evidence for a role of ABCs in resistance to plant allelochemicals is scarce. In the only known example, the *Cp*MRP transporter of the Chrysomelid leaf beetle *Chrysomela populi* is involved in the sequestration of salicin, a toxic phenolic glucoside found in willow and poplar leaves. CpMRP shuttles salicin from the hemolymph into specialized defensive glands, which play a role against predators. Reduction of *CpRMP* expression by RNAi abolished salicin excretion and rendered leaf beetles defenseless (Strauss *et al.*, 2013).

Escaping detection or anticipating defenses

As a striking example of adaptation, larvae of the velvetbean caterpillar produce a modified form of the cyclic peptide inceptin, a HAMP found in OS of the generalist Fall armyworm (see section on HAMPs). Through yet unknown modification of a gut protease, digestion of chloroplastic ATP synthase of the host plant cowpea generates a peptide lacking the C-terminal amino acid, *Vu*-In^{-A} (Schmelz *et al.*, 2012). Velvetbean OS induced a significantly weaker ET production and volatile emission in cowpea leaves, suggesting that the truncated inceptin evades recognition by a (unknown) plant receptor (Schmelz *et al.*, 2012).

A lag phase between ingestion/perception of plant toxins and transcriptional activation of detoxification genes may be detrimental to optimal larval development. An interesting study reported that treatment of *H. zea* larvae with the plant defense signals JA and SA induced the expression of four CYP450s that metabolize furanocoumarins and other toxins (Li *et al.*, 2002b). This induction was shown to provide an advantage to larvae, which performed better on furanocoumarin-containing plants or diets. "Eavesdropping" on defense signals seems thus an effective way of anticipating the production of defense compounds but the generality is this phenomenon amongst arthropods has yet to be established.

Coevolution

The seminal publication by Ehrlich and Raven (1964) stressed the importance of reciprocal relationship between butterflies and plant hosts in shaping the evolution and diversification of each group, and by extension supported the notion that plant-enemy interactions are responsible for much of global biological diversity. This has stimulated decades of research to test these predictions and provide experimental data for such scenario. Evidence is however scarce, because evolution is such a slow process that it is difficult to catch it in action and because several environmental, biogeographical and ecological factors may confound interpretations (reviewed in Futuyma and Agrawal, 2009). For example, removal of herbivore pressure in replicate fields of the evening primrose *Oenothera biennis* caused a rapid evolutionary divergence (Agrawal *et al.*, 2012). Phylogenetic reconstructions of plant and arthropods lineages have however generated useful hints that evolution of defense chemistry responds to herbivore pressure and that counteradaptation drives arthropod diversity. A convincing example is the stepwise evolution of GS complexity in Brassicales, mirrored with the radiation of Pierinae butterfly species (Wheat *et al.*, 2007; Edger *et al.*, 2015). A robust phylogenetic analysis of 14 families from the Brassicales revealed that this order originated ~90 million years ago (Ma) and that plants only synthesized aromatic Phe-GS. Indole-GS appeared after a whole-genome duplication (WGD) ~77 Ma, followed by the occurrence and diversification of aliphatic-GS-containing families ~60 Ma. Finally, after a second WGD, Brassicaceae appeared ~30 Ma and coincided with the greatest GS and species diversification (Edger *et al.*, 2015). Pierinae colonized Brassicales 68 Ma, approximately 10 million years after indole-GS appearance, and radiated through the acquisition of NSPs. Again, shortly after occurrence of Brassicaceae, new lineages of Pierinae evolved and diversified. Strikingly, independent nitrile-specifier gene lineages could be associated with independent colonization of Brassicaceae by two Pierinae lineages (Edger *et al.*, 2015).

Comparative phylogenies of *Bursera* sp. and *Blepharida* sp. indicated that both groups diversified synchronously, showing that plant lineages possessing the defensive trait (resin under high pressure) coevolved with beetles lineages equipped with vein severing ability (Becerra, 2003). In addition, escalation of species and chemical diversity through time was observed in *Bursera*, providing support for herbivore-plant coevolution theory (Becerra *et al.*, 2009). Similarly, diversification of milkweeds was correlated with increased phenolic production (Agrawal *et al.*, 2009). For evolution of herbivores, a phylogenetic study of the leaf miner fly *Phytomyza* provided evidence that repeated shifts to host plants with different chemistry during 40 million years of evolution led to elevated diversification (Winkler *et al.*, 2009). Remarkably, beak length of the seed-eater soapberry bug *Jadera haemotoloma* has adapted within 40-150 generations after shifting to novel host species of Sapindaceae from North America (Carroll, 1992).

Although adaptation of specialist arthropods to plant defenses is well documented, evidence for plant resistance to specialists is less frequent. Interestingly, some Brassicaceae contain other defense compounds besides GS, including alkaloids (camalexin in Arabidopsis and cochlearine in *Cochlera* sp.) and the steroid cucurbitacin in *Iberis amara* (Tsuji *et al.*, 1992; Sachdev-Gupta *et al.*, 1993; Brock *et al.*, 2006). Cucurbitacin has some antifeedant activity on *P. rapae* (Sachdev-Gupta *et al.*, 1993) and a study on natural variation in resistance to *P. brassicae* in Arabidopsis accessions identified QTLs that are not linked to GS biosynthesis (Pfalz *et al.*, 2007). In a beautiful example of coevolution, some cyanogenic glycoside-containing species of *Passiflora* have counteradapted to the specialist *Heliconius* butterfly by the development of egg mimics that repel oviposition (Williams and Gilbert, 1981). Egg mimics have also evolved in the GS-containing crucifer *Strepthanthus breweri* to fend off the specialist *Pieris sisymbrii* (Shapiro, 1981). Many plants face the problem of attracting pollinators without being a target for herbivory. *N. attenuata* is a night-flowering tobacco whose flowers emit benzyl acetone that attracts pollinators, including the adapted herbivore moth *M. sexta*. In response to *M. sexta* feeding, *N. attenuata* shows a striking change of phenology by generating flowers that produce low levels of benzyl acetone and open during the day, attracting hummingbird as novel pollinators (Kessler *et al.*, 2010).

Open questions

Although many assumptions still rely on correlative evidence, progress has been made in the understanding of evolutionary forces that drive escalation of chemical defenses and arthropod adaptations to these chemicals. A recurring issue is to know the exact chain of events and causative agents that result in apparent defense-adaptation-counterdefense scenarios. Improved and additional plant/arthropod phylogenies are needed as well as experimental evolution experiments.

PLANT-ARTHROPOD COLLABORATIONS

Interactions between plants and arthropods are not always antagonistic. Insects pollinate about two-third of flowering plant species. In reward of nutrient-rich pollen and nectar, insects offer this service as a mutualistic engagement (Schoonhoven *et al.*, 2005). Seed dispersal by arthropods, mainly ants, helps colonization while providing food for the carrier (Howe and Smallwood, 1982). However, the most sophisticated collaboration is the association of plants with beneficial arthropods to fend off herbivores. Plants have evolved exquisite ways to "cry for help", which rely on offering refuge or food for guarding predatory mites and ants, or on emitting complex volatiles to attract carnivores (reviewed in Romero and Benson, 2005; Heil, 2008; Stam *et al.*, 2014; Heil, 2015; Hilker and Fatouros, 2015).

Leaf domatia are cavities or hair tufts on the lower surface of leaves and create shelter for mites that are predators of phytophagous mites. Several studies have proven that these structures benefit plants by decreasing herbivore pressure (reviewed in Romero and Benson, 2005). Extrafloral nectar, food bodies on leaflets and hollow thorns are attributes found in certain acacia trees that host ants, providing nutrition and housing (Heil, 2008). This intimate association is maintained because ants constantly patrol trees and aggressively remove unwanted herbivores. Extrafloral nectar production is induced in response to herbivory, showing that plants keep control of this energy demanding process. In an elegant and long-term experiment in an African savanna, removing large herbivores for 10 years reduced nectar production and thorns by *Acacia drepanolobium,* and increased antagonistic behavior of the ant mutualist *Crematogaster mimosae*, which ultimately led to a decreased tree defense and growth (Palmer *et al.*, 2008).

Upon herbivory and detection of HAMPs in OS, plants emit a complex blend of volatiles that attract parasitic wasps or predators (reviewed in Dicke and Loon, 2000; Stam *et al.*, 2014). Volatiles generally consist of terpenes, phenylpropanoids/benzenoids, and fatty acid derivatives (green leaf volatiles) (Pare and (Tumlinson, 1999; Dudareva *et al.*, 2004). This tritrophic interaction is an efficient defense mechanism since carnivores either kill their prey directly or parasitize them, therefore dramatically reduce feeding activity (Dicke and Loon, 2000). Qualitative and quantitative differences in volatile emission explain the specific attraction of parasitoids to their host. For instance, the specialist parasitic wasp *Cardiochiles nigriceps* was significantly more attracted by the volatile blend produced by tobacco and cotton plants infested with his host *H. virescens* than by volatiles produced by plants infested with *H. zea* (De Moraes *et al.*, 1998). Similarly, oviposition triggers volatile release and attraction of egg parasitoids, illustrating the specificity of the emitted blend (Hilker and Fatouros, 2015). Strikingly, indirect defense was also discovered belowground. Upon feeding by the rootworm *Diabrotica virgifera virgifera*, maize roots emit the sesquiterperne (*E*)-β-caryophyllene. However, this response not attract arthropods but entomopathogenic nematodes (Fig.1) (Rasmann *et al.*, 2005).

Open questions

One of the fascinating yet poorly studied question about plant-arthropod mutualism is how indirect defense evolved. Evidence that plants benefit from attraction of parasitoids suggests that genes involved in volatile biosynthesis are under positive selection. Comparative genomic analyses of biosynthesis pathways across plant taxa and their correlation with associated parasitoids will be necessary to have a better understanding of how indirect defense appeared and was maintained. Whether roots attract beneficial arthropods is another unsolved question. On the parasitoid side, advent of more sequenced genomes may offer a resource for identifying genes important for volatile recognition and association with the host. Finally, the contribution of parasitoids to plant-arthropod coevolution is also a question that deserves more research.

CONCLUSIONS AND OUTLOOK

Decades of research on plant-arthropod interactions have revealed that these organisms are engaged in a battle for survival that rely on sophisticated mechanisms of perception, signaling and defense activation on the plant side, and on effective suppression of defenses and chemical/behavioral adaptations on the arthropod side. Although it appears that nature has reached an equilibrium, since both plants and arthropods are abundant, evidence has accumulated that there is constant innovation to generate novel plant defenses strategies and that this exerts a selection pressure on arthropods to evolve novel effectors or detoxification solutions. This arms race has thus no winner and the coevolution process may continue for millions of years.

Although substantial progress has been made in identifying genes and molecules involved in the molecular dialogue between plants and arthropods, as well as some evolutionary processes that underlie their coevolution, we have identified open questions that deserve further research. In addition, root herbivory (Johnson and Rasmann, 2015), insect galls (Stone, 2003), the role of leaf and arthropod microbiomes (Pineda *et al.*, 2010; Sugio *et al.*, 2015), and the outcome of multiple biotic interactions (Pieterse and Dicke, 2007) are clearly understudied. In times when stability of ecosystems, emergence of invasive species and sustainable control of insect pests in agriculture provide challenges to a growing human population, future research on plant-arthropod interactions may contribute viable solutions to these problems.

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AUTHOR CONTRIBUTION

ES and PR wrote the paper. OH provided feedback on the text and designed the figures.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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TABLES

Table 1. HAMPs and effectors from arthropods

Name	Origin	Response	Reference
HAMPs			
FAC (volicitin)	*Spodoptera exigua* OS	Volatiles attract parasitoids	Alborn *et al.*, 1997
2-HOT	*Manduca sexta* OS	Volatiles attract parasitoids	Gaquerel *et al.*, 2009
Caeliferins	*Schistocera americana* OS	Volatiles attract parasitoids	Alborn *et al.*, 2007
β-glucosidase	*Pieris brassica*e OS	Volatiles attract parasitoids	Mattiacci *et al.*, 1995
Inceptin	*Spodoptera frugiperda* OS	Volatile and defense gene induction	Schmelz *et al.*, 2006
Lipase	*Schistocera gregaria* OS	Release of esterified OPDA	Schäfer *et al.*, 2011
β-galactofuranose polysaccharide	*Spodoptera littorali*s OS	Plasma membrane depolarization	Bricchi *et al.*, 2013
Bacterial porin-like	*Spodoptera littoralis* OS	Channel-forming activity	Guo *et al.*, 2013
Protein (<10 kDa)	*Myzus persicae* saliva	Defense gene induction	De Vos and Jander, 2009
Mp56, Mp57, Mp58	*Myzus persicae* saliva	Lower aphid fecundity	Elzinga *et al.*, 2014
Bacterial GroEL	*Macrosiphum euphorbiae* OS	Lower aphid fecundity	Chaudhary *et al.*, 2014
Phosphatidylcholine	*Sogatella furcifera* female	Production of ovicidal compound	Yang *et al.*, 2014
12 kDa protein	*Diprion pini* oviduct secretion	Egg parasitoids attraction	Hilker *et al.*, 2005
Benzyl cyanide	*Pieris brassicae* ARG	Arrest of egg parasitoids	Fatouros *et al.*, 2008
Indole	*Pieris rapae* ARG	Arrest of egg parasitoids	Fatouros *et al.*, 2009
Lipid extract	*Pieris brassicae* eggs	Defense gene induction, necrosis	Bruessow *et al.*, 2010
Bruchin	*Callosobruchus maculatus* female	Neoplasm formation under eggs	Doss *et al.*, 2000
Effectors			
Modified inceptin	*Anticarsia gemmatalis* OS	Plant defense suppression	Schmelz *et al.*, 2012
Bacteria (flagellin)	*Leptinotarsa decemlineata* OS	Inhibition of the JA pathway	Chung *et al.*, 2013
Apyrase	*Helicoverpa zea* saliva	Lower defense gene expression	Wu *et al.*, 2012
Glucose oxidase	*Helicoverpa zea* saliva	Lower nicotine production	Musser *et al.*, 2002
Unknown (<3 kDa)	*Spodoptera littoralis*, *Pieris rapae* OS	Reduced defense gene expression	Consales *et al.*, 2012
Unknown (10-30 kDa)	*Leptinotarsa decemlineata* OS	Reduced defense gene expression	Lawrence *et al.*, 2007
Unknown	*Manduca sexta* OS	Reduced gene expression	Schittko *et al.*, 2001
FACs	*Manduca sexta* OS	Reduced volatile emission	Gaquerel *et al.*, 2009
Chitinases	*Spodoptera exigua* frass	Increased larval performance	Ray *et al.*, 2016
MIF (cytokine)	*Acyrthosiphon pisum* saliva	Plant defense suppression	Naessens *et al.*, 2015
Ca^{++}-binding protein	*Megoura viciae* saliva	Inhibition of sieve tube plugging	Will *et al.*, 2007
Me23, Me10 (unknown)	*Megoura euphorbiae* saliva	Higher aphid fecundity	Atamian *et al.*, 2013
Mp1 (unknown)	*Myzus persicae* saliva	Higher aphid fecundity, targets VSP52	Rodriguez *et al.*, 2017
Mp10 (CSP)	*Myzus persicae* saliva	Suppress ROS production	Bos *et al.*, 2010
MpC002 (unknown)	*Acyrthosipho pisum* saliva	Higher aphid performance	Mutti *et al.*, 2008
Mp55 (unknown)	*Myzus persicae* saliva	Higher aphid fecundity	Elzinga *et al.*, 2014
Tu28, Tu84 (unknown)	*Tetranychus urticae* heads	Higher mite performance	Villarroel *et al.*, 2016
F-box-LRR proteins	*Mayetiola destructor* saliva	Induce ETI in HF-resistant wheat	Zhao *et al.*, 2015
Lipid extract	*Pieris brassicae* eggs	Inhibition of the JA pathway	Bruessow *et al.*, 2010

ARG, accessory reproductive gland secretion; CSP, chemosensory protein; ETI, effector-triggered immunity; FAC, fatty acid-amino acid conjugate; GmSubPep, Glycine max subtilase peptide; GPX, glutathione peroxidase; GroEL, chaperone; HAMP, herbivore-associated molecular pattern; HF, Hessian fly; 2-HOT, 2-hydroxy-octadecatrieonic acid; MIF, migration inhibitory factor; OS; oral secretions; SAR, systemic acquired resistance; VSP52, Vacuolar Protein Sorting Associated Protein52.

Table 2. Plant-derived metabolites with direct insecticidal activity

Metabolite	Plant species	Arthropod species	Mode of action (mutant lines)	Reference
Glucosinolates	Brassicaceae	*Mamestra brassicae,* *Trichoplusia ni,* *Manduca sexta,* *Spodoptera littoralis*	Myrosinase-dependent hydrolysis generates nitriles, thiocyanates, and isothiocyanates (ITC) that react with biological nucleophiles and modify proteins and nucleic acids. (*tgg1/tgg2*, *quadGS*, *myc234*)	Beekwilder et al., 2008 Barth and Jander, 2006 Brown and Hampton, 2011 Schweizer et al., 2013b
Azadirachtin[1]	*Azadirachta indica*	*Spodoptera littoralis,* *Spodoptera frugiperda,* *Schistocerca gregaria*	Disruption of the endocrine system and inhibition of cell division.	Mordue Luntz et al., 1998
Benzoxazinoids[7]	*Zea mays*	*Rhopalosiphum maidis*	Unknown (*Bx13*NIL-Oh43)	Handrick et al., 2016
Benzyl benzoate	*Oryza sativa*	*Sogatella furcifera*	Egg-killing substance.	Seino et al., 1996
Calcium Oxalate	*Medicago truncatula*	*Spodoptera exigua*	Physical abrasion of mandibles. Ingested calcium oxalate interferes with larval development (*cod5*, *cod6*)	Korth et al., 2006.
Camalexin[3]	*Arabidopsis thaliana*	*Myzus persicae*	Unknown (*pad3*, *cyp79b2/cyp79b3*)	Kettles et al., 2013
GABA[2]	All plant species	*Choristoneura rosaceana,* *Meloidogyne hapla,* *Heliothis virescens*	Suppression of neurotransmission	Hosie et al., 1997 Bown et al., 2002, 2006
Hydrogen cyanide (HCN)	*Trifolium repens*, *Lotus corniculatus* *Hypera postica*	*Capnodis tenebrionis*, *Heterobostrychus brunneus*,	Inhibition of mitochondrial respiration	Vetter, 2000
Kaempferol[4]	*Arabidopsis thaliana*	*Pieris brsassicae* *Nicotiana tabacum*	Unknown (oxMYB75)	Onkokesung et al., 2014
Kauralexins[1]	*Zea mays*	*Ostrinia nubilalis*	Unknown	Schmelz et al., 2011
Lactone taraxinic acid[1]	*Taraxacum officinale*	*Melolontha melolontha*	Unknown (*ToGAS1*)	Huber et al., 2016.
L-Canavanine[2]	Fabaceae	*Manduca sexta*	Integration of L-canavanine into proteins	Rosenthal et al., 1976 Rosenthal, 2001
Nicotine[5]	*Nicotiana tabacum* *Nicotiana attenuata*	*Spodoptera exigua*, *Trimerotropis spp.*, *Diabrotica undecimpunctata*	Agonist for acetylcholine receptors, disruption of nervous system (*IRpmt, nic1, nic2, nic1/nic2*)	Gepner et al., 1978 Steppuhn et al., 2004 Katoh et al., 2005
Pyrethrin[1]	*Chrysanthemum cinerariifolium*	Tetranychidae, Pseudococcidae, Auchenorrhyncha, Coleoptera, Caelifera, Aleyrodidae	Inactivation of sodium channels along nerve cells	Casida et al., 1983
Rotenone[4]	*Derris eliptica*, *Pachyrrhizus erosus*	Brought spectrum insecticide	Inhibition of mitochondrial respiration	Dayan et al., 2009
Scopoletin[6]	*Artemisia annua*	*Spilartia obliqua*	Unknown	Tripathi et al., 2011
Teucrein[1]	*Teucrium marum*	*Monomorium pharaonis*, *Phormia regina*, *Periplaneta americana*	Unknown	Eisner et al., 2000

[1] Terpenoid, [2] Amino acid, [3] Indole, [4] Flavonoid, [5] Alkaloid, [6] Coumarin, [7] Hydroxamic acid,

Table 3. Plant-derived proteins with direct insecticidal activity

Protein	Plant species	Arthropod species	Mode of action (mutant lines)	Reference
α-Amylase inhibitors	Fabaceae, Poaceae, Caryophyllales	Coloptera, Hemiptera, Blattidae	Inhibition of digestive α-amylases	Franco et al., 2002
Acrelins	*Phaseolus vulgaris*	*Zabrotes subfasciatus*	Binding to complex glycans disrupts midgut epithelial structure	Fabre et al., 1998
Canatoxins	*Canavalia ensifonnis*	*Callosobruchus chinensis,* *Rhodnius prolixus,* *Nezara viridula,* *Dysdercus peruvianus*	Interfere with serotonin processes and disrupt fluid transport across anterior midgut epithelium	Carlini et al., 1997 Stanisçuaski and Carlini, 2012
Cyclotides	*Oldenlandia affinis* Rubiaceae, Violaceae	*Helicoverpa punctigera,* *Helicoverpa armigera*	Disrupt larval midgut membranes	Jennings et al., 2001 Barbeta et al., 2008
Cysteine protease	*Zea mays* L.	*Spodoptera frugiperda*	Disrupts caterpillar peritrophic matrix	Pechan et al., 2002
Cysteine protease inhibitors	*Oryza sativa* *Glycine max* *Arabidopsis thaliana*	Coleoptera, Hemiptera	Inhibition of digestive gut proteases	Kuroda et al., 1996 Koiwa et al., 1998 Delledonne et al., 2001
Lectins	Leguminosae	Coleoptera, Lepidoptera, Homoptera	Binding to glycosyl groups attached to digestive tract	Vandenborre et al., 2011
Ribosome-inactivating proteins (RIPs)	Fabaceae, Asparagaceae. Passifloraceae	*Anthomonus grandis* *Callosobruchus maculatus* *Anthomonus grandis*	Inactivation of 60S ribosomal subunit	Olsnes et al., 1974 Carlini and Grossi-de-Sá, 2002
Serine protease inhibitors	Solanaceae	*Spodoptera exigua*	Inhibition of digestive gut proteases	Green and Ryan, 1972 Hartl et al., 2010
Threonine deaminase	*Solanum lycopersicum*	*Spodoptera exigua*	Deprivation of essential Thr (TDAs15, TDAs7)	Gonzales-Vigil et al., 2011
Vegetative Storage Protein 2 (VSP2)	*Arabidopsis thaliana*	*Diabrotica undecimpunctata howardi* *Callosobruchus maculatus*, *Drosophila melanogaster*	Insecticidal activity correlated with acid phosphatase activity (*vsp2*)	Liu et al., 2005

Table 4. Coevolution between plants and arthropods

Plant defense	Arthropod adaptation	Plant counterdefense	Reference
Cardenolides *Asclepias syriaca*	Leaf vein cutting *Danaus gilippus* and others		Dussourd and Eisner, 1987
High-pressure resin *Bursera sp.*	Leaf vein severing *Blepharida sp.*		Becerra, 2003
JA-dependent defenses Arabidopsis	Avoiding induced tissue *Helicoverpa armigera*		Perkins *et al*., 2013
Trichomes *Solanum hirtum*	Silk threads over spines *Mechanitis isthmia*		Rathcke and Poole, 1975
Attraction of parasitoids *Lolium multiflorum*	Host shift, escape behavior (?) *Listronotus bonariensis*		Tomasetto *et al*., 2017
Attraction of parasitoids *Physalis angulata*	Eating fruit, no volicitin in OS *Heliothis subflexa*		De Moraes and Mescher, 2004
Cardenolides Apocynaceae	ATPase N122H substitution *Danaus plexxipus* and others		Dobler *et al*., 2012
Protease inhibitors (PI) potato	PI-insensitive protease *Helicoverpa zea*		Bayés *et al*., 2005
L-canavanine (Arg analog) *Dioglea megacarpa*	Discriminating tRNA synthetase *Caryedes brasiliensis*		Rosenthal *et al*., 1976
Cyanogenic glycoside *Passiflora sp.*	Detoxification *Heliconius cydno*	Egg mimicry *Passiflora cyanea*	Williams and Gilbert, 1981
Cyanogenic glycoside *Phaseolus lunatus*	Bacterial β−cyanoalanine synthase *Tetranychus urticae*		Wybouw *et al*., 2014
Alkaloid *Nicotiana attenuata*	Nicotine excretion and metabolism *Manduca sexta*	Altered flower phenology *Nicotiana attenuata*	Kessler *et al*., 2010
Glucosinolates Brassicales	Nitrile-specifier proteins *Pieris rapae* and other Pierinae	GS diversification Brassicales	Edger *et al*., 2015
Glucosinolates Brassicales	Nitrile-specifier protein (?) *Pieris sysimbrii*	Egg mimicry *Streptanthus brewerii*	Shapiro, 1981
Glucosinolates Arabidopsis	Induction of detoxification genes *Heliothis virescens*		Schweizer *et al*., 2017
Furanocoumarins Apiaceae	Detoxification by CYP6B1 *Papilio polyxenes*		Hung *et al*., 1997
HAMP detection (inceptin) *Vigna unguiculata*	Inceptin modification *Anticarsia gemmatalis*		Schmelz *et al*., 2012
Defense signaling *Apium graveolens*	Induction of CYP450s by JA, SA *Helicoverpa zea*		Li *et al*., 2002b

Arg, arginine; GS, glucosinolates; HAMP, herbivore-associated molecular pattern. Question marks indicate no experimental evidence for the adaptation.

FIGURE LEGENDS

Figure 1. Overview of plant responses to herbivory.

Upon perception of herbivorous larvae or eggs, plants activate direct defenses (synthesis of toxic metabolites and proteins, localized cell death (HR)) and indirect defenses (emission of volatiles to attract larval or egg parasitoids and root nematodes). These responses occur both above- and belowground. HIPVs, herbivore-induced plant volatiles; EIPVs, egg-induced plant volatiles; HR, hypersensitive-response.

Figure 2. Signaling of plant responses to herbivory in Arabidopsis.

Current model for signaling steps activated by feeding larvae (a) and oviposition (b). (a) Upon recognition of HAMPs from larval oral secretions by yet unknown receptors, a signal transduction cascade generates the bioactive hormone JA-Ile. JA-Ile induces the interaction of SCF^{COI1} with JAZs transcriptional repressors, which are further ubiquitinated and degraded. MYC2,3,4 can then regulate the transcription of numerous genes, including glucosinolate biosynthesis genes. (b) Egg-derived HAMPs are perceived by yet unknown receptors, which trigger both reactive oxygen species accumulation and activation of SA-biosynthesis enzyme ICS1 through lipase-related EDS1 and PAD4. SA accumulation provokes a redox change that leads to monomerization of NPR1, entry in the nucleus and activation of transcription factors. Expression of *PR-1* is associated with a HR-like response that culminates in localized cell death, presumed to inhibit egg development. In addition, local and distal accumulation of Pip is mediated by the biosynthesis enzyme ALD1 and triggers inhibition of infection by biotroph pathogens in local and distal tissues through SAR. There is evidence for a general conservation of both models in other plant species.

HAMPs, herbivore-associated molecular patterns; RLK, receptor-like kinase; LOX, lipoxygenases; AOS, allene oxide synthase; AOC, allene oxide cyclase; OPDA, 12-oxo-oxophytodienoic acid; OPR3, OPDA-reductase 3; □-ox., □ -oxidation; JA, jasmonic acid; JAR1, Jasmonate-resistant 1; JA-Ile, jasmonate-isoleucine; $\mathrm{SCF}^{\mathrm{COI1}}$, SCF complex with F-box Coronatine-insentive 1 receptor for JA-Ile; JAZs, Jasmonate-ZIM domain proteins; MYC2,3,4, MYC2, MYC3, MYC4 bHLH transcription factors; EDS1, Enhanced-disease susceptibility 1; PAD4, Phytoalexin-deficient 4; ICS1, Isochorismate synthase 1; SA, salicylic acid; NPR1, Non-expressor of pathogenesis-related genes1, TFs, transcription factors; HR, hypersensitive response; *PR-1*, pathogenesis-related 1; Pip, pipecolic acid; SAR, systemic acquired resistance.

Figure 3. Systemic responses to herbivory.

(a) Current model of long-distance signaling in response to herbivory. Both GLR-dependent electrical signaling and JA/JA-Ile movement have been shown to trigger JA-dependent defenses in systemic leaves in response to local feeding. (b) Oviposition triggers release of HIPVs in local and systemic leaves from several plant species, although the nature of the systemic signal is unknown. ALD1-dependent Pip accumulation in local and systemic leaves triggers a SAR against plant pathogens. Whether Pip is the mobile SAR signal has not been demonstrated. JA, jasmonic acid; JA-Ile, JA-isoleucine; GLR, Glutamate receptor-like; ALD1, AGD2-like defense response protein 1; Pip, pipecolic acid; SAR, systemic acquired resistance; HIPVs, herbivore-induced plant volatiles.

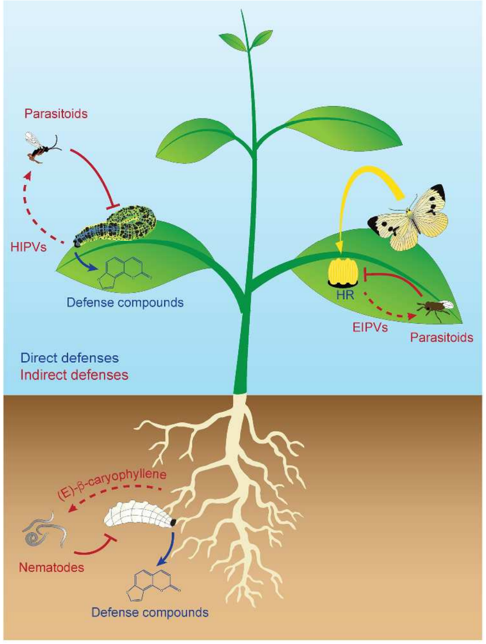

Figure 1

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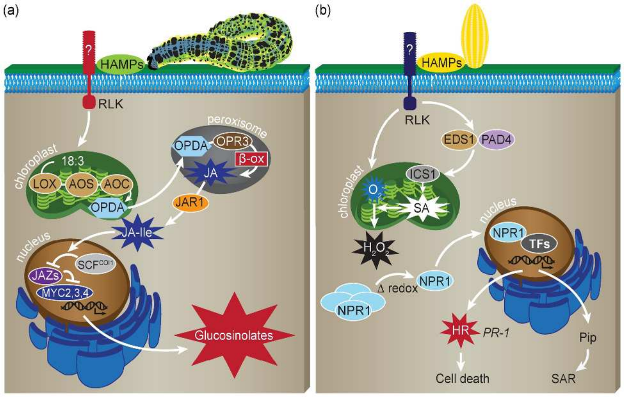

Figure 2

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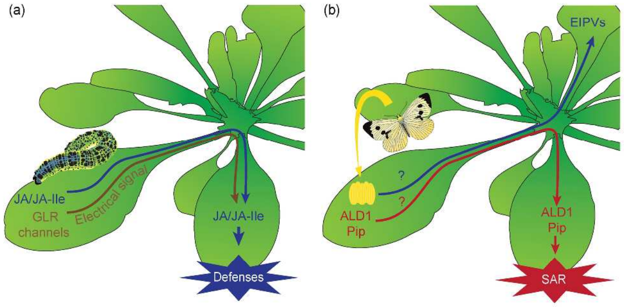

Figure 3

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