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*the plant journal*

# Plant-arthropod interactions: who is the winner?

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|---|---|
| Journal: | *The Plant Journal* |
| Manuscript ID | TPJ-00766-2017.R1 |
| Manuscript Type: | SI Plant Biotic Interactions 2018 |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Stahl, Elia; University of Lausanne, Department of Plant Molecular Biology Hilfiker, Olivier; University of Lausanne, Department of Plant Molecular Biology Reymond, Philippe; University of Lausanne, Department of Plant Molecular Biology |
| Key Words: | arthropods, plant defense signaling, elicitors, effectors, defense metabolites, coevolution, arms race |

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Manuscripts

1    Running title: Plant-arthropod interactions

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5    Plant-arthropod interactions: who is the winner?

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7    Elia Stahl, Olivier Hilfiker and Philippe Reymond*

8

9    Department of Plant Molecular Biology, University of Lausanne, Biophore Building,
10   1015 Lausanne, Switzerland
11

12

13   *For correspondence (e-mail philippe.reymond@unil.ch)
14

15   E. S., elia.stahl@unil.ch; O. H., olivier.hilfiker@gmail.com
16

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18   coevolution, arms race

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22  **SUMMARY**

23  Herbivorous arthropods have interacted with plants for millions of years. During

24  feeding they release chemical cues that allow plants to detect the attack and mount an

25  efficient defense response. A signaling cascade triggers the expression of hundreds of

26  genes, which encode defensive proteins and enzymes for synthesis of toxic metabolites.

27  This direct defense is often complemented by emission of volatiles that attract

28  beneficial parasitoids. In return, arthropods have evolved strategies to interfere with

29  plant defenses, either by producing effectors to inhibit detection and downstream

30  signaling steps, or by adapting to their detrimental effect. In this review, we address the

31  current knowledge on the molecular and chemical dialogue between plants and

32  herbivores, with an emphasis on coevolutionary aspects.

33

34    **INTRODUCTION**

35    Plants and herbivorous arthropods have coevolved for millions of years and it is

36    commonly believed that these interactions have generated the large variety of plant and

37    arthropod species that inhabit our planet. Although a large fraction of arthropods

38    provide service to plants in the form of pollination or protection against enemies, they

39    also constitute a threat since they are generally herbivorous. Whether they chew leaf or

40    root material, feed on cell content, mine mesophyll tissue or suck phloem, arthropods

41    from different feeding guilds impose a stress that plants have to resist. Depending on the

42    type of attack, plants have a battery of strategies that include preexisting constitutive

43    defenses complemented by the induction of direct (toxic secondary metabolites and

44    proteins) and indirect (emission of volatiles to attract predators) defenses (Fig. 1). These

45    responses depend on precise perception of the aggressor, followed by a signal

46    transduction cascade that culminates in a transcriptional reprogramming and synthesis

47    of specific defense compounds. Efficient plant resistance imposes a selection pressure

48    on herbivores, which in turn develop ways to interfere with defense mechanisms or

49    adapt to the detrimental effect of toxins. In recent years, a wealth of information has

50    accumulated on molecular components that control this on-going arms race. Several

51    aspects of plant-arthropod interactions have been reviewed elsewhere (Schoonhoven *et*

52    *al.*, 2005; Zhu-Salzman *et al.*, 2005; Will and van Bel, 2006; Howe and Jander, 2008;

53    Wu and Baldwin, 2010; Hogenhout and Bos, 2011; Farmer, 2014; Jouannet *et al.*, 2014;

54    Hilker and Fatouros, 2015; Schuman and Baldwin, 2016). In this review, we place

55    emphasis on the molecular and chemical dialogue that underlies these interactions. We

56    present the current knowledge on arthropods elicitors and effectors, provide examples

57    of plant defense compounds and adaptations by arthropods, to illustrate a fascinating

58    coevolution between organisms that are generally foes but can also engage in

59    mutualistic relationships.

60

## PERCEPTION OF FEEDING HERBIVORES

62    Plants have evolved exquisite ways to detect their enemies. When infected by bacterial

63    or fungal pathogens, hosts recognize pathogen-derived molecules from the attacker that

64    have been termed pathogen- or microbe-associated molecular patterns

65    (PAMPs/MAMPs). These PAMPs are highly conserved and are generally associated

66    with a class of attacker. PAMP perception is achieved by plasma membrane-bound

67    pattern recognition receptors (PRRs), which are either receptor-like kinases (RLKs) or

68    receptor-like proteins (RLPs) that lack a cytoplasmic kinase domain (Boller and Felix,

69    2009; Couto and Zipfel, 2016). Upon ligand binding, PRRs associate with regulatory

70    receptor kinases, including the well-studied BRI1-ASSOCIATED RECEPTOR

71    KINASE 1 (BAK1) (Couto and Zipfel, 2016). PAMP recognition leads to a

72    transcriptional defense program called pattern-triggered immunity (PTI), which restricts

73    growth of the invading pathogens through local and systemic production of defenses

74    proteins and metabolites (Li *et al.*, 2016). In analogy to plant-pathogen interactions,

75    scientists have identified herbivore-associated molecular patterns (HAMPs) (Mithöfer

76    and Boland, 2008; Bonaventure *et al.*, 2011; Hogenhout and Bos, 2011; Jouannet *et al.*,

77    2014; Acevedo *et al.* 2015) but knowledge about their corresponding PRRs is scarce.

78

### Arthropod-derived HAMPs

80    Initially termed "elicitors" because they elicited defense responses from the plant,

81    HAMPs have been found in a variety of sources, including saliva, oral secretions (OS),

82    reproductive glands, whole body or eggs (Table 1). HAMPs (like PAMPs) constitute

83    essential patterns, making it difficult for herbivores to eliminate them and hence avoid

84    recognition.

85         One of the first and best-known example is volicitin, a fatty acid-amino acid

86    conjugate (FAC) purified from OS of the beet armyworm caterpillar *Spodoptera exigua*

87    (Alborn *et al.*, 1997). When applied to maize leaves, volicitin triggers the emission of a

88    bouquet of volatile terpenoids and indoles that attract parasitic wasps. Volicitin is

89    composed of 17-hydroxylinolenic acid coupled to glutamine. Interestingly, chemical

90    analysis established that linolenic acid originates from the plant and is further

91    hydroxylated and conjugated to glutamine by the insect (Lait *et al.*, 2003; Pare *et al.*,

92    1998). Volicitin and related FACs (fatty acids of different length and saturation coupled

93    to glutamine or glutamate) were further identified in OS from different Lepidoptera

94    (Pohnert *et al.*, 1999; Halitschke *et al.*, 2001; Mori *et al.*, 2003) and even in other

95    insects (Yoshinaga *et al.*, 2007). The physiological role of FACs is not yet clear but it

96    has been suggested that they are important for nitrogen assimilation in larvae

97    (Yoshinaga *et al.*, 2008). In addition, the amphiphilic nature of these molecules might

98    emulsify the ingested food.

99         Caeliferins are sulfated hydroxy fatty acids isolated from OS of the grasshopper

100   *Shistocera americana*. In maize, they elicit emission of volatiles similar to those

101   triggered by volicitin, although there is no evidence for natural enemies of grasshoppers

102   (Alborn *et al.*, 2007). 2-hydroxy octadecatrieonic acid (2-HOT) was detected in OS of

103   the tobacco hornworm *Manduca sexta* and triggers the emission of the sesquiterpene

104   trans-α-bergamotene in wild tobacco *Nicotiana attenuata*. In plants, 2-HOT is produced

105   from linolenic acid by the action of α-dioxygenases. Occurrence of 2-HOT in *M. sexta*

106  OS may allow plants to sense herbivore feeding by the presence of a modified

107  membrane constituent (Gaquerel *et al.*, 2009). Bruchins are fatty acid derived long-

108  chain α,ω-diols, esterified at one or both ends with 3-hydroxypropanoic acid. They

109  were isolated from pea and cowpea weevil oviposition fluid and induce tumor-like

110  growth of undifferentiated cells (neoplasms) on pea pods, like naturally deposited eggs.

111  Neoplasms serve as direct defense by blocking larval entry (Doss *et al.*, 2000). Eggs of

112  the white backed planthopper *Sogatella furcifera* stimulate the production of the

113  ovicidal substance benzyl benzoate in certain rice varieties. Purification of female

114  extracts yielded active phospholipids, including phosphatidylcholine and

115  phosphatidylethanolamine (Yang *et al.*, 2014). Finally, oviposition by the large white

116  *Pieris brassicae* induces defense gene expression, local necrosis and production of

117  reactive oxygen species in Arabidopsis (Little *et al.*, 2007). The inducing activity is

118  found in egg extracts from different insects and is enriched in the lipid fraction

119  (Bruessow *et al.*, 2010).

120      All the above examples seem to indicate that lipid-derived HAMPs are prevalent

121  in OS from chewing herbivores. However, known HAMPs also include proteins,

122  peptides and small metabolites. A β-glucosidase in *P. brassicae* OS is responsible for

123  volatile emission in cabbage (Mattiacci *et al.*, 1995), a lipase in the grasshopper

124  *Schistocera gregaria* OS induces defense gene expression (Schäfer *et al.*, 2011), and an

125  uncharacterized 12kDa protein from oviduct secretions of the sawfly *Diprion pini*

126  induces volatile emission in pine (Hilker *et al.*, 2005). Inceptin is a peptide that

127  originates from the digestion of plant proteins, illustrating plants' ability to detect

128  feeding-dependent modification of self. This cyclic peptide of eleven amino acids was

129  purified from OS of the fall armyworm *S. frugiperda* and derives from proteolytic

130    cleavage of a plant chloroplastic ATPase in the insect midgut (Schmelz *et al.*, 2006).

131    When applied to cowpea (*Vigna unguiculata*) or maize, inceptin induces the production

132    of defense-related hormones, volatiles and defense compounds. Small metabolites

133    include for example benzyl cyanide and indole from reproductive accessory glands of *P.*

134    *brassicae* and *Pieris rapae*, respectively. They are associated with eggs and induce

135    indirect plant defense by arresting egg parasitoids at the oviposition site (Fatouros *et al.*,

136    2008; Fatouros *et al.*, 2009).

137         The feeding mode and physiology of phloem-sucking aphids have rendered

138    HAMPs isolation difficult. Aphids deliver minute amounts of saliva with their syringe-

139    like stylet when probing and navigating through different cell layers to reach sieve

140    elements. Proteomic and genomic analyses of secreted proteins from the green peach

141    aphid *Myzus persicae* salivary glands have nevertheless identified candidate HAMPs

142    that induced defense gene expression or lowered aphid fecundity when overexpressed in

143    Arabidopsis (Table 1) (de Vos and Jander, 2009; Elzinga *et al.*, 2014). In addition,

144    Thrips and phytophagous mites have different feeding mode than chewing herbivores or

145    aphids. Although they belong to different classes (insects or arachnids), both pierce

146    plant tissues and feed on cell content. The Western flower thrips *Frankliniella*

147    *occidendalis* and the two-spotted spider mite *Tetranychus urticae* have been used as a

148    model to study Arabidopsis and tomato plant defenses. Whereas transcriptional changes

149    similar to those induced by lepidopteran herbivores were observed, the nature of the

150    eliciting activity is still unknown (de Vos *et al.*, 2005; Abe *et al.*, 2008; Kant *et al.*,

151    2008; Zhurov *et al.*, 2014).

152         Interestingly, recognition can be mediated through bacterial PAMPs that are

153    present in OS. A porin-like protein from *Ralstonia* was purified from *S. littoralis* OS

154    and activated early defense responses, including channel formation and calcium fluxes

155    (Guo *et al.*, 2013). The bacterial chaperonin GroEL was identified in saliva of the potato

156    aphid *Macrosiphum euphorbiae*. This protein originated from the endosymbiont

157    *Buchnera aphidicola* and induced PTI responses that depended on BAK1 in

158    Arabidopsis (Chaudhary *et al.*, 2014). These two examples expand the range of

159    potential sources of HAMPs to the gut microbiome.

160

161    **HAMP recognition by potential PRRs**

162    Strikingly, contrary to the case of bacterial and fungal PAMPs where direct binding to a

163    PRR has been demonstrated (Boller and Felix, 2009; Couto and Zipfel, 2016), there is

164    yet no evidence for a *bona fide* PRR that perceives a HAMP. However, *M. persicae*-

165    derived HAMPs were shown to elicit defenses characteristic of PTI responses in a

166    BAK1-dependent manner (Prince *et al.*, 2014; Vincent *et al.*, 2017). These studies

167    provide evidence for detection of aphid HAMPs by (unknown) PRRs that are distinct

168    from PRRs that detect bacterial and fungal PAMPs (Prince *et al.*, 2014). More than a

169    decade ago, a biochemical study using a radiolabelled form of volicitin reported binding

170    to a plasma-membrane protein from maize leaves (Truitt *et al.*, 2004). However, this

171    protein has not been further characterized and no gene has been cloned. A cluster of

172    three lectin receptor kinase (LecRK) genes conferred resistance to the brown

173    planthopper (BPH) in rice, but whether these LecRK bind to yet unknown HAMPs from

174    BPH or mediate downstream events is unknown (Liu *et al.*, 2015). Arabidopsis LecRK-

175    I.8 is involved in the perception of egg-derived HAMPs. Indeed, a *lecRK-I.8* mutant

176    displayed a significantly reduced expression of the defense gene *PR1* in response to egg

177    extract treatment (Gouhier-Darimont *et al.*, 2013). This interesting observation will

178    however await chemical identification of the lipid-derived HAMP and binding assays.

179        Recently, a LecRK receptor for extracellular ATP was discovered in

180    Arabidopsis. DORN1 (LecRK-I.9) bound ATP with high affinity and ectopic expression

181    triggered plant responses associated with wounding. It was concluded that DORN1 may

182    mediate perception of feeding herbivores by detecting ATP liberated from cell content

183    after physical damage (Choi *et al.*, 2014). Although ATP is not formerly a HAMP but

184    rather a damage-associated molecular pattern (DAMP), this finding reinforces the

185    hypothesis that LecRKs may be important components of HAMP perception.

186

187    **Wound responses**

188    It has long been recognized that wounding is an important component of plant responses

189    to chewing herbivores (Green and Ryan, 1972; Howe and Jander; 2008). Early work in

190    Solanaceae identified systemin, a 18-aa polypeptide wound signal that regulates the

191    production of anti-insect proteinase inhibitors (reviewed in Ryan and Pierce, 1998).

192    Although some early responses to herbivory are not or only partially mimicked by

193    mechanical damage (Brichi *et al.*, 2010) and emission of volatiles is specifically

194    triggered by insect-derived cues (Alborn *et al.*, 1997), wounding and feeding activate

195    overlapping sets of genes (Reymond *et al.*, 2000; Major *et al.*, 2006). In addition,

196    jasmonic acid (JA), the main signal controling defenses (see below), rapidly

197    accumulates in response to mechanical damage (Reymond *et al.*, 2000; Glauser *et al.*,

198    2008). For aphids, turgor changes associated with stylet penetration of the phloem may

199    also contribute to some defense responses, like for instance the rapid plugging of sieve

200    plates by callose or protein aggregates (reviewed in Will and van Bel, 2006).

201    Since many studies on the role of HAMPs involve exogenous application of OS

202    on wounded leaves, conclusions from such experiments have to be assessed critically.

203    Future experiments aiming at removing HAMPs genetically or physically from the

204    herbivore, as in the case of salivary gland ablation (Musser *et al.*, 2002), will be

205    necessary to demontrate the specific role of these elicitors.

206

207    **Open questions**

208    In several cases, the defense inducing activity of HAMPs is associated with crude

209    extracts or unknown proteins, but their exact chemical nature is unknown. For most

210    HAMPs, information on their role in arthropod biology is lacking and future work

211    should elucidate why they have been kept since they alert the plant about the attack. In

212    addition, genes responsible for HAMP synthesis need to be identified. Host specificity

213    and distribution in different arthropod taxa should also be addressed. For instance,

214    FACs have a broad-range activity but do not elicit volatile emission in lima bean and

215    cotton (Spiteller *et al.*, 2001; Schmelz *et al.*, 2009). Inceptin action is restricted to

216    Fabaceae while Arabidopsis only responds to caeliferins (Schmelz *et al.*, 2009). Finally,

217    there is a clear lack of knowledge on potential PRRs and efforts should be placed in

218    finding ligand/binding pairs and defining downstream steps to establish if plants use the

219    same molecular machinery to detect HAMPs and PAMPS.

220

221    **SIGNALING**

222    Upon feeding, early signaling events include membrane depolarization, $Ca^{2+}$ influx,

223    production of reactive oxygen species (ROS), and activation of mitogen-activated

224    protein kinases (MAPK) (Howe and Jander, 2008; Wu and Baldwin, 2010; Vincent *et*

225  *al.*, 2017). These fast responses have been observed in different plant species and thus

226  seem to constitute a general mechanism to transduce HAMP perception. Since $Ca^{2+}$,

227  ROS, and MAPK are also involved in plant responses to pathogens, how they

228  specifically trigger anti-herbivore defense is currently unknown. For oviposition, there

229  is little information on early signaling steps, however ROS accumulation under eggs has

230  been reported (reviewed in Reymond, 2013; Hilker and Fatouros, 2015). Following

231  early responses to arthropods, alteration in hormonal profile plays a crucial role. JA is

232  the predominant signal that regulates downstream defense steps. Depending on the

233  attacker and on its developmental stage, a role for salicylic acid (SA), ethylene (ET),

234  and other plant hormones as primary signals or modulators has also been reported.

235

236  **JA pathway**

237  A large body of literature has detailed the importance of the JA pathway in response to

238  necrotrophs and herbivores (Howe and Jander, 2008; Browse, 2009; Acosta and Farmer,

239  2010; Wu and Baldwin, 2010; Pieterse *et al.*, 2012). In brief, upon damage fatty acids

240  are released from plastidic galactolipids. 13-lipoxygenases ogygenate 18:3 and 16:3

241  fatty acids to produce hydroperoxides, which are further converted by allene oxide

242  synthase and allene oxide cyclase to 12-oxo-phytodienoic acid (OPDA) and dinor-oxo-

243  phytodienoic acid (dnOPDA), respectively. OPDA and dnOPDA are transferred to

244  peroxisomes where they are reduced by OPDA reductase 3 (OPR3) and subjected to a

245  series of β-oxidation cycles to yield JA (Acosta and Farmer, 2010). Conjugation with

246  Ile by the enzyme JAR1 in the cytosol generates the bioactive (+)-7-iso-JA-Ile (JA-Ile)

247  (Staswick and Tiryaki, 2004; Fonseca *et al.*, 2009). After import in the nucleus, JA-Ile

248  forms a complex with its receptor, the F-box CORONATINE INSENSITIVE 1 (COI1),

249 and a JASMONATE-ZIM DOMAIN PROTEIN (JAZ). This leads to ubiquitination and

250 degradation of the JAZ proteins by the proteasome. JAZs are repressors of transcription

251 factors, including the Arabidopsis bHLH MYC2, MYC3 and MYC4, which control JA-

252 dependent responses additively (Chini *et al.*, 2007; Thines *et al.*, 2007; Browse, 2009;

253 Fernández-Calvo *et al.*, 2011) (Fig. 2). In Arabidopsis, transcriptome analyses revealed

254 that herbivory alters the expression of hundreds of genes and that a majority of these

255 genes are regulated by COI1 and MYC2/3/4 (Reymond *et al.*, 2004; de Vos *et al.*, 2005;

256 Schweizer *et al.*, 2013a; Schweizer *et al.*, 2013b). As a consequence, *coi1-1* and *myc234*

257 mutants were significantly more susceptible to herbivory by the generalist herbivore *S.*

258 *littoralis* (Fernández-Calvo *et al.*, 2011; Schweizer *et al.*, 2013b). In addition, role of the

259 JAZ1/3/4/9/10-MYC2/3/4 Arabidopsis module in resistance against the generalist

260 *Trichoplusia ni* was recently demonstrated (Major *et al.*, 2017).

261      That the JA pathway is central to resistance against arthropods in plants was

262 demonstrated using mutants. An original study using the Arabidopsis *fad3–2 fad7–2*

263 *fad8* triple mutant deficient in the jasmonate precursor linolenic acid showed that it was

264 highly susceptible to larvae of the saprophagous fungal gnat, *Bradysia impatiens*

265 (McConn *et al.*, 1997). Loss of function of the COI1 homologue in tomato increased

266 susceptibility to the two-spotted spider mite *T. urticae* (Li *et al.*, 2004b), and to the

267 lepidopteran herbivores *M. sexta* (Chen *et al.*, 2005) and *T. ni* (Herde and Howe, 2014).

268 Silencing COI1 in *N. attenuata* improved performance of *M. sexta,* and of the stem

269 weevil *Trichobaris mucorea* (Paschold *et al.*, 2007; Diezel *et al.*, 2011); the silverleaf

270 whitefly *B. tabaci* accelerated nymphal development on Arabidopsis *coi1-1* (Zarate *et*

271 *al.*, 2007); the isopod crustacean *Porcellio scaber* completely devoured Arabidopsis *aos*

272 whereas wild-type plants remained intact (Farmer and Dubugnon, 2009); silencing LOX

273     and AOC in rice plants increased root herbivory by the generalist cucumber beetle

274     *Diabrotica balteata*, and the specialist rice water weevil *Lissorhoptrus oryzophilus* (Lu

275     *et al.*, 2015); in maize, mutants of *OPR7* and *OPR8*, two close homologues of *OPR3*,

276     were more susceptibile to *S. exigua* (Yan *et al.*, 2012); the tomato jasmonate

277     biosynthesis mutant *def-1* that is impaired in volatile emission did not attract predatory

278     mites when infested with *T. urticae,* indicating that the JA pathway is also essential for

279     indirect defense (Ament *et al.*, 2004). For aphids, Ellis *et al.* (2002) showed that

280     Arabidopsis mutants with constitutive activation of JA-signaling were more resistant to

281     *M. persicae.*

282

### Other hormones

284     The SA pathway is generally important to fend off biotrophic pathogens and plays a

285     major role in PTI/ETI (Pieterse *et al.*, 2012). SA is a phenolic compound that is mainly

286     synthesized from the precursor chorismate by ISOCHORISMATE SYNTHASE 1

287     (ICS1/SID2). Activation of the lipase-like protein ENHANCED DISEASE

288     SUSCEPTIBILITY 1 (EDS1) and its related interacting partner PHYTOALEXIN

289     DEFICIENT 4 (PAD4) by biotrophic pathogens trigger SA accumulation (Vlot *et al.*,

290     2009). Consequently, change in the redox state of the cell redirects the transcriptional

291     coactivator NON EXPRESSOR OF *PR* GENES 1 (NPR1) from the cytosol to the

292     nucleus, where it regulates expression of numerous defense genes, including the SA

293     marker gene *PR-1* (Vlot *et al.*, 2009; Pieterse *et al.*, 2012).

294          The role of the SA pathway in resistance to arthropods has received some

295     attention. Aphid feeding induced expression of SA-marker genes, but no SA

296     accumulation was observed and studies with SA-pathway mutants in Arabidopsis

297 generated contrasting data on arthropod performance (reviewed in Jaouannet *et al.*,

298 2014). For example, in one study (Mewis et al., 2005) *npr1* and NahG were less

299 susceptible to the green peach aphid *M. persicae*, whereas this difference was not found

300 by Pegadaraju *et al.* (2005). However, *pad4* showed increased performance to *M.*

301 *persicae* but this effect was independent on EDS1 (Pegadaraju *et al.*, 2005, 2007). By

302 suppressing *PAD4* expression, *BOTRYTIS*-INDUCED KINASE1 (BIK1) was also

303 shown to confer enhanced susceptibility to *M. persicae*, indicating that this PTI

304 modulator and target of BAK1 acted as a negative regulator of the plant defense to

305 aphids (Lei *et al.*, 2014). Finally, *M. persica*e infestation triggered a transient trehalose

306 accumulation in Arabidopsis, which was shown to enhance PAD4 expression (Singh *et*

307 *al.*, 2011). PAD4 seems thus to constitute an important component mediating defense

308 against aphids but its connection to the SA pathway remains elusive (Shah and Louis,

309 2015).

310 For chewing herbivores, *S. littoralis* larvae were smaller when feeding on *ics1*

311 and *npr1-1*, implying a negative role of SA (Stotz *et al.*, 2002; Bodenhausen and

312 Reymond, 2007). Since the SA pathway is known to antagonize the JA pathway

313 (Pieterse *et al.*, 2012), these findings suggest that the enhanced resistance of the mutants

314 is due to a lack of inhibition of the JA pathway rather than a direct effect of SA

315 (Koornneef and Pieterse, 2008). Spider mite performance was higher on SA-deficient

316 tomato line NahG than on wild type (Villarroel *et al.*, 2016). When the brown

317 planthopper *Nilaparvata lugens* infested a rice line that overexpresses the resistance

318 gene *Bph14,* there was an induced expression of SA-related genes (Du *et al.*, 2009).

319 Finally, SA accumulated in resistant willow genotypes when attacked by the gall midge

320 *Dasineura marginemtorquens* (Ollerstam and Larsson, 2003).

321     *P. brassicae* oviposition on Arabidopsis triggered SA accumulation and

322     expression of SA-responsive genes (Little *et al.*, 2007). Follow-up studies using SA-

323     signaling mutants indicated that Arabidopsis responses to egg extract, including defense

324     gene expression, ROS accumulation and local cell death, share similarities with PTI and

325     requires a functional SA pathway (Gouhier-Darimont *et al.*, 2013) (Fig. 2).

326     ET is a modulator of SA and JA pathways. For instance, the ET pathway has a

327     synergistic effect on the JA pathway to fight necrotrophic pathogens or acts with NPR1

328     to enable SA antagonistic action on the JA pathway (reviewed in Pieterse *et al.*, 2012).

329     Information on the role of ET against arthropods is however incomplete or inconclusive.

330     The ET-insensitive Arabidopsis mutant *ein2-1* is more resistant to *S. littoralis* feeding

331     (Bodenhausen and Reymond, 2007; Stotz *et al.*, 2000). On the contrary, inhibition of

332     ET perception in maize enhances feeding by *S. frugiperda* (Harfouche *et al.*, 2006).

333     Treatment with HAMPs induced ET production in different plant species (Schmelz *et

334     al.*, 2009). Similarly, FACs elicited ET burst in *N. attenuata* and this prevented SA

335     accumulation, hence reducing a potential inhibitory effect of SA on the JA pathway

336     (Diezel *et al.*, 2009). Whitefly-induced interference of parasitoid attraction triggered by

337     *Plutella xylostella* feeding was abolished in *ein2-1* (Zhang *et al.*, 2013). Finally,

338     inhibition of the JA pathway after *P. brassicae* oviposition-induced SA accumulation in

339     Arabidopsis is dependent on both NPR1 and EIN2 (Schmiesing *et al.*, 2016).

340     Involvement of abscisic acid (ABA), auxin, gibberellins, brassinosteroids and

341     cytokinins in response to herbivory has been adressed in several studies (reviewed in

342     Erb *et al.*, 2012). The emerging picture is that these hormones primarily act as

343     modulators of the JA pathway and thus do not play a direct role in defense (reviewed in

344     Erb *et al.*, 2012).

345

**Systemic responses**

347 Evidence for a long-distance activation of defenses in response to herbivory has

348 accumulated over years. It requires activation of the JA pathway in local and distal

349 tissues but the nature of the systemic signal (hydraulic, chemical or electrical) has been

350 the subject of controversy (reviewed in Farmer *et al.*, 2014; Huber and Bauerle, 2016).

351 That JA or a precursor is the mobile signal was postulated but not demonstrated (Li *et*

352 *al.*, 2002a; Stratmann, 2003; Koo *et al.*, 2009). On the other hand, rapid voltage changes

353 in local and distal Arabidopsis leaves in response to *S. littoralis* feeding were recently

354 reported and depended on *GLUTAMATE RECEPTOR-LIKE (GLR)* genes *GLR3.3* and

355 *GLR3.6* (Mousavi *et al.*, 2013; Salvador-Recatalà *et al.*, 2014). Implanting platinum

356 wires in the petiole of a leaf and injecting current triggered JA and JA-Ile accumulation,

357 and defense gene expression in the leaf lamina distal to the treatment site, providing

358 strong evidence for the role of electrical signaling in systemic response to herbivory

359 (Mousavi *et al.*, 2013). Similar electrophysiological changes were further observed in

360 monocotyledonous and dicotyledonous species after challenge with *S. littoralis* and *M.*

361 *sexta* (Zimmermann *et al.*, 2016). Interestingly, aphid-induced $Ca^{2+}$ accumulation in

362 Arabidopsis was shown to depend on GLR3.3 and GLR3.6, but here a role in long-

363 distance signaling is unlikely (Vincent *et al.*, 2017). In contrast, systemic responses

364 from wounded Arabidopsis cotyledons to roots was shown to be independent of GLRs

365 and electrical signaling but more probably due to JA transport (Gasperini *et al.*, 2015).

366 Similarly, JA but not JA-Ile was identified as a long-distance transmissible signal in *N.*

367 *attenuata* response to *M. sexta* using stem-to-stem grafted plants (Bozorov *et al.*, 2017).

368 In tomato, application of isotope-labeled precursors in wounded leaves indicated that

369　JA-Ile may be a mobile signal (Matsuura et al., 2012). It thus appears that a

370　combination of electrical signaling and hormone transport may be responsible for

371　systemic induction of JA-related defenses, but that the contribution of each signal may

372　depend on the organ or plant species considered (Fig. 3).

373　　　　Oviposition also triggers changes in distal leaves. Egg deposition by the elm leaf

374　beetle *Xanthogaleruca luteola*, the sawfly *D. pini*, and the stemborer moth *Chilo*

375　*partellus* induced the release of volatiles in local and distal leaves of *Ulmus minor*,

376　*Pinus sylvestris*, and maize respectively (Meiners and Hilker, 2000; Hilker *et al.*, 2002;

377　Tamiru *et al.*, 2011). Recently, *P. brassicae* oviposition on Arabidopsis leaves inhibited

378　infection by the bacterial pathogen *Pseudomonas syringae*, both in local and distal

379　leaves (Hilfiker *et al.*, 2014). This systemic acquired resistance (SAR) depended on the

380　metabolic SAR signal pipecolic acid. Indeed, pipecolic acid accumulated in local and

381　distal leaves after oviposition and mutation in the biosynthesis gene *ALD1* abolished

382　egg-induced SAR (Hilfiker *et al.*, 2014). For all these examples, the nature of the

383　systemic signal is however unknown (Fig. 3).

384

**Open questions**

385

386　The precise connection between detection of herbivory or egg deposition and the

387　following activation of different signaling pathways is currently unknown. Although the

388　JA pathway is crucial to fend off a majority of herbivores, which downstream defenses

389　genes are critical for resistance is still unresolved in most plant species. The SA

390　pathway may be important in some plant-arthropod interactions, but further experiments

391　should demonstrate SA accumulation and altered performance on SA mutants.

392　Similarly, more work will be necessary to understand the exact molecular contribution

393    of the ET pathway. Modulation of defenses against herbivory by other plant hormones

394    will also have to be better explored (Erb *et al.*, 2012). Finally, a better knowledge on the

395    nature of systemic signals that activate defenses in distal tissues is needed.

396

397    **DEFENSE COMPOUNDS**

398    **Metabolites**

399    The plant multilayered immune system is accompanied by the endogenous production

400    of metabolites with direct antimicrobial or/and insecticidal activity, whereas some

401    metabolites act as signals and contribute to plant immunity by regulatory means

402    (Mithöfer and Boland, 2012). Examples of plant-derived metabolites with a direct

403    insecticidal activity are given in Table 2.

404         Plants produce non-protein amino acids that function in response to herbivory

405    (reviewed in Huang *et al.*, 2011). One of the best-studied example is L-canavanine, a

406    major nitrogen storage compound in seeds of many species of Leguminosae and a

407    structural analog of L-arginine. L-canavanine is integrated in proteins, which results in

408    the synthesis of dysfunctional proteins and poor larval development (Rosenthal *et al.*,

409    1976, Rosenthal, 2001). Tobacco and soybean plants respond rapidly to herbivore attack

410    with a production of γ-aminobutyric acid (GABA) (Bown *et al.*, 2002). Larvae of the

411    oblique-banded leafroller *Choristoneura rosaceana* raised on GABA-containing

412    artificial diets showed decreased growth and survival rates, indicating that GABA

413    possess direct insecticidal activity (Bown *et al.*, 2006). This insecticidal activity could

414    result from inhibition of neurotransmission via GABA-regulated fast-acting chloride

415    channels (Hosie *et al.*, 1997, Bown *et al.*, 2006).

416	Terpenoid-based compounds with insecticidal properties are widely spread in the

417	plant kingdom. Azadirachtin is synthesized by the neem tree *Azadirachta indica* and

418	reduces growth of *Spodoptera littoralis*, *Spodoptera frugiperda*, and *Schistocerca*

419	*gregaria* by negatively influencing cell division and disruption of the endocrine system

420	(Mordue Luntz *et al.*, 1998). Pyrethrin from *Chrysanthemum cinerariifolium* inactivates

421	sodium channels along nerve cells and thereby harm insects from different orders and

422	families, including Tetranychidae, Pseudococcidae, Auchenorrhyncha, Coleoptera,

423	Caelifera, and Aleyrodidae (Casida *et al.*, 1983). In response to JA, ET, and attack by

424	the European corn borer *Ostrinia nubilalis*, *Zea mays* produces *ent*-kaurane–related

425	diterpenoids, collectively termed kauralexins, which exhibit antifeedant activity on *O.*

426	*nubilalis* (Schmelz *et al.*, 2011). Moreover, the lactone taraxinic acid β-D-

427	glucopyranosyl ester (TA-G) in latex protects the dandelion *Taraxacum officinale*

428	against its major root herbivore, the cockchafer *Melolontha melolontha*. Silencing of the

429	germacrene A synthase ToGAS1 resulted in decreased levels of TA-G in *T. officinale*

430	and in increased *M. melolontha* feeding (Huber *et al.*, 2016).

431	Nicotine is one of the best-studied plant-derived alkaloid with insecticidal

432	activity and is produced by native tobacco species, such as *N. attenuata* and *Nicotiana*

433	*sylvestris*. It is structurally related to acetylcholine and can thereby target acetylcholine

434	receptors in the nervous system of insects (Gepner *et al.*, 1978). Silencing putrescine N-

435	methyltransferase (PMT), which is involved in nicotine biosynthesis, results in

436	decreased constitutive and inducible nicotine levels in *N. attenuata*. Consequently,

437	IR*pmt* plants grown in field experiments were more frequently attacked by the *S. exigua*

438	and *Trimerotropis* spp. grasshoppers (Steppuhn *et al.*, 2004). The medicinal plant

439	*Catharanthus roseus* produces more than a hundred different monoterpene indole

440    alkaloids (MIAs), which are well described as anticancer drugs in chemotherapy.

441    Catharanthine accumulates in leaf wax exudates and exhibits insect toxicity on *Bombyx*

442    *mori* larvae when included in artificial diet (Roepke *et al.*, 2010). Furthermore,

443    transcriptomic and metabolic analysis showed that *C. roseus* respond to *M. sexta*

444    feeding with the biosynthesis of specific MIAs. Interestingly, *C. roseus* leaf

445    consumption resulted in a rapid death of *M. sexta* larvae, which could be linked to MIA

446    generation and dimerization (Dugé de Bernonville *et al.*, 2017). Other examples of

447    insecticidal alkaloids include caffeine, colchicine, strychnine, and swainsonine (Wink *et*

448    *al.*, 1998, Mithöfer and Boland, 2012).

449        Flavonoids, derived from the phenylpropanoid metabolism, are a diverse group

450    of plant secondary metabolites found in all plant species and they display some

451    antiherbivore effects (Ververidis *et al.*, 2007). Rotenone is produced in roots of tropical

452    legumes, such as *Derris eliptica* and *Lonchocarpus*, and is a mitochondrial poison that

453    blocks the electron transport chain and disrupts energy production (Isman *et al.*, 2006).

454    Kaempferol-3,7-dirhamnoside (KRR) accumulates in Arabidopsis in response to *P.*

455    *brassicae* feeding (Onkokesung *et al.*, 2016). Overexpression of *MYB75*, a transcription

456    factor that activates the anthocyanin pathway, resulted in decreased KRR levels in

457    Arabidopsis plants and increased susceptibility to *P. brassicae*. Furthermore, *P.*

458    *brassicae* gained less weight when reared on artificial diet containing KRR

459    (Onkokesung *et al.*, 2014).

460        Aliphatic- and indole-glucosinolates (GS) belong to the best-studied insecticidal

461    metabolites in Brassicaceae, including the model plant Arabidopsis. Aliphatic-GS and

462    indole-GS are derived from methionine and tryptophan, respectively. They are produced

463    in leaves constitutively and act as phytoanticipins in basal immunity against arthropods,

464    but their synthesis can also be induced in response to various pathogen attacks. Thereby,

465    GS biosynthesis relies on a complex regulatory network, controlled by several MYB

466    and MYC transcription factors (Schweizer *et al.*, 2013b; Frerigmann, 2016). Upon

467    plant-tissue disruption, β-thioglucoside glucohydrolase-dependent GS hydrolysis leads

468    to the generation of chemically unstable aglycones, such as toxic nitriles, thiocyanates,

469    and isothiocyanates. These aglycones can react spontaneously with biological

470    nucleophiles and modify proteins and nucleic acids (reviewed Pastorczyk and Bednarek,

471    2016). Strikingly, GS-deficient Arabidopsis mutants are highly susceptible to arthropod

472    feeding, including chewing larvae, spider mites, and aphids (Mewis *et al.*, 2005;

473    Beekwilder *et al.*, 2008; Schlaeppi *et al.*, 2008; Schweizer *et al.*, 2013b; Zhurov *et al.*,

474    2014; Madsen *et al.*, 2015). Tryptophan can also serve as a precursor for several indolic

475    alkaloids, which act as defense-related metabolites in Arabidopsis. Camalexin is

476    produced in Arabidopsis upon infestation by the phloem feeding green peach aphid *M.*

477    *persicae*. Consequently, *M. persicae* grows more successfully on camalexin-deficient

478    *pad3* mutant, indicating that camalexin functions in defense against phloem sap sucking

479    insects (Kettles *et al.*, 2013). Similarly, camalexin accumulated in response to

480    infestation by the cabbage aphid *Brevicoryne brassicae* and aphid performance was

481    augmented on *pad3* (Kusnierczyk *et al.*, 2008).

482         Many defense compounds are stored in developmental structures, including

483    glandular trichomes, laticifers, resin ducts, and specialized cell types or tissues

484    (Mithöfer and Boland, 2012). Genetic evidence for the role of trichomes as a source of

485    defense against herbivores was provided for tomato (Kang *et al.*, 2010; Bleeker *et al.*,

486    2012), Arabidopis (Mauricio, 1998), *Arabidopsis lyrata* (Kivimäki et al., 2007) and

487    *Nicotiana attenuata* (Luu *et al.*, 2017). Induction of terpene-containing traumatic resin

488 ducts by JA in Norway spruce provides support for a defensive role of these structures

489 against conifer pests (Martin *et al.*, 2002).

490      In addition to ingested defense metabolites that target physiological processes in

491 arthropods, plants produce metabolites that harm feeding herbivores physically. In the

492 barrel medic *Medicago truncatula,* calcium oxalate crystals accumulate around

493 secondary veins and act as physical abrasive of *S. exigua* mandibles. Consistent with

494 this, larvae showed a feeding preference for the calcium oxalate-defective mutants *cod5*

495 and *cod6* (Korth *et al.*, 2006). Silica constitutes another important physical defense

496 compound, particularly in grasses (reviewed in Hartley and DeGrabriel, 2016). For

497 example, *Spodoptera exempta* larvae exposed to silica-rich diet displayed mandible

498 wear and reduced growth (Massey and Hartley, 2009).

499

500 **Proteins and peptides**

501 Besides toxic metabolites, plants produce numerous proteins and peptides with direct

502 insecticidal activity (Table 3). Acrelin-1 is a 60 kDa dimeric glycoprotein found in

503 seeds of the wild kidney bean *Phaseolus vulgaris*. Acrelin-1 is highly resistant to

504 proteolytic degradation and binds to complex glycans, which leads to disruption of the

505 epithelial structure in the midgut of the Mexican bean weevil *Zabrotes subfasciatus*

506 (Fabre *et al.*, 1998). Plant-derived lectins are a heterogenous group of proteins found in

507 many members of Leguminosae. They can bind to specific carbohydrate structures in

508 the insect digestive tract, which leads to harmful effects in the whole insect body.

509 Insecticidal activity of lectins was reported against members of Coleoptera,

510 Lepidoptera, and Homoptera (Vandenborre *et al.*, 2011).

511     Cyclotides represent a group of small peptides found in Rubiaceae and

512 Violaceae. A cyclic peptide backbone in combination with a cysteine knot confer strong

513 chemical and biological stability. Cyclotides inhibit larval growth and development of

514 the native budworm *Helicoverpa punctigera* and leads to disruption of microvilli and

515 cellular rupture in the gut epithelium of *H. armigera* larvae (Jennings *et al.*, 2001;

516 Barbeta *et al.*, 2008). Canatoxin (CNTX) is an urease found in seeds of the jack bean

517 *Canavalia ensiformis.* Proteolytic activation of CNTX releases a 10 Kda peptide that

518 interferes with serotine-related processes in *Callosobruchus maculatus* and *Rhodnius*

519 *prolixus* (Stanisçuaski and Carlini, 2012). In tomato, threonine deaminase TD2 has

520 insecticidal properties by depriving herbivores from the essential Thr. Proteolytic

521 activation of TD2 is catalyzed by chymotrypsin in the gut of lepidopteran herbivores,

522 such as *S. exigua*, but not in coleopteran herbivores. Consequently, *S. exigua* larvae

523 performed better on TD2-deficient tomato plants (Gonzales-Vigil *et al.*, 2011).

524     Arthropod digestion and nutrient acquisition relies on enzymes such as α-

525 amylases, cysteine proteases, and serine proteases. So far, numerous plant protease and

526 amylase inhibitors have been reported that inhibit digestive enzymes and thereby

527 interfere with larval development. For instance, expression of an Arabidopsis cysteine

528 protease inhibitor (*Atcys*) in transgenic white poplar plants is sufficient to inhibit most

529 of the digestive proteinase activity of the leaf beetle *Chrysomela populi* and confers

530 resistance to this insect (Delledonne *et al.*, 2001)**.**

531

532 **Open questions**

533 Numerous plant-derived insecticides have been identified and some of them are of great

534 interest in agriculture for plant protection. However, activity of most of them has just

535 been studied in artificial diets. We need better knowledge of biosynthetic pathways and

536 generation of knock-out mutants to test their role *in vivo*. Moreover, target sites for

537 many of the known insecticides are poorly characterized.

538

539 **SUPPRESSION OF DEFENSES**

540 Effective plant PTI exerts as strong selection pressure on aggressors. Bacterial and

541 fungal pathogens have thus evolved numerous effectors to interfere with PTI (Dodds *et*

542 *al.*, 2009; Deslandes and Rivas, 2012;). These effectors are secreted and transferred or

543 directly injected into plant cells. In return, plants have developed strategies to directly or

544 indirectly detect effectors by intracellular nucleotide-binding, leucine-rich-repeat

545 receptors (NB-LRRs) that trigger an enhanced defense response called effector-

546 triggered immunity (ETI)(Jones and Dangl, 2006). This process illustrates the on-going

547 arms race that has been the driving force for generating a multitude of effectors and

548 defense proteins during plant-pathogen coevolution. Similarly, plant defense

549 suppression by arthropods has been reported in several studies (Table 1).

550

551 **Arthropod-derived effectors**

552 A seminal discovery by Musser et al. (2002) reported that glucose oxidase (GOX) in *H.*

553 *zea* salivary glands inhibited nicotine production in tobacco. Elegant experiments using

554 ablation of the secretory apparatus, the spinneret, and ectopic application of active or

555 inactive GOX demonstrated that this enzyme is responsible for a lower accumulation of

556 nicotine upon feeding. Since GOX generates $H_2O_2$ from D-Glucose, it was further

557 shown that this ROS may interfere with plant defense signaling (Bede *et al.*, 2006;

558 Diezel *et al.*, 2009). An ATP-hydrolyzing apyrase activity was found in *H. zea* saliva.

559 Tomato plants treated with this enzyme showed reduced defense gene expression (Wu

560 *et al.*, 2012). Since ATP can be perceived as a DAMP by plant PRRs, it is tempting to

561 speculate that some insects have evolved a way to reduce ATP levels in their host.

562 Unknown proteins or peptides from lepidopteran OS inhibited wound-induced defense

563 gene expression in Arabidopsis and tomato, and this was correlated with enhanced

564 insect performance in the case of Arabidopsis (Lawrence *et al.*, 2007; Consales *et al.*,

565 2012).

566 Although they act as HAMPs in several insects, FACs may have dual roles.

567 Emission of some volatiles was reduced when *M. sexta* FACs were applied to *N.*

568 *attenuata* plants. Whether this interfered with parasitoid attraction was however not

569 tested (Gaquerel *et al.*, 2009). Heat-stable components of *M. sexta* OS suppressed

570 wound-induced accumulation of *N. attenuata* transcripts but their chemical nature was

571 not studied (Schittko *et al.*, 2001). Another striking example of a modified HAMP

572 activity is found in the legume-specialist velvetbean caterpillar *Anticarsia gemmatalis*.

573 OS of this insect contain a modified inceptin that does not induce plant defenses and

574 furthermore acts as an antagonist of the normally active inceptin, probably by

575 competing with inceptin-PRR binding (Schmelz *et al.*, 2012).

576 For spider mites and aphids, examples of effective suppression of defenses exist.

577 In the spider-mite *T. urticae*, two proteins of unknown function suppressed defenses and

578 increased mite performance when expressed in *N. benthamiana* (Villarroel *et al.*, 2016).

579 A salivary component with high homology to human macrophage migration inhibitory

580 factor (MIF) was identified in the pea aphid *Acyrthosiphon pisum* (Naessens *et al.*,

581 2015). MIFs are important pro-inflammatory cytokines modulating immunity and

582 inflammation in vertebrates. Interestingly, RNAi of *ApMIF1* reduced survival and

583     fecundity of *A. pisum*. In addition, ectopic expression of MIF1 reduced plant defenses in

584     *N. benthamiana* (Naessens *et al.*, 2015). Since MIFs form heterocomplexes and

585     homologues have been recently identified in plant genomes (Panstruga *et al.*, 2015),

586     aphid MIF may interfere with endogenous MIFs to alter plant defenses (Naessens *et al.*,

587     2015; Reymond and Calandra, 2015). A salivary calcium-binding protein from

588     *Megoura viciae* prevented sieve plate occlusion, a known defense mechanism against

589     phloem-feeding that is triggered by calcium release (Will and van Bel, 2006; Will *et al.*,

590     2007). *A. pisum,* in which expression of the salivary protein C002 was reduced by

591     RNAi, was impaired in phloem feeding (Mutti *et al.*, 2008). Attempts to identify more

592     aphid effectors have relied on the same proteomic and genomic approaches that

593     sucessfully isolated secreted HAMPs. A series of proteins of unknown function have

594     been tested and were shown to suppress PTI responses and increase aphid performance

595     when expressed *in planta* (Bos *et al.*, 2010; Atamian *et al.*, 2013; Elzinga *et al.*, 2014).

596     For example, the *M. persicae* Mp10 effector suppressed flg22-induced but not chitin-

597     induced ROS production (Bos *et al.*, 2010). Furthermore, Mp10 was shown to act in the

598     BAK1 pathway (Drurey *et al.*, 2017). *M. persicae* Mp1 promoted aphid virulence by

599     targeting a vacuolar sorting protein (VSP52) from its preferred host plants Arabidopis

600     and potato, but not with VSP52 from poor-host barley and *Medicago truncaluta*

601     (Rodriguez *et al.*, 2017). Similarly, a comparative study on aphid effectors revealed that

602     they act in a plant-specific way and that sequences displayed high nonsynonymous

603     substitution rates, indicative of positive selection (Pitino and Hohenhout; 2013).

604          The Hessian fly *Mayetiola destructor* is an economically important pest of

605     wheat and a well-studied member of the plant parasitic gall midges (Stuart *et al.*, 2012).

606     The Hessian fly genome revealed a large family of secreted proteins (SSGP-71) that

607   resemble ubiquitin E3 ligases in plants (Zhao *et al.*, 2015). They contain a F-box

608   domain and variable leucine-rich repeats (LRR). In plants, the F box interacts with Skp,

609   a component of the SCF-E3-ubiquitin-ligase complex that targets proteins for

610   degradation. Interestingly, two Hessian fly F-box-LRR effectors were shown to directly

611   bind to wheat Skp proteins, suggesting that the role of these effectors is to highjack the

612   plant proteasome in order to block defenses (Zhao *et al.*, 2015). As further evidence that

613   F-box-LRRs are true effectors that can be recognized by NB-LRRs and trigger ETI,

614   mutations in two SSGP-71 genes were associated with regained virulence on wheat

615   cultivars containing the respective *H* resistance genes (Zhao *et al.*, 2015).

616   As discussed above, JA and SA signaling pathways generally modulate plant

617   defenses against arthropods and pathogens, respectively. These pathways are

618   antagonistic to each other and this property has been highjacked by bacterial effectors to

619   effectively suppress SA-dependent defenses (Pieterse *et al.*, 2012; Zheng *et al.*, 2012;

620   Gimenez-Ibanez *et al.*, 2014). Interestingly, effectors from arthropods also exploit

621   antagonism between SA and JA pathways. In Arabidopsis, defense gene expression and

622   JA levels were lower in response to *S. exigua* larvae with intact salivary glands

623   compared to larvae with ablated spinneret. This effect was lost in a mutant that does not

624   accumulate SA, implying a role for SA in inhibiting JA accumulation (Weech *et al.*,

625   2008). Silverleaf whitefly induced SA defenses while suppressing JA defenses in

626   Arabidopsis and lima bean (Zarate *et al.*, 2007; Zhang *et al.*, 2009). Similarly, the

627   mealybug *Phenacoccus solenopsis* inhibited JA accumulation and JA-dependent

628   defenses in tomato and this suppression was due to SA accumulation (Zhang *et al.*,

629   2015). A somewhat twisted example comes from the Colorado potato beetle (CPB)

630   *Leptinotarsa decemlineata* that uses microbe-derived flagellin to trigger SA-dependent

631    inhibition of the JA pathway in tomato. Indeed, bacteria in CPB OS decreased JA-

632    responsive defenses and increased SA and SA-related gene expression. These responses

633    were lost when using antibiotic-treated larvae and a SA-mutant (Chung *et al.*, 2013).

634    The observation that chitinase in larval frass of the fall armyworm *S. frugiperda*

635    suppress maize defenses through induction of the SA-dependent gene expression

636    provides another intriguing evidence of indirect effector-like activity. Finally, *P.*

637    *brassicae* oviposition or egg extract-treatment triggered SA accumulation, suppressed

638    larval-induced JA-dependent gene expression, and enhanced larval performance in

639    Arabidopsis (Little *et al.*, 2007; Bruessow *et al.*, 2010). This egg-induced inhibition of

640    the JA pathway is achieved through SA-dependent destruction of MYC2, MYC3 and

641    MYC4 transcription factors that control JA defense gene expression (Schmiesing *et al.*,

642    2016). Intriguingly, *P. brassicae* oviposition also triggers a SAR against bacterial

643    pathogens, a response that may benefit hatching larvae (Hilfiker *et al.*, 2014). This latter

644    phenomenon does not seem to be strictly related to suppression of defenses but

645    illustrates a manipulation of plant signaling pathways by an egg-derived effector, to the

646    potential benefit of the attacker.

647

648    **Defense suppression by insect-vectored viruses and phytoplasma**

649    Plant pathogens like viruses and phytoplasma are often transmitted by arthropods and

650    thus engage in mutualistic interactions with their vector to ensure dispersal and survival.

651    Improved performance and reproduction of the carrier is thus crucial for the pathogen

652    and consequently compromising plant defenses has obvious advantages. The

653    pathogenesis protein βC1 of *Tomato yellow leaf curl China virus* (TYLCCNV), a

654    begomovirus transmitted by the whitefly *B. tabaci*, binds to the plant transcription

655   factor AS1, triggering a reduced expression of JA-responsive genes (Yang *et al.*, 2008).

656   βC1 interacted with MYC2 and interfered with expression of TPS genes, which are

657   responsible for biosynthesis of defensive terpenoids (Li *et al.*, 2014). Consequently,

658   virus-infected whiteflies displayed a significantly higher survival and reproduction on

659   tobacco plants than non-infected ones (Luan *et al.*, 2013). The C2 protein from the

660   *Tomato yellow leaf curl Sardinia virus* (TYLCSV) and *Tomato yellow leaf curl virus*

661   (TYLCV) was shown to interfere with the activity of COP9 signalosome complex,

662   which subsequently compromised the function of several CUL1-based SCF ubiquitin

663   E3 ligases. Jasmonate responses were altered in Arabidopsis expressing C2 from

664   TYLCSV or TYLCV, suggesting that SCF$^{COI1}$ is one target of this virulence factor

665   (Lozano-Durán *et al.* 2011; Rosas-Díaz *et al.*, 2016). The 2b protein of aphid-

666   transmitted *Cucumber mosaic virus* inhibited expression of JA-regulated genes

667   downstream of JA production (Lewsey *et al.*, 2010). *M. persicae* aphid fecundity was

668   enhanced by *Turnip mosaic virus* infection of Arabidopsis, which showed increased

669   callose deposition. This effect depended on ET-signaling and was caused by the Nuclear

670   Inclusion a-Protease domain (Casteel *et al.*, 2015).

671       Phytoplasma are obligate bacterial pathogens that develop in plant phloem. The

672   Aster Yellows phytoplasma strain Witches' Broom (AY-WB) secretes the SAP11

673   protein that destabilizes class II CIN-TCP transcription factors, some of which are

674   positive regulators of the JA-biosynthesis enzyme LOX2. As a consequence,

675   Arabidopsis lines expressing SP11 or AY-WB infected plants produced less JA and

676   allowed enhanced performance of the leafhopper vector *Macrosteles quadrilineatus*

677   (Sugio *et al.*, 2011).

678

679 **Arthropod resistance genes**

680 ETI triggered by pathogen or fungal effectors is driven by NB-LRRs. These resistance

681 proteins usually contain a Toll-Interleukin-1 receptor-Resistance protein (TIR) or a

682 coiled-coil (CC) domain at the amino terminus. They are encoded by numerous

683 resistance (*R*) genes usually clustered in plant genomes, allowing recombination-based

684 diversification to respond to the evolution of pathogen effectors (Jones and Dangl,

685 2006; McHale *et al.*, 2006). In contrast to *R* genes associated with bacterial and fungal

686 pathogens, only a few arthropod-directed *R* genes have been cloned and characterized

687 (Gururani *et al.*, 2012). *Mi-1.2* from tomato encodes a CC-NB-LRR and confers

688 resistance to the potato aphid, the whitefly *B. tabaci*, the psyllid *Bactericerca cockerelli*,

689 and the root-knot nematode *Meloidogyne incognita*, illustrating the first example of a

690 resistance gene acting against distantly related pests (Milligan *et al.*, 1998; Rossi *et al.*,

691 1998; Nombela *et al.*, 2003; Casteel *et al.*, 2006). In the presence of potato aphid saliva

692 *Mi-1.2* was shown to interact with *SlSERK1,* a receptor kinase related to Arabidopsis

693 BAK1, and this complex formation is suggested to confer aphid resistance (Peng *et al.*,

694 2016). *Vat* from melon is also a CC-NB-LRR and, interestingly, provides dual

695 resistance against the aphid *Aphis gossypii* and viruses transmitted by this vector

696 (Dogimont *et al.*, 2014). Resistance to the brown planthopper (BPH) *Nilaparvata*

697 *lugens,* a sucking insect attacking rice plants, is conferred by two CC-NB-LRR genes,

698 *Bph14* and *Bph16* (Du *et al.*, 2009; Tamura *et al.*, 2014). In lettuce, *Ra* is part of a large

699 CC-NB-LRR gene cluster and provides resistance against the root aphid *Pemphigus*

700 *bursarius* (Wroblewski *et al.*, 2007). The *AIN* locus in *M. truncatula* is associated with

701 resistance against the bluegreen aphid *Acyrthosiphon kondoi* and resides in a cluster of

702 CC-NB-LRR genes (Klingler *et al.*, 2009). Similarly, *Hdic* is embedded in a family of

703    NB-LRR *H* resistance genes that are active against the Hessian fly *M. destructor* (Stuart

704    *et al.*, 2012).

705

**Open questions**

707    Chemical identity, mode of action, and molecular target(s) of several effectors are

708    poorly characterized. Whether each type of effector represents an evolutionary response

709    to PTI and appears in only a subset of related arthropod species or biotypes, similar to

710    bacterial or fungal effectors, remains an open question. When effectors inhibit defenses

711    via SA-dependent inhibition of the JA pathway, it is unclear whether activation of the

712    SA pathway by arthropod-derived cues illustrates a strategy evolved by the attacker to

713    indirectly target the JA pathway or whether this is a trade-off, since the SA pathway

714    may be needed for defense.

715        Strikingly, all examples of cloned resistance genes are CC-NB-LRRs that target

716    phloem-feeding insects. Whether there is a mechanistic reason for such specificity or

717    whether this is explained by a lack of success in cloning resistance genes against

718    members of other feeding guilds will await future experiments. Indeed, many loci

719    providing resistance against different orders of arthropods have been identified in

720    different crop species and need to be characterized (Smith and Clement, 2011; Gururani

721    *et al.*, 2012). Alternatively, other feeding guilds that rapidly consume leaf material may

722    avoid recognition by "eating the evidence". Also, besides F-box-LRR effectors and H

723    resistance proteins in Hessian fly/wheat interaction, information about the nature of

724    effectors interacting with known arthropod NB-LRRs is currently lacking.

725

**PLANT-ARTHROPOD COEVOLUTION**

727 Plants and herbivores are engaged in a continuous battle for survival and rely on

728 different strategies to counteract the evolution of resistance or adaptation to defense

729 compounds. In addition to PTI and ETI immunity responses, which are based on HAMP

730 recognition and inhibition of HAMP-triggered defenses by arthropod effectors (see

731 previous sections), there are numerous examples of behavioral or metabolic responses

732 that overcome plant defenses (Table 4). In a few cases, a successive appearance of

733 defense and counterdefense mechanisms can be observed and nicely illustrates

734 coevolutionary processes that underlie plant-arthropod interactions.

735

**Behavioral adaptations**

737 Capability of arthropods to circumvent plant defenses by specialized feeding behavior

738 has been documented (reviewed in Dussourd, 2017). Cardenolides are toxic cardiac

739 glycosides that inhibit Na/K-ATPase and are stored in latex from several plant families.

740 Larvae of the queen butterfly *Danaus gilippus* cut trenches on leaves of the milkweed

741 *Asclepias syriaca*, releasing a flow of cardenolide-containing latex and thus rendering

742 the plant more palatable (Dussourd and Eisner, 1987). In some *Bursera* species,

743 terpene-containing resin is stored under pressure in leaf canals. Upon feeding, the toxic

744 resin is ejected and solidifies around small herbivores. Adapted members of

745 chrysomelid beetles of the genus *Blepharida* puncture leaf veins to stop the flow before

746 feeding (Becerra, 2003). Leaf vein severing or trench cutting is frequent and found in

747 several arthropod families (Dussourd, 2017).

748     To avoid defensive trichomes in *Solanum* sp., larvae of the ithomiid butterfly

749 *Mechanitis isthmia* spin a fine silk fabric over spines, allowing them to move and feed

750 safely (Rathcke and Poole, 1975). Another behavioral adaptation is to minimize contact

751 with induced plant defenses. When carefully studying movement of *H. armigera*

752 caterpillars feeding on Arabidopsis, Perkins *et al.* (2013) noticed that larvae moved

753 away from elicited and closely connected leaves, suggesting that they are capable of

754 detecting a signal that triggers this response. The nature of the warning signal is

755 unknown but depends on activation of the JA pathway (Perkins *et al.*, 2013). There are

756 also examples of behaviors that reduce attraction of parasitoids. Larvae of *Heliothis*

757 *subflexa* have specialized on their host plant *Physalis angulata* by feeding exclusively

758 on fruits, which lack linolenic acid. As a consequence, no volicitin is produced in *H.*

759 *subflexa* OS and feeding does not trigger volatile emission (De Moraes and Mescher,

760 2004). Since linolenic acid is required for development of most insect larvae, this

761 physiological adaptation is remarkable and provides both a protection against

762 parasitoids and an exclusive access to a food source. Interestingly, linolenic acid is also

763 a precursor for JA and there is the possibility that *P. angulata* fruits are unable to trigger

764 JA-dependent defenses against herbivores. This hypothesis was however not tested in

765 the study. Recently, the first evidence of insect resistance against an introduced

766 parasitoid wasp was reported (Tomasetto *et al.*, 2017). The Argentine stem weevil

767 *Listronotus bonariensis* was discovered in New Zealand in 1927 and cause intensive

768 damage to pasture grass. Since the introduction of a natural parasitoid of the stem

769 weevil in the 90's there has been a gradual decline in parasitism rate from 80-90% to 10-

770 20%. This sharp reduction is attributed to a host shift from *Lolium multiflorum* to the

771 more widely cultivated *Lolium perenne*, which is potentially impaired in herbivore-

772 induced volatile emission (Tomasetto *et al.*, 2017).

773

774 **Metabolic resistance**

775  Target modification and metabolism of plant toxins are the main strategies to overcome

776  plant defenses and have been the subject of numerous studies, which in some instances

777  have revealed the molecular mechanism (reviewed in Després *et al.*, 2007; Li *et al.*,

778  2007; Heidel-Fischer and Vogel, 2015).

779  Insensitivity of the monarch butterfly *Danaus plexxipus* to cardenolides was

780  attributed to an amino acid substitution in the binding site of a Na/K-ATPase (Holzinger

781  and Wink, 1996). The same substitution was found in four species that span four insect

782  orders and 300 million years of divergence, providing a stunning example of convergent

783  evolution (Dobler *et al.*, 2012). *H. zea* evolved a structural modification in the binding

784  site of a carboxypeptidase to evade inhibition of the potato carboxypeptidase inhibitor

785  (Bayés *et al.*, 2005). Similarly, a single amino acid substitution in chymotrypsin from

786  *Helicoverpa* larvae removes a binding contact to a tobacco proteinase inhibitor (Dunse

787  *et al.*, 2010). As described above, L-canavanine from legumes is a L-Arg analog with

788  insecticidal properties. Larvae of the bruchid beetle *Caryedes brasiliensis* have evolved

789  a discriminating arginyl-tRNA synthetase that does not accept L-canavanine as

790  substrate and thus are protected against the toxic effect of this analog (Rosenthal *et al.*,

791  1976).

792  Detoxification of cyanogenic glycosides from *Passiflora* sp. by larvae of the

793  butterfly *Heliconius* is carried out by sequestration and replacement of a nitrile by a

794  thiol group that prevents cyanide release (Engler *et al.*, 2000). However, the enzyme

795  responsible for this reaction has not been identified yet. Another way to avoid cyanide

796  poisoning is to metabolize HCN. Remarkably, the spider mite *T. urticae* has acquired a

797  bacterial gene encoding a β-cyanoalanine synthase (CAS) that can detoxify HCN to β-

798  cyanoalanine (Wybouw *et al.*, 2014). The same activity was found in the lepidopteran

799　herbivore *P. rapae* where CAS genes are also predicted to originate from bacteria

800　through horizontal gene transfer (van Ohlen *et al.*, 2016). Excretion of the alkaloid

801　nicotine by the specialist tobacco hornworm *M. sexta* is thought to be the main method

802　by which this insect can thrive on Solanaceae (Self *et al.*, 1964; Maddrell and Gardiner,

803　1976). Interestingly, it was recently shown that part of the ingested nicotine is

804　transported from *M. sexta* midgut to the hemolymph, from where it is actively exhaled

805　and used as a defensive signal against the spider predator *Camptocosa parallela* (Kumar

806　*et al.*, 2014).

807　　　Arthropod adaptation to the GS-myrosinase system of Brassicaceae has been

808　extensively studied (Winde and Wittstock, 2011). In larvae of *P. rapa*e and *P.*

809　*brassicae,* midgut nitrile-specifier proteins (NSPs) favor GS hydrolysis to less toxic

810　nitriles, instead of isothiocyanates (ITC) (Wittstock *et al.*, 2004). In contrast, the

811　diamondback moth *P. xylostella* and the desert locust *S. gregaria* detoxify intact GS

812　with a sulfatase, preventing formation of hydrolysis products (Ratzka *et al.*, 2002; Falk

813　and Gershenzon, 2007). Remarkably, the cabbage aphid *B. brassicae* sequesters intact

814　GS from its host plants in the haemolymph and produces a myrosinase in microbodies.

815　Upon attack by predators, aphids use this "mustard-oil bomb" to generate bioactive

816　compounds and defend themselves (Bridges et al., 2002; Kazana et al., 2007). Similarly,

817　the crucifer specialist flea beetle *Phyllotreta striolata* accumulates GS when feeding and

818　has acquired a myrosinase gene (Beran *et al.*, 2014).

819　　　Major detoxification gene families from arthropods include cytochrome P450

820　monooxygenases　　　(CYP450s),　　　glutathione-*S*-transferases　　　(GSTs),　　　UDP-

821　glycosyltransferases (UGTs), carboxyl/cholinesterases (CCEs) and ABC transporters

822　(ABCs) (Li *et al.*, 2007; Heidel-Fischer and Vogel, 2015). These enzymes have

823   relatively broad substrate specificity and are generally important for generalist

824   herbivores that face a variety of plant toxins. Using the polyphagous *T. ni* and defense

825   or signaling mutants, Herde and Howe (2014) were the first to demonstrate

826   transcriptional reprogramming and altered expression of detoxification genes in

827   response to GS in Arabidopsis. Similarly, a comparative transcriptomic analysis of

828   larvae of the generalist *Heliothis virescens* and the specialist *P. brassicae* feeding on

829   Arabidopsis genotypes with contrasting GS levels revealed a significant upregulation of

830   detoxification genes from all the above-mentioned families in the generalist, whereas

831   there was a much-reduced transcriptional activation in the specialist (Schweizer *et al.*,

832   2017). Furanocoumarins are DNA-interfering agents primarily found in Apiaceae and

833   Rutaceae. Species of the genus *Papilio*, including the black swallowtail *P. polyxenes*,

834   induce the expression of CYP450s from the CYP6B class upon feeding on

835   furanocoumarin-containing plants. CYP6B proteins were shown to metabolize

836   furanocoumarins and were more active in the specialist *P. polyxenes* than in the

837   generalist *H. zea* (Hung *et al.*, 1997; Li *et al.*, 2004a; Li *et al.*, 2007). The fly genus

838   *Scaptomyza* is closely related to the genus *Drosophila* and has acquired the ability to

839   feed on Brassicaceae. A duplication in the GST gene *GstD1* in *S. nigra* is responsible

840   for an enhanced detoxification activity against isothiocyanates, toxic breakdown

841   products of GS, and is postulated to be linked to the evolutionary transition to herbivory

842   in Drosophilidae (Gloss *et al.*, 2014). Gossypol is a major sesquiterpene defensive

843   compound in cotton. Larvae of the generalist Heliothine moth *H. armigera* can develop

844   on cotton plants and are equipped with two UGTs, UGT41B3 and UGT40D1, which are

845   capable of glycosylating gossypol (Krempl *et al.*, 2016).

846     Although CCEs have been clearly associated with resistance to synthetic

847     insecticides and CCE gene expression is induced after feeding (Li *et al.*, 2007; Teese *et*

848     *al.*, 2010), there is limited information on their role against plant allelochemicals. In

849     different strains of the gypsy moth *Lymantrya dispar*, larval survival on artificial diet

850     containing phenolic glycosides was positively correlated with CCE activity (Lindroth

851     and Weisbrod, 1991). Similarly, ABC transporters have been associated with insecticide

852     resistance, including *Bacillus thuringiensis* insecticidal toxins (Bt). There is an

853     expansion of ABC genes in the *T. urticae* genome and expression of ABC genes is

854     enhanced upon switching to a different host plant or feeding on artificial diet containing

855     plant secondary metabolites (Grbic *et al.*, 2011; Dermauw *et al.*, 2013a; Dermauw *et al.*,

856     2013b; Dermauw and Van Leeuwen, 2014; Tay *et al.*, 2015; Bretschneider *et al.*, 2016).

857     However, direct evidence for a role of ABCs in resistance to plant allelochemicals is

858     scarce. In the only known example, the *Cp*MRP transporter of the Chrysomelid leaf

859     beetle *Chrysomela populi* is involved in the sequestration of salicin, a toxic phenolic

860     glucoside found in willow and poplar leaves. CpMRP shuttles salicin from the

861     hemolymph into specialized defensive glands, which play a role against predators.

862     Reduction of *CpRMP* expression by RNAi abolished salicin excretion and rendered leaf

863     beetles defenseless (Strauss *et al.*, 2013).

864

865     **Escaping detection or anticipating defenses**

866     As a striking example of adaptation, larvae of the velvetbean caterpillar produce a

867     modified form of the cyclic peptide inceptin, a HAMP found in OS of the generalist Fall

868     armyworm (see section on HAMPs). Through yet unknown modification of a gut

869     protease, digestion of chloroplastic ATP synthase of the host plant cowpea generates a

870    peptide lacking the C-terminal amino acid, *Vu*-In[-A] (Schmelz *et al.*, 2012). Velvetbean

871    OS induced a significantly weaker ET production and volatile emission in cowpea

872    leaves, suggesting that the truncated inceptin evades recognition by a (unknown) plant

873    receptor (Schmelz *et al.*, 2012).

874          A lag phase between ingestion/perception of plant toxins and transcriptional

875    activation of detoxification genes may be detrimental to optimal larval development. An

876    interesting study reported that treatment of *H. zea* larvae with the plant defense signals

877    JA and SA induced the expression of four CYP450s that metabolize furanocoumarins

878    and other toxins (Li *et al.*, 2002b). This induction was shown to provide an advantage to

879    larvae, which performed better on furanocoumarin-containing plants or diets.

880    "Eavesdropping" on defense signals seems thus an effective way of anticipating the

881    production of defense compounds but the generality is this phenomenon amongst

882    arthropods has yet to be established.

883

884    **Coevolution**

885    The seminal publication by Ehrlich and Raven (1964) stressed the importance of

886    reciprocal relationship between butterflies and plant hosts in shaping the evolution and

887    diversification of each group, and by extension supported the notion that plant-enemy

888    interactions are responsible for much of global biological diversity. This has stimulated

889    decades of research to test these predictions and provide experimental data for such

890    scenario. Evidence is however scarce, because evolution is such a slow process that it is

891    difficult to catch it in action and because several environmental, biogeographical and

892    ecological factors may confound interpretations (reviewed in Futuyma and Agrawal,

893    2009). For example, removal of herbivore pressure in replicate fields of the evening

894    primrose *Oenothera biennis* caused a rapid evolutionary divergence (Agrawal *et al.*,

895    2012). Phylogenetic reconstructions of plant and arthropods lineages have however

896    generated useful hints that evolution of defense chemistry responds to herbivore

897    pressure and that counteradaptation drives arthropod diversity. A convincing example is

898    the stepwise evolution of GS complexity in Brassicales, mirrored with the radiation of

899    Pierinae butterfly species (Wheat *et al.*, 2007; Edger *et al.*, 2015). A robust

900    phylogenetic analysis of 14 families from the Brassicales revealed that this order

901    originated ~90 million years ago (Ma) and that plants only synthesized aromatic Phe-

902    GS. Indole-GS appeared after a whole-genome duplication (WGD) ~77 Ma, followed

903    by the occurrence and diversification of aliphatic-GS-containing families ~60 Ma.

904    Finally, after a second WGD, Brassicaceae appeared ~30 Ma and coincided with the

905    greatest GS and species diversification (Edger *et al.*, 2015). Pierinae colonized

906    Brassicales 68 Ma, approximately 10 million years after indole-GS appearance, and

907    radiated through the acquisition of NSPs. Again, shortly after occurrence of

908    Brassicaceae, new lineages of Pierinae evolved and diversified. Strikingly, independent

909    nitrile-specifier gene lineages could be associated with independent colonization of

910    Brassicaceae by two Pierinae lineages (Edger *et al.*, 2015).

911        Comparative phylogenies of *Bursera* sp. and *Blepharida* sp. indicated that both

912    groups diversified synchronously, showing that plant lineages possessing the defensive

913    trait (resin under high pressure) coevolved with beetles lineages equipped with vein

914    severing ability (Becerra, 2003). In addition, escalation of species and chemical

915    diversity through time was observed in *Bursera*, providing support for herbivore-plant

916    coevolution theory (Becerra *et al.*, 2009). Similarly, diversification of milkweeds was

917    correlated with increased phenolic production (Agrawal *et al.*, 2009). For evolution of

918     herbivores, a phylogenetic study of the leaf miner fly *Phytomyza* provided evidence that

919     repeated shifts to host plants with different chemistry during 40 million years of

920     evolution led to elevated diversification (Winkler *et al.*, 2009). Remarkably, beak length

921     of the seed-eater soapberry bug *Jadera haemotoloma* has adapted within 40-150

922     generations after shifting to novel host species of Sapindaceae from North America

923     (Carroll, 1992).

924        Although adaptation of specialist arthropods to plant defenses is well

925     documented, evidence for plant resistance to specialists is less frequent. Interestingly,

926     some Brassicaceae contain other defense compounds besides GS, including alkaloids

927     (camalexin in Arabidopsis and cochlearine in *Cochlera* sp.) and the steroid cucurbitacin

928     in *Iberis amara* (Tsuji *et al.*, 1992; Sachdev-Gupta *et al.*, 1993; Brock *et al.*, 2006).

929     Cucurbitacin has some antifeedant activity on *P. rapae* (Sachdev-Gupta *et al.*, 1993)

930     and a study on natural variation in resistance to *P. brassicae* in Arabidopsis accessions

931     identified QTLs that are not linked to GS biosynthesis (Pfalz *et al.*, 2007). In a beautiful

932     example of coevolution, some cyanogenic glycoside-containing species of *Passiflora*

933     have counteradapted to the specialist *Heliconius* butterfly by the development of egg

934     mimics that repel oviposition (Williams and Gilbert, 1981). Egg mimics have also

935     evolved in the GS-containing crucifer *Strepthanthus breweri* to fend off the specialist

936     *Pieris sisymbrii* (Shapiro, 1981). Many plants face the problem of attracting pollinators

937     without being a target for herbivory. *N. attenuata* is a night-flowering tobacco whose

938     flowers emit benzyl acetone that attracts pollinators, including the adapted herbivore

939     moth *M. sexta*. In response to *M. sexta* feeding, *N. attenuata* shows a striking change of

940     phenology by generating flowers that produce low levels of benzyl acetone and open

941     during the day, attracting hummingbird as novel pollinators (Kessler *et al.*, 2010).

942

**Open questions**

944    Although many assumptions still rely on correlative evidence, progress has been made

945    in the understanding of evolutionary forces that drive escalation of chemical defenses

946    and arthropod adaptations to these chemicals. A recurring issue is to know the exact

947    chain of events and causative agents that result in apparent defense-adaptation-

948    counterdefense scenarios. Improved and additional plant/arthropod phylogenies are

949    needed as well as experimental evolution experiments.

950

951    **PLANT-ARTHROPOD COLLABORATIONS**

952    Interactions between plants and arthropods are not always antagonistic. Insects pollinate

953    about two-third of flowering plant species. In reward of nutrient-rich pollen and nectar,

954    insects offer this service as a mutualistic engagement (Schoonhoven *et al.*, 2005). Seed

955    dispersal by arthropods, mainly ants, helps colonization while providing food for the

956    carrier (Howe and Smallwood, 1982). However, the most sophisticated collaboration is

957    the association of plants with beneficial arthropods to fend off herbivores. Plants have

958    evolved exquisite ways to "cry for help", which rely on offering refuge or food for

959    guarding predatory mites and ants, or on emitting complex volatiles to attract carnivores

960    (reviewed in Romero and Benson, 2005; Heil, 2008; Stam *et al.*, 2014; Heil, 2015;

961    Hilker and Fatouros, 2015).

962        Leaf domatia are cavities or hair tufts on the lower surface of leaves and create

963    shelter for mites that are predators of phytophagous mites. Several studies have proven

964    that these structures benefit plants by decreasing herbivore pressure (reviewed in

965    Romero and Benson, 2005). Extrafloral nectar, food bodies on leaflets and hollow

966    thorns are attributes found in certain acacia trees that host ants, providing nutrition and

967    housing (Heil, 2008). This intimate association is maintained because ants constantly

968    patrol trees and aggressively remove unwanted herbivores. Extrafloral nectar production

969    is induced in response to herbivory, showing that plants keep control of this energy

970    demanding process. In an elegant and long-term experiment in an African savanna,

971    removing large herbivores for 10 years reduced nectar production and thorns by *Acacia*

972    *drepanolobium,* and increased antagonistic behavior of the ant mutualist *Crematogaster*

973    *mimosae*, which ultimately led to a decreased tree defense and growth (Palmer *et al.*,

974    2008).

975         Upon herbivory and detection of HAMPs in OS, plants emit a complex blend of

976    volatiles that attract parasitic wasps or predators (reviewed in Dicke and Loon, 2000;

977    Stam      *et      al.*,      2014).      Volatiles      generally      consist      of      terpenes,

978    phenylpropanoids/benzenoids, and fatty acid derivatives (green leaf volatiles) (Pare and

979    (Tumlinson, 1999; Dudareva *et al.*, 2004). This tritrophic interaction is an efficient

980    defense mechanism since carnivores either kill their prey directly or parasitize them,

981    therefore dramatically reduce feeding activity (Dicke and Loon, 2000). Qualitative and

982    quantitative differences in volatile emission explain the specific attraction of parasitoids

983    to their host. For instance, the specialist parasitic wasp *Cardiochiles nigriceps* was

984    significantly more attracted by the volatile blend produced by tobacco and cotton plants

985    infested with his host *H. virescens* than by volatiles produced by plants infested with *H.*

986    *zea* (De Moraes *et al.*, 1998). Similarly, oviposition triggers volatile release and

987    attraction of egg parasitoids, illustrating the specificity of the emitted blend (Hilker and

988    Fatouros, 2015). Strikingly, indirect defense was also discovered belowground. Upon

989    feeding by the rootworm *Diabrotica virgifera virgifera*, maize roots emit the

990    sesquiterperne (*E*)-β-caryophyllene. However, this response not attract arthropods but

991    entomopathogenic nematodes (Fig.1) (Rasmann *et al.*, 2005).

992

993    **Open questions**

994    One of the fascinating yet poorly studied question about plant-arthropod mutualism is

995    how indirect defense evolved. Evidence that plants benefit from attraction of parasitoids

996    suggests that genes involved in volatile biosynthesis are under positive selection.

997    Comparative genomic analyses of biosynthesis pathways across plant taxa and their

998    correlation with associated parasitoids will be necessary to have a better understanding

999    of how indirect defense appeared and was maintained. Whether roots attract beneficial

1000   arthropods is another unsolved question. On the parasitoid side, advent of more

1001   sequenced genomes may offer a resource for identifying genes important for volatile

1002   recognition and association with the host. Finally, the contribution of parasitoids to

1003   plant-arthropod coevolution is also a question that deserves more research.

1004

1005   **CONCLUSIONS AND OUTLOOK**

1006   Decades of research on plant-arthropod interactions have revealed that these organisms

1007   are engaged in a battle for survival that rely on sophisticated mechanisms of perception,

1008   signaling and defense activation on the plant side, and on effective suppression of

1009   defenses and chemical/behavioral adaptations on the arthropod side. Although it appears

1010   that nature has reached an equilibrium, since both plants and arthropods are abundant,

1011   evidence has accumulated that there is constant innovation to generate novel plant

1012   defenses strategies and that this exerts a selection pressure on arthropods to evolve

1013    novel effectors or detoxification solutions. This arms race has thus no winner and the

1014    coevolution process may continue for millions of years.

1015        Although substantial progress has been made in identifying genes and molecules

1016    involved in the molecular dialogue between plants and arthropods, as well as some

1017    evolutionary processes that underlie their coevolution, we have identified open

1018    questions that deserve further research. In addition, root herbivory (Johnson and

1019    Rasmann, 2015), insect galls (Stone, 2003), the role of leaf and arthropod microbiomes

1020    (Pineda *et al.*, 2010; Sugio *et al.*, 2015), and the outcome of multiple biotic interactions

1021    (Pieterse and Dicke, 2007) are clearly understudied. In times when stability of

1022    ecosystems, emergence of invasive species and sustainable control of insect pests in

1023    agriculture provide challenges to a growing human population, future research on plant-

1024    arthropod interactions may contribute viable solutions to these problems.

1025

1026

1027    **ACKNOWLEDGEMENTS**

1032

1033    **AUTHOR CONTRIBUTION**

1034    ES and PR wrote the paper. OH provided feedback on the text and designed the figures.

1035

1036    **CONFLICT OF INTEREST**

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4        1037    The authors declare that they have no conflict of interest.
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1924

## 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 brassicae* 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 littoralis* 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<br>  *Asclepias syriaca* | Leaf vein cutting<br>  *Danaus gilippus* and others | | Dussourd and Eisner, 1987 |
| High-pressure resin<br>  *Bursera sp.* | Leaf vein severing<br>  *Blepharida sp.* | | Becerra, 2003 |
| JA-dependent defenses<br>  Arabidopsis | Avoiding induced tissue<br>  *Helicoverpa armigera* | | Perkins *et al.*, 2013 |
| Trichomes<br>  *Solanum hirtum* | Silk threads over spines<br>  *Mechanitis isthmia* | | Rathcke and Poole, 1975 |
| Attraction of parasitoids<br>  *Lolium multiflorum* | Host shift, escape behavior (?)<br>  *Listronotus bonariensis* | | Tomasetto *et al.*, 2017 |
| Attraction of parasitoids<br>  *Physalis angulata* | Eating fruit, no volicitin in OS<br>  *Heliothis subflexa* | | De Moraes and Mescher, 2004 |
| Cardenolides<br>  Apocynaceae | ATPase N122H substitution<br>  *Danaus plexxipus* and others | | Dobler *et al.*, 2012 |
| Protease inhibitors (PI)<br>  potato | PI-insensitive protease<br>  *Helicoverpa zea* | | Bayés *et al.*, 2005 |
| L-canavanine (Arg analog)<br>  *Dioglea megacarpa* | Discriminating tRNA synthetase<br>  *Caryedes brasiliensis* | | Rosenthal *et al.*, 1976 |
| Cyanogenic glycoside<br>  *Passiflora sp.* | Detoxification<br>  *Heliconius cydno* | Egg mimicry<br>  *Passiflora cyanea* | Williams and Gilbert, 1981 |
| Cyanogenic glycoside<br>  *Phaseolus lunatus* | Bacterial β–cyanoalanine synthase<br>  *Tetranychus urticae* | | Wybouw *et al.*, 2014 |
| Alkaloid<br>  *Nicotiana attenuata* | Nicotine excretion and metabolism<br>  *Manduca sexta* | Altered flower phenology<br>  *Nicotiana attenuata* | Kessler *et al.*, 2010 |
| Glucosinolates<br>  Brassicales | Nitrile-specifier proteins<br>  *Pieris rapae* and other Pierinae | GS diversification<br>  Brassicales | Edger *et al.*, 2015 |
| Glucosinolates<br>  Brassicales | Nitrile-specifier protein (?)<br>  *Pieris sysimbrii* | Egg mimicry<br>  *Streptanthus brewerii* | Shapiro, 1981 |
| Glucosinolates<br>  Arabidopsis | Induction of detoxification genes<br>  *Heliothis virescens* | | Schweizer *et al.*, 2017 |
| Furanocoumarins<br>  Apiaceae | Detoxification by CYP6B1<br>  *Papilio polyxenes* | | Hung *et al.*, 1997 |
| HAMP detection (inceptin)<br>  *Vigna unguiculata* | Inceptin modification<br>  *Anticarsia gemmatalis* | | Schmelz *et al.*, 2012 |
| Defense signaling<br>  *Apium graveolens* | Induction of CYP450s by JA, SA<br>  *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; $SCF^{COI1}$, 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.

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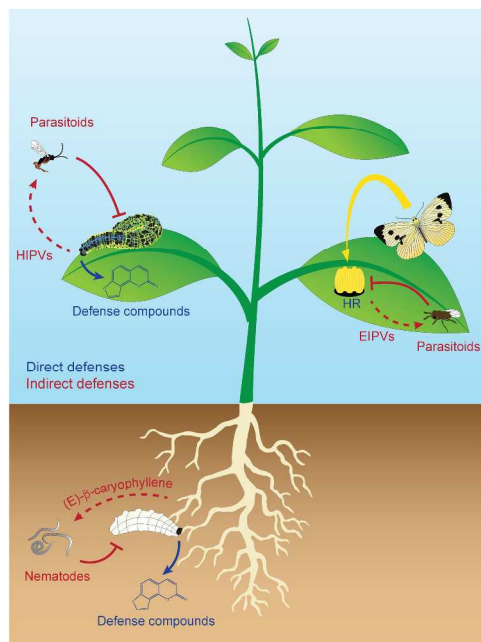52
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Figure 1

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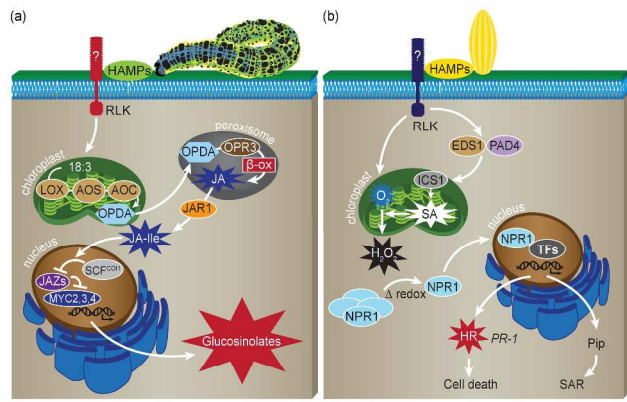41
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Figure 2

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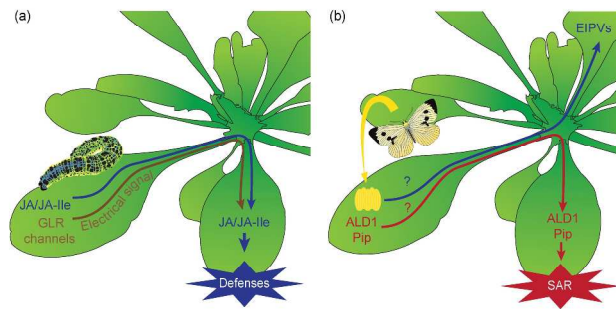31
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Figure 3

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