Phytoparasitic Nematode Control of Plant Hormone Pathways[1][OPEN]

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Plant-parasitic nematodes are microscopically small animals that cause global annual crop losses of at least 80 billion dollars (Nicol et al., 2011). The evolution of nematodes into plant parasites occurred several times, resulting in diverse interaction modes with the plant (Smant et al., 2018). We will focus this review on the sedentary cyst nematodes (CN) and root-knot nematodes (RKN), as they are the foremost studied due to their economic importance (Jones et al., 2013) and fascinating liaison with plants in the form of nematode feeding sites (Box 1).

Nematodes establish feeding sites by recruiting specific plant developmental pathways, involving hormonal cross talk. At the same time, nematodes need to suppress plant defense and its interacting hormone pathways. This interface between development and defense results in a complex pattern in which it is difficult to unravel the specific roles of different plant hormones. Therefore, we present a simplified model for describing the roles of hormones in plant-nematode interactions in this review. Auxin, as the key regulator, and cytokinin, as its modulator, are the primary plant hormones involved in cell division and differentiation (Benková et al., 2003; Pernisová et al., 2009). Jasmonate (JA) and salicylate (SA) are the principal plant defense hormones (Mur et al., 2006). Other hormones modulate and cross talk with these principal hormones and with each other, and can have different effects depending on the specific host-nematode interaction.

Besides the classical phytohormones, small, secreted peptide hormones shape plant development; remarkably, nematodes have evolved plant peptide hormone (PPH) effector mimics to facilitate parasitism. Recent studies have revealed a diversity of these peptides, which we will discuss in the latter half of this review.

NEMATODES MANIPULATE PHYTOHORMONE PATHWAYS FOR FEEDING SITE FORMATION

Auxin is Key to NFS Formation

Auxin, or indole-3 acetic acid (IAA), is a key regulator of plant organogenesis. Hence, it is not surprising that the initiation and maturation of NFS is associated with local accumulation of auxin (Karczmarek et al., 2004). Congruently, auxin mutants are significantly less susceptible to both CN and RKN (for review, see Grunewald et al., 2009b; Gleason et al., 2016). Auxin

ADVANCES

- Cyst nematodes and root-knot nematodes need auxin and cytokinin for the formation of their feeding sites in plant roots. Differences in feeding sites between these nematodes are reflected in the differential roles of plant genes involved in those hormone pathways.
- A cytokinin-synthesizing isopentenyltransferase in the cyst nematode *Heterodera schachtii* is important for syncytium development.
- Similar to fungal pathogens, nematodes secrete chorismate mutase into the plant to decrease salicylic acid-related defense.
- Similar to herbivores, nematodes are countered by jasmonate-induced defense molecules, such as proteinase inhibitors.
- Plant-parasitic nematodes deploy an assortment of plant peptide hormone effector mimics to establish successful parasitism.

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G.G. and M.G.M. conceived the structure and the contents of the paper. G.G. wrote the plant hormone part and M.G.M. focused on the effector part. G.G. and M.G.M. commented on and edited the final text.

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BOX 1. Plant-parasitic nematodes

Plant-parasitic nematodes have mouth spears, called stylets, necessary for cell wall piercing to obtain nutrients from the plant cells. Ectoparasites feed on plants without entering, while migratory endoparasites cause massive necrosis by continuous migration through plant roots. Sedentary endoparasites migrate through the root until they find an adequate location for settling, then induce a nematode feeding site (NFS) containing one or more highly metabolically active cells that provide copious nutrition for nematode growth and reproduction. The diversity of plant-parasitic nematodes also includes semi-endoparasites of roots and shoot-dwelling species. While cyst nematodes (CN) and root-knot nematodes (RKN) are both sedentary endoparasites, their behaviors and their NFS are distinct. The different infection strategies evolved by CN and RKN are exemplified by their unique repertoires of effectors, proteins that are mainly secreted from the oesophageal glands to enable parasitism (Haegeman et al., 2012). After hatching from eggs in the soil, CN and RKN enter plant roots as stage 2 juveniles (J2). CN vigorously move through plant cells, leaving a necrotic path, whereas RKN move between plant cells with minimal root wounding. Upon creation of an NFS, J2 undergo several molts to develop into adult nematodes. The NFS of CN is one large cell, or syncytium, generated by the fusion of more than a hundred cells due to cell wall degradation. RKN stimulate half-dozen cells to enlarge by repeated mitosis without cell division, creating an NFS consisting of several giant cells. The surrounding cells are activated to form a root knot or gall. While the mechanisms of NFS formation are profoundly different between CN and RKN, cell cycle activation is crucial in both cases. Mitosis is one of the first signs of giant cell formation, but does not occur inside syncytia, only in the surrounding cells. Both types of NFS typically develop large nuclei by endoreduplication and contain a dense cytoplasm with fragmented vacuoles and cell wall ingrowths typical of transfer cells. Female CN mature into cysts that hold and protect many eggs, while female RKN deposit their eggs into a gelatinous mass.

could be underpinning many of the changes occurring during feeding site development, such as hypertrophy, cell wall ingrowths, and cell cycle activation (de Almeida Engler et al., 1999). Auxin is known for its role in cell expansion via the up-regulation of cell wall-modifying proteins and plasma membrane proton pumps that regulate acid growth (Majda and Robert, 2018). During transfer cell formation, auxin and ethylene (ET) cooperatively bring about the development of cell wall ingrowths (Yuan et al., 2016). In addition, auxin is not only an important trigger for cell-cycle entry but also acts in various other cell cycle phases (Perrot-Rechenmann, 2010).

Transcriptome and promoter-reporter analyses of NFS reveal a complex temporal and spatial pattern of up- and down-regulation of auxin biosynthesis and signaling-related genes and miRNAs influencing mRNA stability (e.g., Ithal et al., 2007; Barcala et al., 2010; Ji et al., 2013; Hewezi et al., 2014; Cabrera et al., 2015, 2016). Soon after nematode infection, auxin biosynthesis and auxin-response genes are mainly up-regulated, whereas genes encoding repressors are turned off, supporting a role for auxin at this early stage of infection. The accumulation of auxin at the initiating NFS could be due to secretion by the nematodes, locally induced plant biosynthesis, and changes in auxin transport. Auxin, mainly in its conjugated form, has been detected in RKN (*Meloidogyne incognita*) and beet CN (*Heterodera schachtii*) secretions (De Meutter et al., 2005), but its impact on NFS formation is unknown.

The role of auxin transport during nematode infection of Arabidopsis (*Arabidopsis thaliana*) roots has been established by analyses of the involved genes at the levels of expression, protein localization, and mutant phenotypes (Grunewald et al., 2009a; Lee et al., 2011; Kyndt et al., 2016). A substantial amount of auxin is produced in plant shoots, with polar auxin transport generating morphogenic auxin gradients. An interacting network of influx (AUXIN/LIKE AUXIN [AUX/LAX]) and efflux (PIN-formed [PIN]) transmembrane proteins with temporally and spatially adjusted subcellular locations mediate this auxin flow (Vieten et al., 2007). The AUX1 and LAX3 influx proteins appear to be essential to the formation of galls and syncytia, as the expression of corresponding genes is strongly up-regulated in the early infection stages, and mutants are less susceptible to infection. PIN4 is needed for proper expansion of both syncytia and galls, with *pin4* mutants resulting in the development of smaller cysts (Grunewald et al., 2009a; Kyndt et al., 2016). However, the contributions of some other PIN proteins appear to be quite different between the two types of feeding sites. PIN1 is necessary for delivering auxin from the shoots to the initiating syncytium, where its expression is strongly down-regulated to prevent the pumping out of auxin. Inside syncytia, PIN3 is relocated from the basal to the lateral plasma membranes to redirect auxin

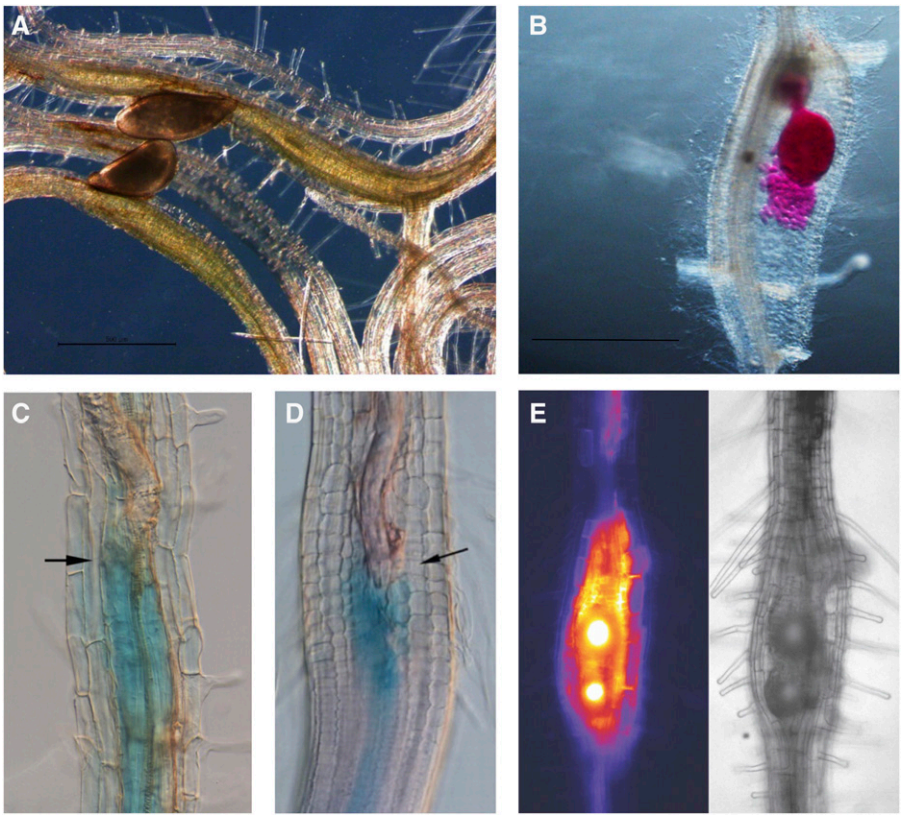

Figure 1. Plant-parasitic nematodes and their impact on plant gene regulation. A, Two females of the beet CN *H. schachtii* feeding on Arabidopsis roots. Picture courtesy of Anju Verma. B, Female of the rice RKN *M. graminicola* on rice roots, with egg mass, stained pink with acid fuchsin staining. Picture courtesy of Zobaida Lahari. C and D, GUS assays on Arabidopsis roots infected with *H. schachtii* showing up-regulation of the *DR5*-promoter (blue color; C) at 24 h after inoculation and the *IAA14*-promoter (D) at 2 d post inoculation. Black arrows point to nematode heads. Reprinted with permission from Grunewald et al., 2008. E, Up-regulation of the *LAX3*-promoter after *H. schachtii* infection in Arabidopsis roots with LAX3-YFP construct: (left) fluorescence image; (right) brightfield image. Pictures courtesy of Chris Lee.

to the neighboring cells, stimulating the radial expansion of the syncytium. While a *pin1* mutant has fewer and smaller cysts than wild-type plants, the *pin3* mutation only affects syncytium and female cyst size (Grunewald et al., 2009a). In contrast to syncytia, giant cells express *PIN1*. The *pin1* mutants only show a slightly reduced number of galls and no difference in nematode development. In contrast to CN, PIN2 and PIN3 appear to be more important for the delivery of auxin into the initiating giant cells induced by RKN, as illustrated by a nearly halved number of galls in the *pin2* and *pin3* mutants but no difference in female development (Kyndt et al., 2016).

How do nematodes manipulate auxin transport and signaling to provoke the necessary changes for NFS development? For the CN *H. schachtii*, two effector proteins have been pinpointed as facilitators of auxin effects in syncytia. The effector 19C07 targets the Arabidopsis LAX3 auxin import protein, possibly increasing its activity and thus enhancing auxin influx into the syncytium and adjacent cells (Lee et al., 2011). The effector 10A07 interacts with the auxin regulator protein INDOLEACETIC ACID-INDUCED16 (IAA16) from Arabidopsis (Hewezi et al., 2015). *AUX/IAA* constitute a gene family of 29 members in Arabidopsis that negatively regulate the auxin response factors (ARFs). Upon removal of specific AUX/IAA by the proteasome, the corresponding ARFs can activate auxin-responsive genes (Chapman and Estelle, 2009). Therefore, binding of 10A07 to IAA16 could prevent it from repressing auxin response genes. Congruently, plants overexpressing *10A07* show enhanced expression of *ARF6-8* and *19* and are more susceptible to *H. schachtii* than control plants. Unexpectedly, however, overexpression of *IAA16* has similar effects, indicating a more complex regulation than anticipated from an IAA repressor.

Cytokinins Modulate NFS Formation

Cytokinins are N6-substituted adenine derivatives that, in concert with auxin, control cell division and differentiation in plants (Schaller et al., 2014; Di Mambro et al., 2017). Cytokinins are critical for cell cycle control, and the timing and amplitude of their oscillating levels may be important for the decision of cells to go into mitosis or endoreduplication. Cytokinins delay senescence and convert tissues into sinks by modulating nutrient translocation.

Due to their involvement in cell cycle control and nutrient mobilization, cytokinins have long been assumed to play a role in NFS development. De Meutter et al. (2003) detected cytokinins in secretions from the CN *H. schachtii* and the RKN *M. incognita*. For *H. schachtii*, this finding was corroborated with the identification of a cytokinin-synthesizing nematode gene being expressed in the early infection stages (Siddique et al., 2015); silencing of this gene results in reduced infectivity by the nematode. On the other

hand, cytokinin biosynthesis Arabidopsis mutants show significantly smaller syncytia compared to wild-type plants (Siddique et al., 2015). This observation implies that both plant- and nematode-produced cytokinins are needed for the optimal formation of syncytia. Such detailed analyses have not been performed for RKN, but a similar scenario is very likely. Cytokinin signaling mutants and plants with reduced cytokinin levels are less susceptible to both types of nematodes (Lohar et al., 2004; Siddique et al., 2015; Shanks et al., 2016; Dowd et al., 2017). Nevertheless, expression of cytokinin biosynthesis, signaling, and catabolism genes is different in syncytia and galls (Dowd et al., 2017), which could be underlying divergent types of cell cycle progression. This hypothesis was confirmed by the analyses of cytokinin perception mutants, demonstrating that *Ahk4* is the main *Ahk* gene (coding for Arabidopsis His kinases) involved in syncytium development, while *Ahk2* and *Ahk3* are important for gall formation (Siddique et al., 2015; Dowd et al., 2017). Comparing gene expression of young syncytia and galls with callus, Cabrera et al. (2015) found that, due to a higher cytokinin/auxin ratio, syncytia resemble shoot-forming calli and galls are similar to solid callus. However, it is still unknown how cytokinin signaling relates to the different abnormal cell cycles in syncytia and giant cells.

ET has Diverse Roles in Plant Susceptibility to CN and RKN

ET ($H_2C = CH_2$) is a gaseous hormone involved in many plant processes, but is famous for its role in senescence and fruit ripening (including the activation of cell wall degradation). In other plant processes, ET can result in different outcomes through its positive cross talk with either the auxin pathway (Strader et al., 2010) or the JA pathway (Nahar et al., 2011).

The available information on the role of ET in nematode infection seems contradictory, but some major features can be distinguished. ET consistently inhibits RKN infection but has a positive effect on CN infection. Early reports by Glazer et al. (1983, 1985) showed that ET has a positive effect on gall weight and giant cell hypertrophy, but this effect does not necessarily equate to increased nematode infection. Indeed, all later studies across multiple plant species convincingly show that ET inhibits RKN infection, possibly through a decrease in nematode attraction to the roots (Nahar et al., 2011; Fudali et al., 2013; Mantelin et al., 2013). Consistent with ET playing a role in plant defense to RKN infection, resistant plants show more up-regulation of ET biosynthesis and response genes than susceptible plants (Kumari et al., 2016; Shukla et al., 2018).

In contrast, ET enhances the attraction of *H. schachtii* to Arabidopsis roots as shown by higher levels of infection in plants with more ET (response), while mutants in ET response (or treated with ET inhibitors) have fewer nematodes (Goverse et al., 2000; Wubben et al., 2001; Kammerhofer et al., 2015). Higher ET levels also have been linked to increased syncytium expansion (Goverse et al., 2000) and Bent et al. (2006) found fewer soybean CN (SCN) *H. glycines* females developing on ET-insensitive soybean roots. On the other hand, detailed attraction studies using SCNs yielded dissimilar results (Hu et al., 2017b). *H. glycines* juveniles are attracted more to soybean root tips pretreated with an ET biosynthesis inhibitor than to control roots. The attraction of *H. glycines* to roots of Arabidopsis (nonhost for SCN) is enhanced in ET-insensitive mutants and diminished in ET-overproducing mutants (Hu et al., 2017b). Recent work by Piya et al. (2018) elucidates how ET perception in Arabidopsis can result in higher or lower susceptibility to *H. schachtii* (measured as the number of developing females), depending on the receptor and its downstream pathway. The canonical ET signaling pathway causes suppression of SA-based defense, resulting in higher susceptibility to the CN, fitting the idea that ET enhances CN infection. The second pathway acts via the ETHYLENE RECEPTOR1, with ET inhibiting cytokinin signaling and thus reducing susceptibility to *H. schachtii* infection (Piya et al., 2018). Depending on the specific host-nematode interaction and timing or location of ET effects, cross talk with other hormone pathways could, therefore, have different effects on the host response to CN infection.

Habash et al. (2017) identified a tyrosinase-like protein secreted by *H. schachtii* (Hs-Tyr) that, upon ectopic expression in Arabidopsis, increases susceptibility to the CN but not to the RKN *M. incognita*. *Hs-Tyr* expression in the plant is correlated with higher auxin (IAA-conjugates) and 1-aminocyclopropane-1-carboxylic acid (ET-precursor) levels, two hormones involved in susceptibility to CN.

DEFENSE HORMONE PATHWAYS ACTIVATED BY THE PLANT AND DAMPENED BY THE PARASITE

An investigation of the plant response to organisms invading aerial plant parts identified SA and JA as important defense hormones interacting either antagonistically or synergistically (Mur et al., 2006). Findings from Arabidopsis led to the paradigm that SA generally protects against biotrophic pathogens, whereas JA inhibits necrotrophic micro-organisms and munching insects (Glazebrook, 2005; Beckers and Spoel, 2006). Gutjahr and Paszkowski (2009) concluded that SA also appears to activate defense against biotrophic pathogens in roots, but JA presented a complex picture, and more research was needed to dissect the role of both hormones in root defense signaling. Ten years and many publications later, this conclusion still stands true for plant-nematode interactions.

SA Activates Basal Defenses Against Nematodes

The application of SA, or chemicals with similar action, reduces nematode infection (e.g., Wubben et al., 2008;

Nahar et al., 2011; Molinari et al., 2014; Kammerhofer et al., 2015; Molinari, 2016). In many cases, the effect is modest and has been explained by the capability of the nematodes to suppress the SA pathway (Sanz-Alférez et al., 2008; Barcala et al., 2010; Uehara et al., 2010; Ji et al., 2013; Shukla et al., 2018). Although the effect is not always significant, mutants and transgenics with lower SA levels or signaling generally are more susceptible to nematodes (Wubben et al., 2008; Nahar et al., 2011), whereas enhanced SA levels or signaling results in lower nematode infections (Priya et al., 2011; Lin et al., 2013; Youssef et al., 2013). Nguyen et al. (2016), however, did not find enhanced susceptibility to *H. schachtii* in Arabidopsis SA signaling mutants.

Many nematode effectors suppress plant defenses (Haegeman et al., 2012), but in only a few cases has this effect been specifically linked to suppression of the SA pathway. Effectors of fungal and oomycete pathogens have been implicated in the manipulation of SA biosynthesis. Some of these microbes secrete chorismate mutase and isochorismatase that convert chorismate and isochorismate, respectively, away from the main SA biosynthesis pathway, in this way lowering SA levels and defenses (Djamei et al., 2011; Liu et al., 2014). Similar genes have been identified in plant-parasitic nematodes (see Table 1). Wang et al. (2018) demonstrated that transient expression of an *M. incognita* chorismate mutase effector in *Nicotiana benthamiana* causes a decline in SA levels and larger

Table 1. *Nematode effectors mimicking PPHs and influencing phytohormone physiology and signaling at feeding sites*

Effector Mimics of PPHs		
CLE-like Peptides		
HgCLE	*Heterodera glycines*	Wang et al., 2001, 2005, 2010a; Gao et al., 2003
HsCLE	*H. schachtii*	Wang et al., 2011
GrCLE	*Globodera rostochiensis*	Lu et al., 2009; Guo et al., 2011; Chen et al., 2015
RrCLE	*Rotylenchulus reniformis*	Wubben et al., 2015
MhCLE	*Meloidogyne hapla*	Bird et al., 2015
CEP-like Peptides		
MhCEP	*M. hapla*	Bobay et al., 2013; Bird et al., 2015
RrCEP	*R. reniformis*	Eves-Van Den Akker et al., 2016
IDA-like Peptides		
MiIDL	*M. incognita*	Tucker and Yang, 2013; Kim et al., 2018
MhIDL	*M. hapla*	Kim et al., 2018
MfIDL	*M. floridensis*	Kim et al., 2018
Effectors Influencing Phytohormone Physiology and Signaling		
Auxins		
Conjugated forms	*H. schachtii*	De Meutter et al., 2005
Conjugated forms	*M. incognita*	De Meutter et al., 2005
Cytokinins		
iP, Z, BA-types	*H. schachtii*	De Meutter et al., 2003; Siddique et al., 2015
iP, Z, BA-types	*M. incognita*	De Meutter et al., 2003
Chorismate Mutase		
HgCM	*H. glycines*	Bekal et al., 2003
HsCM	*H. schachtii*	Vanholme et al., 2009
GrCM	*G. rostochiensis*	Lu et al., 2008
GpCM	*G. pallida*	Jones et al., 2003; Yu et al., 2011
GtCM	*G. tabacum*	Yu et al., 2011
GeCM	*G. ellingtonae*	Chronis et al., 2014
MjCM	*M. javanica*	Lambert et al., 1999; Doyle and Lambert, 2003
MiCM	*M. incognita*	Huang et al., 2005; Wang et al., 2018
MaCM	*M. arenaria*	Long et al., 2006a, 2006b
HoCM	*Hirschmanniella oryzae*	Bauters et al., 2014
PcCM	*Pratylenchus coffeae*	Haegeman et al., 2011
Tyrosinase		
HsTYR	*H. schachtii*	Habash et al., 2017
Isochorismatase		
GrICM	*G. rostochiensis*	Eves-Van Den Akker et al., 2016
MhICM	*M. hapla*	Opperman et al., 2008
RrICM	*R. reniformis*	Wubben et al., 2010
HoICM	*H. oryzae*	Bauters et al., 2014
Novel Proteins		
Hg19C07	*H. glycines*	Gao et al., 2003
Hs19C07	*H. schachtii*	Lee et al., 2011
Hg10A07	*H. glycines*	Hewezi et al., 2015
Hs10A07	*H. schachtii*	Hewezi et al., 2015

lesions upon infection with *Phytophthora capsici*. Transgenic *N. benthamiana* plants expressing *M. incognita* chorismate mutase effector are more susceptible to *M. incognita*. Overexpression of a *Hirschmanniella oryzae* chorismate mutase or an isochorismatase in rice also enhances susceptibility to this nematode (L. Bauters, unpublished data).

The JA Pathway has a Polemical Role in Nematode Infection

The release of JA during plant defense was first discovered as a response to insect attack. JA enhances the expression of protease inhibitors and pathways producing secondary metabolites with antiherbivore activity. Protease inhibitors constrain the proteolytic activity of the insects' digestive enzymes to debilitate their growth and reproduction. Nematodes, being animals, also rely on proteases for obtaining sufficient nutrients from their food source. Therefore, it is not surprising that JA would play a role in defense to plant-parasitic nematodes. However, data on the role of the JA pathway (see Fig. 2 for an overview) in nematode infection are not unequivocal, at least not for RKN.

For CN, the available data are consistent with JA enhancing defense. Application of Methyl-JA to Arabidopsis leaves reduces *H. schachtii* infection on the roots, and the JA biosynthesis mutants *delayed-dehiscence2* (*dde2*) and *lipoxygenase 6* (*lox6*) show enhanced female development compared to control plants (Kammerhofer et al., 2015). Arabidopsis mutants with higher JA levels/signaling are less susceptible to *H. schachtii* (Ali et al., 2013; Nguyen et al., 2016; Sidonskaya et al., 2016), and soybean roots overexpressing (E,E)-a-farnesene synthase (a gene upregulated upon JA treatment) support lower levels of *H. glycines* infection, indicating an additional possible mechanism of JA action (Lin et al., 2017). At first sight, the results of Ozalvo et al. (2014) fit the "JA = defense" picture with the JA biosynthesis mutant *lox4* being more susceptible to *H. schachtii,* but a closer look contradicts this conclusion (see below).

Over the past 10 years, more than 20 papers have been published on the role of JA in RKN infections, and the data overwhelmingly support JA as a defense molecule. Application of MeJA on tomato (*Solanum lycopersicum*), rice (*Oryza sativa*), and soybean (*Glycine max*) invariably reduces RKN infection (Cooper et al., 2005; Shimizu and Mazzafera, 2007; Fujimoto et al., 2011; Nahar et al., 2011; Zhang et al., 2011; Zinovieva et al., 2013; Vieira Dos Santos et al., 2014; Zhou et al., 2015; Hu et al., 2017a; Kyndt et al., 2017), while inhibitors of JA biosynthesis enhance infection (Nahar et al., 2011; Zhou et al., 2015). In contrast, analyses of mutants and transgenics modified in JA signaling or biosynthesis yield brain-twisting results.

The first indication of the complexity of the JA pathway was the report that a JA-insensitive mutant in tomato is less susceptible to *M. incognita* than the wild

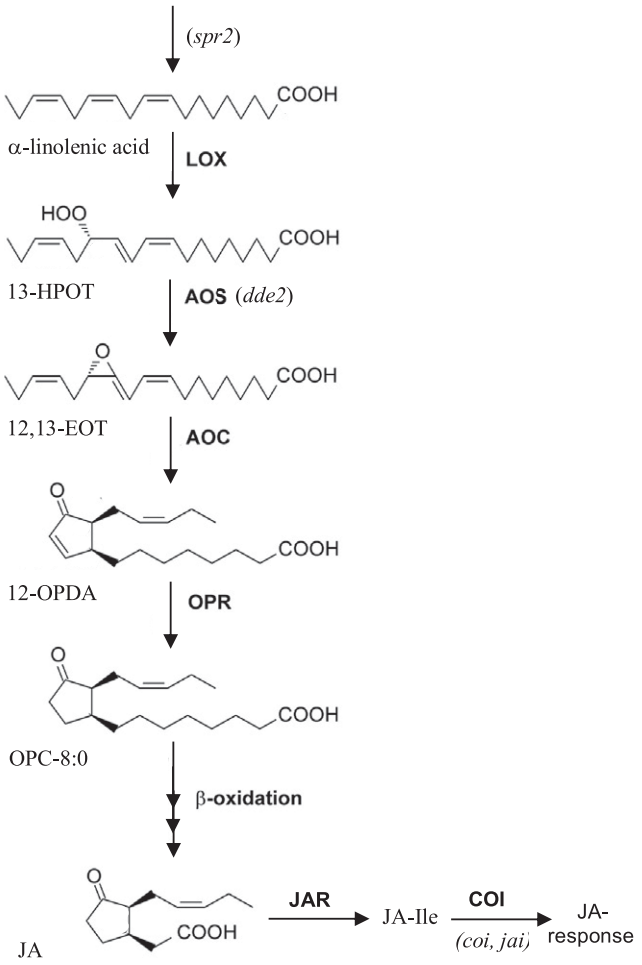

Figure 2. Overview of JA biosynthesis pathway and related mutants. Only the main pathway of oxylipin synthesis to jasmonate is shown. Several branches occur that give rise to many other metabolites. In addition, several enzymes are encoded by multiple genes from a gene family, although only one is shown. Intermediates and derivates: 13-HPOT, 13-hydroperoxy-octadecatrienoic acid; 12,13-EOT, 12,13-epoxy octadecatrienoic acid; OPC-8:0, 3-oxo-2-(2-pentenyl)-cyclopentane-1-octanoic acid; JA-Ile, jasmonoyl-Ile. Enzymes: LOX, 13-lipoxygenase; OPR, 12-oxophytodienoate reductase; JAR, jasmonate response locus encoding a jasmonic acid-amido synthetase that converts JA into the bio-active JA-Ile. Mutants: *spr2, suppressor of prosystemin response 2* mutant; *coi1,* the mutant in COI F-box protein involved in jasmonate signaling; *jai, jasmonate insensitive,* also mutant in COI.

type (Bhattarai et al., 2008). This observation led to the conclusion that, whereas the hormone JA results in defense, JA signaling is needed for successful infection. However, other experiments with JA-signaling mutants do not support this conclusion: specifically, *M. incognita* infection of the Arabidopsis mutant *coronatine insensitive* (*coi*) does not differ from the wild type (Gleason et al., 2016), and the rice mutant *jar1* is slightly more susceptible to the rice RKN *Meloidogyne graminicola* (T Kyndt and R singh, unpublished data). To augment the complexity, Gleason et al. (2016) demonstrated that

coi is not needed for JA-induced defense against *M. incognita* infection in Arabidopsis.

What about mutant/transgenic plants with changes in JA biosynthesis? Tomato *suppressor of prosystemin-mediated responses2* mutants, affected in the production of linolenic acid needed for JA biosynthesis, are more susceptible to *M. incognita* (Sun et al., 2011; Fan et al., 2015). Tomato plants overexpressing *miR319* show lower JA levels and are highly susceptible to *M. incognita* (Zhao et al., 2015). Rice plants overexpressing allene oxide synthase (*AOS*) are less susceptible to *M. graminicola* (Kyndt et al., 2017), and the *Arabidopsis AOS* mutant *dde2* shows more galling by *M. hapla* than wild type (Gleason et al., 2016).

However, not all mutants in JA biosynthesis corroborate the role of JA in defense. Depending on the *Lox* or allene oxide cyclase (*Aoc*) gene, mutants are more (*lox4-1*, Ozalvo et al., 2014; *aoc-3*, Naor et al., 2018) or less (*lox3-1*, Ozalvo et al., 2014) susceptible to RKN infection. As Naor et al. (2018) explain, the oxylipin biosynthesis pathway branches into many metabolites with differing levels of toxicity to RKN; therefore, mutants likely affect more than just the JA level. Gleason et al. (2016), for instance, showed that the intermediate 12-oxo-phytodienoic acid (OPDA) is much more important than JA for defense against RKN, which is consistent with JA and OPDA having different signaling roles (Dave and Graham, 2012). In contrast to Gleason et al. (2016), Naor et al. (2018) found the *Arabidopsis dde2* mutant to be less susceptible to *M. javanica.* Ozalvo et al. (2014) add further to the confusion by demonstrating that the highly susceptible biosynthesis mutant *lox4* has not lower but higher JA levels upon nematode infection and also higher JA, ET, and SA-regulated transcription, all thought to be involved in defense to RKN.

It is difficult to compare the different results, as some papers report gall numbers (the initial infection stage) and others describe female numbers or measure percent female development. In addition, numbers per root system can give a different conclusion compared to numbers per gram of root, especially if using mutants that are affected in their root morphology. Unfortunately, most authors do not describe the root phenotype of the mutants. An example of these complications are the results of Gao et al. (2008) on the *lox3-4* mutant in maize (*Zea mays*). This mutant has elevated JA, SA, and ET levels in its roots and is highly susceptible to *M. incognita* infection, based on increased nematode attraction to roots and a higher number of eggs per gram of root compared to wild type. The *lox3-4* mutant has much shorter roots, but the number of root tips needed for nematode invasion is most likely unaltered or even higher (nematode attraction and invasion per plant are higher). As a consequence, calculation of the number of eggs per invaded nematode is much lower in the *lox3-4* than in wild type, which could be interpreted as less susceptible if susceptibility is measured as the ability of the host to allow nematode multiplication.

In conclusion, while spraying JA enhances plant defense to nematodes, it is not JA itself that is responsible, but its effects on the production of proteins (such as proteinase inhibitors) and metabolites (such as terpenes and oxylipins). Depending on how mutations in JA-related genes affect these antiherbivore compounds, the plant is rendered more or less susceptible to nematode infection.

In view of the importance of JA in defense, we could expect nematode effectors that interfere with this pathway. Indeed, transcriptome analyses have found suppression of JA-related genes in syncytia and giant cells (Ithal et al., 2007; Ji et al., 2013). Nematode-secreted fatty acid and retinol (FAR)-binding proteins have been proposed to interfere with lipid signaling in host defense, for animal (e.g., Garofalo et al., 2003) as well as plant parasites. The FAR protein of the potato (*Solanum tuberosum*) CN *Globodera pallida* is located on the cuticle surface and interferes with plant LOX-mediated defense (Prior et al., 2001). Tomato roots expressing the *M. javanica* MjFAR are more susceptible to RKN infection, and this observation is correlated with lower expression of the JA-responsive proteinase inhibitor2 (Iberkleid et al., 2013); however, some genes in the JA pathway are expressed at higher levels in these roots (Iberkleid et al., 2015).

OTHER PLANT HORMONES PLUG INTO THE DEFENSE CORE

In contrast to the ample studies on the importance of auxin and jasmonate in susceptibility and defense, respectively, very little research has been done on the role of gibberellic acid (GA), abscisic acid (ABA), brassinosteroids, and strigolactones in nematode infection. The available knowledge is limited mainly to the rice-*M. graminicola* system.

GA is well known for its role in stimulating plant growth by the degradation of DELLAs, a class of growth-repressing nuclear proteins. Studies in Arabidopsis revealed that GA antagonizes JA action and promotes SA signaling and/or perception (Navarro et al., 2008). In rice, GA interacts antagonistically with both JA and SA signaling pathways (De Vleesschauwer et al., 2016). Congruently, GA is important for susceptibility of rice to *M. graminicola*, as shown in a detailed study using the application of GA or a GA-biosynthesis inhibitor and a series of mutants (Yimer et al., 2018). In contrast, foliar application of GA to tomato increases resistance against *M. javanica* (Moosavi, 2017). However, these latter results were not confirmed by analysis of GA-mutants, and the GA concentration applied might have influenced the outcome (Bauters et al., 2018; Yimer et al., 2018).

The application of ABA increases the susceptibility of rice and tomato to RKN infection (Kyndt et al., 2017; Moosavi, 2017), and brassinosteroids suppress rice defense to *M. graminicola* (Nahar et al., 2013). In rice, ABA (Kyndt et al., 2017), brassinosteroids (Nahar et al., 2013),

and strigolactones (Lahari et al., 2018) all appear to enhance susceptibility to *M. graminicola* through antagonism with the JA pathway.

NEMATODES SECRETE PPH EFFECTOR MIMICS FOR FEEDING SITE FORMATION

Besides the classical phytohormones discussed so far, small, secreted peptide hormones are also potent modulators of plant growth and development. It has become increasingly evident that secreted peptides play critical roles in mediating a range of plant-microbe interactions, either by induction of PPH gene expression, for instance during legume-rhizobium symbioses, or by secreting PPH effector mimics (Yamaguchi et al., 2016; Ronald and Joe, 2018; Taleski et al., 2018). Here, we focus on PPH effector mimics secreted by nematodes, the first animal-pathogen model identified to secrete such molecules for parasitism. The different classes of PPH effector mimics identified from nematodes have expanded to include CLAVATA3/EMBRYO SURROUNDING REGION (CLE)-like, C-TERMINALLY ENCODED PEPTIDE (CEP)-like, and INFLORESCENCE DEFICIENT IN ABSCISSION (IDA)-like peptides.

CLE-like Peptides

Plant CLEs play important roles in shoot, root, and vascular meristem maintenance and are classified as either A-type or B-type peptides (for review, see Yamaguchi et al., 2016). The A-type peptides promote cell differentiation, whereas the B-type peptides suppress differentiation of tracheary elements and promote procambial cell division. Comprehensive clustering analysis has categorized plant CLEs into groups with potentially shared function (Goad et al., 2017). Aside from plants, CLE-like peptide effector mimics have been identified from multiple genera of CN, RKN, and more recently, from the reniform nematode (a semi-endoparasite that induces syncytia; Fig. 3). In the case of CN and reniform nematodes, the domain architecture of CLE-like peptide effector mimics resembles that of plant CLE proteins (Lu et al., 2009; Wang et al., 2010a, 2011; Wubben et al., 2015). Plant CLEs are produced as prepropeptides harboring an N-terminal secretion signal peptide that directs them through the plant secretory pathway for delivery to the apoplast. A central "pro" domain, referred to as the "variable" domain because of its lack of sequence homology among family members, separates the secretion signal peptide and C-terminal CLE domain. Similarly, CN and reniform produce CLEs as prepropeptides, but this occurs in the dorsal esophageal gland cell of the nematode (Wang et al., 2010a; Wubben et al., 2015). The N-terminal secretion signal peptide directs these effector proteins through the gland cell secretory pathway for packaging into secretory granules. They are then delivered as propeptides (comprised of a central variable domain and a C-terminal CLE domain with homology to plant CLE peptides) to the cytoplasm of host root cells through the stylet (Lu et al., 2009; Wang et al., 2010a; Mitchum et al., 2012, 2013). Once in the cytoplasm of host root cells, they are redirected through the plant secretory pathway to the apoplast by an unknown posttranslational trafficking mechanism mediated by a conserved "cryptic signal peptide" sequence in the N-terminal portion of the variable domain (Wang et al., 2010b). The proteins subsequently undergo posttranslational modification by hydroxyproline (Hyp) arabinosylation and proteolytic cleavage down to the 12-amino acid CLE peptide to release one or more bioactive ligands (Chen et al., 2015). These ligands interact with plant Leu-rich repeat (LRR) receptor kinases,

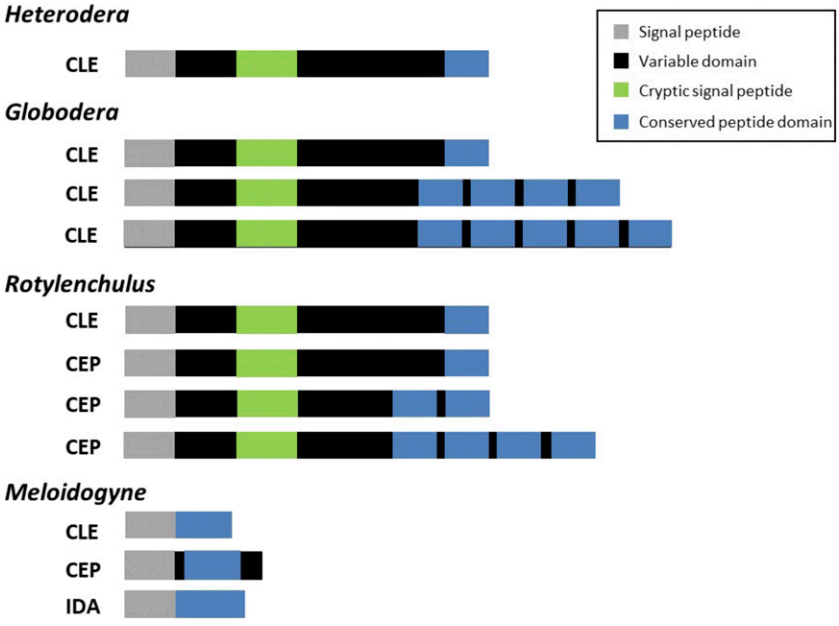

Figure 3. Representative structures of nematode CLE-like, CEP-like, and IDA-like proteins. Cyst and reniform nematode CLE and CEP-like proteins contain an N-terminal signal peptide, a variable domain, and either single or multiple conserved C-terminal peptide motifs similar to plant CLE or CEPs, respectively. The green box in the variable domain of cyst and reniform nematode CLE and CEP-like proteins denotes a cryptic signal peptide sequence. Root-knot nematode CLE, CEP, and IDA-like proteins lack a variable domain sequence.

including CLV1, CLV2, and BARELY ANY MERISTEMs, to positively regulate NFS development (Guo et al., 2010, 2015; Chen et al., 2015). Silencing of nematode *CLE* genes or their cognate plant receptors delays nematode development by impairing NFS formation (Replogle et al., 2011, 2013; Chen et al., 2015; Guo et al., 2015, 2017). In contrast to CN, the absence of a "pro" domain from RKN CLEs suggests this nematode may deliver bioactive CLE peptide mimics directly into the apoplast (Mitchum et al., 2012; Bird et al., 2015).

Based on the findings that nematode CLE peptide effector mimics belong to multigene families, are coordinately expressed, and can encode proteins with multiple CLE domains (Mitchum et al., 2012), it appears that nematodes may require the simultaneous secretion of a mixture of CLE peptide mimics for NFS formation. Multiple single-domain CLEs have been identified from *Heterodera*, RKN, and reniform, whereas *Globodera* species harbor multidomain CLEs. Another fascinating observation is that no two identical CLE sequences have been identified within a single genus or across genera. Whether these differences play a significant role in plant host adaptation is still unknown. Until recently, only A-type CLE-like peptide effector mimics had been identified from nematodes (Mitchum et al., 2012). However, mining of the *H. glycines* early parasitic stage transcriptome (Gardner et al., 2018) revealed B-type CLE peptide effector mimics nearly identical to tracheary element differentiation inhibitory factor (TDIF), encoded by CLE41 and CLE44, in Arabidopsis (Guo et al., 2017). In plants, the TDIF peptide regulates vascular stem cell maintenance through an interaction with the TDIF RECEPTOR (TDR)/PHLOEM INTERCALATED WITH XYLEM receptor kinase to activate two independent downstream pathways. The TDIF-TDR-WOX4 pathway promotes procambial cell proliferation, whereas the TDIF-TDR-Glycogen Synthase Kinase3-BRI1-EMS SUPPRESSOR1 pathway inhibits xylem differentiation from procambial cells. Procambial-associated genes are activated in both CN and RKN feeding sites (Guo et al., 2017; Yamaguchi et al., 2017). The TDIF-TDR-WOX4 procambial cell proliferation pathway is required for CN feeding site formation (Guo et al., 2017); however, further research is needed to assess whether the TDIF-TDR-Glycogen Synthase Kinase3-BRI1-EMS SUPPRESSOR1 signaling is equally important. As of yet, B-type CLE peptide effector mimics have not been identified from RKN, and a potential role of these vascular stem cell signaling pathways in RKN feeding site formation remains to be confirmed. Of note is the low abundance of nematode B-type CLEs relative to A-type CLEs in early CN parasitic stages (Guo et al., 2017). A detailed analysis assessing if nematodes tightly control the expression and release of specific peptide effectors during the phases of NFS formation will help gauge whether there is any potential biological significance of peptide synergism. Other than a role for WOX4, little is known about the downstream intracellular nematode peptide signaling cascades. Additional research is needed to dissect what appears to be a complex network of nematode CLE-receptor interactions to understand fully their specific contribution to NFS formation.

CEP-like Peptides

As the genomes and transcriptomes of more plant-parasitic nematodes have been released, computational scans have identified additional classes of PPH effector mimics, lending further support for peptide hormone mimicry as a signature adaptation to plant parasitism (Bird et al., 2015). CEP-like peptide effector mimics have been identified from *Meloidogyne* genomes and, more recently, from reniform nematode but not from CN genomes. In plants, CEPs are small, secreted peptide hormones implicated in nitrogen-demand signaling, nodulation, and lateral root development (reviewed by Taleski et al., 2018). CEP propeptides are cleaved by amino- and carboxypeptidases to release 15-amino acid bioactive peptides that signal through LRR-RK CEPR1. Like CLEs, CEP activity is regulated by posttranslational modifications in the form of Hyp arabinosylation. Despite the widespread identification of CEPs in plants, downstream signaling mediated by CEP-CEPR remains unknown. Twelve reniform *CEP* gene family members have been identified to date. They are unique in that they harbor one intron per domain sequence, whereas all other CEPs identified from animals and plants are encoded by a single exon, suggesting an independent evolutionary origin (Eves-Van Den Akker et al., 2016). Similar to plant CEPs, the reniform CEPs are produced as prepropeptides. Remarkably, the "pro" domain harbors a cryptic signal peptide with similarity to CN and reniform CLE-like effectors, not only suggesting that these effector proteins may be indirectly routed to the apoplast upon delivery as propeptides to host root cells but that the trafficking mechanism by which this occurs may be conserved across genera and span to different classes of effectors. CEPs are produced within the dorsal gland cell of sedentary reniform females, suggesting a prominent role in NFS formation. Interestingly, the RKN CEPs, like their CLE counterparts, lack the "pro" domain, lending further support for a mechanism of direct delivery to the apoplast to exert their function in giant cell formation (Bobay et al., 2013; Bird et al., 2015). Although the role of CEP-like effector mimics in nematode parasitism remains unknown, Arabidopsis primary root length and lateral root number are inhibited in a dose-dependent manner upon exogenous application of RrCEP1, similar to the application of plant CEP peptides. In addition, feeding sites induced by the CN *H. schachtii* are smaller in size in the RrCEP1-treated roots, suggesting that one potential function of nematode CEPs may be to regulate NFS size (Eves-Van Den Akker et al., 2016). Further studies are needed to clarify the unique role of CEP-like PPH effector mimics in plant-nematode interactions and any potential role in host nitrate uptake like their plant counterparts.

IDA-like Peptides

The broad spectrum of PPH effector mimics identified from *Meloidogyne* species may aid RKN to parasitize a broad range of host plant species. In addition to CLE-like and CEP-like PPH effector mimics, several IDA-like (IDL) family members have been identified from multiple *Meloidogyne* species (Tucker and Yang, 2013; Kim et al., 2018). An exhaustive search of CN and reniform sequence data for IDL peptides remains to be conducted; however, no IDL peptides were identified from existing sequence data for *Heterodera* and *Globodera* spp. (Kim et al., 2018). In plants, IDA signaling through the LRR-RKs HAESA (HAE) and HAESA-like2 activates a MAP kinase signaling cascade that leads to the expression of KNOX transcription factors, which regulate a suite of cell wall-modifying proteins important for cell separation during floral organ abscission and lateral root emergence. More recently, IDL peptides were shown to modulate plant stress and defense responses to pathogens (Vie et al., 2017; Wang et al., 2017). Like CLEs and CEPs, IDAs harbor an N-terminal secretion signal peptide and undergo proteolytic cleavage to 14-amino acid bioactive peptides in the apoplast. RKN IDL effector mimics have a similar domain architecture. A synthetic *M. incognita* IDL1 (MiIDL1) peptide applied exogenously to the Arabidopsis mutant *ida* is able to rescue floral abscission and lateral root phenotypes in an HAE/HAESA-like2-dependent manner (Kim et al., 2018). However, direct binding of MiIDL1 to these receptors has not been demonstrated. Similarly, transgenic *Arabidopsis ida* mutant plants expressing *MiIDL1* exhibit wild-type floral abscission. Host-derived RNAi targeting of MiIDL1 leads to fewer and smaller galls compared to control plants, demonstrating a critical role in parasitism. Together, these data provide evidence of a specific role of IDL PPH mimics in giant cell formation and point to a potentially unique adaptation for RKN parasitism.

INTEGRATION OF PEPTIDE AND HORMONE SIGNALING FOR NFS FORMATION

Cross talk between peptide and hormone signaling regulates developmental processes and responses to external stimuli (for review, see Wang et al., 2016). Evidence for such cross talk governing NFS formation is amassing in the literature. Alterations to phytohormone physiology and signaling, induced in response to nematode feeding, may be coordinately regulated by PPH effector mimics and hormones to fine-tune root developmental programs in favor of NFS formation. Studies showing that a low M_r peptide (s) from *G. rostochiensis* secretions costimulates the proliferation of protoplasts together with auxin and cytokinin, provided some of the first evidence for potential cross talk between nematode-secreted peptides and hormonal signaling (Goverse et al., 1999). Recent studies suggest CN may be co-opting early signaling events in vascular cell patterning, a process controlled by CLE peptides and hormonal signaling, for the successful formation of NFS. For instance, the beet (*Beta vulgaris*) CN *H. schachtii* secretes HsCLE2, an A-type CLE peptide mimic that is identical to AtCLE5/6 while simultaneously secreting HsCLEB, a B-type CLE peptide mimic nearly identical to Arabidopsis CLE41/TDIF (Guo et al., 2017). These peptides act synergistically in an auxin-dependent manner to suppress differentiation and promote vascular stem cell proliferation. They also activate the expression of numerous auxin-responsive genes known to be up-regulated in NFS (Whitford et al., 2008). Though plant CLE peptides exhibit cell-type specific expression patterns, overlapping expression domains may be critical for developmental programs requiring the synergistic action of multiple CLE peptides. Nematodes appear to have adapted to exploit this by controlling both the timing and quantity of A- and B-type peptides secreted into a chosen cell to potentially bypass the plant's own cell type-specific and negative feedback regulation mechanisms. Aside from auxin, there are also reports of intersections among CLE signaling and BR, CK, and GA signaling both locally and systemically. TDIF signaling suppresses xylem differentiation from procambial cells through integration with BR signaling (Kondo et al., 2014); GA positively regulates the expression of CLE6 and overexpression of this peptide partially rescues GA-deficiency (Bidadi et al., 2014); and CLEs are regulators of type-A ARRs to promote CK signaling (Kondo et al., 2011). A similarly complex cross talk is likely at play for other classes of plant peptides and hormones. For instance, the developmental programs underlying lateral root emergence

OUTSTANDING QUESTIONS

- Only a few nematode effectors have been identified as important for NFS formation or suppressing defense hormone pathways. Will the current boom in effector analysis provide insights into how nematodes manipulate plant pathways?
- The role of JA in defense to nematodes is contested and might differ between plant species, such as tomato versus rice. Which metabolites related to the JA pathway are really important to constrain nematode infection? Metabolome analysis of mutants in the JA-pathway could clarify this question. Are JA-independent COI-signaling and COI-independent JA activities also a piece of the puzzle?
- How do the different types and combinations of PPH effector mimics among plant-parasitic nematodes shape host-range and NFS formation?

requires the integration of auxin and IDA signaling to regulate cell-wall–modifying proteins involved in cell separation (Kumpf et al., 2013). These studies illuminate the incredibly complex network of peptide and hormone signaling pathways likely active in NFS formation.

CONCLUSION

Substantial progress has been made in our understanding of how plant hormones shape the interface between plants and nematodes and how nematode effector proteins contribute to this interaction. However, the few effectors that have been identified as participating in NFS formation cannot explain the myriad of complex changes that lead to a mature feeding cell (see "Outstanding Questions"). Undoubtedly, we still have much to learn about the interplay among peptide, phytohormone, and defense signaling pathways in NFS formation. Moreover, the field has expanded, as nematodes are no longer unique among plant pathogens in their ability to secrete mimics of PPHs (Ronald and Joe, 2018). It was recently discovered that the fungal pathogen *Fusarium oxysporum* and the bacterial pathogen *Xanthomonas oryzae* pv. oryzae secrete functional peptide mimics of plant rapid alkalinization factor and plant peptide containing sulfated tyrosine peptides, respectively (Masachis et al., 2016; Pruitt et al., 2017). Thus, as we continue to uncover the complex interplay between peptide and hormone signaling in plant-nematode interactions, the findings are likely to have much broader applicability in molecular plant-microbe interactions than previously thought.

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