Exchanges at the Plant-Oomycete Interface That Influence Disease[1][OPEN]

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The microbial eukaryotes known as oomycetes comprise more than 1,500 species, including many important phytopathogens. Most exhibit filamentous growth and feed osmotrophically. Oomycetes appear fungus-like but are classified as stramenopiles along with brown algae and diatoms (Beakes et al., 2012). Unlike most fungi, oomycetes are diploid, have cell walls made primarily of cellulose and β-glucans instead of chitin, make aseptate hyphae, undergo oogamous reproduction, and produce few secondary metabolites (Fawke et al., 2015).

Oomycetes exhibit diverse lifestyles across terrestrial and aquatic niches. While best known as pathogens of leaves, stems, roots, and fruit, some oomycetes are endophytes, infect animals, or are saprophytes (Lamour and Kamoun, 2009; Ploch and Thines, 2011; Aram and Rizzo, 2018). Many are highly host adapted, unculturable on artificial media, and grow only on living plants as biotrophs. Examples include downy mildew pathogens such as *Plasmopara viticola*, which infects grapevine (*Vitis vinifera*), and *Albugo candida*, which causes white rust on crucifers (Kamoun et al., 2015). The obligate pathogens typically cause minimal damage to the plant but reduce yield and raise susceptibility to secondary infection or abiotic stress.

Many oomycetes are hemibiotrophs, which start infections like biotrophs but cause necrosis late in the disease cycle. Most belong to the genus *Phytophthora*, including *Phytophthora cinnamomi*, which infects hundreds of agricultural, forest, and ornamental hosts; *Phytophthora infestans*, which blights potato (*Solanum tuberosum*) and tomato (*Solanum lycopersicum*); and *Phytophthora sojae*, which colonizes soybean (*Glycine max*) and lupines. Some species, such as *Ph. cinnamomi*, shift to necrotrophy early in infection, while others, such as *Ph. infestans*, make the transition much later, reflecting differences in how the species balance the two trophic behaviors. Unlike many other oomycetes, *Phytophthora* spp. are culturable and amenable to transformation; thus, they have been the subject of many molecular studies.

The largest genus of necrotrophic oomycetes, which feed on nutrients from lysed cells, is *Pythium*. Most members of this group are opportunistic root pathogens with broad host ranges, such as *Pythium ultimum*, which infects vegetables, grains, and trees (Kamoun et al., 2015). Interestingly, some *Pythium* spp. also are mycoparasites (Benhamou et al., 2012). Also appearing to grow as a necrotroph is *Aphanomyces euteiches*, which causes root rot of legumes.

This review focuses on events at the plant-oomycete interface, where exchanges of host and pathogen molecules play critical roles in determining the outcome of the association (Fig. 1). Oomycete pathogens sense, bind, and absorb nutrients from their hosts and also interact with other microbes in the phyllosphere and

ADVANCES

- Differences between the biotrophic, hemibiotrophic, and necrotrophic lifestyles of oomycetes have been attributed to variation in gene content and patterns of gene expression. Such genes include those encoding metabolic enzymes, proteinaceous toxins, and defense-suppressing effectors.
- Haustoria represent a specialized interface for delivering effectors to plants.
- The extrahaustorial matrix seems to be made *de novo* through the polarized delivery of plant cargo, and differs from a typical plasma membrane.
- Effectors have proved to be exquisite tools for probing the plant immune response and understanding host-pathogen evolution.
- Factors that regulate the production, germination, and homing responses of oomycete spores are starting to be defined, including transcription factors and novel G-protein-related signaling pathways.

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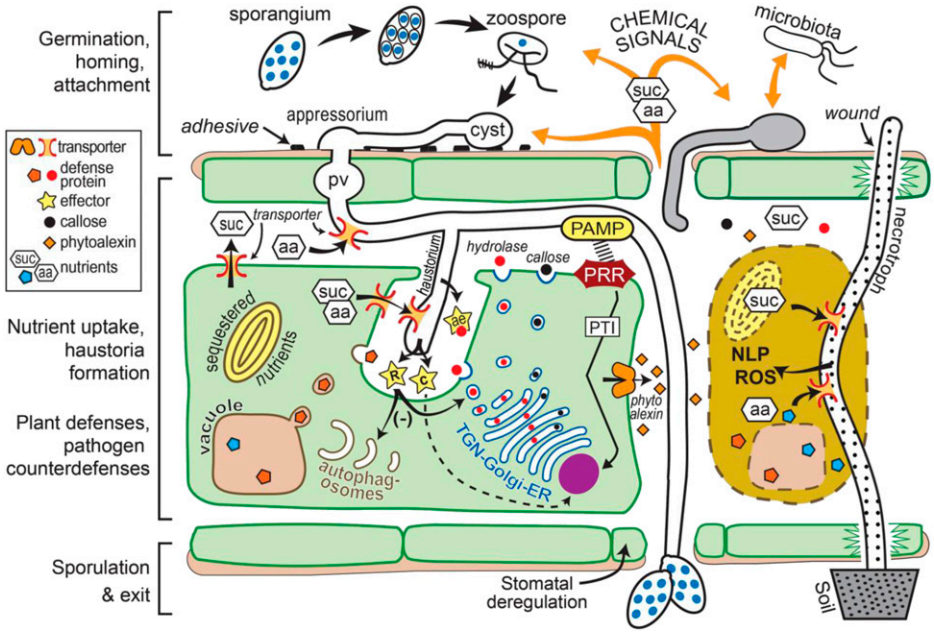


Figure 1. Interactions at plant-oomycete interfaces. Illustrated at center left is a biotrophic infection, starting from a sporangium and involving biflagellated zoospores, an appressorium formed from a germinated cyst, a primary infection vesicle (pv), an intercellular mycelium, and a haustorium. The effects of plant signals such as isoflavones, sucrose (suc), and amino acids (aa) on spore germination and/or homing are indicated. The bacterium at top right represents the effects of the microbiome on spores, as discussed in Box 2. The oval organelle marked "sequestered nutrients" represents a starch granule; this only releases significant carbohydrate to the pathogens during necrotrophy. The turquoise pentagon represents a nutrient such as sulfate that is located primarily in a plant vacuole. Yellow stars represent apoplastic effectors such as protease inhibitors (ae) and cytoplasmic effectors such as Crinklers (C) and RXLRs (R). The latter are shown inhibiting the delivery of defense materials, such as proteases and callose, to the apoplast and EHMx by secretory or autophagosomal vesicles of a mesophyll cell. These defense responses also occur in the epidermis. Shown at top right are the initial stages of infection initiated through a stomata (gray mycelium). Shown at right is an opportunistic necrotroph (spotted mycelium) entering through a wound, feeding from a lysed cell, and exiting into soil. Lysis of the host during infection by the necrotroph occurs due to the absence of defense-suppressing effectors, ROS generation, and early expression of NLPs, as discussed in Box 3.

rhizosphere. Meanwhile, plants detect and deliver defenses against infection. Plant-oomycete interfaces can be dynamic, varying with infection stage and as immune responses are deployed. Here, we discuss insights into these topics yielded by advances in cell biology, genome analysis, transcriptomics, and protein structure analysis.

PLANTS CAN ATTRACT UNWANTED GUESTS

Oomycetes employ several types of spores for dissemination and host infection (Box 1). These include both asexual and sexual spores (McCarren et al., 2005; Granke et al., 2009). Colonization by the majority of oomycetes begins when an asexual sporangium releases zoospores, which encyst and form a germ tube (Fig. 1). As discussed below, many aspects of spore behavior are influenced by plant signals. The microbiome also affects spores and can attenuate or worsen disease, as described in Box 2 (Lioussanne et al., 2008; Windstam and Nelson, 2008; Raaijmakers et al., 2010; Schlatter et al., 2017; Jack and Nelson, 2018).

Host signals can be sensed by the asexual sporangia since they are fully hydrated and metabolically active prior to germination, unlike most fungal spores, which are desiccated. While sporangia require only free water to germinate, this can be hastened by plant signals. Studies have shown that *Pl. viticola* releases zoospores faster on leaves than in a host-free system (Kiefer et al., 2002) and that *Pythium* spp. germination is accelerated by volatiles, sugars, and amino acids from seeds (Nelson, 1987). Root exudates, or sprouted potato tubers in the case of *Ph. infestans*, also stimulate the germination of sexual spores (oospores), which typically stay dormant in soil until a host is present (El-Hamalawi and Erwin, 1986; Pittis and Shattock, 1994). Studies with *Ap. euteiches* indicated that its oospores respond more to host than nonhost exudates (Shang et al., 2000). It is intriguing to consider that in the future, it may be possible to use plant signal mimics to cause oospores to undergo suicide germination before a crop is planted.

Zoospores exhibit several homing responses, including chemotaxis, electrotaxis, host-triggered encystment, and germ tube tropism (Deacon and Donaldson, 1993). These contribute to host specificity, especially with root pathogens. For instance, *Ap. euteiches* zoospores are attracted

BOX 1. A Diversity of Infectious Propagules

Oomycetes produce several forms of spores for survival, dissemination, and infection, with the multiplicity of types contributing to their success as pathogens. The defining feature of the taxonomic group are oospores, which are thick-walled products of sexual reproduction that can survive in plant debris or soil for years. Homothallism (self-fertility), heterothallism, and blended phenotypes are exhibited by different species, even in the same genus. Interestingly, mating hormones made by *Phytophthora* spp. are synthesized from phytol, an acyclic diterpene of plants, which indicates the close dependence of the genus on its hosts. Oospores germinate by producing hyphae that often form sporangia capable of discharging zoospores.

Most oomycetes also produce zoospores from asexual sporangia, which cause the majority of infections within a growing season. Many foliar pathogens such as *Ph. infestans* and *Pl. viticola* are well-suited to wind dispersal since their sporangia detach easily from the sporangiophore, and are lemon-shaped which retards their fall from air. After landing on a moist surface such as a dew-covered leaf, zoospores are released that later encyst and send out a germ tube, although these sometimes extend directly from sporangia. Other species such as *Ph. capsici* make sporangia that require greater force to be dislodged, and thus are spread more by rain, wind-driven rain, or flowing water (Granke et al., 2009).

Many root pathogens such as *Ph. sojae* and most *Pythium* spp. produce sporangia that are inseparable from the sporangiophore, and in such cases zoospores are liberated directly from lesions. This also occurs with *Aphanomyces* spp., but from sporangia that resemble normal hyphae. The motility of zoospores expands the potential space for infection, even though the maximum swimming range may only be a few centimeters. Remarkably, zoospores of some species that fail to infect a host can encyst and later produce a second zoospore, thus providing two chances for colonizing a plant. Despite its potential benefits, the motile stage is absent from certain foliar downy mildews, which instead extend germ tubes from their asexual spores (conidia). Genes for flagellar proteins are absent or degraded in such species (Judelson et al., 2012).

Some *Phytophthora* and *Pythium* spp. also produce chlamydospores, which are thick-walled asexual cells. When conditions become suited to growth, these can germinate and cause infections vegetatively or through sporangia (McCarren et al., 2005). Otherwise, most oomycetes do not initiate natural infections from mycelia except for most members of *Pythium* and a few species of *Phytophthora* (Aram and Rizzo, 2018).

specifically to prunetin (Sekizaki et al., 1993), while *Ph. sojae* responds to daizein and genistein, which are produced by their respective hosts (Hosseini et al., 2014). These isoflavones also influence encystment and germ tube orientation (Morris et al., 1998). Recent data point to a role for G-proteins in these responses. Silencing of the *Ph. sojae* gene encoding its G-protein α-subunit interfered with zoospore motility and chemotaxis (Hua et al., 2008), and knockdowns of a G-protein α-subunit-interacting His triad protein inhibited chemotaxis (Zhang et al., 2016). In addition, encystment was stimulated and cyst germination was impaired by knocking down the expression of a protein that consists of a G-protein-coupled receptor domain coupled to a phosphatidylinositol phosphate kinase domain (Yang et al., 2013). Oomycetes express several novel G-protein-coupled receptor-like proteins with C-terminal accessory domains (van den Hoogen et al., 2018).

Pharmacological studies have shown that calcium influences most aspects of zoospore behavior. This explains the biology behind the strategy of reducing root diseases by adding gypsum (calcium sulfate) to soil, which impairs zoosporogenesis or causes encystment before a plant is reached (Mostowfizadeh-Ghalamfarsa et al., 2018). Many spore-specific calcium channels and calcium-regulated protein phosphatases and kinases have been identified, although none have been tested for function (Ah-Fong et al., 2017b).

Chemotaxis also occurs in foliar pathogens, where amino acids such as Gln attract zoospores, a process that also appears to involve G-proteins (Latijnhouwers et al., 2004). Amino acid signaling may explain why zoospores of *Ph. infestans* and many relatives concentrate near stomata (Dale and Irwin, 1991). Few *Pl. viticola* zoospores were drawn to stomata closed by exogenous abscisic acid, suggesting that the attractants are soluble or volatile substomatal chemicals. Such behavior is critical to *Pl. viticola*, which enters leaves only through stomata (Kiefer et al., 2002).

OOMYCETES ENTER PLANTS THROUGH MULTIPLE ROUTES

As water molds, most oomycetes prefer to grow in moist environments such as the apoplast. Entry into

BOX 2. Other Microbes at the Interface: Friend Or Foe?

A plant-oomycete interaction does not occur in a biological vacuum. It is long known that bacteria and fungi in soil and the phyllosphere produce compounds that antagonize oomycetes, such as lipopeptide surfactants that disrupt the zoospore plasma membrane (Raaijmakers et al., 2010; Schlatter et al., 2017). Microbes can also attenuate or promote maladies caused by oomycetes in less direct ways. Bacteria recruited to seedlings have been shown to reduce infection by metabolizing fatty acids in plant exudates that would otherwise stimulate *Py. ultimum* sporangia to germinate, or by hampering the homing responses of *Py. aphanidermatum* zoospores (Windstam and Nelson, 2008; Jack and Nelson, 2018). Interference with zoospore behavior was also reported for *Glomus intraradices* mycorrhizae on tomato, which reduced infection and produced zoospore repellants such as isocitric acid (Lioussanne et al., 2008). Some microbial interactions may benefit the oomycete. Although its significance requires further investigation, *Phytophthora* spp. produce the bacterial quorum-sensing signal AI-2, which was proposed to recruit bacteria that improve the infection potential of zoospores (Kong and Hong, 2016).

Oomycetes can even attack other oomycetes, with the best-described example being *Py. oligandrum* (Benhamou et al., 2012). This species parasitizes other oomycetes and fungi. An interesting question is how *Py. oligandrum* distinguishes self from non-self during such interactions. *Py. oligandrum* has also been proposed to grow as an endophyte, and was shown to reduce diseases in sugarbeet, cotton, and other plants. This is believed to be due to the combined effects of mycoparasitism and the priming of host defenses, since plants recognize several *Py. oligandrum* proteins including its elicitins (Takenaka et al., 2011). *Py. oligandrum* has also been shown to stimulate plant growth, possibly because it makes the auxin precursor trypamine, and produces auxins when grown on root exudates (Benhamou et al., 2012). Many *Albugo* species are also reported to grow as asymptomatic endophytes on crucifers, but whether these benefit the plant is unknown (Ploch and Thines, 2011).

the plant may occur when zoospores or germ tubes pass through stomata or other natural openings, transit through wounds, or grow between root epidermal cells. Examples include *Pl. viticola*, which enters through stomata, *Ph. cinnamomi*, which can move through peridermal gaps, and *Ph. infestans*, which often enters tubers through lenticels. *Ph. infestans,* downy mildews, white rusts, and many *Pythium* spp. also penetrate tissue using appressoria. These swellings form when cyst germ tubes contact hydrophobic surfaces such as the cuticle, especially if epidermal cell boundaries or their topographic mimics are sensed (Bircher and Hohl, 1997).

Insight into the biology of oomycete appressoria has lagged behind that of fungi. However, a study in *Ph. infestans* using GFP-labeled F-actin identified an aster-like structure where appressoria contact the leaf, which may focus cargo transport to the penetration peg (Kots et al., 2017). Also, a basic leucine zipper domain transcription factor and mitogen-activated protein kinase were shown to regulate appressorium formation (Blanco and Judelson, 2005; Li et al., 2010). Genes induced in the appressorium stage by *Phytophthora* spp. include cell wall-degrading enzymes (CWDEs), defense-suppressing effectors, and potential adhesion proteins (Kebdani et al., 2010).

Mirroring the complexity of the plant cell wall, a typical oomycete expresses CWDEs belonging to as many as 28 glycosyl hydrolase groups (Blackman et al., 2015). A typical species of *Phytophthora* expresses about 200 genes encoding such proteins. Some of the (hemi)cellulases are predicted to bear glycophosphatidylinositol anchors and probably serve to expand the oomycete wall, which contains mostly cellulose plus β-1,3- and β-1,6-glucans (Mélida et al., 2013). Fewer types of CWDEs are expressed by biotrophs, as in the case of *Albugo laibachii*, which lacks pectate lyase and pectin esterase (Kemen et al., 2011). Studies in *Ph. infestans* and relatives show that CWDEs are expressed in stages during sporulation, germination, and in planta growth (Kebdani et al., 2010; Blackman et al., 2015). A less ordered pattern of expression was reported for *Py. ultimum*, which also expressed fewer CWDEs (Ah-Fong et al., 2017b). Other differences between *Phytophthora* and *Pythium* spp. are highlighted in Box 3. The pattern of CWDE expression in *Py. ultimum* suggests that the enzymes of this necrotroph may be used primarily to burst host cells rather than to digest plant walls for carbon. Indeed, cellulose is a poor carbon source for most oomycetes (Zerillo et al., 2013). Perhaps advanced

imaging techniques such as superresolution confocal microscopy with specific organic fluorophores could be employed to obtain information about carbohydrate structure at penetration sites, the effects of CWDEs at different stages of infection, and polymer rearrangements resulting from plant defenses.

Most stages of infection require adherence of the pathogen to the host. Zoospores turn their ventral grooves toward the host prior to encystment, allowing vesicles to discharge a glue-like thrombospondin repeat protein toward the plant interface (Robold and Hardham, 2005). A protein containing a Sushi domain, which in animals mediates cell-cell adhesion, reaches the plant surface from other zoospore vesicles by kiss-and-run exocytosis (Zhang et al., 2013). Sticky substances also are released from germ tubes. The downy mildew *Hyaloperonospora arabidopsidis* was shown to secrete proteins and fibrillar β-1,3-glucans

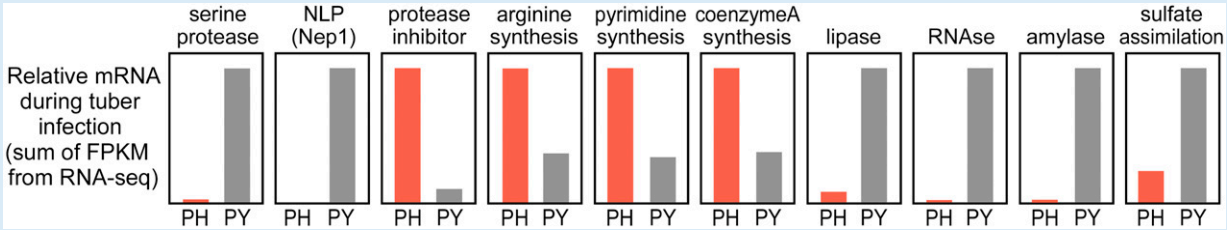
BOX 3. Stealthy *Phytophthora* versus aggressive *Pythium*

These two genera have distinct lifestyles despite being close neighbors in oomycete phylogenies. While most *Pythium* spp. are aggressive cosmopolitan necrotrophs, *Phytophthora* spp. are hemibiotrophs and are often host-specific. *Phytophthora* spp. grow primarily in the apoplast, which limits injuries to host cells and minimizes the production of damage-associated molecular patterns (DAMPs), which would otherwise induce host defenses. Host damage during the formation of haustoria, which are not made by *Pythium*, is also minimal since the openings in the plant wall are only a few microns in diameter. Imm une responses are also reduced since PRRs are excluded from the EHM. Only towards the end of the disease cycle do *Phytophthora* spp. exhibit signs of necrotrophy. In contrast, *Pythium* spp. seem to go full-speed ahead with a strategy of lysing host cells and extracting nutrients.

Some differences between the taxa are due to variation in gene content. For example, *Pythium* spp. lack the RXLR and CRN proteins that *Phytophthora* use to suppress host defenses. Moreover, only *Pythium* spp. encode the pore-forming toxins known as perforins. Other differences are reflected in the expression patterns of genes shared by *Ph. infestans* and *Py. ultimum*, as seen during potato tuber colonization (Ah-Fong et al., 2017b).

For example, *Py. ultimum* expresses its secreted proteases and necrosis-inducing NLP proteins at much higher levels than *Ph. infestans* (Fig. 2). In contrast, inhibitors of host proteases are expressed more by *Ph. infestans*. Catalase genes are expressed less by *Py. ultimum,* which suggests that eliminating peroxide delivered by the host to the pathogenic interface is not critical to its lifestyle.

Patterns of metabolic gene expression in *Ph. infestans* and *Py. ultimum* also reflect their divergent lifestyles. A consequence of the stealthy apoplastic mode of growth of *Phytophthora* is restricted access to nutrients. Thus, *Ph. infestans* expresses at higher levels many genes needed to synthesize metabolites that are at low concentrations in the apoplast. Examples include genes that encode enzymes for making amino acids such as arginine, nucleotides, and cofactors such as coenzyme A (Fig. 2; Ah-Fong et al., 2017b and H. Judelson and A. Ah-Fong, unpublished results). In contrast, mRNA levels of genes encoding enzymes that use nutrients that are normally sequestered in plant cells but released during necrotrophy are much higher in *Py. ultimum* than *Ph. infestans.* Examples include lipase, RNase, amylase for digesting starch, and enzymes for assimilating sulfate.



that bind its germ tubes to the substratum (Carzaniga et al., 2001). This may help resist detachment by wind or rain or protect against desiccation. Other potential adhesion proteins include mucin-like proteins (Larousse et al., 2014), jacalin-like and cellulose-binding elicitor (CBEL) lectins (Gaulin et al., 2002), and the ACWP family of acidic wall proteins (Resjö et al., 2017). Abnormal appressoria resulted from the knockdown of ACWP genes, suggesting that they contribute to adhesion or wall integrity. Knockdowns of CBEL showed that it helped hyphae bind to cellulosic substances but was not essential for pathogenicity (Gaulin et al., 2002). One of the few oomycete proteins known to concentrate in haustoria, Hmp1, is membrane anchored and weakly resembles lectins. Silencing *Hmp1* in *Ph. infestans* impaired the formation of infection vesicles in epidermal cells and haustoria, suggesting that the protein helps the pathogen bind to host interfaces (Avrova et al., 2008).

PLANTS CAN DETECT OOMYCETES AND BRING DEFENSES TO THE INTERFACE

Plants have evolved sophisticated systems for detecting microbes. One involves the binding of pathogen-associated molecular patterns (PAMPs) to plasmalemma-spanning pattern recognition receptors (PRRs), which activates PAMP-triggered immunity (PTI; Saijo et al., 2018). The salicylic acid (SA) and jasmonic acid pathways both participate in PTI against necrotrophic and (hemi)biotrophic oomycetes (Halim et al., 2009). Disrupting jasmonate production in Arabidopsis (*Arabidopsis thaliana*) allowed *Pythium irregulare*, which typically infects wounded or otherwise compromised hosts, to become a more severe pathogen (Staswick et al., 1998).

Constituents of the cell wall or plasma membrane were among the first oomycete PAMPs to be identified. These include β-1,3- and β-1,6-glucans and arachidonic acid (Fawke et al., 2015; Robinson and Bostock, 2015). *Medicago truncatula* also responds to a chitosaccharide from *Ap. euteiches*; most other oomycete phytopathogens lack this PAMP, since they do not make chitin (Mélida et al., 2013; Nars et al., 2013). Proteinaceous PAMPs include a cell wall transglutaminase (Brunner et al., 2002), the glycosyl hydrolase domain of the oligopeptide elicitor (OPEL) protein (Chang et al., 2015), the cellulose-binding protein CBEL, the elicitin family of sterol-binding proteins (Takenaka et al., 2011; Derevnina et al., 2016), and the XEG1 endoglucanase (Wang et al., 2018). The latter are proposed to be used for sterol acquisition by *Phytophthora* and *Pythium* spp., which are sterol autotrophs. It is notable that Nep1-like proteins (NLPs) were classified recently as PAMPs by some researchers. Most NLPs in *Phytophthora* spp. are expressed late in infection and have been linked to necrotrophic growth (Feng et al., 2014). Analysis of crystal structures identified similarity with pore-forming cytotoxins of sea anemones, which suggests that NLPs destabilize the host plasmalemma (Lenarčič et al., 2017). Oomycetes are immune to NLPs, since the latter are specific for dicotyledonous sphingolipids. An NLP from *Phytophthora parasitica* was shown to elicit defenses in crucifers, which suggests that some NLPs affect plant cells both as pore-forming toxins and inducers of PTI (Böhm et al., 2014).

Receptors for three oomycete PAMPs are known. The infestin elicitin of *Ph. infestans* and related proteins are recognized in potato by elicitin response protein (ELR), a plasmalemma-associated factor that associates with SUPPRESSOR OF BIR1-1 (SOBIR1), which is a leucine-rich repeat (LRR) receptor kinase (Domazakis et al., 2018). This pairing is needed since ELR lacks an intracellular kinase domain. When infestin is detected, the ELR-SOBIR1 complex recruits the LRR receptor-like kinase BRI1-ASSOCIATED KINASE-1, which is a known hub in defense responses. SOBIR1 also participates in the reaction of Arabidopsis to NLPs, which are recognized by the LRR receptor RLP23 (Albert et al., 2015). Recently identified was Response to XEG1 (RXEG1), an LLR protein that recognizes XEG1, a glycoside hydrolase 12 endoglucanase that is made by *Phytophthora* spp. RXEG1also forms a complex with BRI1-ASSOCIATED KINASE-1 and SOBIR1 to transduce the defense signal (Wang et al., 2018). Interestingly, fungal glycoside hydrolase 12 proteins also have been shown to serve as PAMPS and act through the same signaling hub (Gui et al., 2017).

Once PTI is activated, defense molecules are delivered to plant-oomycete interfaces, including pathogenesis-related (PR) proteins, callose for thickening cell walls, and microbial toxins. Effector-triggered immunity reinforces and expands these responses and often leads to hypersensitive cell death. Since PTI and effector-triggered immunity are not oomycete specific, readers seeking more information are directed to other reviews (Kourelis and van der Hoorn, 2018; Saijo et al., 2018). However, oomycetes were used in many early studies of the cytoskeletal dynamics that occur during infection, which showed that plant actin microfilaments focused rapidly near penetration sites (Takemoto et al., 2003). This causes peroxisomes, nuclei, and the endomembrane transport network to move toward the infection, which may help deliver defenses (Li and Staiger, 2018). Some (hemi)biotrophic oomycetes have evolved counter defenses against these trafficking pathways and may have hijacked some to support haustoria.

While the delivery of proteases, glucanases, and callose to oomycete-plant interfaces through canonical secretory and exocytosis pathways is long established, autophagic vesicles were shown recently to surround *Ph. infestans* haustoria and also may convey defenses (Dagdas et al., 2018). It is unknown whether plants use exosomes against oomycetes, for example by transporting inhibitory small RNAs, as shown recently with fungi (Cai et al., 2018). Nevertheless, there are reports of lettuce (*Lactuca sativa*) and potato being engineered to resist *Bremia lactucae* and *Ph. infestans* by host-induced

gene silencing using small RNAs targeting oomycete genes (Govindarajulu et al., 2015; Jahan et al., 2015).

Reactive oxygen species (ROS) are delivered to plant-oomycete interfaces through several pathways. ROS are derived from wall-bound peroxidases, respiratory burst oxidase homologs in plasmalemma, and glycolate oxidase in peroxisomes, which move to infection sites during cytoskeletal remodeling (Marino et al., 2012). ROS from tobacco (*Nicotiana tabacum*) roots have been implicated in blocking infection by *Ph. parasitica* zoospores, which interestingly die through programmed cell death (Galiana et al., 2005). Besides being antimicrobial, ROS strengthens cell walls by initiating lignin polymerization (Barros et al., 2015). Several other enzymes that fortify plant walls also are induced during PTI against oomycetes, including cinnamyl alcohol dehydrogenase and callose synthase (Wang et al., 2013; Hosseini et al., 2015).

Toxic isoflavonoids, sesquiterpenes, polyacetylenes, and other molecules that are collectively named phytoalexins are believed to be delivered to the pathogen by ATP-binding cassette (ABC) transporters. The export of capsidiol during the elicitin-triggered defense response of *Nicotiana benthamiana* against *Ph. infestans* involves ABCG1 and ABCG2, which are up-regulated during PTI (Rin et al., 2017). Some phytoalexins, such as α-tomatine of tomato, are preformed in plants, while others are induced by infection, such as capsidiol of *Nicotiana* spp. and pepper (*Capsicum annuum*), glyceollin of soybean, and camalexin of crucifers (Hahn et al., 1985; Bednarek et al., 2005).

These defenses may combine to produce apoplastic (or intracellular) environments that are unfavorable to oomycetes. This may explain why necrotrophy begins earlier in some *Phytophthora*-plant pathosystems than others, although the water soaking that is often associated with plant cell death may keep the pathogen hydrated. The low level of free water resulting from silicon polymerization in the apoplast also was invoked to explain why soybean grown at high silicon concentrations was less susceptible to *Ph. sojae* (Rasoolizadeh et al., 2018).

MANY OOMYCETES HAVE EVOLVED ELABORATE COUNTER DEFENSES

Oomycetes exhibit stealthy behaviors during biotrophic growth that minimize the immune response and maintain host integrity, which helps these pathogens feed from living cells. This is not an issue for necrotrophs such as *Pythium* spp. (Box 3). The (hemi)biotrophs resist host defenses using cytoplasmic and apoplastic effector proteins that are secreted toward their interface with plants. Oomycetes also produce enzymes that may degrade phytoalexins or immune-response hormones. The existence of these enzymes and effectors highlights the power of selection in the pathogen and the importance of their plant targets to the host defense response.

One example involves the plant apoplastic Cys proteases Rcr3 and C14, which were shown by mutation and knockdowns in tomato and *N. benthamiana* to defend against *Ph. infestans* (Song et al., 2009; Kaschani et al., 2010). *Ph. infestans* and relatives antagonize these using effectors such as extracellular cystatin-like protease inhibitor 1 (EPIC1). Studies of EPIC1 from *Ph. infestans* and *Phytophthora mirabilis* (which infects *Mirabilis jalapa*) and the host proteases were performed, guided by the crystal structure of a related protease-inhibitor complex. Amino acid changes in EPIC1 were implicated in helping the pathogens jump to new host species (Dong et al., 2014). Orthologs of EPIC1 genes occur in downy mildew, white rust, and *Pythium* spp. genomes. Most oomycetes also can inhibit plant Ser proteases, and one from *Phytophthora palmivora* was shown to contribute to virulence against the rubber tree (*Hevea brasiliensis*; Ekchaweng et al., 2017).

Another example of host-pathogen coevolution in the apoplast comes from studies of the endoglucanase XEG1 from *Ph. sojae*. Soybean produces an inhibitor of this CWDE, which binds XEG1 and blocks its contribution to virulence. To counteract the plant, *Ph. sojae* secretes an inactive enzyme as a decoy (Ma et al., 2017). With the defense protein unproductively bound to this trap, *Ph. sojae* can invade soybean more easily. Orthologs of XEG1 and its decoy are conserved throughout the *Phytophthora* genus.

Another apoplastic effector that counteracts host defenses is the in planta-induced protein (IPI-O) of *Ph. infestans*. IPI-O contains an Arg-Gly-Asp motif that is believed to disrupt adhesion between the plant's cell wall and plasmalemma by binding the lectin receptor kinase LecRK-I.9, thus promoting disease by reducing wall integrity (Bouwmeester et al., 2011). Intriguingly, IPI-O contains an RxLR motif (Arg-x-Leu-Arg) that is shared by many oomycete effectors that enter plant cells to interfere with plant defenses. In planta expression of IPI-O minus its signal peptide caused expanded lesions, suggesting that IPI-O acts both at the host plasmalemma and intracellularly (Chen and Halterman, 2017). The intracellular target, apparently, is resistance protein Rpi-blb1 (Champouret et al., 2009).

RxLRs along with CRN (Crinkler) proteins represent the known cytoplasmic effectors of oomycetes. These are absent from *Pythium* spp. (Box 3) but are encoded by large gene families in *Phytophthora* spp., downy mildews, and white rusts, albeit with divergent signature motifs in some species (Kemen et al., 2011). How these proteins move into plants is not fully clarified, but RxLR uptake may involve binding a receptor on lipid rafts, as shown for a host-targeted protein from the animal pathogenic oomycete *Saprolegnia parasitica* (Trusch et al., 2018). RxLRs and CRNs are known to defeat plant immune responses through many routes, which include reprogramming host gene expression, altering RNA metabolism, and binding to host proteins involved in signaling (Wang and Wang, 2018). In this review, mention will be made only of RxLRs that act at the oomycete-plant interface.

Many RxLRs affect the trafficking of defense molecules. AVRblb2 accumulates in plants near haustoria and blocks

the secretion of C14 protease (Bozkurt et al., 2011). RxLR24 of *Phytophthora brassicae* interferes with the delivery of antimicrobial proteins such as PR-1 by attaching to a GTPase involved in exocytosis (Tomczynska et al., 2018). Trafficking also is blocked by Avr1 of *Ph. infestans*, which binds exocyst protein SEC5 (Du et al., 2015), REX3 of *Ph. palmivora*, which interferes with brefeldin-sensitive secretion (Evangelisti et al., 2017), and PexRD54 of *Ph. infestans*, which depletes the Joka2 cargo protein from the autophagosomal membrane-forming ATG8 complex (Dagdas et al., 2016). The latter is interesting since the pathogen may be hijacking autophagosomes to destroy defense molecules through selective autophagy.

Although their functions are unidentified, the RxLRs Avh241 of *Ph. sojae* and HaRxL77 of *H. arabidopsidis* localize to the plant plasmalemma and are hypothesized to bind PRRs at the plant-oomycete interface (Caillaud et al., 2012; Yu et al., 2012). Causing auxin levels to rise at the interface is Penetration Specific Effector1 of *Ph. parasitica*, which is made in appressoria and interferes with auxin carriers (Evangelisti et al., 2013). This may elevate plant susceptibility since auxin inhibits SA signaling.

Interestingly, some species of *Pythium* are known to produce the auxin indole-3-acetic acid (Gravel et al., 2007). While there is no proof that oomycetes make other plant hormones, the sunflower (*Helianthus annuus*) downy mildew *Plasmopara halstedii* apparently encodes all enzymes for synthesizing cytokinin, which some bacteria make to direct host nutrients to infection sites (Sharma et al., 2015). *Pl. halstedii* also seems capable of producing brassinolide from phytosterols, which would negatively regulate the immune response. Many oomycetes also encode a predicted isochorismatase, which may disrupt SA signaling by breaking down its precursor. Interestingly, the enzyme in *Ph. sojae* localizes to haustoria (Liu et al., 2014).

Unlike fungi, most oomycetes have a limited capacity to degrade phytoalexins. Perhaps to compensate, oomycetes encode many more ABC transporters, which may expel the toxins (Ah-Fong et al., 2017b). While many fungi can degrade α-tomatine, *Phytophthora* and *Pythium* spp. that are pathogenic on tomato fail to degrade this glycoalkaloid (Sandrock and Vanetten, 1998). *Ph. sojae* can break down some soybean phytoalexins but not the most bioactive, glyceollin (Stossel, 1983). Whether *Pythium* spp. have special mechanisms to counteract plant defenses is unknown. However, during tuber infection, mRNA levels of *Py. ultimum* ABC transporters were about twice those of their counterparts in *Ph. infestans*, suggesting that the transporters might help eliminate phytoalexins liberated from lysing cells (Ah-Fong et al., 2017b). Cytochrome P450 enzymes also were more highly expressed in *Py. ultimum*.

HAUSTORIA REPRESENT A SPECIALIZED INTERFACE

Biotrophic and hemibiotrophic oomycetes form intimate associations with their hosts using haustoria (Fig. 1). These specialized hyphae breach host cell walls and become enveloped by a host membrane called the extrahaustorial membrane (EHM). Between the haustorium and EHM is a carbohydrate-rich amorphous layer called the extrahaustorial matrix (EHMx), which likely is of plant and pathogen origin (Caillaud et al., 2014). Little is known about how haustoria form and function in oomycetes, including how the host machinery is coopted during their genesis and what limits their expansion; most haustoria are less than 25 μm long.

Recent studies with *Ph. infestans* and *H. arabidopsidis* indicated that the EHM is assembled de novo, as suggested for fungi (Lu et al., 2012; Bozkurt et al., 2015). Secretory vesicles are abundant near developing haustoria, along with trans-Golgi and late endosomal markers such as Rab5 and Rab7 GTPases (Caillaud et al., 2014; Inada et al., 2016). Within the EHM are plasmalemma proteins such as the Pen1 syntaxin, synaptotagmin, and remorin, which would be needed to deliver membrane material to growing haustoria. Some plant proteins are excluded from the EHM, including a calcium ATPase and at least some PRRs (Lu et al., 2012). Reduced ATPase activity could favor nutrient flow to the pathogen by reducing the plant's capacity to retrieve nutrients from the EHMx, while PRR exclusion may minimize defense responses. Haustoria accommodation also causes host cells to reorganize their contents, with changes including endoplasmic reticulum aggregation, Golgi accumulation, and nuclear migration toward the haustoria (Lu et al., 2012). The nuclear shift might be part of a defense response or may be induced by the pathogen to facilitate the transport of CRN effectors, many of which act by reprogramming transcription (Song et al., 2015). Whether the reorganized endomembrane system delivers more transporters and/or nutrients to the EHM is an interesting question.

There are dissimilarities between haustoria of different species. While haustoria made by *Phytophthora* spp. are typically short and finger-like, those of downy mildews and white rusts are bulbous. Moreover, while *Ph. infestans* haustoria are anucleate and contain few mitochondria and endoplasmic reticulum, those of *H. arabidopsidis* have nuclei and many mitochondria and Golgi bodies (Mims et al., 2004). While the FLS2 PRR was excluded from the EHM with *Ph. infestans*, this was not the case with *H. arabidopsidis* (Lu et al., 2012). Downy mildew haustoria also are more likely to be surrounded by a callose collar than those of *Phytophthora* spp.

Several aspects of haustoria formation resemble plant defense responses. Deposition of the β-glucans that form callose collars involves secretory vesicles, multivesicular bodies, and Plasmodesmata-located-protein1 (PDLP1), which also is used to seal plasmodesmata during infection by other pathogens (Caillaud et al., 2014). Also possibly related to defense are haustorial encasements, which are double-layered membranes that often surround older haustoria (Lu et al., 2012).

These are common with *H. arabidopsidis* but are seen less with *Ph. infestans*. Encasements might restrict the pathogen's uptake of nutrients, impair effector translocation, or concentrate plant-derived antimicrobials. The EHM appears to have small invaginations, which also may promote its stability (Mims et al., 2004). The formation of these convolutions appears to involve PDLP1, since they increased when PDLP1 was overexpressed (Caillaud et al., 2014).

Although the contribution of oomycete haustoria to nutrient uptake is unclear, as discussed in the next section, the role of this structure in transporting proteins to the EHMx is demonstrated. Effectors are discharged from haustoria through at least two mechanisms. Secretion of the EPIC1 protease inhibitor was blocked by brefeldin A, indicating that it reaches the apoplast by the classic Golgi-mediated pathway (Wang et al., 2017). However, the delivery of RxLR Pi04314 was brefeldin A insensitive, suggesting that this cytoplasmic effector follows an alternative route even though it contains a classic signal peptide. Isochorismatases also are secreted but lack signal peptides, suggesting that they use the unconventional secretion pathway that has been documented in nonoomycetes (Liu et al., 2014).

NUTRIENT ACQUISITION AT THE PLANT-OOMYCETE INTERFACE

Although not proven, oomycete haustoria often are assumed to play a major role in nutrition. Nevertheless, they lack the neckband that encircles fungal haustoria, which is thought to help establish electrochemical gradients for nutrient transport by sealing the EHMx (Mims et al., 2004). *Al. candida* and *H. arabidopsidis* contain an electron-dense layer near their callose collars, which might function like a neckband, however (Soylu, 2004). In *Ph. infestans*, EHMx continuity with the apoplast was confirmed by studying the distribution of fluorescently tagged Avr3a (Whisson et al., 2007). Also unlike fungi, no haustoria-specific transporters are identified in oomycetes. While *Ph. infestans* and *Py. ultimum* both express ~410 nutrient transporters, very few are specific to the haustoria-forming species (Ah-Fong et al., 2017b). Most nutrients may be drawn from the apoplast, considering that analyses of images of potato leaves infected by *Ph. infestans* indicate that its haustoria represent only about 2% of the total pathogen surface area (H. Judelson, unpublished data).

Regardless of where nutrients are acquired, plants contain myriad compounds to support pathogen growth. Metabolic models based on genome data indicate that most oomycetes can utilize the major plant hexoses, disaccharides, organic acids, starch, and sugar alcohols, although pentose utilization is restricted by the absence of arabinose isomerase (Rodenburg et al., 2018). Most oomycetes also can use the major nitrogen sources found in planta, including amino acids, ammonium, and nitrate. However, the biotrophs have reduced metabolic capabilities and, thus, a greater reliance on the host. While species of *Phytophthora* and *Pythium* each encode approximately 850 enzyme activities based on Enzyme Commission numbers, *H. arabidopsidis* and *Al. candida* encode only about 740 and 650, respectively (Judelson, 2017). These obligate biotrophs lack genes for nitrate assimilation and have impaired abilities to incorporate inorganic sulfur due to a lack of sulfite oxidase or reductase.

The metabolic deficiencies in the (hemi)biotrophs may help suppress immune responses, besides providing potential energy savings to the pathogen. The biotrophs are unable to make unsaturated fatty acids such as arachidonate, which are PAMPs in *Phytophthora* and *Pythium* spp. (Robinson and Bostock, 2015). The haustoria-forming oomycetes lack molybdopterin-utilizing pathways and consequently must acquire thiamine from the host. This may be beneficial, since this vitamin can up-regulate plant defenses, as demonstrated in the *Pl. viticola*-grape system (Boubakri et al., 2013).

It is important to differentiate the theoretical metabolism of oomycetes from what occurs in planta, since not all nutrients are at each plant-oomycete interface. While biotrophs are restricted to apoplastic nutrients, necrotrophs can access all compounds. Examples include starch and sulfate, which are sequestered within starch granules and vacuoles, respectively. Data from a study of *Ph. infestans* and *Py. ultimum* on potato tubers (Ah-Fong et al., 2017b) showed that while both encode α-amylase for starch utilization and adenylyl-sulfate kinase for incorporating sulfate, the *Py. ultimum* genes were expressed at greater than 10-fold higher levels (Box 3). This is the logical outcome of substrate-level induction. This situation changed during late infection when tissue colonized by *Ph. infestans* became necrotic, and mRNA levels for these enzymes equalized between the two pathogens. Similar patterns were observed for enzymes that act on other nutrients sequestered during biotrophic growth, such as phytate and lipids. This indicates that the terminal lifestyle of *Ph. infestans* is necrotrophic and not just necrogenic, thus addressing a debate in *Phytophthora*-host interactions. One position has been that plant necrosis does not benefit the pathogen and occurs simply because the pathogen no longer needs to suppress host defenses. The other viewpoint, which is supported by these results, is that necrosis is induced to liberate additional nutrients.

OOMYCETES HAVE AN EXIT STRATEGY

The final chapter in disease involves the pathogen's egress from its host. Necrotrophs such as *Pythium* spp. can simply extend hyphae from macerated plant tissue into soil and transition to survival through saprophytic growth; sporulation is optional. In contrast, most (hemi)biotrophs must produce asexual spores. These are typically formed by root-rotting species at the crown, surface-exposed roots, or subterranean spaces

OUTSTANDING QUESTIONS

- Are there effectors that cause nutrients to flow to the oomycete-plant interface?
- Do oomycete haustoria play a major role in nutrient uptake, or is protein secretion their main function?
- What cargo is carried by plant exosomes to the oomycete-host interface?
- Why does the shift from biotrophy to necrotrophy occur early during infection by some *Phytophthora* spp. and later in others?
- Can genome-scale modeling of metabolism yield insight into the basis of obligate biotrophy?
- What are the molecular and environmental (including *in planta*) factors that trigger sporulation?
- Considering that much of our knowledge of oomycete-plant interactions comes from studies of *Phytophthora* spp., what is needed to accelerate investigations of other oomycetes?

adjoining roots. The task is more complicated for foliage-infecting (hemi)biotrophs, which usually sporulate from sporangiophores that pass through stomata (Farrell et al., 1969; Allègre et al., 2007). Most foliage-infecting oomycetes sporulate at night. This maximizes survival of the spores, which are prone to desiccation and lack UV-blocking pigments. Nocturnal sporulation is proposed to be regulated by cryptochromes in response to blue light (Xiang and Judelson, 2014) and requires modulating guard cell behavior, since stomata would normally be closed at night. Stomatal deregulation in the *Pl. viticola*-grape leaf interaction was proposed to be determined by a secreted glycoprotein, which caused stomata in colonized areas to remain open during darkness, water stress, and abscisic acid treatment (Allègre et al., 2007; Guillier et al., 2015). This effect resembles that caused by the bacterial toxin coronatine (Melotto et al., 2006).

Substantial genomic resources are devoted to sporulation. In *Ph. infestans*, this involves the up-regulation of more than 3,000 genes (~20% of the total), including those encoding storage, effector, and adhesion proteins, and several hundred components of flagella (Judelson et al., 2012; Ah-Fong et al., 2017a). Genes proven to regulate sporulation include MADS box and Myb transcription factors, a mitogen-activated protein kinase, and a cell cycle phosphatase (Ah-Fong and Judelson, 2011; Li et al., 2014; Xiang and Judelson, 2014). However, the primary trigger for sporulation is unknown. Nutrient limitation is thought to play a role, which is concordant with the finding that the nitrogen metabolite repression regulator NMRA is down-regulated near the onset of sporulation in *Ph. infestans* (Ah-Fong et al., 2017a). NMRA also was proposed to control the transcription of late-induced effectors in *Phytophthora capsici* (Pham et al., 2018). Spiking at the same time are mRNAs for genes used to assimilate nitrate, which is a nonpreferred nitrogen source compared with amino acids (Abrahamian et al., 2016). Since a study in *Phytophthora cactorum* found that adding amino acids or ammonium to media did not retard sporulation, the process also may be prompted by an accumulated metabolite (Elliott, 1989). The plant also may affect sporulation, since its metabolic pathways are linked to those of the pathogen during colonization. A dual-species systems approach to metabolism may help understand what influences sporulation, effector expression, phytohormone levels, and other aspects of plant-oomycete interactions.

CONCLUSION

Oomycetes have developed diverse lifestyles over their 400+ million years of evolution (Taylor et al., 2006). The (hemi)biotrophs have learned to coopt their hosts by suppressing defenses and coercing plants to form interfaces for effector and nutrient delivery. Such lifestyles may have evolved by exploiting pathways used by plants to harbor mutualists, since mutants of *M. truncatula* deficient in mycorrhizae formation were shown to have reduced susceptibility to *Ph. palmivora* (Rey et al., 2015). Many oomycetes have become host-adapted to the extent that they depend on plant metabolites for growth or reproduction. In contrast, necrotrophs have less-specialized lifestyles, as they can grow as saprophytes or pathogens, overpowering their hosts and perhaps even profiting from the plant immune response. Most oomycetes also have retained a flagellated life stage, which expands their access to new hosts, although this comes with a large genomic burden. Meanwhile, plants have evolved complex multilayered defenses that balance survival against the growth penalty that comes from activating the immune response (Ning et al., 2017).

Many of the defenses, counter defenses, spore behaviors, and interactions with other microbes that we have described have small individual effects on disease outcomes but are significant from an epidemiological perspective. The infection potential of an oomycete spore on plant tissue is usually much less than 100%, similar to the situation in fungi (Mellersh and Heath, 2002; Kong and Hong, 2016). The progress of an epidemic will be influenced by factors that raise or lower this infection potential or the time between penetration and sporulation (Willocquet et al., 2017). While many plant scientists aim to develop strong resistance against pathogens, natural defenses (as well as changes in pathogens that enhance fitness) need not have blockbuster effects to be retained during evolution.

Our knowledge of interactions involving *Phytophthora* spp. has grown dramatically due to the availability of genome sequences and tools for functional

genomics, but research into other oomycetes has lagged. It is unfortunate that *Pythium* spp. have remained little studied despite their large agricultural impact, for example. Most *Pythium* spp. are easily cultured, so it should be possible for a new generation of researchers to improve our understanding of the genus. Studying the breadth of oomycetes is important since crop protection solutions developed for one group may not translate to others.

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