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Oomycete Interactions with Plants: Infection Strategies and Resistance Principles

Stuart Fawke, Mehdi Doumane,* Sebastian Schornack

Sainsbury Laboratory (SLCU), University of Cambridge, Cambridge, United Kingdom

SUMMARY

The Oomycota include many economically significant microbial pathogens of crop species. Understanding the mechanisms by which oomycetes infect plants and identifying methods to provide durable resistance are major research goals. Over the last few years, many elicitors that trigger plant immunity have been identified, as well as host genes that mediate susceptibility to oomycete pathogens. The mechanisms behind these processes have subsequently been investigated and many new discoveries made, marking a period of exciting research in the oomycete pathology field. This review provides an introduction to our current knowledge of the pathogenic mechanisms used by oomycetes, including elicitors and effectors, plus an overview of the major principles of host resistance: the established R gene hypothesis and the more recently defined susceptibility (S) gene model. Future directions for development of oomycete-resistant plants are discussed, along with ways that recent discoveries in the field of oomycete-plant interactions are generating novel means of studying how pathogen and symbiont colonizations overlap.

INTRODUCTION

The Oomycota are a distinct class of fungus-like eukaryotic microbes, many of which are highly destructive plant or animal pathogens. They share a range of morphological features with fungi, but they possess various unique characteristics which set them apart (1). Cellulose is a major component of oomycete cell walls. In contrast, chitin, not cellulose, is a major cell wall component of true fungi. However, oomycetes also possess chitin synthases that are activated during tip morphogenesis (2, 3). Oomycetes are diploid during their vegetative mycelial stage, whereas fungi predominantly produce haploid thalli, although exceptions do exist (2, 4). Cells of oomycetes can be distinguished morphologically from true fungi by their mitochondria, as they possess tubular cristae as opposed to the flattened cristae of fungi (5), or by their hyphae, which are always nonseptate (6).

Typical structural features guided the identification of oomycetes in the fossil record. The oldest existing evidence for oomycete-like structures dates back to the Devonian period, i.e., ca. 400 to 360 Ma (7), and there is evidence of oomycete parasitism occurring during the Carboniferous period, ca. 300 Ma (8). Molecular clock estimates position the origin of oomycetes as early as the Silurian period, i.e., ca. 430 to 400 Ma (9).

This review provides an overview of our current knowledge of oomycete plant pathogens. We introduce the elicitors, effector proteins, and disease resistance and susceptibility principles involved in our current understanding of how oomycetes interact with their plant hosts. We also present strategies for developing oomycete-resistant crop plants and highlight the potential of oomycetes as tools to investigate common and contrasting mechanisms of pathogenic and mutualistic filamentous microbes.

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Address correspondence to Sebastian Schornack, sebastian.schornack@slcu.cam.ac.uk.

* Present address: Mehdi Doumane, Department of Biology, École Normale Supérieure de Lyon, Lyon, France.

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TABLE 1 Plant-pathogenic oomycete genome sequence resources

Order and species	Genome size (Mb)	Reference(s)
Peronosporales		
Albugo laibachii	37.0	137
Albugo candida	45.3	184
Bremia lactucae	Transcriptome only	138; http://web.science.uu.nl/pmi/data/bremia/
Hyaloperonospora arabidopsidis	81.6	125
Phytophthora cactorum	Transcriptome only	185
Phytophthora capsici	64.0	139
Phytophthora cinnamomi	78.0	http://genome.jgi.doe.gov/Phyci1/Phyci1.home.html
Phytophthora infestans	240.0	124
Phytophthora ipomoeae	Alignment to *P. infestans*	186
Phytophthora fragariae var. *fragariae*	73.6	187
Phytophthora mirabilis	Alignment to *P. infestans*	186
Phytophthora palmivora		Sequencing project in progress (USDA, 2012); http://www.ars.usda.gov/research/projects/projects.htm?accn_no=422621
Phytophthora parasitica	82.4	*Phytophthora parasitica* Assembly Development Initiative, Broad Institute (https://olive.broadinstitute.org/projects/phytophthora_parasitica)
Phytophthora phaseoli		186
Phytophthora ramorum	65.0	126
Phytophthora sojae	95.0	126
Plasmopara halstedii		Sequencing project in progress (INRA, 2012); http://www6.bordeaux-aquitaine.inra.fr/sante-agroecologie-vignoble/Personnel/Scientifiques/Francois-Delmotte/Downy-mildew-genomics
Plasmopara viticola		Sequencing project in progress (INRA, 2012); http://www6.bordeaux-aquitaine.inra.fr/sante-agroecologie-vignoble/Personnel/Scientifiques/Francois-Delmotte/Downy-mildew-genomics
Pseudoperonospora cubensis	Transcriptome only	140
Pythiales		
Pythium ultimum	42.8	2
Pythium aphanidermatum	35.9	2, 141
Pythium arrhenomanes	44.7	2, 141
Pythium irregulare	42.9	2, 141
Pythium iwayamai	43.3	2, 141
Pythium ultimum var. *sporangiiferum*	37.7	2, 141
Pythium vexans	33.9	2, 141
Saprolegniales		
Aphanomyces euteiches		Sequencing project in progress (Genoscope, 2009); http://www.polebio.lrsv.ups-tlse.fr/aphano/

PHYLOGENY

Analyses of conserved DNA sequences, such as mitochondrial *COX2* (10–12), large-subunit ribosomal DNA (LSU rDNA) (13), and small-subunit rDNA (SSU rDNA) (14), have confirmed that oomycetes belong outside the fungal kingdom, within the Chromalveolata. The Chromalveolata kingdom contains mainly photosynthetic species, a result of ancestral "enslavement" of red algae (15), but oomycetes have since lost their chloroplasts (16). The availability of several sequenced genomes for some genera (Table 1), in particular *Phytophthora*, has greatly facilitated multilocus assessments of oomycete taxonomic relationships (17). The Oomycota are broadly divided into two subclasses. The Saprolegniomycetidae, referred to as the "water molds," include the orders Eurychasmales, Leptomitales, and Saprolegniales, while the Peronosporomycetidae are mostly plant pathogen orders and consist of the Rhipidiales, Pythiales, and Peronosporales. The existence of early diverging genera of marine parasites within the mainly terrestrial Saprolegniales and Peronosporales orders has led evolutionary biologists to suggest that oomycetes made their migration onto the land and into the soil via parasitism of nematode hosts or by switching from colonization of estuarine seaweed to the roots or shoots of early coastal vegetation (18).

EARLY LIFE CYCLE STAGES: ASEXUAL REPRODUCTION AND INFECTION STRUCTURES

Dispersal of oomycetes by wind or water is achieved through asexual sporangia. Germination of sporangia can occur either directly, forming invasive hyphae, or indirectly, releasing motile zoospores, which are chemotactically and electrotactically attracted to the surfaces of host plants (19). Zoospores swim until reaching the plant surface, at which point they shed their flagella and encyst, firmly attaching themselves to the plant surface via secretion of adhesion molecules (20), as visualized in Fig. 1.

Upon germination of a zoospore, a germ tube emerges and grows across the plant surface until the development of an appressorium is induced by surface topology and/or hydrophobicity (6).

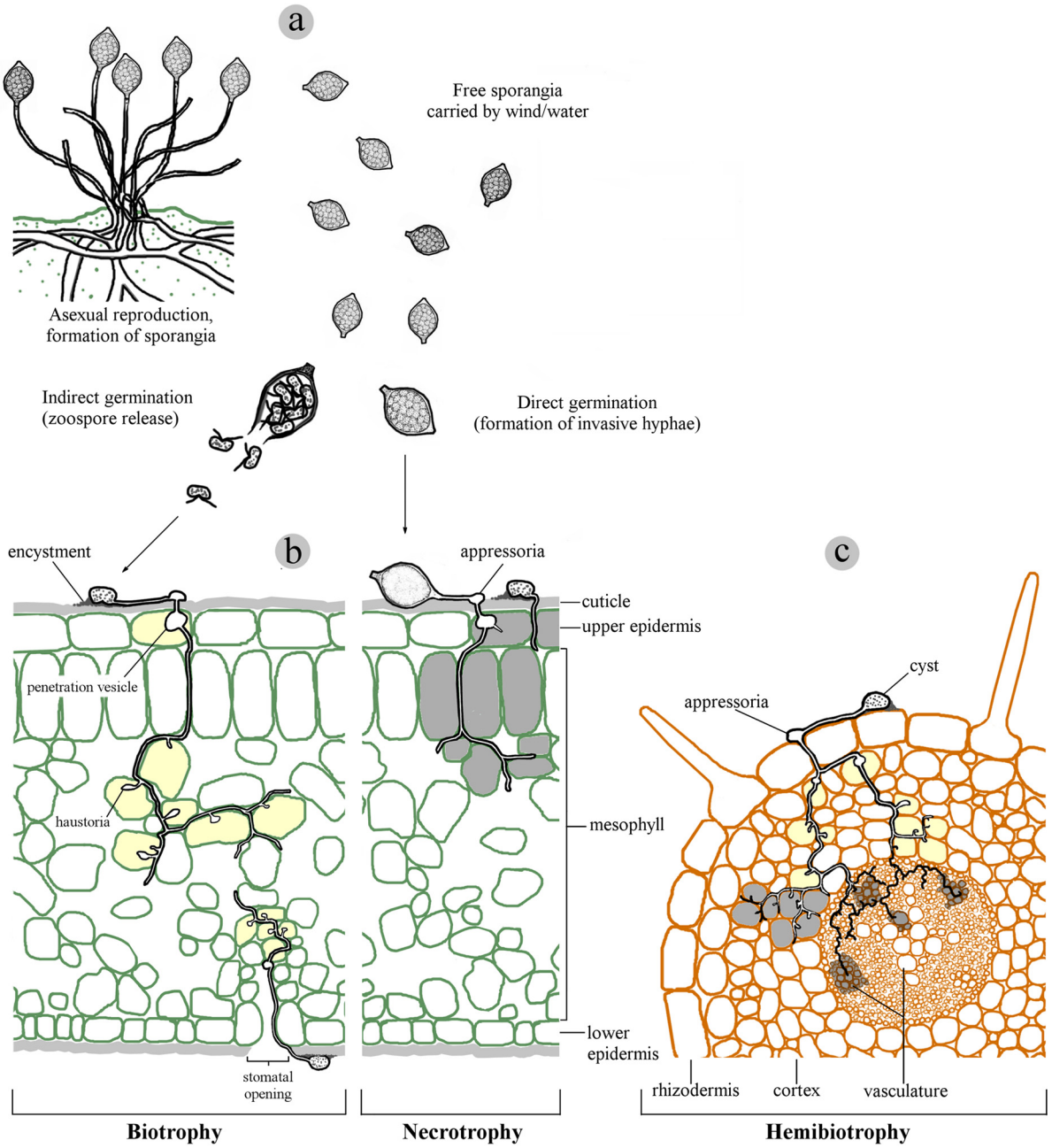

FIG 1 Infection strategies and lifestyles of selected oomycetes. (a) Typical asexual *Phytophthora* dispersal structures. (b) Leaf colonization. (c) Root colonization. Two methods of germination (direct germination from deciduous sporangia and indirect germination from zoospores) are depicted. Other germination strategies are not displayed. Following germination, depending on the species, oomycetes perform biotrophy (e.g., *Hyaloperonospora arabidopsidis* or *Albugo laibachii*, the latter often entering through stomata and then forming appressoria), necrotrophy (e.g., *Pythium ultimum*), or hemibiotrophy (e.g., *Phytophthora sojae* or *Phytophthora palmivora*). Notably, oomycete entry occurs through epidermal cells or between cells. Cells which have been colonized by a biotrophic pathogen are highlighted in yellow, while those that are undergoing cell death as a result of necrotrophy are shaded gray. In the case of a hemibiotrophic oomycete colonizing a root, the interaction is initially biotrophic, while the oomycete spreads through the cortex, but once the oomycete is established and hyphae have entered the endodermis and vasculature, necrotrophy can be observed.

In general, oomycete appressoria function in the penetration of the outermost, epidermal cell layers. Exceptions to this include *Albugo candida*, a leaf-infecting pathogen of *Arabidopsis thaliana*, which enters through stomata and then forms appressoria in order to penetrate the mesophyll cells below (21), and *Aphanomyces euteiches*, which does not form distinct appressoria.

Oomycete plant pathogens exhibit biotrophic, necrotrophic, or hemibiotrophic (a combination of both) lifestyles. Many biotrophic oomycetes are completely reliant on host tissues (obligate biotrophy). This is a feature of the downy mildews *Hyaloperonospora arabidopsidis*, *Hyaloperonospora parasitica*, and *Plasmopara viticola*, as well as *A. candida*, which causes white rust.

TABLE 2 Lifestyles, host ranges, and infection structures of important plant-infecting oomycete species

Species	Lifestyle[a]	Host(s) [organ(s)]	Infection structure(s)
Albugo candida	B	*Arabidopsis thaliana* and other Brassicaceae plants (leaves)	Enter through stomata and then form appressoria and haustoria
Aphanomyces euteiches	B	Legumes: *Medicago truncatula*, *Pisum sativum*, *Medicago sativa* (roots)	Hyphae only
Hyaloperonospora arabidopsidis	B	*Arabidopsis thaliana* (leaves)	Appressoria, haustoria
Hyaloperonospora parasitica	B	*Capsella bursa-pastoris* and Brassicaceae, including *Arabidopsis thaliana* (leaves)	Appressoria, penetration hyphae, haustoria
Peronospora manshurica	B	*Glycine max* (leaves)	Appressoria, haustoria
Plasmopara viticola	B	*Vitis* spp. (leaves)	Appressoria, haustoria
Phytophthora cinnamomi	HB	Very broad range, including most annual and herbaceous perennial species (roots)	Appressoria, haustoria
Phytophthora capsici	HB	*Capsicum annuum*, members of the Cucurbitaceae, Fabaceae, and Solanaceae (stems and fruit)	Appressoria, haustoria
Phytophthora infestans	HB	Potato, tomato, wild tobaccos (shoots)	Appressoria, haustoria
Phytophthora palmivora	HB	Very broad range, including palm and fruit tree species, *Medicago truncatula*, *Nicotiana benthamiana* (roots, trunks, buds, leaves)	Appressoria, haustoria
Phytophthora parasitica	HB	Very broad range, including *Solanum lycopersicum*, *Solanum tuberosum*, *Capsicum annuum* (roots and leaves)	Appressoria, haustoria
Phytophthora ramorum	HB	Very broad range, including *Quercus agrifolia*, *Notholithocarpus densiflorus* (phloem and inner bark)	Appressorium-like structures (haustoria not yet observed)
Phytophthora sojae	HB	*Glycine max*, *Glycine soja*, *Lupinus* spp. (roots)	Appressoria, haustoria
Pythium ultimum	N	Very broad range, including *Zea mays*, *Glycine max*, *Solanum tuberosum*, and *Triticum* spp. (roots)	Appressoria only

[a] B, obligate biotroph; HB, hemibiotroph; N, necrotroph.

Hemibiotrophs, such as *Phytophthora* spp., commonly have the ability to survive in axenic culture (facultative), as do necrotrophs, such as *Pythium ultimum*. A summary of the lifestyles of important plant-colonizing oomycetes is provided in Table 2.

Obligate biotrophs, such as *H. parasitica*, must maintain a close interaction with their hosts while keeping the plant alive for their own survival, meaning that highly specific infection mechanisms exist, significantly restricting their host range. This is in contrast to hemibiotrophic pathogens, for example, those of the *Phytophthora* genus, some of which have the ability to infect hundreds of different plant species, growing initially as biotrophs but later switching to a necrotrophic phase. Following penetration of the cell wall by appressoria, oomycetes generate vegetative hyphae that grow intercellularly, and haustoria develop as side branches from intercellular and epicuticular hyphae, terminating inside penetrated host cells (22, 23) (Fig. 1 and 2). Haustoria can be observed during colonization by most obligate biotrophs (24) and have been implicated in nutrient uptake in fungi for which haustorium-specific sugar transporters have been described (25), although little is known about haustorium-specific transport processes in oomycetes. However, a number of hemibiotrophs and necrotrophs do not form haustoria, for example, *Aphanomyces euteiches* and *Pythium ultimum*.

PLANTS RECOGNIZE OOMYCETE-DERIVED MOLECULES

Elicitors are molecules which stimulate a defense response in a host plant (Table 3). Most of them constitute pathogen-associated molecular patterns (PAMPs) (26) because they are structurally conserved and thought to be indispensable components or products of a pathogen's life cycle or infection process. Elicitors are perceived by some plants as a microbial signature, likely through peripheral receptors, some of which require BAK1/SERK3 for their activity (27, 28). The following paragraphs describe a number of oomycete elicitors and their receptors, if known.

The elicitor Pep-13 was isolated from *Phytophthora sojae* and is a 13-amino-acid peptide of a surface-exposed stretch of a transglutaminase protein (29–31). Mutation of just one of these amino acids is sufficient to impair transglutaminase-mediated recognition of *P. sojae* and to avoid induction of plant defense responses (29). Although Pep-13 was identified over 10 years ago, its plant receptor(s) has yet to be discovered.

Some parasitic oomycetes, including *Phytophthora* species, have lost the ability to synthesize their own sterols, which are essential molecules for many cellular functions. They must therefore acquire sterols from host cell membranes (32). *Phytophthora infestans* INF1 is a member of a family of conserved lipid transfer proteins with sterol-binding and elicitor capacities, including cryptogein from *Phytophthora cryptogea*, CAP1 from *Phytophthora capsici*, and PAL1 from *Phytophthora palmivora*, among others. INF1 binds dehydroergosterol *in vitro* and catalyzes sterol transfer between liposomes (33). However, there is still no *in vivo* evidence of INF1 involvement in sterol uptake, and INF1-lacking *P. infestans* strains remain pathogenic (34, 35). INF1 is known to be secreted by *P. infestans* through its N-terminal signal peptide,

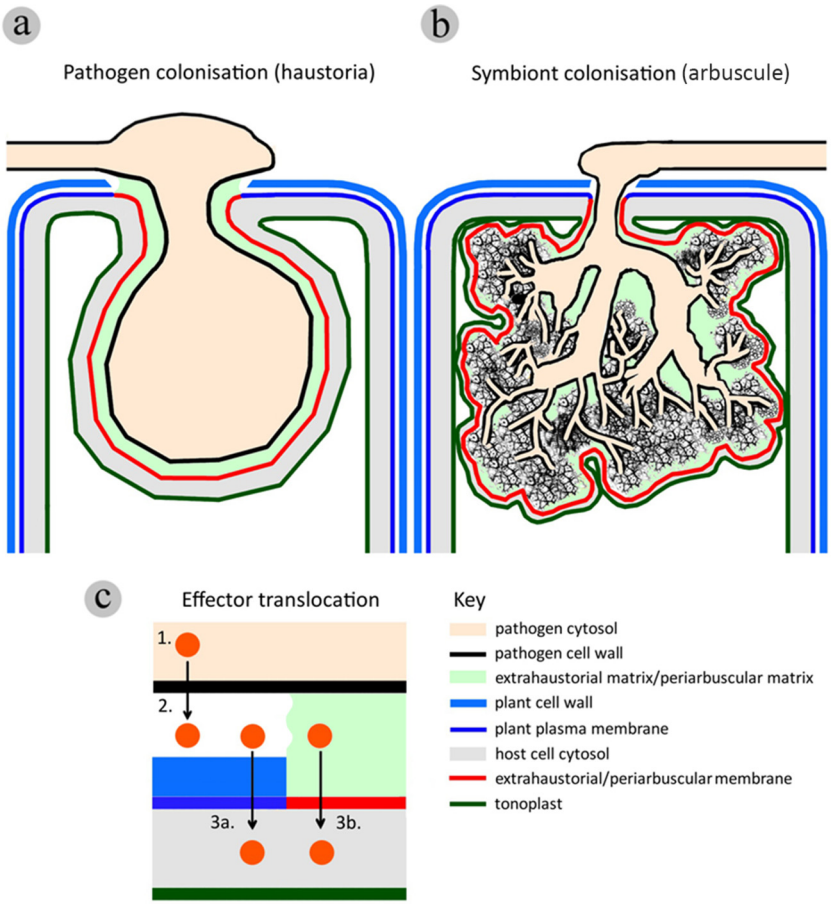

FIG 2 Filamentous plant-microbe interfaces and membrane barriers for effector translocation. Haustoria (a) and arbuscules (b) both represent invaginations of the plant cell protoplast caused by microbial ingrowth. Both are surrounded by specialized membranes, termed the extrahaustorial membrane (EHM) or the periarbuscular membrane (PAM) (red). (c) Cytoplasmic effectors must pass several membrane barriers. Originating in the pathogen cytosol (1), effectors are thought to be secreted across the pathogen cell wall (2), either into the space adjacent to the plant cell wall or into the extrahaustorial matrix/periarbuscular matrix (EHM/PAM). The EHM/PAM is an environment that may be modified by other pathogen-secreted molecules to stabilize the effector protein or, alternatively, may contain host plant proteases which target effectors for hydrolysis. Some plant membrane molecules may act as receptors for effectors, assisting their transport to the host cell, while effectors themselves may interact to aid translocation into the host cytosol. Movement across the host plasma membrane may or may not involve first crossing the plant cell wall (3a and 3b, respectively), depending on where an effector is secreted from the microbe. This movement may occur either by endocytosis or via a translocon (pathogen-specific translocation mechanism). Focal host defense responses may inhibit the entry of effectors, while pathogen factors may prepare host cells for their uptake.

initially localizing to the extracellular space (36), and it has been shown by *in vitro* immunocytochemistry that the INF1-like quercinin protein of *Phytophthora quercina* appears to be transported inside the host (29). INF1 was reported to interact with the cytoplasmic domain of NbLRK1, a lectin-like receptor kinase that is localized to the plasma membrane (37). However, the requirement of BAK1/SERK3 for INF1-triggered immune responses rather points to an LRR-containing receptor (27, 28), leaving open whether it is a receptor-like protein (RLP) or a receptor-like kinase (RLK). The identification of *SlSOBIR1* as a required component for responses elicited by the *P. parasitica* INF1-like protein ParA1 (38) suggested that INF1 perception is mediated through an RLP rather than an RLK, since SOBIR1 was previously reported to be a coreceptor of RLPs (39). Then, the discovery of ELR, a wild

TABLE 3 Examples of known oomycete elicitors

Elicitor	Type	Plant receptor	Reference(s)
INF1	Protein, sterol binding	BAK1/SERK3-dependent ELR	28, 34, 35, 40
OPEL	Protein	Unknown monomeric, 100-kDa integral plasma membrane protein	30, 41, 142
CBEL	Protein	Unknown, but cellulose dependent	44
Pep-13	Peptide	Unknown	29, 30
Arachidonic acid	Unsaturated fatty acid	Unknown	143
Beta-glucans	Carbohydrate	Glucan-dependent CEBiP CERK1	46, 48, 144, 145

potato RLP that associates with BAK1/SERK3, mediating broad-spectrum recognition and induction of cell death after triggering by four *P. infestans* elicitins (INF1, INF2A, INF5, and INF6) as well as 11 elicitins of diverse other *Phytophthora* species, added a new chapter to our understanding of INF1 perception (40).

OPEL is a recently described secreted protein from culture filtrates of *Phytophthora parasitica* with homologs in other oomycetes but not in fungi (41). This 556-amino-acid protein is inducibly expressed during plant invasion. Infiltration of OPEL proteins into *Nicotiana tabacum* leaves led to callose deposition, cell death, synthesis of reactive oxygen species (ROS), and induction of PAMP-triggered immunity (PTI) response marker genes as well as salicylic acid-responsive defense genes (41), all of which are characteristics of a plant defense response. OPEL is therefore considered a microbial signature that is recognized in tobacco leaves. Infiltration of OPEL also stimulates resistance to viruses, bacteria, and the oomycete pathogen *P. parasitica*. OPEL contains the following three domains in addition to its signal peptide: a thaumatin-like domain, a glycine-rich protein domain, and a glycosyl hydrolase (GH) domain with laminarinase activity. Recombinant OPEL protein infiltration resulted in an enhanced plant immune response and resistance to *P. parasitica*. Chang et al. (41) concluded that the predicted laminarinase activity of OPEL triggers plant immune responses, presumably by generating degradation products in the apoplast that act as damage-associated molecular patterns (DAMPs). However, they were unable to show any enzymatic activity from the wild-type OPEL protein by using laminarin or 1,3-β-glucan as a substrate. OPEL might have a specific polysaccharide substrate in the plant cell wall whose degradation is detected by plant immunity. Alternatively, coevolution of plants and oomycetes may have led to the perception of OPEL via its enzymatic active site.

The cellulose-binding elicitor lectin (CBEL) of *P. parasitica* is an apoplastic elicitor that possesses two carbohydrate-binding modules belonging to family 1 (CBM1) domains, allowing binding to cellulose and lectin-like hemagglutinating activity (42). CBM1 domains occur commonly in oomycete and fungal proteins, although CBM1-containing fungal proteins function in plant cellulose degradation, whereas those of oomycetes (including CBEL) play a role in adhesion (43). There is downstream signaling following CBEL perception in tobacco cells but not in cell wall-lacking protoplasts, suggesting that plant cell wall binding is required for CBEL-induced defense reactions (44). Alternatively, CBEL detection might require other cell wall-dependent processes, such as polar exo- or endocytosis, which cannot properly take place in nonpolar protoplasts (45).

β-Glucans represent PAMPs originating from cell wall fractions of filamentous pathogens (fungi and oomycetes). Soybean plants perceive branched heptaglucans with β(1-6) backbone linkages from *Phytophthora sojae* and, in particular, its three nonreducing terminal glycosyl residues (46). Conversely, this glucan does not elicit defense responses in tobacco cells, but a linear β(1-3) glucan does (47). Branched glucan-chitosaccharides from cell wall fractions of *Aphanomyces euteiches* induce defense gene expression and nuclear calcium oscillation in *Medicago truncatula* root epidermis (48), similar but not identical to those elicited by lipochito-oligosaccharides produced by arbuscular mycorrhizal fungi.

EFFECTORS SUPPRESS HOST IMMUNITY

In order to sustain an intimate association with the host plant, oomycetes must suppress immune responses triggered by their own elicitors. By secreting effector proteins that can act in many different cellular compartments, pathogens alter the plant's physiological state to benefit colonization. Descriptions of effector function are often defined by the available approaches used to study them. Here we mention some recent effector studies that focus on the localization and stability of effectors and their target proteins, as well as overall transcriptional changes and virulence effects, all of which are summarized in Table 4.

The *P. infestans* effector AVR3a suppresses perception of the PAMP INF1 through stabilization of the U-box protein CMPG1 (49). AVR3a was also found to interact with dynamin-related protein 2 (DRP2), a plant GTPase implicated in receptor-mediated endocytosis that, when overexpressed, attenuated PAMP-triggered ROS accumulation (50). It appears from these findings that AVR3a can suppress BAK1/SERK3-mediated immunity via two different methods.

P. infestans PexRD2 interacts with the kinase domain of MAPKKKε, a positive regulator of cell death associated with plant immunity. This in turn disrupts the signaling pathways triggered by or dependent on MAPKKKε, increasing the susceptibility of *Nicotiana benthamiana* to *P. infestans* (51).

When expressed in plant cells, *P. infestans* AVRblb2 displays an intriguing localization at haustoria and renders plants more susceptible to infection. Furthermore, AVRblb2 prevents secretion of the plant defense protease C14, resulting in lower C14 levels in the apoplast and an accumulation of C14-loaded secretory compartments around haustoria (52).

The nucleus-localized effector HaRxL44 of *H. arabidopsidis* interacts with Mediator subunit 19a (MED19a), resulting in degradation of MED19a. The Mediator complex consists of around 25 protein subunits and is broadly conserved in eukaryotes, functioning as a mediator in the interaction between transcriptional regulators and RNA polymerase II. MED19a was found to be a positive regulator of immunity against *H. arabidopsidis* and to be responsible for transcriptional changes resembling jasmonic acid/ethylene (JA/ET) signaling in the presence of HaRxL44. It was concluded that HaRxL44 attenuates salicylic acid-triggered immunity in *Arabidopsis* by degrading MED19, shifting the balance of defense transcription to JA/ET signaling (53).

Two *P. sojae* effectors, PsCRN63 and PsCRN115 (for crinkling- and necrosis-inducing proteins), which are suggested to be secreted, were shown to regulate plant programmed cell death and H_2O_2 homeostasis. These effectors act through direct interaction with catalases to overcome host immune responses (54).

The identification of two putative membrane-associated NAC transcription factors (TFs) as the host targets of the effector Pi03192 is one example of oomycete effectors targeting transcriptional responses. The effector interacts with NAC targeted by *Phytophthora* 1 (NTP1) and NTP2 at the endoplasmic reticulum (ER) membrane, where these proteins are localized. The proposed mechanism by which Pi03192 promotes disease progression is the prevention of relocalization of NTP1 and -2 from the ER to the nucleus, which appears to be key for immunity. Few plant pathogen effectors have been shown to influence such relocalization events or to target transcriptional regulators of plant immunity (55).

TABLE 4 Examples of oomycete effectors that suppress host immunity

Effector (oomycete species)	Known host target(s)	Virulence effect(s)	Reference
AVR3a (*P. infestans*)	Stabilization of potato CMPG1	When overexpressed in *N. benthamiana*, suppresses perception of INF1, attenuates flg22- and INF1-triggered ROS accumulation	49
	Interaction with *Nicotiana benthamiana* dynamin-related protein 2 (DRP2)		50
PexRD2 (*P. infestans*)	Interaction with the kinase domain of potato MAPKKKε	Suppressor of cell death triggered by MAPKKKε signaling pathway; when overexpressed, increases susceptibility of *N. benthamiana* to *P. infestans*	51
AVRblb2 (*P. infestans*)	Associates with papain-like cysteine protease C14 from *N. benthamiana* and tomato	Prevents secretion of the plant defense protease C14 in *N. benthamiana* and tomato; when overexpressed, enhances susceptibility of *N. benthamiana* plants to *P. infestans*	52
Pi03192 (*P. infestans*)	Interaction with the potato transcription factors NAC targeted by *Phytophthora* 1 (NTP1) and NTP2	Prevention of relocalization of NTP1 and -2 from the ER to the nucleus, which appears to be key for immunity; silencing of NTP1 or NTP2 in *N. benthamiana* increases its susceptibility to *P. infestans*	55
HaRxL44 (*H. arabidopsidis*)	Degradation of *Arabidopsis* Mediator subunit 19a (MED19a), a mediator in the interaction between transcriptional regulators and RNA polymerase II	Attenuates salicylic acid-triggered immunity in *Arabidopsis*, shifting the balance of defense transcription to JA/ET signaling	53
PsCRN63 (*P. sojae*)	Direct interaction with catalases from *N. benthamiana* (*NbCAT1*) and *Glycine max* (*GmCAT1*)	When overexpressed, cell death and accumulation of H_2O_2 in *N. benthamiana* leaves	54
PsCRN115 (*P. sojae*)	Direct interaction with catalases from *N. benthamiana* (*NbCAT1*) and *Glycine max* (*GmCAT1*)	When coexpressed with PsCRN63, suppression of cell death and H_2O_2 accumulation in *N. benthamiana* leaves; suggested to suppress cell death by inhibiting PsCRN63-induced effects	54
PSR1 (*P. sojae*)	Interaction with *Arabidopsis* PINP1 helicase domain-containing protein; inhibition of the biogenesis of small RNAs	When overexpressed, enhances susceptibility of *N. benthamiana* to potato virus X and *P. infestans*	56
		When overexpressed, enhances susceptibility of *Arabidopsis* to *P. capsici*	57
PSR2 (*P. sojae*)	Unknown target; inhibition of the biogenesis of small RNAs	Suppression of RNA silencing in *N. benthamiana*; when silenced, reduction in virulence of *P. sojae* on soybean plants	56
PsIsc1 (*P. sojae*)	Hydrolyzes isochorismate (the direct precursor of salicylic acid)	Disruption of salicylate metabolism pathway; suppression of salicylate-mediated innate immunity in *N. benthamiana*	62

Two effectors from *P. sojae*, PSR1 and PSR2, suppress RNA silencing by inhibiting the biogenesis of small RNAs (56). Very recently, the host target of PSR1, PSR1-interacting protein 1 (PINP1), was identified and shown to regulate the accumulation of microRNAs and small interfering RNAs in *Arabidopsis* (57). When overexpressed, PSR1 enhanced the susceptibility of *Arabidopsis* to *P. capsici* and also enhanced the susceptibility of *N. benthamiana* to *P. infestans*. A target for PSR2 has yet to be discovered, although PSR2 is known to be required for full virulence of *P. sojae* on soybean plants (56).

Recent research also established that numerous *Phytophthora* and *Hyaloperonospora* effectors can suppress PTI against the bacterial PAMP-derived peptide flg22 at different steps of the downstream signal cascade (58, 59). Other features of effector interference with plant defenses are protease and peroxidase inhibition, targeting of the ubiquitination system, salicylate signaling, and disruption of the attachment of the plant cell wall to the plasma membrane (60–63).

HOW ARE EFFECTORS DEPLOYED IN THE HOST?

By definition, effectors are encoded by the oomycete but act inside the host. Accordingly, the majority of identified oomycete effectors carry an N-terminal signal peptide that mediates secretion from the microbe. A notable exception is the *P. sojae* effector PsIsc1, a putative isochorismatase that does not have a predicted secretory leader peptide but nevertheless can be detected in *P. sojae* secretion supernatants (62).

Once secreted, apoplastic effectors act in the apoplast surrounding plant and microbial cells, while cytoplasmic effectors enter the plant cell and have to cross the plant cell wall and the plant plasma membrane or, alternatively, the extrahaustorial matrix and the extrahaustorial membrane (Fig. 2c). Fusions of the *P. infestans* effector AVR3a with red fluorescent protein (RFP) accumulate only at haustoria (23). These interfaces are presumably a specific site of secretion of AVR3a, or RFP is very stable in the extrahaustorial matrix space surrounding haustoria. Notably, a similar distribution was observed when AVR3a was fused to green

fluorescent protein (GFP) and secreted from *P. capsici* (64). Given this indirect evidence, haustoria have been hypothesized to be a site of translocation for cytoplasmic effectors. However, not all oomycetes form haustoria, and studies have shown internalization of effectors into plant cells even in the absence of the pathogen from which they originated (65), suggesting that specific microbial structures for delivery of effectors may not always be required.

The majority of cytoplasmic oomycete effectors characterized to date contain an RXLR (arginine-any amino acid-leucine-arginine) motif following an N-terminal signal peptide, which is thought to allow translocation into plant cells (23, 66). The RXLR motif can be followed by an EER motif, and furthermore, similar motifs, such as QXLR (67) and RXLQ (61), can replace the RXLR motif, or it can be absent, such as in the case of ATR5 (68). A second class of effectors, CRNs, named for their crinkling- and necrosis-inducing activity (69), are also common in oomycetes and may perform a similar translocation function via conserved LXLFLAK motifs (64). It has been suggested that RXLRs may be an adaptation to facilitate biotrophy, because their expression is induced during preinfection and biotrophic phases of infection (23), whereas certain other species, e.g., *Pythium* spp., may employ predominantly CRNs as a result of their adaptation to necrotrophy (2). However, many biotrophic oomycete species exist which secrete both RXLRs and CRNs, implying that a connection between effector class and lifestyle is not easily defined.

There are two main experimental approaches that have been used in an attempt to conclusively demonstrate the functions of host-targeting domains, such as RXLRs, in effectors. The first, cell reentry assays, involves expression of a full-length effector protein from a pathogen, including its secretion signal peptide, in a plant cell. Once expressed, this effector passes through the plant secretory system and is secreted into the extracellular space (apoplast); its subsequent reentry into the plant cell can then be traced microscopically via fusion to a fluorescent protein (70). Through the generation of mutations in specific domains suspected to function in delivery of effectors into plant cells and by employing cell reentry assays, it has been possible to identify putative domains required for entry (65, 71, 72). However, this assay cannot unequivocally demonstrate that when the effector is expressed, it is assuredly secreted into the apoplast prior to reentry. To address this weakness of cell reentry experiments, a second assay was devised in which purified effector proteins labeled by a fluorescent tag are applied to plant tissues and their entry tracked via microscopy (65, 72, 73). The assay of purified effector protein uptake into roots is currently under debate. Protein internalization by root cells is nonspecific (74), and fluorescent proteins are taken up by the plant at a rate comparable to that of their effector-fused derivatives (75). Thus, this assay cannot be used to properly assess specific effector entry. Conversely, Tyler et al. observed a differential uptake of fluorescent proteins when effector motifs implicated in uptake were fused to them (76). A detailed list of supporting and conflicting experimental data on this topic was recently published (77).

Whisson et al. (23) demonstrated that the N terminus of the *P. infestans* AVR3a effector, i.e., the RXLR domain, is required for translocation into potato cells, implying that this domain functions as a leader sequence that mediates host cell targeting. The RXLR domains of oomycete effectors have been reported to bind extracellular phosphatidylinositol-3-phosphate (PI3P) to mediate effector endocytosis (72). Bhattacharjee et al. (78) produced data in support of strong RXLR-PI3P binding, albeit in the *Plasmodium* endoplasmic reticulum, while investigating the *P. infestans* host translocation motif of the candidate effector NUK10. However, their experiments, alongside studies of plants by Yaeno et al. (79), also led them to conclude that this binding takes place inside the pathogen and is required for stabilization and secretion of the effector. There have also been multiple publications claiming that, in contrast to the idea that an N-terminal RXLR is required for PI3P binding, it may in fact be the C-terminal domain of the effector that is responsible. Wawra et al. (80) reported C-terminally mediated PI3P binding of AVR3a from *P. infestans*, while Sun et al. (81) found similar binding properties within the Avh5 effector of *P. sojae*, although the latter concluded that both regions were involved in effector entry into cells. Notably, Zhang et al. (54) showed that phospholipid binding of the RXLR effector AVR3a can occur even with denatured proteins, but mutants in the C terminus of AVR3a (79), known to impair phospholipid binding, were not assessed in that study. Our idea of a conserved host-targeting domain within effectors continues to be challenged by these conflicting findings on the functional relevance of such a domain.

PLANT INNATE IMMUNITY

Oomycete-plant interactions are characterized by molecular coevolution, with each side battling for control over the other. Plant cell membrane-resident pattern recognition receptors (PRRs) expose their PAMP recognition domains to the apoplast to detect conserved oomycete PAMPs and subsequently trigger PAMP-triggered immunity (PTI). Intracellular disease resistance proteins mediate recognition of effectors entering the host cell and elicit effector-triggered immunity (ETI). Both plant immune responses aim at interfering with pathogen ingress and spread. Researchers score pH alkalinization, callose deposition, and defense gene activation as markers of PTI. ETI responses are often concomitant with a visible controlled cell death, the hypersensitive response (HR). However, some conserved PAMPs can also trigger cell death responses, such as in the case of *P. infestans* INF1 infiltrated as a protein or expressed inside *N. benthamiana* (28).

In order to fully colonize the host, a pathogen must overcome plant immunity. As reported earlier, many effector proteins have been shown to suppress PTI responses (23, 61, 65, 82), namely, three tested variants of the *P. infestans* effector AVR3a suppressed flg22-triggered responses when overexpressed *in planta* (50). One way to avoid effector overexpression and achieve more targeted application is to deliver effectors via a bacterial pathogen, such as *Pseudomonas syringae* (61). A large-scale investigation of candidate oomycete effectors and their effects on PTI utilized the type III secretion system of *P. syringae* to deliver candidate effectors. Since delivering effectors by using *P. syringae* is still not a flawless experimental setup—the effector protein might block secretion of other *P. syringae* type III effectors, thereby reducing *P. syringae* virulence and affecting subsequent symptoms—the authors followed up by generating stable transgenic plants expressing single effectors and showing that they had enhanced susceptibility to *H. arabidopsidis*.

While PTI is thought to be triggered by conserved PAMPs across a range of pathogen species, ETI provides race-specific resistance, because different races of a pathogen secrete different arrays of effectors and therefore may lack, or may possess variants

TABLE 5 Cloned resistance (R) and susceptibility (S) genes affecting oomycete-plant interactions

Species	Cloned R gene(s) [cognate Avr gene(s)] [references(s)]	Cloned S gene(s) [reference(s)]
Albugo candida	*Arabidopsis WRR4* (146)	
Hyaloperonospora arabidopsidis	*Arabidopsis RPP1* (*ATR1*) (147–149), *RPP2* (150), *RPP4* (150), *RPP5* (151), *RPP7* (150), *RPP8* (152), *RPP13* (*ATR13*) (149, 153)	*Arabidopsis AGD5* (104), *IOS1* (106), *PUB22/23/24* (154, 155), *SON1* (112), *EDR2* (113, 114), *SNI1* (115, 156), *Cdd1* (116), *DMR1* (117, 157), *RSP1/2* (118), *PMR4* (158), *DMR6* (188, 189)
Peronospora manshurica	Soybean *Rpm* (159)	*MPK4* (108, 109)
Phytophthora cinnamomi	*Arabidopsis TIR1* (160)	
Phytophthora infestans	Potato *R1* (87, 161), *R2* (*AVR2*) (162–164), *R3a* (*AVR3a*) (165, 166), *R3b* (*AVR3b*) (96, 167), *R4* (*AVR4*) (168, 169), *R6* and *R7* (170), *R10* and *R11* (171), *RB/Rpi-Blb1* (*AVR-Blb1/IPI-O1*) (119, 172, 173), *Rpi-Blb2* (174), *Ph-3* (175), *Rpi-vnt1* (176), *Rpi-blb3* (162), *Rpi-abpt* (162)	*StREM1.3* and *N. benthamiana REM1.3* orthologs (177)
Phytophthora palmivora		*Medicago RAM2* (100), *LATD* (133)
Phytophthora sojae	Soybean *Rps1d* (*AVR1d*) (178), *Rps1b* (*AVR1b*) (179)	
Plasmopara viticola	Grape *Rpv1* and *Rpv2* (180), *Rpv3* (*avrRpv3*) (181, 182), *Rpv10* (183)	

of, the effectors necessary to trigger ETI. Again, oomycetes have developed effectors to suppress this alternative recognition principle. Examples include *P. infestans* SNE1 and the *P. sojae* effectors CRN70 and Avr1k, which have all been shown to suppress R3a/AVR3a-triggered HR in *N. benthamiana* leaves (83, 84), although transient coexpression assays are not always fully conclusive, because the effector in question may, to some extent, suppress overall gene expression, including expression of the HR reporter constructs.

R GENE-MEDIATED RESISTANCE

According to the gene-for-gene model (85), a plant will be resistant to a pathogen when it possesses a dominant R gene that is complementary to the pathogen's avirulence (Avr) gene; this is referred to as an incompatible interaction. In a compatible interaction, there is no corresponding R gene for an Avr gene (or vice versa), resulting in disease. In the years shortly after the introduction of the gene-for-gene hypothesis, Black et al. generated 11 potato R gene differentials (86) via introgression and named them MaR1 to MaR11. The R1, R3a, and R10 genes have been used extensively and successfully in European breeding programs, and R1 and R3a have been cloned for investigations of their functions (87). The cytoplasmic RXLR effector *AVR3a* of *Phytophthora infestans* confers avirulence on potato plants carrying the *R3a* gene (25). Many other cloned R genes providing resistance to important oomycetes are listed in Table 5 (along with their cognate Avr genes, if known).

The existence of PTI and ETI responses due to perception means that in order to retain the ability to infect a host species, pathogens constantly vary their repertoire of effector molecules to avoid Avr activity. As a result, R gene-based resistance, which relies on the presence of singular effectors which are not essential to the pathogen's success, can easily be overcome by rapid sequence diversification or loss. This has caused problems in agricultural contexts where R genes were employed to provide resistance to crop pathogens because the resistance has only been durable if the required Avr gene is essential to the pathogen's success. However, there have been various attempts to improve the chances of durability, namely, stacking multiple R genes within one variety (88) and/or using variety mixtures (89) or multilines (90), as well as engineered R genes with extended recognition spectra (91, 92). The use of variety mixtures involves sowing several varieties containing different R genes and different parental backgrounds together in the same field. Multilines contain lines of the same variety, but with different combinations of R genes, thereby creating a mosaic and preventing takeover of the field by a single pathogen isolate.

Identifying effectors which are required to maintain full pathogen virulence can aid in the search for cognate disease resistance genes in wild varieties of host crop plant species (93). Several oomycete effectors have been shown to contribute to pathogen virulence. Variations in the copy numbers of *P. sojae AvrI* and *Avr3a* (94), as well as knockdown of transcript levels of *Avr3a* (49), *PsAvh172*, *PsAvh238* (95), *PsAvr3b* (96), *PsCRN63*, and *PsCRN115* (97), have negative impacts on virulence.

S GENE-MEDIATED RESISTANCE

All plant genes that facilitate infection and support compatibility can be considered susceptibility (S) genes. Mutation or loss of an S gene thus reduces the ability of the pathogen to cause disease. This can result in pathogen-specific resistance if the gene is involved in production of a component required for host penetration or in broad-spectrum resistance if the gene suppresses constitutive defenses. The concept of susceptibility genes was first explored in 2002 (98), after the identification of *PMR6* (*powdery mildew resistance 6*) in *Arabidopsis* (99). S genes that have been identified as susceptibility factors for colonization by important oomycetes are included in Table 5. S genes can be classified into the following three groups based on the point at which they act during infection: those involved in early pathogen establishment, those involved in modulation of host defenses, and those involved in pathogen sustenance.

Early Pathogen Establishment

The *Medicago truncatula ram2* mutant has an altered composition of cutin, a key component of the plant cuticle, due to a mutation in a gene encoding a cutin biosynthesis enzyme, namely, glycerol-3-phosphate acyl transferase. *ram2* mutants display reduced susceptibility to *Phytophthora palmivora*, with a significant disruption of appressorium formation (100). This example, together with other examples of plant-fungus interactions, implies that the leaf cuticle provides essential developmental cues for pathogenicity (101–103). Proteins involved in controlling cytoskeleton dynamics and vesicle trafficking, such as GTPase-activating proteins (GAPs), also appear to be key susceptibility factors. For example, an ARF-GAP protein, AGD5, of *A. thaliana* was recently found to be a susceptibility factor for *H. arabidopsidis* infection (104). It may be that rearrangements of the cytoskeleton mediated by AGD5 ensure susceptibility to the adapted pathogen *H. arabidopsidis*.

Modulation of Host Defenses

Although callose deposition is primarily an induced defense response that occurs at sites where the pathogen attempts to penetrate, providing a physical barrier to entry, it has also been implicated in suppression of PTI. Overexpression of *PMR4* leads to increased callose deposition and is associated with complete resistance of *A. thaliana* to the nonadapted fungal pathogen *Blumeria graminis* (105). Surprisingly, a mutation causing loss of function of *PMR4* also provides resistance to *B. graminis*, as well as to the oomycete *H. arabidopsidis*, but via a different mechanism. The mechanism by which *PMR4* acts as a susceptibility gene seems to lie in suppression of salicylic acid signaling, which causes a moderate increase in defense gene expression (105).

A. thaliana plants are less susceptible to *H. arabidopsidis* in the absence of the gene *IOS1* (*impaired oomycete susceptibility*), encoding a malectin-like, leucine-rich repeat receptor-like kinase (106). In support of this finding, it appears that transcription of *IOS1* promotes susceptibility and is localized to the area surrounding penetration by *H. arabidopsidis*, suggesting that it may be either a residual PAMP-triggered response or a component of a defense mechanism that has been interfered with by the oomycete to benefit infection. In *ios1* mutants, PTI-responsive genes showed delayed induction upon infection with *H. arabidopsidis*, but their expression levels were increased, implying that *IOS1* negatively regulates the activation of PTI responses, possibly through involvement in FLS2/BAK1 protein complex formation (107).

The *mitogen-activated protein kinase 4* (*MPK4*) gene acts downstream of immune receptors to regulate the transduction of extracellular stimuli into adaptive, intracellular responses and has been found to act as a negative regulator of these defense responses (108). Silencing of *Glycine max* (soybean) *MPK4* (*GmMPK4*) leads to enhanced resistance to the downy mildew *Peronospora manshurica* (109). Suggestions have been made that *GmMPK4* silencing causes increased lignin biosynthesis, which may indirectly provide a physical barrier at the epidermal cells, such that the oomycete cannot penetrate into the mesophyll. Further evidence for the role of *MPK4* as a susceptibility gene lies in a complex of BAK1/BRI1 (BRI1-associated receptor kinase 1/brassinosteroid insensitive 1), which is required for the activation of MPK4 (110). BRI1 was found to associate with BAK1 *in vivo*, and both components appear to work cooperatively to negatively regulate cell death and defense responses to *H. parasitica*. The majority of susceptibility genes were identified through studies of interactions between plants and *H. arabidopsidis* or *H. parasitica*. Many of these S genes function in a defense suppression (mutant plants exhibiting constitutive defense responses) that leads to dwarf phenotypes or developmental defects. However, there are some S genes for which mutant plants exhibit no significant dwarf phenotype and show no developmental defects. These include a number of genes encoding negative regulators of defense responses, such as PTI, salicylic acid signaling, and/or systemic acquired resistance (SAR); examples include the genes for plant U-box E3 ubiquitin ligases (PUB22/23/24) and suppressor of *nim1-1* (SON1), which are involved in ubiquitination and protein degradation (111, 112). Other negative regulators of defense include enhanced disease resistance 2 (EDR2), suppressor of *npr1-1* inducible 1 (SNI1), and constitutive defense without defect in growth and development 1 (Cdd1) (113–116).

Pathogen Sustenance

A. thaliana mutants have also been identified which display a loss of susceptibility to *H. arabidopsidis* due to perturbations in enzymes that function in amino acid metabolism. For example, the *dmr1* strain carries a mutation in a gene encoding homoserine kinase, an enzyme catalyst of the synthesis pathway for Met, Thr, and Ile (117). When the activity of homoserine kinase is fully knocked out, the effect is lethal, but knockdown provides resistance to *H. arabidopsidis*. Other mutants, the *rsp1* and *rsp2* mutants, have a disrupted aspartate kinase function, which is also important for Met, Thr, and Ile synthesis, but also for Lys synthesis. In an attempt to elucidate the mechanism of reduced susceptibility in these mutants, Thr and homoserine were applied exogenously, which resulted in reduced *H. arabidopsidis* conidiophore formation (118). This supports the hypothesis that metabolites downstream of or induced by Thr and homoserine are toxic to the oomycete. The availability of each of these amino acids has also been implicated in the induction of resistance (117, 118).

FUTURE DIRECTIONS FOR DEVELOPMENT OF OOMYCETE-RESISTANT PLANTS

Strategies to tackle economic losses caused by oomycete pathogens are numerous and diverse in their approaches, but the following three main areas can be seen as having the greatest potential for success in the near future: tactical deployment of natural or engineered R genes, S gene knockouts/mutations, and transgenic hairpin RNA silencing of essential pathogen transcripts.

Applying the R gene hypothesis to breeding for resistance leads to only short-lived success, as the resistance is overcome quickly by the pathogen as it varies its effector repertoire. Identifying and accurately screening for new R genes by using molecular markers is laborious, expensive, and sometimes problematic due to epistatic interactions between resistance genes. An alternative to marker-assisted screens for identification of novel R proteins are effector-based, high-throughput, *in planta* expression assays (119). Combined with plant disease epidemiology studies and comparative genomics, these expression assays could aid in the prioritization of effectors present in emerging virulent strains as well as those abundant in numerous other isolates (120).

Only in the last few years have researchers begun to adopt structural biology to fully investigate functional relationships between interacting pathogen and plant proteins (121). Knowledge of how immune receptors function on a molecular level has already begun to

fuel development of engineered receptors that detect a broader range of oomycete effectors (91, 92). The function of an R gene and its specificity for a given effector can also be validated via transient coexpression with effectors in plants that do not carry the candidate resistance gene. Once identified, these R genes must be applied carefully in the field so as to extend the durability of the resistance they provide, though techniques such as R gene stacking, use of variety mixtures, or use of multilines. However, these techniques have their limitations when it comes to implementation in a large-scale agricultural context. Once stably engineered R proteins with extended recognition spectra (91, 92) have been shown to perform well in the field, they may provide alternative solutions.

A second approach aims at removing key plant genes required for infection. These S gene mutation-based resistance mechanisms should provide much greater durability than the use of R genes because they involve a component that is essential for pathogen survival. Many of the S genes identified in plant-oomycete interactions to date have been found through studies of downy mildews infecting the model species *A. thaliana*. There are, however, S genes that show promise as a means to provide resistance to more economically significant oomycetes, for example, *ram2*-mediated resistance to *Phytophthora palmivora* and *Aphanomyces euteiches* (100, 122).

Unfortunately, the large majority of S genes are involved in essential plant processes, which constitutes a significant downside to their use in a disease resistance context. Knockouts of some S genes, namely, *DMR1*, are expected to result in lethal phenotypes (117). Mutation of *RAM2* in *M. truncatula* results in altered water permeability of the seed coat, which might affect its shelf life (100). Therefore, for such S genes to be useful agriculturally, different alleles must be identified that encode proteins with reduced but not fully abolished activity. To achieve this, "artificial evolution," i.e., targeted mutagenesis, or assessments of natural variation using haplotype-specific markers (123) could be applied.

Alongside the discovery of novel susceptibility gene alleles, it is important to combine this research with a greater understanding of oomycete pathogenicity mechanisms. A number of oomycete genomes have been sequenced to date (Table 1), including those of *H. arabidopsidis*, *P. ultimum*, *P. infestans*, *Phytophthora ramorum*, *P. sojae*, and *P. capsici* (2, 124–126). The four *Phytophthora* species here are all hemibiotrophs and therefore can be cultured *in vitro*, making them more amenable to transformation and gene disruption. As a result, in future, these species will serve as tools to discover more about how oomycetes interact with their hosts and, ultimately, which genes encode effectors, resistance proteins, or susceptibility proteins.

A third strategy, termed host-induced gene silencing, is based on transgenic plants which produce hairpin RNA constructs targeting pathogen transcripts essential for virulence. This principle has been demonstrated to work in fungi, and accumulating evidence suggests its transferability to *Phytophthora* and *Bremia* spp. (127–129).

POTENTIAL FOR COMPARATIVE PATHOGEN-MUTUALIST STUDIES

Our growing knowledge of oomycete interactions with plants opens up exciting possibilities for investigating the commonalities and differences between pathogenic and mutualistic lifestyles. For example, the important model legume species *Medicago truncatula* can be colonized by both arbuscular mycorrhizal fungi, such as *Rhizophagus irregularis*, and the oomycete pathogens *Aphanomyces euteiches* and *P. palmivora* (130). The advantage of a common host species for these distinct groups of filamentous microorganisms is the ability to genetically dissect common and contrasting elements required for their colonization processes. Oomycete pathogens and mutualists share similarities with respect to intracellular structures in plants, i.e., they both feature host cell plasma membrane invaginations (haustoria and arbuscules, respectively) (Fig. 2), driven by the invading microbes, which penetrate the cell wall and then become surrounded by a specialized membrane (termed the extrahaustorial membrane and the periarbuscular membrane, respectively) (131). Whether arbuscules are translocation sites of the recently identified SP7 effector (132) or other effectors of arbuscular mycorrhiza fungi remains to be clarified. In a recent publication by Rey et al. (133), genetic elements of the common symbiosis signaling pathway required for arbuscule formation in *M. truncatula* were found to have no functional overlap with the formation of *P. palmivora* haustoria, indicating that different mechanisms are operating during their formation. Common elements found in both mutualistic and pathogenic membrane formation interfaces are v-SNAREs of the VAMP72 family that are involved in exocytotic vesicle trafficking (134). Furthermore, marker localization studies of oomycete haustoria suggest that rerouting of vacuole-targeted late endosomal compartments, labeled by the small Rab7-type GTPase RabG3c, seems to contribute to extrahaustorial membrane formation (135). Notably, the corresponding *Medicago* Rab7a2 protein can be found in the cytoplasm of arbuscule-containing root cells (136). It is thus important to study the distribution of this and other markers in a more comparative way, using the same plant tissue for haustoria and arbuscules.

CONCLUSIONS

Considering the continued negative impact of oomycetes on agriculture, understanding their biology is imperative to reveal new strategies for their control. It is exciting to see that oomycete research is in full bloom and that the numbers of genetic, genomic, and cell biology resources are continuously growing. Comparative studies with unrelated microbes that share colonization strategies should enable us to extend our range of applicable resistance principles while maintaining the agronomic benefits of mutualist fungi.

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Stuart Fawke obtained a degree in natural sciences (2012) from the University of Birmingham and an M.Sc. (2013) in plant genetics from the University of East Anglia, Norwich, with a research project at The John Innes Centre. He is currently a Ph.D. student at the University of Cambridge, where he studies the role of cutin biosynthesis enzymes in plant-microbe interactions and development.

Mehdi Doumane obtained a B.Sc. in biology (2013) from the École Normale Supérieure (ENS) de Lyon, France. He is currently an M.Sc. student at the École Normale Supérieure (ENS) de Lyon. In 2014, he undertook a 4-month internship at the University of Cambridge, Sainsbury Laboratory, in the group of Sebastian Schornack, where he studied *Phytophthora*-plant interactions.

Sebastian Schornack obtained a diploma in genetics (2000) and a Ph.D. in plant genetics (2006) from Martin Luther University Halle-Wittenberg, Germany, working on *Xanthomonas* TAL effectors and disease resistance genes, and he continued there for postdoctoral research with Thomas Lahaye, discovering the TAL effector code in 2007. He then moved to the United Kingdom for a postdoctoral post with Sophien Kamoun at The Sainsbury Laboratory, Norwich (2008–2012), where he worked on *Phytophthora infestans* effectors. In 2013, he moved to the University of Cambridge, where he is currently a Gatsby Group Leader and Royal Society UR Fellow in the Sainsbury Laboratory (SLCU). His main interests are common and contrasting principles of plant colonization by pathogenic and beneficial filamentous microbes.