Oomycete Interactions with Plants: Infection Strategies and Resistance Principles

Stuart Fawke[1], Mehdi Doumane[1*], Sebastian Schornack[1#]

[1]Sainsbury Laboratory (SLCU), University of Cambridge, United Kingdom

[*]Current address: Department of Biology, École Normale Supérieure de Lyon, Lyon, France

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

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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.

Abstract

The Oomycota include many economically significant microbial pathogens of crop species. Understanding the mechanisms by which oomycetes infect and identifying methods to provide durable resistance is a major research goal. 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 developing oomycete-resistant plants will be discussed, alongside how recent discoveries in the oomycete-plant interactions field are generating novel ways of studying how pathogen and symbiont colonisations overlap.

Introduction

The Oomycota are a distinct class of fungal-like eukaryotic microbes, many of which are highly destructive plant or animal pathogens. They share a range of morphological features with fungi, but possess various unique characteristics which set them apart (1). Cellulose is a major component of oomycete cell walls. By contrast, chitin, but 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, possessing tubular cristae as opposed to the flattened cristae of fungi (5) or their hyphae which are always non-septate (6).

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

Phylogeny

Analysis of conserved DNA sequences such as mitochondrial *COX2* (10-12), LSU rDNA (13) and 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). Availability of several sequenced genomes for some genera (see Table 1), in particular *Phytophthora*, has greatly facilitated multilocus assessment of oomycete taxonomic relationships (17). The Oomycota are broadly divided into two subclasses. The Saprolegniomycetidae, referred to as the 'water moulds', include the orders Eurychasmales, Leptomitales and Saprolegniales, whilst 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 colonisation 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 either occur 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 visualised in Figure 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). 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, H. parasitica,* and *Plasmopara viticola* as well as *A. candida* that causes white rust. Hemibiotrophs commonly have the ability to survive in axenic culture (facultative) such as *Phytophthora spp*, as do necrotrophs like *Pythium ultimum*. A summary of the lifestyles of important plant-colonising oomycetes is provided in Table 2.

Obligate biotrophs such as *H. parasitica* must maintain a close interaction with their hosts whilst 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 a biotroph 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) (Figure 1; Figure 2). Haustoria can be observed during colonisation by most obligate biotrophs (24) and have been implied in nutrient uptake in fungi where haustorium-specific sugar transporters have been described (25), although in oomycetes little is known about haustorium-specific transport processes. However, a

number of hemibiotrophs and necrotrophs do not form haustoria, for example *Aphanomyces euteiches* and *Pythium ultimum*.

Plants recognise oomycete-derived molecules

Elicitors are molecules which stimulate a defence response in a host plant (Table 3). Most of them constitute PAMPs (pathogen associated molecular patterns) (26) because they are structurally conserved and thought to be indispensable components or products of a pathogen's lifecycle 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 thirteen amino acid peptide of a surface exposed stretch of a transglutaminase protein (29-31). Mutation in just one of these amino acids is sufficient to impair transglutaminase-mediated recognition of *P. sojae* and to avoid induction of plant-defence responses (29). Although Pep-13 was identified over 10 years ago, its plant receptor(s) have yet to be discovered.

Some parasitic oomycetes, including *Phytophthora* species, have lost the ability to synthesise 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 capacity including Cryptogein from *Phytophthora cryptogea*, CAP1 from *Phytophthora capsici* and PAL1 from *Phytophthora palmivora,* amongst others. INF1 binds *in vitro* dehydroergosterol and catalyses 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, initially localising to the extracellular space (36), and it has been shown by *in vitro* immunocytochemistry that the INF1-like Quercinin 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 localised to the plasma membrane (37). However, requirement of BAK1/SERK3 for INF1-triggered immune responses rather points to a 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 ParA1 (38) suggested that INF1 perception is mediated through a receptor-like protein (RLP) rather than

a receptor like-kinase (RLK), since SOBIR1 was previously reported to be a co-receptor of RLPs (39). Then, the discovery of ELR, a wild potato RLP that associates with BAK1/SERK3, mediating broad-spectrum recognition and induction of cell death, triggered by four *P. infestans* elicitins (INF1, INF2A, INF5 and INF6) as well as eleven elicitins of diverse other *Phytophthora* species, added a new chapter in 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 PTI response marker genes as well as salicylic acid-responsive defence genes (41); all characteristics of a plant defence response. OPEL is therefore considered a microbial signature that is recognised in tobacco leaves. Infiltration of OPEL also stimulates resistance to viruses, bacteria and the oomycete pathogen *P. parasitica*. OPEL contains 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 enhanced plant immune reponse and resistance to *P. parasitica.* Chang et al. (41) conclude 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, the authors were unable to show any enzymatic activity from the wildtype OPEL protein 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, co-evolution of plant and oomycete may have led to 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 signalling following CBEL perception in tobacco cells, but not in cell wall-lacking protoplasts, suggesting that plant cell wall binding is required for CBEL-induced defence reactions (44). Alternatively, CBEL detection might require other cell wall-dependent processes such as polar exo- or endocytosis which cannot properly take place in non-polar protoplasts (45).

β-glucans represent PAMPs originating from cell wall fractions of filamentous pathogens (fungi and oomycetes). Soybean perceives branched heptaglucans with β(1-6) backbone linkages from *Phytophthora sojae*, and, in particular, its three non-reducing terminal glycosyl residues (46). Conversely, this glucan does not elicit defence responses in tobacco cells, but a linear β(1-3) glucan does (47). Branched glucan-chitosaccharides from cell wall fractions of *Aphanomyces euteiches* induce defence 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 mycorrhiza 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 colonisation. 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 localisation and stability of effectors and their target proteins, as well as overall transcriptional changes and virulence effects, all of which are summarised in Table 4.

The *P. infestans* effector AVR3a suppresses perception of the PAMP, INF1, through stabilisation 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 signalling pathways triggered by, or dependent on, MAPKKKε, increasing the susceptibility of *N. benthamiana* to *P. infestans* (51).

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

The nuclear-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 responsible for transcriptional changes resembling jasmonic acid/ethylene (JA/ET) signalling when in the presence of HaRxL44. It was concluded that HaRxL44 attenuates salicylic acid–triggered immunity in Arabidopsis by degrading MED19, shifting the balance of defence transcription to JA/ET-signalling. (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. The effectors act through direct interaction with catalases to overcome host immune responses (54).

The identification of two putative membrane-associated NAC transcription factors (TF) 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* (NTP) 1 and NTP2 at the endoplasmic reticulum (ER) membrane, where these proteins are localised. The proposed mechanism by which Pi03192 promotes disease progression is the prevention of relocalisation of NTP1 and 2 from the ER to the nucleus, that appears to be key for immunity. Few plant pathogen effectors have been shown to influence such re-localisation events or target transcriptional regulators of plant immunity (55).

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 accumulation of microRNAs and small interfering RNAs in *Arabidopsis* (57). When overexpressed, PSR1 enhanced susceptibility of *Arabidopsis* to *P. capsici* and also enhanced 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 (56).

Recent research has 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 defences are protease and peroxidase inhibition, targeting of the ubiquitination system, salicylate signalling or the disruption of plant cell wall to plasma membrane attachment (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 would 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 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 has been observed when AVR3a was fused to GFP and secreted from *P. capsici* (64). Given this indirect evidence, haustoria have been hypothesised to be a site of translocation for cytoplasmic effectors. However, not all oomycetes form haustoria and studies have shown internalisation 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 characterised 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 known as 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 pre-infection and biotrophic phases of infection (23), whereas certain other species may employ CRNs predominantly as a result of their adaptation to necrotrophy, e.g. *Pythium spp* (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 function of host-targeting domains, such as RXLRs, in effectors. The first, cell re-entry 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 passages through the plant secretory system and is secreted into the extracellular space (apoplast); its subsequent re-entry 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 employing cell re-entry 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 re-entry. To address this weakness of cell re-entry experiments, a second assay was devised in which purified effector proteins, labelled by a fluorescent tag, are applied to plant tissues and their entry tracked via microscopy (65, 72, 73). The purified effector protein uptake assay into roots is currently under debate. Protein internalisation by root cells is non-specific (74) and fluorescent proteins are taken up by the plant at a comparable rate to their effector-fused derivatives (75). Thus, this assay cannot be used to properly assess specific effector entry. Conversely, Tyler et al (2013) observed differential uptake of fluorescent proteins when effector motifs implied in uptake were fused to them (76). A detailed list of supporting and conflicting experimental data on this topic has recently been 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) with Bhattacharjee et al (78) producing data in support of strong RXLR-PI3P binding, albeit in the *Plasmodium* endoplasmic reticulum, when investigating the *P. infestans* host translocation motif of the candidate effector NUK10. However, their experiments, alongside others by Yaeno et. al. in plants (79) also led them to conclude that this binding takes place inside the pathogen and is required for stabilisation and secretion of the effector. There have also been multiple publications claiming that, contrary 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-terminal mediated PI3P binding of AVR3a from *P. infestans*, whilst 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, Wawra 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, have not been assessed in this study. Our idea of a conserved host-

targeting domain within effectors continues to be challenged by these conflicting findings as to their functional relevance.

Plant innate immunity

Oomycete-plant interactions are characterised 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 for pH alkalinisation, callose deposition and defence gene activation as markers for 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 when infiltrated as protein or when expressed inside *N. benthamiana* (28).

In order to fully colonise 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 suppress 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). This large scale investigation of candidate oomycete effectors and their effects on PTI utilised the type III secretion system of *P. syringae* to deliver candidate effectors. Since delivering effectors 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 enhance 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 possess variants 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 these transient co-expression 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, Mastenbroek and others generated eleven potato R gene differentials (86) via introgression and named them MaR1 to MaR11. The R1, R3a and R10 genes have been extensively and successfully used in European breeding programmes and R1 and R3a cloned to investigate 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, in brackets).

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, relying on presence of singular effectors which are not essential to the pathogen's success, can be easily overcome by rapid sequence diversification or loss. This has caused problems in an agricultural context 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 take-over of the field by a single pathogen isolate.

Identifying effectors which are required to maintain full pathogen virulence can aid 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. Variation in copy number of *P. sojae Avr1* and *Avr3a* (94) as well as knock-down of

transcript levels of *Avr3a* (49), PsAvh172, PsAvh238 (95), PsAvr3b (96), PsCRN63 and PsCRN115 (97) negatively impact 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 broad-spectrum resistance if the gene suppresses constitutive defences. 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 colonisation by important oomycetes are included in Table 5. S genes can be classified into three groups based on the point at which they act during infection; early pathogen establishment, modulation of host defences and pathogen sustenance.

Early pathogen establishment: The *Medicago truncatula* mutant *ram2* has altered cutin composition, a key component of the plant cuticle, due to a mutation in a gene encoding a cutin biosynthesis enzyme, glycerol-3-phosphate acyl transferase. *ram2* mutants display reduced susceptibility to *Phytophthora palmivora* with significant disruption of appressoria formation (100). This example, together with others in 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 (GAP), also appear to be key susceptibility factors. For example, an ARF-GAP protein, AGD5, of *A. thaliana* has recently been 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 defences: Although callose deposition is primarily an induced defence 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 in *A. thaliana* to the non-adapted fungal pathogen *Blumeria graminis* (105). Surprisingly, a mutation causing loss-of-function of *PMR4* also provides resistance to *B. graminis*, as well as 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 signalling which causes a moderate increase in defence 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 localised to the area surrounding penetration by *H. arabidopsidis*, suggesting that it may either be a residual PAMP-triggered response, or a component of a defence mechanism that has been interfered with by the oomycete to benefit infection. In *ios1* mutants PTI-responsive genes were delayed in their 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 defence responses (108). Silencing of *MPK4* in *Glycine max* (soybean) 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 defence responses to *H. parasitica.* The majority of susceptibility genes were identified through study of interactions between plants and *H. arabidopsidis, and H. parasitica*. Many of these S genes function in defence suppression (mutant plants exhibiting constitutive defence 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 defence responses such as PTI, salicylic acid signalling and/or SAR (systemic acquired resistance), for example, '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 defence include 'enhanced disease resistance 2' (EDR2), 'suppressor of npr1-1 inducible 1' (SNI1) and 'constitutive defence without defect in growth and development 1*'* (Cdd1) (113-116).

Pathogen sustenance: A. thaliana mutants have also been identified which display loss of susceptibility to *H. arabidopsidis* due to perturbations in enzymes that function in amino acid metabolism. For example, *dmr1* carries a mutation in a gene encoding homoserine kinase,

494 an enzyme catalyst of the synthesis pathway for Met, Thr and Ile (117). When the activity of
495 homoserine kinase is fully knocked out, the effect is lethal, but knockdown provides
496 resistance to *H. arabidopsidis*. Other mutants, *rsp1* and *rsp2*, have disrupted aspartate
497 kinase function which is again important for Met, Thr and Ile synthesis, but also for Lys. In an
498 attempt to elucidate the mechanism of reduced susceptibility in these mutants, Thr and
499 homoserine were applied exogenously, which resulted in reduced *H. arabidopsidis*
500 conidiphore formation (118). This supports the hypothesis that metabolites downstream of,
501 or induced by, Thr and homoserine are toxic to the oomycete. The availability of each of
502 these amino acids has also been implicated in the induction of resistance (117, 118).

503

504 **Future directions for developing oomycete-resistant plants**

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

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

519

520 Only in the last few years have researchers begun to adopt structural biology to fully
521 investigate functional relationships between interacting pathogen and plant proteins (121).
522 Knowledge of how immune receptors function on a molecular level has already begun to fuel
523 development of engineered receptors that detect a broader range of oomycete effectors (91,
524 92). The function of an R gene and its specificity for a given effector can also be validated
525 via transient co-expression with effectors in plants that do not carry the candidate resistance
526 gene. Once identified these R genes must be carefully applied in the field so as to extend
527 the durability of the resistance they provide though techniques such as R gene stacking,
528 variety mixtures or 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 the infection. These S gene mutation-based resistance mechanisms should provide much greater durability than R genes because they involve a component that is essential for pathogen survival. Many of the S genes identified to date in plant-oomycete interactions have been found through study of model species *A. thaliana*-infecting downy mildews. 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* spp. (100, 122).

The large majority of S genes are unfortunately 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). For such S genes to be useful agriculturally therefore, 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 assessment of natural variation using haplotype-specific markers (123) could be applied.

Alongside discovering 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 *H. arabidopsidis, P. ultimum, P. infestans, P. 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 these species will, in the future, 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* (127-129)

Potential for comparative pathogen-mutualist studies

Our growing knowledge of oomycete interactions with plants opens up exciting possibilities to investigate the commonalities and differences between pathogenic and mutualistic lifestyles. For example, the important model legume species *Medicago truncatula* is able to be colonised by both arbuscular mycorrhizal fungi, such as *Rhizophagus irregularis*, as well as 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 colonisation 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, Figure 2), driven by the invading microbes, which penetrate the cell wall and then become surrounded by a specialised membrane (termed extra haustorial membrane and periarbuscular membrane, respectively, (131)). Whether arbuscules are translocation sites of the recently identified SP7 (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 signalling 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 interface membrane formation are v-SNAREs of the VAMP72 family involved in exocytotic vesicle trafficking (134). Furthermore, marker localisation studies at oomycete haustoria suggest that rerouting of vacuolar-targeted late endosomal compartments, labelled by the small Rab7 type GTPase RabG3c, seems to contribute to extrahaustorial membrane formation (135). Notably, the corresponding Medicago Rab7a2 can be found in the cytoplasm of arbuscule containing root cells (136). It thus would be important to study distribution of this and other markers in a more comparative way using the same plant tissue for haustoria and arbuscules.

Summary

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 colonisation strategies should enable us to extend our range of applicable resistance principles whilst maintaining the agronomic benefits of mutualist fungi.

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606 **Table 1. Plant pathogenic oomycete genome sequence resources**

Species	Genome size [Mb]	References
Order 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)
Phytophtora 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 Dev Initiative, Broad Institute (broadinstitute.org)
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)
Order Pythiales		
Pythium ultimum	42.8	(2)

Pythium aphanidermatum	35.9	(2, 141)
Pythium arrhenomanes	44.7	
Pythium irregulare	42.9	
Pythium iwayamai	43.3	
Pythium ultimum var. sporangiiferum	37.7	
Pythium vexans	33.9	
Order Saprolegniales		
Aphanomyces euteiches	-	Sequencing project in progress (Genoscope, 2009); http://www.polebio.lrsv.ups-tlse.fr/aphano/

607

608 **Table 2. Lifestyle, host range and infection structures of important plant-infecting**
609 **oomycete species.** Lifestyle abbreviations: B – obligate biotroph; HB – hemibiotroph; N –
610 necrotroph.

Species	Lifestyle	Hosts (organ)	Infection structures
Albugo candida	B	*Arabidopsis thaliana* and other Brassicacea (leaves)	Enter through stomata then form appressoria, 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: inc. most annual and herbaceous perennial species (roots)	Appressoria, haustoria
Phytophthora capsici	HB	*Capsicum annuum,* members of 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 : inc. palm and fruit tree species**,** *Medicago truncatula, Nicotiana benthamiana* (roots, trunks,	Appressoria, haustoria

		buds, leaves)	
Phytophthora parasitica	HB	Very broad range: inc. *Solanum lycopersicum, Solanum tuberosum, Capsicum annuum* (roots and leaves)	Appressoria, haustoria
Phytophthora ramorum	HB	Very broad range: inc. *Quercus agrifolia, Notholithocarpus densiflorus* (phloem and inner bark)	Appressoria-like structures. (Haustoria not yet observed)
Phytophthora sojae	HB	*Glycine max, Glycine soja, Lupinus spp* (roots)	Appressoria, haustoria
Pythium ultimum	N	Very broad range: inc. *Zea mays, Glycine max, Solanum tuberosum* and *Triticum spp* (roots)	Appressoria only

611

612 **Table 3. Examples of known oomycete elicitors**

Name	Type	Plant receptor	References
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 acids	Unknown	(143)
Beta-glucans	Carbohydrate	Glucan-dependent CEBiP CERK1	(46, 48, 144, 145)

613

614 **Table 4. Examples of oomycete effectors that suppress host immunity**

Effector (Oomycete species)	Known host target(s)	Virulence effects	References
AVR3a (*P. infestans*)	Stabilisation 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 signalling 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 defence protease C14 in *N. benthamiana* and tomato. When overexpressed, enhanced susceptibility of *N. benthamiana* plants to *P. infestans*	(52)
Pi03192 (*P. infestans*)	Interaction with the potato transcription factors NAC Targeted by *Phytophthora* (NTP) 1 and NTP2	Prevention of relocalisation of NTP1 and 2 from the ER to the nucleus, that appears to be key for immunity. Silencing of NTP1 or NTP2 in *N. benthamiana* increases 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 defence transcription to JA/ET-signalling	(53)
PsCRN63 (*P. sojae*)	Direct interaction with catalases from *N. benthamiana* (*NbCAT1*) and *Glycine max* (*GmCAT1*)	When overexpressed, cell death and accumulation of H2O2 in N. benthamiana leaves	(54)
PsCRN115 (*P. sojae*)		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	
PSR1 (*P. sojae*)	Interaction with Arabidopsis PINP1 helicase domain containing protein. Inhibition of the biogenesis of small RNAs	When overexpressed, enhanced susceptibility of *N. benthamiana* to Potato Virus X and *P. infestans*	(56)
		When overexpressed, enhanced susceptibility of *Arabidopsis* to *P. capsici*	(57)
PSR2 (*P. sojae*)	Target unknown. Inhibition of the biogenesis of small RNAs	Suppression of RNA silencing in *N. benthamiana*. When silenced, reduction in virulence of *P. sojae* on soybean	(56)
PsIsc1 (*P. sojae*)	Hydrolyses isochorismate (the direct precursor of salicylic acid)	Disruption of salicylate metabolism pathway. Suppression of salicylate-mediated innate immunity in *N. benthamiana*.	(62)

Table 5. Cloned resistance (R) and susceptibility (S) genes affecting oomycete plant interactions

Species	Cloned R genes (cognate Avr genes)	Cloned S genes
Albugo candida	*Arabidopsis WRR4 (146)*	
Hyaloperonospora arabidopsidis	*Arabidopsis RPP1 (147) (ATR1) (148, 149), RPP2 (150) , RPP4 (150), RPP5 (151), RPP7 (150), RPP8 (152), RPP13 (153) (ATR13) (149),*	*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* (162, 163) *(AVR2)* (163, 164), *R3a (165) (Avr3a) (166), R3b (167) (Avr3b) (96), R4 and (AVR4) (168)* (169), *R6 and R7 (170), R10 and R11 (171), RB/Rpi-Blb1 (172, 173) (Avr-Blb1/IPI-O1) (119), 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 and (Avr1d) (178), Rps1b and (AVR1b) (179)*	
Plasmopara viticola	Grape *Rpv1 Rpv2 (180), Rpv3 (181) (avrRpv3) (182), Rpv10 (183)*	

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619

620 **Figure 1.** Infection strategies and lifestyles of selected oomycetes.

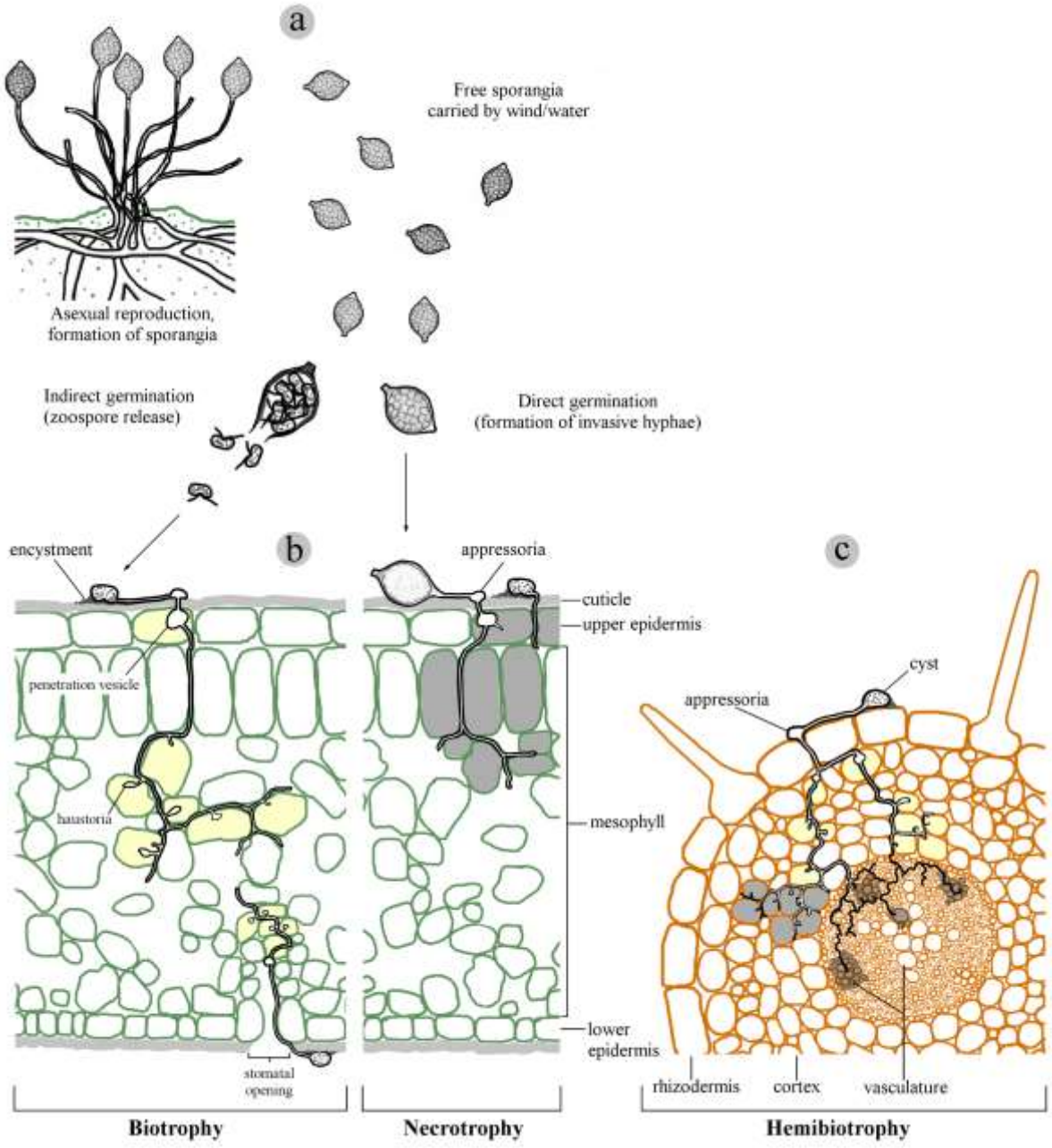

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Figure 2 – Filamentous plant microbe interfaces and membrane barriers for effector translocation.

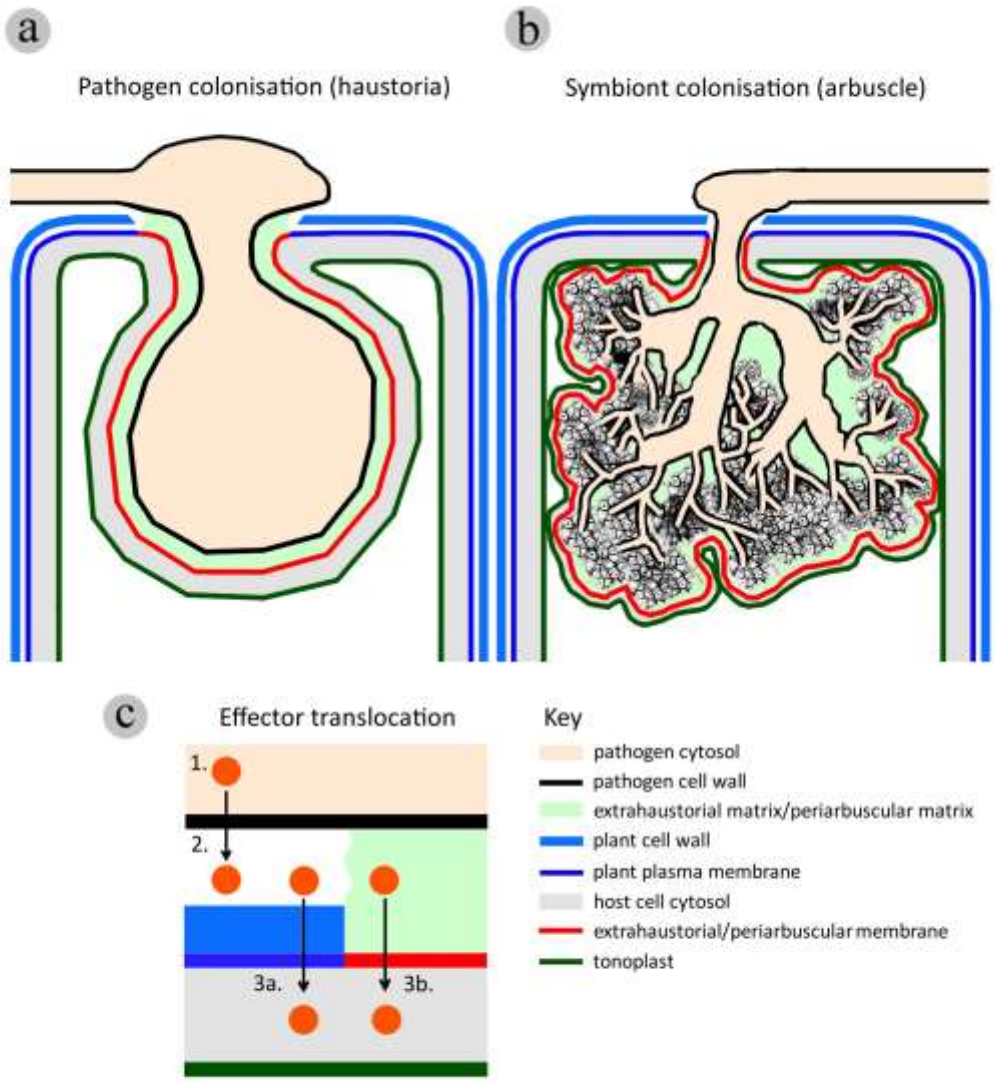

Figure Legends

Figure 1. Infection strategies and lifestyles of selected oomycetes.

(a) Typical asexual *Phytophthora* dispersal structures **(b)** leaf colonisation **(c)** root colonisation. Two alternative methods of germination (direct germination from deciduous sporangia or indirect germination from zoospores) are depicted. Other alternative 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 colonised by a biotrophic pathogen are highlighted in yellow, whilst those that are undergoing cell death as a result of necrotrophy are shaded grey. In the case of a hemibiotrophic oomycete colonising a root, the interaction is initially biotrophic whilst the oomycete spreads through the cortex, but once established, and hyphae have entered the endodermis and vasculature, necrotrophy can be observed.

Figure 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 specialised membranes termed extrahaustorial membrane (EHM) or periarbuscular membrane (PAM), labelled in red. Cytoplasmic effectors have to pass several membrane barriers **(c)**. 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 stabilise the effector protein, or alternatively, 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 whilst 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 defence responses may inhibit the entry of effectors, whilst pathogen factors may prepare host cells for their uptake.

References

1. **Judelson H, Blanco F.** 2005. The spores of Phytophthora: weapons of the plant destroyer. Nature Reviews Microbiology **3:**47-58.
2. **Lévesque CA, Brouwer H, Cano L, Hamilton JP, Holt C, Huitema E, Raffaele S, Robideau GP, Thines M, Win J, Zerillo MM, Beakes GW, Boore JL, Busam D, Dumas B, Ferriera S, Fuerstenberg SI, Gachon CM, Gaulin E, Govers F, Grenville-Briggs L, Horner N, Hostetler J, Jiang RH, Johnson J, Krajaejun T, Lin H, Meijer HJ, Moore B, Morris P, Phuntmart V, Puiu D, Shetty J, Stajich JE, Tripathy S, Wawra S, van West P, Whitty BR, Coutinho PM, Henrissat B, Martin F, Thomas PD, Tyler BM, De Vries RP, Kamoun S, Yandell M, Tisserat N, Buell CR.** 2010. Genome sequence of the necrotrophic plant pathogen Pythium ultimum reveals original pathogenicity mechanisms and effector repertoire. Genome Biol **11:**R73.
3. **Guerriero G, Avino M, Zhou Q, Fugelstad J, Clergeot PH, Bulone V.** 2010. Chitin synthases from Saprolegnia are involved in tip growth and represent a potential target for anti-oomycete drugs. PLoS Pathog **6:**e1001070.
4. **Emerson R.** 1941. An experimental study of the life cycles and taxonomy of Allomyces. Lloydia **4:**77-144.
5. **Taylor F.** 1978. Problems in the development of a specific hypothetical phylogeny of the lower eukaryotes. BioSystems **10:**67-89.
6. **Latijnhouwers M, de Wit PJ, Govers F.** 2003. Oomycetes and fungi: similar weaponry to attack plants. Trends Microbiol **11:**462-469.
7. **Krings M, Taylor TN, Dotzler N.** 2011. The fossil record of the Peronosporomycetes (Oomycota). Mycologia **103:**455-457.
8. **Strullu-Derrien C, Kenrick P, Rioult JP, Strullu DG.** 2011. Evidence of parasitic Oomycetes (Peronosporomycetes) infecting the stem cortex of the Carboniferous seed fern Lyginopteris oldhamia. Proc Biol Sci **278:**675-680.
9. **Matari NH, Blair JE.** 2014. A multilocus timescale for oomycete evolution estimated under three distinct molecular clock models. BMC Evol Biol **14:**101.
10. **Thines M, Göker M, Telle S, Ryley M, Mathur K, Narayana YD, Spring O, Thakur RP.** 2008. Phylogenetic relationships of graminicolous downy mildews based on cox2 sequence data. Mycol Res **112:**345-351.
11. **Hudspeth DSS NS, Hudspeth MES.** 2000. **A COX2 molecular phylogeny of the peronosporomycetes**. *Mycologia* **92:**674-684.
12. **Hudspeth DSS SD, Hudspeth MES.** 2003. **A cox2 phylogenetic hypothesis for the downy mildews and white rusts**. Fungal Diversity **13:**47-57.
13. **Leclerc MC, Guillot J, Deville M.** 2000. Taxonomic and phylogenetic analysis of Saprolegniaceae (Oomycetes) inferred from LSU rDNA and ITS sequence comparisons. Antonie Van Leeuwenhoek **77:**369-377.
14. **Forster H, Coffey M, Elwood H, Sogin M.** 1990. Sequence analysis of the small subunit ribosomal RNAs of three zoosporic fungi and implications for fungal evolution. Mycologia **82:**306-312.
15. **Cavalier-Smith T.** 2010. Deep phylogeny, ancestral groups and the four ages of life. Philos Trans R Soc Lond B Biol Sci **365:**111-132.
16. **Lamour KH, Win J, Kamoun S.** 2007. Oomycete genomics: new insights and future directions. FEMS Microbiol Lett **274:**1-8.
17. **Blair J, Coffey M, Park S, Geiser D, Kang S.** 2008. A multi-locus phylogeny for *Phytophthora* utilizing markers derived from complete genome sequences. Fungal Genetics and Biology **45:**266-277.
18. **Beakes GW, Glockling SL, Sekimoto S.** 2012. The evolutionary phylogeny of the oomycete "fungi". Protoplasma **249:**3-19.

19. **Tyler BM.** 2002. Molecular basis of recognition between phytophthora pathogens and their hosts. Annu Rev Phytopathol **40:**137-167.
20. **Hardham AR SW.** 2009. Cellular and molecular biology of *Phytophthora*-Plant Interactions (in Plant Relationships: A Comprehensive Treatise on Fungi As Experimental Systems for Basic and Applied Research by Holger B. Deising, p 3-28, 2nd Edition ed.
21. **Kemen E, Jones JD.** 2012. Obligate biotroph parasitism: can we link genomes to lifestyles? Trends Plant Sci **17:**448-457.
22. **O'Connell RJ, Panstruga R.** 2006. Tête à tête inside a plant cell: establishing compatibility between plants and biotrophic fungi and oomycetes. New Phytol **171:**699-718.
23. **Whisson SC, Boevink PC, Moleleki L, Avrova AO, Morales JG, Gilroy EM, Armstrong MR, Grouffaud S, van West P, Chapman S, Hein I, Toth IK, Pritchard L, Birch PR.** 2007. A translocation signal for delivery of oomycete effector proteins into host plant cells. Nature **450:**115-118.
24. **Hardham AR.** 2007. Cell biology of plant-oomycete interactions. Cell Microbiol **9:**31-39.
25. **Voegele RT, Struck C, Hahn M, Mendgen K.** 2001. The role of haustoria in sugar supply during infection of broad bean by the rust fungus Uromyces fabae. Proc Natl Acad Sci U S A **98:**8133-8138.
26. **Henry G TP, Ongena M.** 2012. **PAMPs, MAMPs, DAMPs and others: an update on the diversity of plant immunity elicitors**. Biotechnologie Agronomie Societe Et Environnement **16:**257-268.
27. **Heese A, Hann DR, Gimenez-Ibanez S, Jones AM, He K, Li J, Schroeder JI, Peck SC, Rathjen JP.** 2007. The receptor-like kinase SERK3/BAK1 is a central regulator of innate immunity in plants. Proc Natl Acad Sci U S A **104:**12217-12222.
28. **Chaparro-Garcia A, Wilkinson RC, Gimenez-Ibanez S, Findlay K, Coffey MD, Zipfel C, Rathjen JP, Kamoun S, Schornack S.** 2011. The receptor-like kinase SERK3/BAK1 is required for basal resistance against the late blight pathogen phytophthora infestans in Nicotiana benthamiana. PLoS One **6:**e16608.
29. **Brunner F, Rosahl S, Lee J, Rudd JJ, Geiler C, Kauppinen S, Rasmussen G, Scheel D, Nürnberger T.** 2002. Pep-13, a plant defense-inducing pathogen-associated pattern from Phytophthora transglutaminases. EMBO J **21:**6681-6688.
30. **Nürnberger T, Nennstiel D, Jabs T, Sacks WR, Hahlbrock K, Scheel D.** 1994. High affinity binding of a fungal oligopeptide elicitor to parsley plasma membranes triggers multiple defense responses. Cell **78:**449-460.
31. **Sacks W, Nürnberger T, Hahlbrock K, Scheel D.** 1995. Molecular characterization of nucleotide sequences encoding the extracellular glycoprotein elicitor from Phytophthora megasperma. Mol Gen Genet **246:**45-55.
32. **Gaulin E, Bottin A, Dumas B.** 2010. Sterol biosynthesis in oomycete pathogens. Plant Signal Behav **5:**258-260.
33. **Mikes V, Milat ML, Ponchet M, Panabières F, Ricci P, Blein JP.** 1998. Elicitins, proteinaceous elicitors of plant defense, are a new class of sterol carrier proteins. Biochem Biophys Res Commun **245:**133-139.
34. **Kamoun S, van West P, de Jong AJ, de Groot KE, Vleeshouwers VG, Govers F.** 1997. A gene encoding a protein elicitor of Phytophthora infestans is down-regulated during infection of potato. Mol Plant Microbe Interact **10:**13-20.
35. **Kamoun S, van West P, Vleeshouwers VG, de Groot KE, Govers F.** 1998. Resistance of nicotiana benthamiana to phytophthora infestans is mediated by the recognition of the elicitor protein INF1. Plant Cell **10:**1413-1426.
36. **Kamoun S, Klucher KM, Coffey MD, Tyler BM.** 1993. A gene encoding a host-specific elicitor protein of Phytophthora parasitica. Mol Plant Microbe Interact **6:**573-581.

37. **Kanzaki H, Saitoh H, Takahashi Y, Berberich T, Ito A, Kamoun S, Terauchi R.** 2008. NbLRK1, a lectin-like receptor kinase protein of Nicotiana benthamiana, interacts with Phytophthora infestans INF1 elicitin and mediates INF1-induced cell death. Planta **228:**977-987.
38. **Peng KC, Wang CW, Wu CH, Huang CT, Liou RF.** 2015. Tomato SOBIR1/EVR homologs are involved in elicitin perception and plant defense against the oomycete pathogen Phytophthora parasitica. Mol Plant Microbe Interact doi:10.1094/MPMI-12-14-0405-R.
39. **Liebrand TW, van den Berg GC, Zhang Z, Smit P, Cordewener JH, America AH, Sklenar J, Jones AM, Tameling WI, Robatzek S, Thomma BP, Joosten MH.** 2013. Receptor-like kinase SOBIR1/EVR interacts with receptor-like proteins in plant immunity against fungal infection. Proc Natl Acad Sci U S A **110:**10010-10015.
40. **Du J, Verzaux E, Chaparro-Garcia A, Bijsterbosch G, Keizer L, Zhou J, Liebrand T, Xie C, Govers F, Robatzek S, van der Vossen E, Jacobsen E, Visser R, Kamoun S, Vleeshouwers V.** 2015. Elicitin recognition confers enhanced resistance to *Phytophthora infestans* in potato. Nature Plants (Letter) **1:**Article number 15034.
41. **Chang YH, Yan HZ, Liou RF.** 2015. A novel elicitor protein from Phytophthora parasitica induces plant basal immunity and systemic acquired resistance. Mol Plant Pathol **16:**123-136.
42. **Mateos FV, Rickauer M, Esquerré-Tugayé MT.** 1997. Cloning and characterization of a cDNA encoding an elicitor of Phytophthora parasitica var. nicotianae that shows cellulose-binding and lectin-like activities. Mol Plant Microbe Interact **10:**1045-1053.
43. **Larroque M, Barriot R, Bottin A, Barre A, Rougé P, Dumas B, Gaulin E.** 2012. The unique architecture and function of cellulose-interacting proteins in oomycetes revealed by genomic and structural analyses. BMC Genomics **13:**605.
44. **Gaulin E, Dramé N, Lafitte C, Torto-Alalibo T, Martinez Y, Ameline-Torregrosa C, Khatib M, Mazarguil H, Villalba-Mateos F, Kamoun S, Mazars C, Dumas B, Bottin A, Esquerré-Tugayé MT, Rickauer M.** 2006. Cellulose binding domains of a Phytophthora cell wall protein are novel pathogen-associated molecular patterns. Plant Cell **18:**1766-1777.
45. **Denecke J, Aniento F, Frigerio L, Hawes C, Hwang I, Mathur J, Neuhaus J, Robinson D.** 2012. Secretory Pathway Research: The More Experimental Systems the Better. The Plant Cell **24:**1316-1326.
46. **Cheong JJ, Birberg W, Fügedi P, Pilotti A, Garegg PJ, Hong N, Ogawa T, Hahn MG.** 1991. Structure-activity relationships of oligo-beta-glucoside elicitors of phytoalexin accumulation in soybean. Plant Cell **3:**127-136.
47. **Klarzynski O, Plesse B, Joubert JM, Yvin JC, Kopp M, Kloareg B, Fritig B.** 2000. Linear beta-1,3 glucans are elicitors of defense responses in tobacco. Plant Physiol **124:**1027-1038.
48. **Nars A, Lafitte C, Chabaud M, Drouillard S, Mélida H, Danoun S, Le Costaouëc T, Rey T, Benedetti J, Bulone V, Barker DG, Bono JJ, Dumas B, Jacquet C, Heux L, Fliegmann J, Bottin A.** 2013. Aphanomyces euteiches cell wall fractions containing novel glucan-chitosaccharides induce defense genes and nuclear calcium oscillations in the plant host Medicago truncatula. PLoS One **8:**e75039.
49. **Bos JI, Armstrong MR, Gilroy EM, Boevink PC, Hein I, Taylor RM, Zhendong T, Engelhardt S, Vetukuri RR, Harrower B, Dixelius C, Bryan G, Sadanandom A, Whisson SC, Kamoun S, Birch PR.** 2010. Phytophthora infestans effector AVR3a is essential for virulence and manipulates plant immunity by stabilizing host E3 ligase CMPG1. Proc Natl Acad Sci U S A **107:**9909-9914.
50. **Chaparro-Garcia A, Schwizer S, Sklenar J, Yoshida K, Bos J, Schornack S, Jones A, Bozkurt T, Kamoun S.** 2014. Phytophthora infestans RXLR-WY effector AVR3a associates with a Dynamin-Related Protein involved in endocytosis of a plant pattern recognition receptor. BioRxiv

51. **King SR, McLellan H, Boevink PC, Armstrong MR, Bukharova T, Sukarta O, Win J, Kamoun S, Birch PR, Banfield MJ.** 2014. Phytophthora infestans RXLR effector PexRD2 interacts with host MAPKKK ε to suppress plant immune signaling. Plant Cell **26:**1345-1359.
52. **Bozkurt TO, Schornack S, Win J, Shindo T, Ilyas M, Oliva R, Cano LM, Jones AM, Huitema E, van der Hoorn RA, Kamoun S.** 2011. Phytophthora infestans effector AVRblb2 prevents secretion of a plant immune protease at the haustorial interface. Proc Natl Acad Sci U S A **108:**20832-20837.
53. **Caillaud MC, Asai S, Rallapalli G, Piquerez S, Fabro G, Jones JD.** 2013. A downy mildew effector attenuates salicylic acid-triggered immunity in Arabidopsis by interacting with the host mediator complex. PLoS Biol **11:**e1001732.
54. **Zhang M, Li Q, Liu T, Liu L, Shen D, Zhu Y, Liu P, Zhou JM, Dou D.** 2015. Two cytoplasmic effectors of Phytophthora sojae regulate plant cell death via interactions with plant catalases. Plant Physiol **167:**164-175.
55. **McLellan H, Boevink PC, Armstrong MR, Pritchard L, Gomez S, Morales J, Whisson SC, Beynon JL, Birch PR.** 2013. An RxLR effector from Phytophthora infestans prevents re-localisation of two plant NAC transcription factors from the endoplasmic reticulum to the nucleus. PLoS Pathog **9:**e1003670.
56. **Qiao Y, Liu L, Xiong Q, Flores C, Wong J, Shi J, Wang X, Liu X, Xiang Q, Jiang S, Zhang F, Wang Y, Judelson H, Chen X, Ma W.** 2013. Oomycete pathogens encode RNA silencing suppressors. Nature Genetics **45:**330–333.
57. **Qiao Y, Shi J, Zhai Y, Hou Y, Ma W.** 2015. Phytophthora effector targets a novel component of small RNA pathway in plants to promote infection. PNAS **doi: 10.1073/pnas.1421475112**.
58. **Zheng X, McLellan H, Fraiture M, Liu X, Boevink PC, Gilroy EM, Chen Y, Kandel K, Sessa G, Birch PR, Brunner F.** 2014. Functionally redundant RXLR effectors from Phytophthora infestans act at different steps to suppress early flg22-triggered immunity. PLoS Pathog **10:**e1004057.
59. **Pel MJ, Wintermans PC, Cabral A, Robroek BJ, Seidl MF, Bautor J, Parker JE, Van den Ackerveken G, Pieterse CM.** 2014. Functional analysis of Hyaloperonospora arabidopsidis RXLR effectors. PLoS One **9:**e110624.
60. **Schornack S, Huitema E, Cano LM, Bozkurt TO, Oliva R, Van Damme M, Schwizer S, Raffaele S, Chaparro-Garcia A, Farrer R, Segretin ME, Bos J, Haas BJ, Zody MC, Nusbaum C, Win J, Thines M, Kamoun S.** 2009. Ten things to know about oomycete effectors. Mol Plant Pathol **10:**795-803.
61. **Fabro G, Steinbrenner J, Coates M, Ishaque N, Baxter L, Studholme DJ, Körner E, Allen RL, Piquerez SJ, Rougon-Cardoso A, Greenshields D, Lei R, Badel JL, Caillaud MC, Sohn KH, Van den Ackerveken G, Parker JE, Beynon J, Jones JD.** 2011. Multiple candidate effectors from the oomycete pathogen Hyaloperonospora arabidopsidis suppress host plant immunity. PLoS Pathog **7:**e1002348.
62. **Liu T, Song T, Zhang X, Yuan H, Su L, Li W, Xu J, Liu S, Chen L, Chen T, Zhang M, Gu L, Zhang B, Dou D.** 2014. Unconventionally secreted effectors of two filamentous pathogens target plant salicylate biosynthesis. Nat Commun **5:**4686.
63. **Giraldo MC, Valent B.** 2013. Filamentous plant pathogen effectors in action. Nat Rev Microbiol **11:**800-814.
64. **Schornack S, van Damme M, Bozkurt TO, Cano LM, Smoker M, Thines M, Gaulin E, Kamoun S, Huitema E.** 2010. Ancient class of translocated oomycete effectors targets the host nucleus. Proc Natl Acad Sci U S A **107:**17421-17426.
65. **Dou D, Kale SD, Wang X, Jiang RH, Bruce NA, Arredondo FD, Zhang X, Tyler BM.** 2008. RXLR-mediated entry of Phytophthora sojae effector Avr1b into soybean cells does not require pathogen-encoded machinery. Plant Cell **20:**1930-1947.
66. **Rehmany AP, Gordon A, Rose LE, Allen RL, Armstrong MR, Whisson SC, Kamoun S, Tyler BM, Birch PR, Beynon JL.** 2005. Differential recognition of highly divergent downy mildew

avirulence gene alleles by RPP1 resistance genes from two Arabidopsis lines. Plant Cell **17:**1839-1850.

67. **Tian M, Win J, Savory E, Burkhardt A, Held M, Brandizzi F, Day B.** 2011. 454 Genome sequencing of Pseudoperonospora cubensis reveals effector proteins with a QXLR translocation motif. Mol Plant Microbe Interact **24:**543-553.
68. **Bailey K, Cevik V, Holton N, Byrne-Richardson J, Sohn KH, Coates M, Woods-Tör A, Aksoy HM, Hughes L, Baxter L, Jones JD, Beynon J, Holub EB, Tör M.** 2011. Molecular cloning of ATR5(Emoy2) from Hyaloperonospora arabidopsidis, an avirulence determinant that triggers RPP5-mediated defense in Arabidopsis. Mol Plant Microbe Interact **24:**827-838.
69. **Torto TA, Li S, Styer A, Huitema E, Testa A, Gow NA, van West P, Kamoun S.** 2003. EST mining and functional expression assays identify extracellular effector proteins from the plant pathogen Phytophthora. Genome Res **13:**1675-1685.
70. **Catanzariti AM, Dodds PN, Lawrence GJ, Ayliffe MA, Ellis JG.** 2006. Haustorially expressed secreted proteins from flax rust are highly enriched for avirulence elicitors. Plant Cell **18:**243-256.
71. **Rafiqi M, Gan PH, Ravensdale M, Lawrence GJ, Ellis JG, Jones DA, Hardham AR, Dodds PN.** 2010. Internalization of flax rust avirulence proteins into flax and tobacco cells can occur in the absence of the pathogen. Plant Cell **22:**2017-2032.
72. **Kale SD, Gu B, Capelluto DG, Dou D, Feldman E, Rumore A, Arredondo FD, Hanlon R, Fudal I, Rouxel T, Lawrence CB, Shan W, Tyler BM.** 2010. External lipid PI3P mediates entry of eukaryotic pathogen effectors into plant and animal host cells. Cell **142:**284-295.
73. **Plett JM, Kemppainen M, Kale SD, Kohler A, Legué V, Brun A, Tyler BM, Pardo AG, Martin F.** 2011. A secreted effector protein of Laccaria bicolor is required for symbiosis development. Curr Biol **21:**1197-1203.
74. **Paungfoo-Lonhienne C, Lonhienne T, Rentsch D, Robinson N, Christie M, Webb R, Gamage H, Carroll B, Schenk P, Schmidt S.** 2008. Plants can use protein as a nitrogen source without assistance from other organisms. PNAS **105:**4524 – 4529.
75. **Wawra S, Djamei A, Albert I, Nürnberger T, Kahmann R, van West P.** 2013. In vitro translocation experiments with RxLR-reporter fusion proteins of Avr1b from Phytophthora sojae and AVR3a from Phytophthora infestans fail to demonstrate specific autonomous uptake in plant and animal cells. Mol Plant Microbe Interact **26:**528-536.
76. **Tyler BM, Kale SD, Wang Q, Tao K, Clark HR, Drews K, Antignani V, Rumore A, Hayes T, Plett JM, Fudal I, Gu B, Chen Q, Affeldt KJ, Berthier E, Fischer GJ, Dou D, Shan W, Keller NP, Martin F, Rouxel T, Lawrence CB.** 2013. Microbe-independent entry of oomycete RxLR effectors and fungal RxLR-like effectors into plant and animal cells is specific and reproducible. Mol Plant Microbe Interact **26:**611-616.
77. **Petre B, Kamoun S.** 2014. How Do Filamentous Pathogens Deliver Effector Proteins into Plant Cells? PLoS Biol **12:**e1001801.
78. **Bhattacharjee S, Stahelin RV, Speicher KD, Speicher DW, Haldar K.** 2012. Endoplasmic reticulum PI(3)P lipid binding targets malaria proteins to the host cell. Cell **148:**201-212.
79. **Yaeno T, Li H, Chaparro-Garcia A, Schornack S, Koshiba S, Watanabe S, Kigawa T, Kamoun S, Shirasu K.** 2011. Phosphatidylinositol monophosphate-binding interface in the oomycete RXLR effector AVR3a is required for its stability in host cells to modulate plant immunity. Proc Natl Acad Sci U S A **108:**14682-14687.
80. **Wawra S, Agacan M, Boddey JA, Davidson I, Gachon CM, Zanda M, Grouffaud S, Whisson SC, Birch PR, Porter AJ, van West P.** 2012. Avirulence protein 3a (AVR3a) from the potato pathogen Phytophthora infestans forms homodimers through its predicted translocation region and does not specifically bind phospholipids. J Biol Chem **287:**38101-38109.
81. **Sun F, Kale SD, Azurmendi HF, Li D, Tyler BM, Capelluto DG.** 2013. Structural basis for interactions of the Phytophthora sojae RxLR effector Avh5 with phosphatidylinositol 3-phosphate and for host cell entry. Mol Plant Microbe Interact **26:**330-344.

82. **Bos JI, Kanneganti TD, Young C, Cakir C, Huitema E, Win J, Armstrong MR, Birch PR, Kamoun S.** 2006. The C-terminal half of Phytophthora infestans RXLR effector AVR3a is sufficient to trigger R3a-mediated hypersensitivity and suppress INF1-induced cell death in Nicotiana benthamiana. Plant J **48:**165-176.
83. **Kelley B, Lee S, Damasceno C, Chakravarthy S, Kim B, Martin G, Rose J.** 2010. A secreted effector protein (SNE1) from Phytophthora infestans is a broadly acting suppressor of programmed cell death. The Plant Journal **62:**357-366.
84. **Rajput NA, Zhang M, Ru Y, Liu T, Xu J, Liu L, Mafurah JJ, Dou D.** 2014. Phytophthora sojae effector PsCRN70 suppresses plant defenses in Nicotiana benthamiana. PLoS One **9:**e98114.
85. **Flor H.** 1954. Identification of races of flax rust by species with single rust-conditioning gene. US Dept Agr Tech Bull **1087**.
86. **Black W MC, Mills WR, Peterson LC.** 1953. **A proposal for an international nomenclature of races of *Phytophthora infestans* and of genes controlling immunity in *Solanum demissum* derivatives**. Euphytica **2:**173–178.
87. **Ballvora A, Ercolano MR, Weiss J, Meksem K, Bormann CA, Oberhagemann P, Salamini F, Gebhardt C.** 2002. The R1 gene for potato resistance to late blight (Phytophthora infestans) belongs to the leucine zipper/NBS/LRR class of plant resistance genes. Plant J **30:**361-371.
88. **Zhu S, Li Y, Vossen JH, Visser RG, Jacobsen E.** 2012. Functional stacking of three resistance genes against Phytophthora infestans in potato. Transgenic Res **21:**89-99.
89. **Zhu Y, Chen H, Fan J, Wang Y, Li Y, Chen J, Yang S, Hu L, Leung H, Mew TW, Teng PS, Wang Z, Mundt CC.** 2000. Genetic diversity and disease control in rice. Nature **406:**718-722.
90. **Brunner S, Stirnweis D, Diaz Quijano C, Buesing G, Herren G, Parlange F, Barret P, Tassy C, Sautter C, Winzeler M, Keller B.** 2012. Transgenic Pm3 multilines of wheat show increased powdery mildew resistance in the field. Plant Biotechnol J **10:**398-409.
91. **Segretin ME, Pais M, Franceschetti M, Chaparro-Garcia A, Bos JI, Banfield MJ, Kamoun S.** 2014. Single amino acid mutations in the potato immune receptor R3a expand response to Phytophthora effectors. Mol Plant Microbe Interact **27:**624-637.
92. **Chapman S, Stevens LJ, Boevink PC, Engelhardt S, Alexander CJ, Harrower B, Champouret N, McGeachy K, Van Weymers PS, Chen X, Birch PR, Hein I.** 2014. Detection of the virulent form of AVR3a from Phytophthora infestans following artificial evolution of potato resistance gene R3a. PLoS One **9:**e110158.
93. **Vleeshouwers VG, Raffaele S, Vossen JH, Champouret N, Oliva R, Segretin ME, Rietman H, Cano LM, Lokossou A, Kessel G, Pel MA, Kamoun S.** 2011. Understanding and exploiting late blight resistance in the age of effectors. Annu Rev Phytopathol **49:**507-531.
94. **Qutob D, Tedman-Jones J, Dong S, Kuflu K, Pham H, Wang Y, Dou D, Kale SD, Arredondo FD, Tyler BM, Gijzen M.** 2009. Copy number variation and transcriptional polymorphisms of Phytophthora sojae RXLR effector genes Avr1a and Avr3a. PLoS One **4:**e5066.
95. **Wang Q, Han C, Ferreira AO, Yu X, Ye W, Tripathy S, Kale SD, Gu B, Sheng Y, Sui Y, Wang X, Zhang Z, Cheng B, Dong S, Shan W, Zheng X, Dou D, Tyler BM, Wang Y.** 2011. Transcriptional programming and functional interactions within the Phytophthora sojae RXLR effector repertoire. Plant Cell **23:**2064-2086.
96. **Dong S, Yin W, Kong G, Yang X, Qutob D, Chen Q, Kale SD, Sui Y, Zhang Z, Dou D, Zheng X, Gijzen M, Tyler BM, Wang Y.** 2011. Phytophthora sojae avirulence effector Avr3b is a secreted NADH and ADP-ribose pyrophosphorylase that modulates plant immunity. PLoS Pathog **7:**e1002353.
97. **Liu T, Ye W, Ru Y, Yang X, Gu B, Tao K, Lu S, Dong S, Zheng X, Shan W, Wang Y, Dou D.** 2011. Two host cytoplasmic effectors are required for pathogenesis of Phytophthora sojae by suppression of host defenses. Plant Physiol **155:**490-501.
98. **Eckardt NA.** 2002. Plant disease susceptibility genes? Plant Cell **14:**1983-1986.
99. **Vogel JP, Raab TK, Schiff C, Somerville SC.** 2002. PMR6, a pectate lyase-like gene required for powdery mildew susceptibility in Arabidopsis. Plant Cell **14:**2095-2106.

100. **Wang E, Schornack S, Marsh JF, Gobbato E, Schwessinger B, Eastmond P, Schultze M, Kamoun S, Oldroyd GE.** 2012. A common signaling process that promotes mycorrhizal and oomycete colonization of plants. Curr Biol **22:**2242-2246.
101. **Reisige K GC, Daniels U, Moerschbacher BM.** 2006. **The C28 aldehyde octacosanal is a morphogenetically active component involved in host plant recognition and infection structure differentiation in the wheat stem rust fungus**. Molecular Plant Pathology **68**.
102. **Mendoza-Mendoza A, Berndt P, Djamei A, Weise C, Linne U, Marahiel M, Vranes M, Kämper J, Kahmann R.** 2009. Physical-chemical plant-derived signals induce differentiation in Ustilago maydis. Mol Microbiol **71:**895-911.
103. **Skamnioti P, Gurr SJ.** 2007. Magnaporthe grisea cutinase2 mediates appressorium differentiation and host penetration and is required for full virulence. Plant Cell **19:**2674-2689.
104. **Schmidt SM, Kuhn H, Micali C, Liller C, Kwaaitaal M, Panstruga R.** 2014. Interaction of a Blumeria graminis f. sp. hordei effector candidate with a barley ARF-GAP suggests that host vesicle trafficking is a fungal pathogenicity target. Mol Plant Pathol **15:**535-549.
105. **Ellinger D, Naumann M, Falter C, Zwikowics C, Jamrow T, Manisseri C, Somerville SC, Voigt CA.** 2013. Elevated early callose deposition results in complete penetration resistance to powdery mildew in Arabidopsis. Plant Physiol **161:**1433-1444.
106. **Hok S, Danchin EG, Allasia V, Panabières F, Attard A, Keller H.** 2011. An Arabidopsis (malectin-like) leucine-rich repeat receptor-like kinase contributes to downy mildew disease. Plant Cell Environ **34:**1944-1957.
107. **Chen CW, Panzeri D, Yeh YH, Kadota Y, Huang PY, Tao CN, Roux M, Chien SC, Chin TC, Chu PW, Zipfel C, Zimmerli L.** 2014. The Arabidopsis malectin-like leucine-rich repeat receptor-like kinase IOS1 associates with the pattern recognition receptors FLS2 and EFR and is critical for priming of pattern-triggered immunity. Plant Cell **26:**3201-3219.
108. **Petersen M, Brodersen P, Naested H, Andreasson E, Lindhart U, Johansen B, Nielsen HB, Lacy M, Austin MJ, Parker JE, Sharma SB, Klessig DF, Martienssen R, Mattsson O, Jensen AB, Mundy J.** 2000. Arabidopsis map kinase 4 negatively regulates systemic acquired resistance. Cell **103:**1111-1120.
109. **Liu JZ, Horstman HD, Braun E, Graham MA, Zhang C, Navarre D, Qiu WL, Lee Y, Nettleton D, Hill JH, Whitham SA.** 2011. Soybean homologs of MPK4 negatively regulate defense responses and positively regulate growth and development. Plant Physiol **157:**1363-1378.
110. **Gao M, Wang X, Wang D, Xu F, Ding X, Zhang Z, Bi D, Cheng YT, Chen S, Li X, Zhang Y.** 2009. Regulation of cell death and innate immunity by two receptor-like kinases in Arabidopsis. Cell Host Microbe **6:**34-44.
111. **Trujillo M, Ichimura K, Casais C, Shirasu K.** 2008. Negative regulation of PAMP-triggered immunity by an E3 ubiquitin ligase triplet in Arabidopsis. Curr Biol **18:**1396-1401.
112. **Kim HS, Delaney TP.** 2002. Arabidopsis SON1 is an F-box protein that regulates a novel induced defense response independent of both salicylic acid and systemic acquired resistance. Plant Cell **14:**1469-1482.
113. **Tang D, Ade J, Frye CA, Innes RW.** 2005. Regulation of plant defense responses in Arabidopsis by EDR2, a PH and START domain-containing protein. Plant J **44:**245-257.
114. **Vorwerk S, Schiff C, Santamaria M, Koh S, Nishimura M, Vogel J, Somerville C, Somerville S.** 2007. EDR2 negatively regulates salicylic acid-based defenses and cell death during powdery mildew infections of Arabidopsis thaliana. BMC Plant Biol **7:**35.
115. **Li X, Zhang Y, Clarke JD, Li Y, Dong X.** 1999. Identification and cloning of a negative regulator of systemic acquired resistance, SNI1, through a screen for suppressors of npr1-1. Cell **98:**329-339.
116. **Swain S, Roy S, Shah J, Van Wees S, Pieterse CM, Nandi AK.** 2011. Arabidopsis thaliana cdd1 mutant uncouples the constitutive activation of salicylic acid signalling from growth defects. Mol Plant Pathol **12:**855-865.

117. **van Damme M, Zeilmaker T, Elberse J, Andel A, de Sain-van der Velden M, van den Ackerveken G.** 2009. Downy mildew resistance in Arabidopsis by mutation of HOMOSERINE KINASE. Plant Cell **21:**2179-2189.
118. **Stuttmann J, Hubberten HM, Rietz S, Kaur J, Muskett P, Guerois R, Bednarek P, Hoefgen R, Parker JE.** 2011. Perturbation of Arabidopsis amino acid metabolism causes incompatibility with the adapted biotrophic pathogen Hyaloperonospora arabidopsidis. Plant Cell **23:**2788-2803.
119. **Vleeshouwers VG, Rietman H, Krenek P, Champouret N, Young C, Oh SK, Wang M, Bouwmeester K, Vosman B, Visser RG, Jacobsen E, Govers F, Kamoun S, Van der Vossen EA.** 2008. Effector genomics accelerates discovery and functional profiling of potato disease resistance and phytophthora infestans avirulence genes. PLoS One **3:**e2875.
120. **Kamoun S, Furzer O, Jones J, Judelson H, Ali G, Dalio R, Roy S, Schena L, Zambounis A, Panabières F, Cahill D, Ruocco M, Figueiredo A, Chen X, Hulvey J, Stam R, Lamour K, Gijzen M, Tyler B, Grünwald N, Mukhtar M, Tomé D, Tör M, Van Den Ackerveken G, McDowell J, Daayf F, Fry W, Lindqvist-Kreuze H, Meijer H, Petre B, Ristaino J, Yoshida K, Birch P, Govers F.** 2014. The Top 10 oomycete pathogens in molecular plant pathology. Molecular Plant Pathology **doi: 10.1111/mpp.12190**.
121. **Wirthmueller L, Maqbool A, Banfield MJ.** 2013. On the front line: structural insights into plant-pathogen interactions. Nat Rev Microbiol **11:**761-776.
122. **Gobbato E, Wang E, Higgins G, Bano SA, Henry C, Schultze M, Oldroyd GE.** 2013. RAM1 and RAM2 function and expression during arbuscular mycorrhizal symbiosis and Aphanomyces euteiches colonization. Plant Signal Behav **8**.
123. **Bhullar NK, Zhang Z, Wicker T, Keller B.** 2010. Wheat gene bank accessions as a source of new alleles of the powdery mildew resistance gene Pm3: a large scale allele mining project. BMC Plant Biol **10:**88.
124. **Haas BJ, Kamoun S, Zody MC, Jiang RH, Handsaker RE, Cano LM, Grabherr M, Kodira CD, Raffaele S, Torto-Alalibo T, Bozkurt TO, Ah-Fong AM, Alvarado L, Anderson VL, Armstrong MR, Avrova A, Baxter L, Beynon J, Boevink PC, Bollmann SR, Bos JI, Bulone V, Cai G, Cakir C, Carrington JC, Chawner M, Conti L, Costanzo S, Ewan R, Fahlgren N, Fischbach MA, Fugelstad J, Gilroy EM, Gnerre S, Green PJ, Grenville-Briggs LJ, Griffith J, Grünwald NJ, Horn K, Horner NR, Hu CH, Huitema E, Jeong DH, Jones AM, Jones JD, Jones RW, Karlsson EK, Kunjeti SG, Lamour K, Liu Z, et al.** 2009. Genome sequence and analysis of the Irish potato famine pathogen Phytophthora infestans. Nature **461:**393-398.
125. **Baxter L, Tripathy S, Ishaque N, Boot N, Cabral A, Kemen E, Thines M, Ah-Fong A, Anderson R, Badejoko W, Bittner-Eddy P, Boore JL, Chibucos MC, Coates M, Dehal P, Delehaunty K, Dong S, Downton P, Dumas B, Fabro G, Fronick C, Fuerstenberg SI, Fulton L, Gaulin E, Govers F, Hughes L, Humphray S, Jiang RH, Judelson H, Kamoun S, Kyung K, Meijer H, Minx P, Morris P, Nelson J, Phuntumart V, Qutob D, Rehmany A, Rougon-Cardoso A, Ryden P, Torto-Alalibo T, Studholme D, Wang Y, Win J, Wood J, Clifton SW, Rogers J, Van den Ackerveken G, Jones JD, McDowell JM, et al.** 2010. Signatures of adaptation to obligate biotrophy in the Hyaloperonospora arabidopsidis genome. Science **330:**1549-1551.
126. **Tyler BM, Tripathy S, Zhang X, Dehal P, Jiang RH, Aerts A, Arredondo FD, Baxter L, Bensasson D, Beynon JL, Chapman J, Damasceno CM, Dorrance AE, Dou D, Dickerman AW, Dubchak IL, Garbelotto M, Gijzen M, Gordon SG, Govers F, Grunwald NJ, Huang W, Ivors KL, Jones RW, Kamoun S, Krampis K, Lamour KH, Lee MK, McDonald WH, Medina M, Meijer HJ, Nordberg EK, Maclean DJ, Ospina-Giraldo MD, Morris PF, Phuntumart V, Putnam NH, Rash S, Rose JK, Sakihama Y, Salamov AA, Savidor A, Scheuring CF, Smith BM, Sobral BW, Terry A, Torto-Alalibo TA, Win J, Xu Z, Zhang H, et al.** 2006. Phytophthora genome sequences uncover evolutionary origins and mechanisms of pathogenesis. Science **313:**1261-1266.

127. **Vega-Arreguín JC, Jalloh A, Bos JI, Moffett P.** 2014. Recognition of an Avr3a homologue plays a major role in mediating nonhost resistance to Phytophthora capsici in Nicotiana species. Mol Plant Microbe Interact **27:**770-780.
128. **Govindarajulu M, Epstein L, Wroblewski T, Michelmore RW.** 2014. Host-induced gene silencing inhibits the biotrophic pathogen causing downy mildew of lettuce. Plant Biotechnol J doi:10.1111/pbi.12307.
129. **Jahan SN, Åsman AK, Corcoran P, Fogelqvist J, Vetukuri RR, Dixelius C.** 2015. Plant-mediated gene silencing restricts growth of the potato late blight pathogen Phytophthora infestans. J Exp Bot **doi:10.1093/jxb/erv094**.
130. **Rey T, Schornack S.** 2013. Interactions of beneficial and detrimental root-colonizing filamentous microbes with plant hosts. Genome Biol **14:**121.
131. **Evangelisti E, Rey T, Schornack S.** 2014. Cross-interference of plant development and plant-microbe interactions. Curr Opin Plant Biol **20:**118-126.
132. **Kloppholz S, Kuhn H, Requena N.** 2011. A secreted fungal effector of Glomus intraradices promotes symbiotic biotrophy. Curr Biol **21:**1204-1209.
133. **Rey T, Chatterjee A, Buttay M, Toulotte J, Schornack S.** 2014. Medicago truncatula symbiosis mutants affected in the interaction with a biotrophic root pathogen. New Phytol doi:10.1111/nph.13233.
134. **Kwon C, Neu C, Pajonk S, Yun HS, Lipka U, Humphry M, Bau S, Straus M, Kwaaitaal M, Rampelt H, El Kasmi F, Jürgens G, Parker J, Panstruga R, Lipka V, Schulze-Lefert P.** 2008. Co-option of a default secretory pathway for plant immune responses. Nature **451:**835-840.
135. **Bozkurt TO, Belhaj K, Dagdas YF, Chaparro-Garcia A, Wu CH, Cano LM, Kamoun S.** 2015. Rerouting of plant late endocytic trafficking toward a pathogen interface. Traffic **16:**204-226.
136. **Ivanov S, Harrison MJ.** 2014. A set of fluorescent protein-based markers expressed from constitutive and arbuscular mycorrhiza-inducible promoters to label organelles, membranes and cytoskeletal elements in Medicago truncatula. Plant J **80:**1151-1163.
137. **Kemen E, Gardiner A, Schultz-Larsen T, Kemen AC, Balmuth AL, Robert-Seilaniantz A, Bailey K, Holub E, Studholme DJ, Maclean D, Jones JD.** 2011. Gene gain and loss during evolution of obligate parasitism in the white rust pathogen of Arabidopsis thaliana. PLoS Biol **9:**e1001094.
138. **Stassen JH, Seidl MF, Vergeer PW, Nijman IJ, Snel B, Cuppen E, Van den Ackerveken G.** 2012. Effector identification in the lettuce downy mildew Bremia lactucae by massively parallel transcriptome sequencing. Mol Plant Pathol **13:**719-731.
139. **Lamour KH, Mudge J, Gobena D, Hurtado-Gonzales OP, Schmutz J, Kuo A, Miller NA, Rice BJ, Raffaele S, Cano LM, Bharti AK, Donahoo RS, Finley S, Huitema E, Hulvey J, Platt D, Salamov A, Savidor A, Sharma R, Stam R, Storey D, Thines M, Win J, Haas BJ, Dinwiddie DL, Jenkins J, Knight JR, Affourtit JP, Han CS, Chertkov O, Lindquist EA, Detter C, Grigoriev IV, Kamoun S, Kingsmore SF.** 2012. Genome sequencing and mapping reveal loss of heterozygosity as a mechanism for rapid adaptation in the vegetable pathogen Phytophthora capsici. Mol Plant Microbe Interact **25:**1350-1360.
140. **Savory EA, Adhikari BN, Hamilton JP, Vaillancourt B, Buell CR, Day B.** 2012. mRNA-Seq analysis of the Pseudoperonospora cubensis transcriptome during cucumber (Cucumis sativus L.) infection. PLoS One **7:**e35796.
141. **Adhikari BN, Hamilton JP, Zerillo MM, Tisserat N, Lévesque CA, Buell CR.** 2013. Comparative genomics reveals insight into virulence strategies of plant pathogenic oomycetes. PLoS One **8:**e75072.
142. **Nennstiel D, Scheel D, Nürnberger T.** 1998. Characterization and partial purification of an oligopeptide elicitor receptor from parsley (Petroselinum crispum). FEBS Lett **431:**405-410.
143. **Bostock RM, Laine RA, Kuć JA.** 1982. Factors affecting the elicitation of sesquiterpenoid phytoalexin accumulation by eicosapentaenoic and arachidonic acids in potato. Plant Physiol **70:**1417-1424.

144. **Kaku H, Nishizawa Y, Ishii-Minami N, Akimoto-Tomiyama C, Dohmae N, Takio K, Minami E, Shibuya N.** 2006. Plant cells recognize chitin fragments for defense signaling through a plasma membrane receptor. Proc Natl Acad Sci U S A **103:**11086-11091.
145. **Miya A, Albert P, Shinya T, Desaki Y, Ichimura K, Shirasu K, Narusaka Y, Kawakami N, Kaku H, Shibuya N.** 2007. CERK1, a LysM receptor kinase, is essential for chitin elicitor signaling in Arabidopsis. Proc Natl Acad Sci U S A **104:**19613-19618.
146. **Borhan MH, Gunn N, Cooper A, Gulden S, Tör M, Rimmer SR, Holub EB.** 2008. WRR4 encodes a TIR-NB-LRR protein that confers broad-spectrum white rust resistance in Arabidopsis thaliana to four physiological races of Albugo candida. Mol Plant Microbe Interact **21:**757-768.
147. **Botella MA, Parker JE, Frost LN, Bittner-Eddy PD, Beynon JL, Daniels MJ, Holub EB, Jones JD.** 1998. Three genes of the Arabidopsis RPP1 complex resistance locus recognize distinct Peronospora parasitica avirulence determinants. Plant Cell **10:**1847-1860.
148. **Krasileva KV, Dahlbeck D, Staskawicz BJ.** 2010. Activation of an Arabidopsis resistance protein is specified by the in planta association of its leucine-rich repeat domain with the cognate oomycete effector. Plant Cell **22:**2444-2458.
149. **Sohn KH, Lei R, Nemri A, Jones JD.** 2007. The downy mildew effector proteins ATR1 and ATR13 promote disease susceptibility in Arabidopsis thaliana. Plant Cell **19:**4077-4090.
150. ***Tör M*, *Holub E*, *Brose E*, *Musker R*, *Gunn N*, *Can C*, *Crute I*, *Beynon J*.** 1994. *Map positions of three loci in Arabidopsis thaliana associated with isolate-specific recognition of Peronospora parasitica (downy mildew)*. *Mol Plant-Microbe Interact* **7:**214-222.
151. **Parker JE, Coleman MJ, Szabò V, Frost LN, Schmidt R, van der Biezen EA, Moores T, Dean C, Daniels MJ, Jones JD.** 1997. The Arabidopsis downy mildew resistance gene RPP5 shares similarity to the toll and interleukin-1 receptors with N and L6. Plant Cell **9:**879-894.
152. **McDowell JM, Dhandaydham M, Long TA, Aarts MG, Goff S, Holub EB, Dangl JL.** 1998. Intragenic recombination and diversifying selection contribute to the evolution of downy mildew resistance at the RPP8 locus of Arabidopsis. Plant Cell **10:**1861-1874.
153. **Bittner-Eddy PD, Crute IR, Holub EB, Beynon JL.** 2000. RPP13 is a simple locus in Arabidopsis thaliana for alleles that specify downy mildew resistance to different avirulence determinants in Peronospora parasitica. Plant J **21:**177-188.
154. **Cho SK, Ryu MY, Song C, Kwak JM, Kim WT.** 2008. Arabidopsis PUB22 and PUB23 are homologous U-Box E3 ubiquitin ligases that play combinatory roles in response to drought stress. Plant Cell **20:**1899-1914.
155. **Bond DM, Dennis ES, Pogson BJ, Finnegan EJ.** 2009. Histone acetylation, VERNALIZATION INSENSITIVE 3, FLOWERING LOCUS C, and the vernalization response. Mol Plant **2:**724-737.
156. **Wubben MJ, Jin J, Baum TJ.** 2008. Cyst nematode parasitism of Arabidopsis thaliana is inhibited by salicylic acid (SA) and elicits uncoupled SA-independent pathogenesis-related gene expression in roots. Mol Plant Microbe Interact **21:**424-432.
157. **Van Damme M, Andel A, Huibers RP, Panstruga R, Weisbeek PJ, Van den Ackerveken G.** 2005. Identification of arabidopsis loci required for susceptibility to the downy mildew pathogen Hyaloperonospora parasitica. Mol Plant Microbe Interact **18:**583-592.
158. **Nishimura MT, Stein M, Hou BH, Vogel JP, Edwards H, Somerville SC.** 2003. Loss of a callose synthase results in salicylic acid-dependent disease resistance. Science **301:**969-972.
159. **Lim S, Bernard R, Nickell C, Grey L.** 1984. New physiological race of *Peronospora manschurica* virulent to the gene Rpm in soybeans. Plant Dis **68:**71-72.
160. **Ruegger M, Dewey E, Gray WM, Hobbie L, Turner J, Estelle M.** 1998. The TIR1 protein of Arabidopsis functions in auxin response and is related to human SKP2 and yeast grr1p. Genes Dev **12:**198-207.
161. **Leonards-Schippers C, Gieffers W, Salamini F, Gebhardt C.** 1992. The R1 gene conferring race-specific resistance to Phytophthora infestans in potato is located on potato chromosome V. Mol Gen Genet **233:**278-283.

162. **Lokossou AA, Park TH, van Arkel G, Arens M, Ruyter-Spira C, Morales J, Whisson SC, Birch PR, Visser RG, Jacobsen E, van der Vossen EA.** 2009. Exploiting knowledge of R/Avr genes to rapidly clone a new LZ-NBS-LRR family of late blight resistance genes from potato linkage group IV. Mol Plant Microbe Interact **22:**630-641.
163. **Saunders DG, Breen S, Win J, Schornack S, Hein I, Bozkurt TO, Champouret N, Vleeshouwers VG, Birch PR, Gilroy EM, Kamoun S.** 2012. Host protein BSL1 associates with Phytophthora infestans RXLR effector AVR2 and the Solanum demissum Immune receptor R2 to mediate disease resistance. Plant Cell **24:**3420-3434.
164. **Gilroy EM, Breen S, Whisson SC, Squires J, Hein I, Kaczmarek M, Turnbull D, Boevink PC, Lokossou A, Cano LM, Morales J, Avrova AO, Pritchard L, Randall E, Lees A, Govers F, van West P, Kamoun S, Vleeshouwers VG, Cooke DE, Birch PR.** 2011. Presence/absence, differential expression and sequence polymorphisms between PiAVR2 and PiAVR2-like in Phytophthora infestans determine virulence on R2 plants. New Phytol **191:**763-776.
165. **el-Kharbotly A, Leonards-Schippers C, Huigen DJ, Jacobsen E, Pereira A, Stiekema WJ, Salamini F, Gebhardt C.** 1994. Segregation analysis and RFLP mapping of the R1 and R3 alleles conferring race-specific resistance to Phytophthora infestans in progeny of dihaploid potato parents. Mol Gen Genet **242:**749-754.
166. **Armstrong MR, Whisson SC, Pritchard L, Bos JI, Venter E, Avrova AO, Rehmany AP, Böhme U, Brooks K, Cherevach I, Hamlin N, White B, Fraser A, Lord A, Quail MA, Churcher C, Hall N, Berriman M, Huang S, Kamoun S, Beynon JL, Birch PR.** 2005. An ancestral oomycete locus contains late blight avirulence gene Avr3a, encoding a protein that is recognized in the host cytoplasm. Proc Natl Acad Sci U S A **102:**7766-7771.
167. **Li G, Huang S, Guo X, Li Y, Yang Y, Guo Z, Kuang H, Rietman H, Bergervoet M, Vleeshouwers VG, van der Vossen EA, Qu D, Visser RG, Jacobsen E, Vossen JH.** 2011. Cloning and characterization of r3b; members of the r3 superfamily of late blight resistance genes show sequence and functional divergence. Mol Plant Microbe Interact **24:**1132-1142.
168. **van Poppel P.** 2010. The *Phytophthora infestans* avirulence gene Avr4 and its potato counterpart R4. PhD Thesis. Wageningen University.
169. **van Poppel PM, Guo J, van de Vondervoort PJ, Jung MW, Birch PR, Whisson SC, Govers F.** 2008. The Phytophthora infestans avirulence gene Avr4 encodes an RXLR-dEER effector. Mol Plant Microbe Interact **21:**1460-1470.
170. **El-Kharbotly A, Palomino-Sánchez C, Salamini F, Jacobsen E, Gebhardt C.** 1996. R6 and R7 alleles of potato conferring race-specific resistance to Phytophthora infestans (Mont.) de Bary identified genetic loci clustering with the R3 locus on chromosome XI. Theor Appl Genet **92:**880-884.
171. **Bradshaw JE, Bryan GJ, Lees AK, McLean K, Solomon-Blackburn RM.** 2006. Mapping the R10 and R11 genes for resistance to late blight (Phytophthora infestans) present in the potato (Solanum tuberosum) R-gene differentials of black. Theor Appl Genet **112:**744-751.
172. **Song J, Bradeen JM, Naess SK, Raasch JA, Wielgus SM, Haberlach GT, Liu J, Kuang H, Austin-Phillips S, Buell CR, Helgeson JP, Jiang J.** 2003. Gene RB cloned from Solanum bulbocastanum confers broad spectrum resistance to potato late blight. Proc Natl Acad Sci U S A **100:**9128-9133.
173. **van der Vossen E, Sikkema A, Hekkert B, Gros J, Stevens P, Muskens M, Wouters D, Pereira A, Stiekema W, Allefs S.** 2003. An ancient R gene from the wild potato species Solanum bulbocastanum confers broad-spectrum resistance to Phytophthora infestans in cultivated potato and tomato. Plant J **36:**867-882.
174. **van der Vossen EA, Gros J, Sikkema A, Muskens M, Wouters D, Wolters P, Pereira A, Allefs S.** 2005. The Rpi-blb2 gene from Solanum bulbocastanum is an Mi-1 gene homolog conferring broad-spectrum late blight resistance in potato. Plant J **44:**208-222.

175. **Zhang C, Liu L, Wang X, Vossen J, Li G, Li T, Zheng Z, Gao J, Guo Y, Visser RG, Li J, Bai Y, Du Y.** 2014. The Ph-3 gene from Solanum pimpinellifolium encodes CC-NBS-LRR protein conferring resistance to Phytophthora infestans. Theor Appl Genet **127:**1353-1364.
176. **Foster SJ, Park TH, Pel M, Brigneti G, Sliwka J, Jagger L, van der Vossen E, Jones JD.** 2009. Rpi-vnt1.1, a Tm-2(2) homolog from Solanum venturii, confers resistance to potato late blight. Mol Plant Microbe Interact **22:**589-600.
177. **Bozkurt TO, Richardson A, Dagdas YF, Mongrand S, Kamoun S, Raffaele S.** 2014. The Plant Membrane-Associated REMORIN1.3 Accumulates in Discrete Perihaustorial Domains and Enhances Susceptibility to Phytophthora infestans. Plant Physiol **165:**1005-1018.
178. **Na R, Yu D, Qutob D, Zhao J, Gijzen M.** 2013. Deletion of the Phytophthora sojae avirulence gene Avr1d causes gain of virulence on Rps1d. Mol Plant Microbe Interact **26:**969-976.
179. **Shan W, Cao M, Leung D, Tyler BM.** 2004. The Avr1b locus of Phytophthora sojae encodes an elicitor and a regulator required for avirulence on soybean plants carrying resistance gene Rps1b. Mol Plant Microbe Interact **17:**394-403.
180. **Merdinoglu D, Wiedemann-Merdinoglu S, Coste P, Dumas V, Haetty S, Butterlin G, Greif C.** 2003. **Genetic analysis of downy mildew resistance derived from *Muscadinia rotundifolia*.** Acta Hort**:**527-533.
181. **Bellin D, Peressotti E, Merdinoglu D, Wiedemann-Merdinoglu S, Adam-Blondon AF, Cipriani G, Morgante M, Testolin R, Di Gaspero G.** 2009. Resistance to Plasmopara viticola in grapevine 'Bianca' is controlled by a major dominant gene causing localised necrosis at the infection site. Theor Appl Genet **120:**163-176.
182. **Casagrande K, Falginella L, Castellarin SD, Testolin R, Di Gaspero G.** 2011. Defence responses in Rpv3-dependent resistance to grapevine downy mildew. Planta **234:**1097-1109.
183. **Schwander F, Eibach R, Fechter I, Hausmann L, Zyprian E, Töpfer R.** 2012. Rpv10: a new locus from the Asian Vitis gene pool for pyramiding downy mildew resistance loci in grapevine. Theor Appl Genet **124:**163-176.

Biographical Text

Stuart Fawke obtained a degree in Natural Sciences (2012) from the University of Birmingham and an MSc (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 BSc in Biology (2013) from the École Normale Supérieure (ENS) de Lyon, France. He is currently a MSc student at the École Normale Supérieure (ENS) de Lyon. In 2014 he undertook a four-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 continued there for postdoctoral research with Prof. Thomas Lahaye, discovering the TAL effector code (2007). He then moved to the UK to for a postdoc with Prof. Sophien Kamoun at The Sainsbury Laboratory, Norwich (2008-2012), working 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 colonisation by pathogenic and beneficial filamentous microbes.