Resistance to oomycetes: a general role for the hypersensitive response?

Sophien Kamoun, Edgar Huitema and Vivianne G.A.A. Vleeshouwers

Oomycete plant pathogens, such as Phytophthora, downy mildews and Pythium, have devastating disease effects on numerous crop and ornamental plants. Various types of genetic resistance to oomycetes occur in plants, and can be determined at the subspecific or varietal level (race or cultivar-specific resistance), or at the species or genus level (nonhost resistance). In addition, resistance might be a quantitative phenotype (partial resistance). Resistance reactions are often associated with the hypersensitive response – a programed cell death pathway. Recent advances in the genetic, biochemical and cytological characterization of disease resistance suggests that the hypersensitive response is associated with all forms of resistance to Phytophthora and downy mildews. Identification of the resistance genes involved in nonhost and partial resistance to oomycetes remains an important challenge.

Oomycetes are a diverse group of organisms, many of which are plant pathogens, including ~60 species of the genus *Phytophthora*, numerous genera of the biotrophic downy mildews and more than 100 species of the genus *Pythium*. These cause devastating disease symptoms on numerous crop and ornamental plants, and are notoriously difficult to manage. For example, *Phytophthora infestans*, which causes late blight of potato, devastated potato production in the mid-19th century, and remains the most serious constraint to potato production[1]. Worldwide losses due to late blight are estimated to exceed $2 billion annually. Other economically important diseases include root and stem rot caused by *Phytophthora sojae*, which hampers soybean production in several continents, and black pod of cocoa caused by *Phytophthora palmivora*, which is a recurring threat to worldwide chocolate production. The use of chemicals targeted against oomycetes can provide some level of disease control. However, in the long term, the development of crops that possess durable genetic resistance, whether by classical breeding methods or by genetic engineering, provides the best prospect for effective, economical and environmentally sound control of oomycete diseases.

Disease resistance processes in plants are diverse. Resistance might occur at the subspecific or varietal level (race or cultivar-specific resistance) or at the species or genus level (nonhost resistance). In addition, resistance might be a quantitative phenotype (partial resistance) with a partial reduction in disease severity. On the one hand, it has been argued that these various types of resistance might have distinct values in disease management strategies because of differences in durability in the field. For example, race or cultivar-specific resistance mediated by single resistance (*R*) genes is thought to be of limited value in the field, because of the rapid evolution of new virulent races of the pathogens. On the other hand, nonhost and partial resistance appear more durable (Fig. 1). However, the extent to which durable nonhost or partial resistance involves genetic components that are distinct from *R* genes remains unclear.

The hypersensitive response (HR) of plants is often associated with disease resistance[2]. The HR generally occurs as a rapid, localized necrosis, a form of programed cell death. It follows perception by the plant of pathogen signal molecules (elicitors) encoded by avirulence (*Avr*) genes[3]. Specific receptors, encoded by *R* genes, interact directly or indirectly with elicitors, thereby initiating signal transduction pathways that lead to the HR and the expression of the disease resistance response. One consequence of this, is that races of the pathogen that contain a mutation in their *Avr* gene(s) can arise and become virulent on particular plant genotypes. The *R* genes from unrelated plant species share similar structural domains, suggesting conserved mechanisms of pathogen recognition and signaling of defense responses in the plant kingdom[3,4]. Some of these domains, such as the Toll-interleukin 1-resistance (TIR) domain, also occur in mammalian and invertebrate proteins involved in innate immunity, suggesting an ancient origin for mechanisms of cellular defense[4].

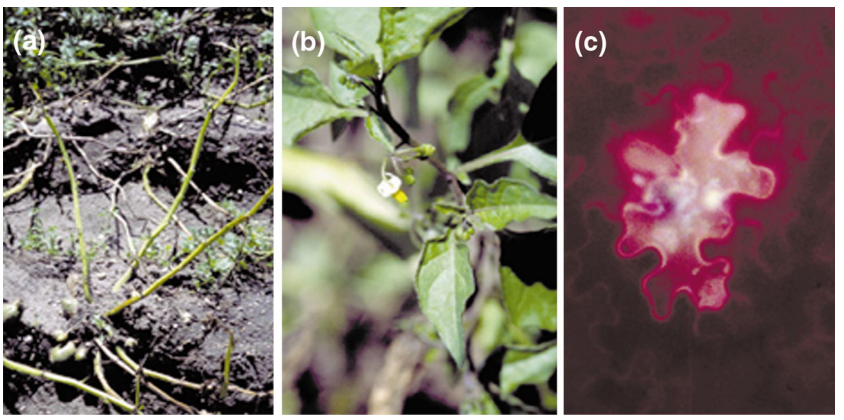

Fig. 1. Nonhost resistance in weeds. Late blight, caused by the 'Irish famine fungus' *Phytophthora infestans* (*Phytophthora* is Greek for plant destroyer), is the most devastating disease of potato worldwide. An entire field can be destroyed within a few weeks. (a) Infected potato plants that were not treated with chemicals and were under highly favorable environmental conditions show systemic blight symptoms. The leaves turn black and drop to earth, and ultimately the plants will die. When the field is examined in more detail, healthy green weeds can be seen among the blighted potatoes. These weeds exhibit nonhost resistance to the late blight pathogen. One indigenous weed seen commonly in infected European fields is black nightshade (*Solanum nigrum*) (b). Even though this plant has been continuously exposed to late blight since the introduction of *P. infestans* to Europe 150 years ago, it has remained resistant. Laboratory inoculation of *S. nigrum* with *P. infestans* shows penetration of the leaf epidermis accompanied by rapid cell death [hypersensitive response (HR)] of the penetrated plant cells (c). Phenolic compounds that accumulate in HR cells show a bright autofluorescence when illuminated with UV (1000× magnification). A future challenge is to engineer potatoes into nonhosts of *P. infestans*, just like all the weeds that grow in infected fields.

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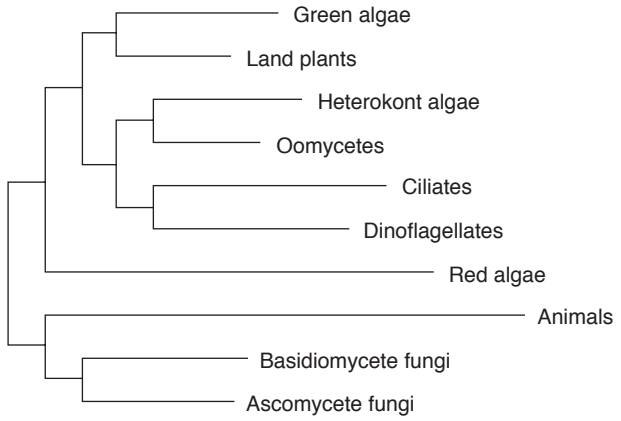

Fig. 2. Phylogenetic tree showing the evolutionary relationships between the major eukaryotic groups (adapted from Ref. 6). Note the position of the oomycetes compared with the other eukaryotic plant pathogens (filamentous fungi in the basidiomycetes and ascomycetes). Oomycetes appear as an independent group of plant pathogenic eukaryotes.

An improved understanding of the molecular basis of the various types of disease resistance is essential to achieve durable resistance. Here we review our current knowledge of resistance to oomycetes and illustrate the frequent association of the HR with resistance responses in interactions between plants and oomycete pathogens, particularly *Phytophthora* and downy mildews.

The oomycetes

Oomycetes exhibit a filamentous growth habit, and are often inaccurately referred to as fungi. Biochemical analyses, in conjunction with phylogenetic analyses of ribosomal and mitochondrial gene sequences, suggest that oomycetes share little taxonomic affinity to filamentous fungi, but are more closely related to golden-brown algae and heterokont algae in the Kingdom Protista[5–7]. Therefore, oomycetes include a unique group of eukaryotic plant pathogens that have evolved the ability to infect plants independently of true fungi (Fig. 2). This suggests that oomycetes might have distinct genetic and biochemical mechanisms for interacting with plants. For example, in contrast to filamentous fungi[8,9], oomycetes contain little or no membrane sterols, which are the target of toxic saponins, and are therefore unaffected by these compounds, which are abundant in plants.

Resistance to oomycetes

Infection events

The disease cycle of several plant pathogenic oomycetes is well characterized. Early infection events are similar in both susceptible and resistance interactions. Typically, infection starts when zoospores (motile spores) encyst and germinate on root or leaf surfaces (Figs 3 and 4). Alternatively, in some species, sporangia (asexual spores) might germinate directly. Germ tubes penetrate an epidermal cell to form an infection vesicle. In susceptible plants, branching hyphae with feeding structures known as haustoria, expand from the site of penetration to neighboring cells through the intercellular space (Fig. 4a). In resistant plants, the major defense reaction is the HR (Fig. 4b). The timing and extent of the HR varies depending on the interacting pathogen and plant genotypes. In some cases, such as with many nonhost interactions, the HR remains limited to one or a few cells (Fig. 1c). In other cases, such as *P. infestans* infection of resistant potato cultivars carrying the *Solanum demissum R* genes, or potato cultivars with high resistance levels, a group of cells display the HR and the infection is stopped at a later stage (Fig. 4c). Interestingly, interactions displaying partial resistance are sometimes also associated with HR lesions (Fig. 4d). In these cases, the HR appears ineffective in blocking the pathogen, resulting in numerous escaping hyphae and a typical phenotype of trailing HR, in which the pathogen hyphae remain ahead of the plant response.

Race or cultivar-specific resistance

A number of *R* genes targeted against the downy mildews *Peronospora parasitica* (*RPP* genes)[10–12] and *Bremia lactucae* (*Dm* genes)[13] have been isolated from *Arabidopsis* and lettuce, respectively. All identified genes encode receptor-like proteins that contain a nucleotide binding site and several leucine-rich-repeats (LRR). This structure is typical of *R* genes active against other pathogens. At least three classes of *R* proteins targeted against oomycetes are known, and are distinguished by their N-terminal regions, which show homology to the TIR domain (*RPP1* and *RPP5* clusters), leucine-zipper motifs (*RPP8* cluster) or have no obvious homology to known domains (*Dm3* cluster). However, specificity of recognition might lie in the hypervariable LRR regions[11–13]. These *R* genes are thought to interact with pathogen *Avr* factors that have yet to be identified. Resistance mediated by *R* genes in *Arabidopsis* and lettuce is always associated with the HR, which is generally visible as a distinct necrosis and correlates with the accumulation of autofluorescent compounds and irreversible membrane damage[14,15]. The extent, timing and severity of the HR varies depending on the *R* gene examined and the pathogen strain.

Nonhost resistance

Parsley is a nonhost of *Phytophthora sojae* and *Phytophthora infestans*. Following inoculation with *Phytophthora*, parsley cells exhibit a complex and coordinated series of morphological and biochemical defense responses that culminate in HR cell death[16–18]. An extracellular 42 kDa glycoprotein elicitor from *P. sojae* or a 13 amino-acid oligopeptide (Pep-13) derived from this protein are sufficient to induce changes in plasma membrane permeability, an oxidative burst, activation of defense genes and accumulation of defense compounds[19]. In addition to signaling molecules, local mechanical stimulation, perhaps similar in nature to that caused by the invading pathogen, induces some of the early morphological reactions and potentiates the response to the elicitor[20]. However, the signal(s) that lead to activation of the HR in the parsley system remain unknown.

In tobacco and other species of the genus *Nicotiana*, resistance to *P. infestans* is diverse and the HR varies in intensity depending on the plant species examined[21]. *P. infestans*, as well as other *Phytophthora* species, produce 10 kDa extracellular proteins, termed elicitins, which induce the HR and other biochemical changes associated with defense responses in *Nicotiana*[22–24]. *P. infestans* strains deficient in the elicitin protein INF1, induce disease lesions on *Nicotiana benthamiana*, suggesting that INF1 functions as an *Avr* factor that conditions resistance in this species[21]. In contrast, INF1 deficient strains remain unable to infect other *Nicotiana* species, such as tobacco. In this example, tobacco might react to additional elicitors, perhaps other members of the complex INF elicitin family of *P. infestans*[25]. Similar to the phenotypic expression of resistance, the genetic basis of *Nicotiana* resistance to *P. infestans* could be diverse. In the case of *N. benthamiana*, a single component, the recognition of INF1, is the main determinant of resistance, but in other *Nicotiana* species a more complex genetic control, perhaps an array of *R* genes with different specificities, might be responsible. In the light of this diversity, the *P. infestans–Nicotiana* system appears an ideal model to dissect and compare the molecular basis of nonhost recognition in closely related species.

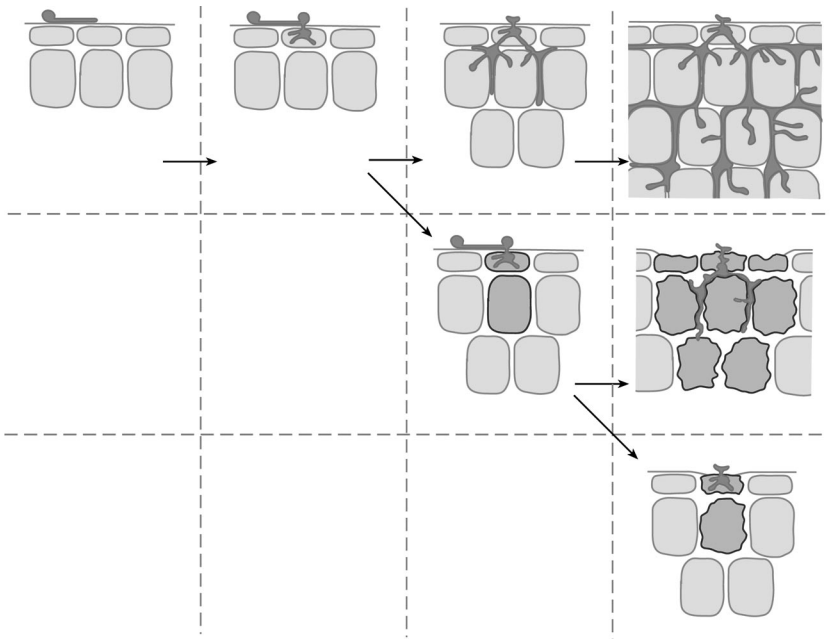

Fig. 3. Schematic view of the early infection events in susceptible and resistance interactions between *Phytophthora infestans* and plants. Early stages are similar in all types of interactions. In susceptible plants, no visible defense responses occur (upper row), secondary hyphae grow into the intercellular space and form haustoria inside mesophyll cells. The hyphae branch and rapidly colonize the mesophyll tissue, which will finally result in disease. In resistant plants, cells are activated after penetration by the pathogen (middle row). The hypersensitive response (HR) is induced and the pathogen is contained within a group of dead plant cells (middle row) or within the penetrated epidermal cell (lower row) depending on the genotypes of the interacting plant and pathogen. The HR lesions in the middle row are visible macroscopically as brownish–black spots. In many nonhost plants (lower row), the HR is induced extremely fast, and only one or two plant cells are sacrificed. Macroscopically no symptoms are visible.

Phytophthora mirabilis, a host-specific species closely related to *P. infestans*, infects *Mirabilis jalapa* but is unable to infect potato and tomato. Interspecific hybrids between these two *Phytophthora* species are essentially unable to infect the original host plants, suggesting that avirulence on the nonhosts is dominant[26]. In contrast to the parental strains, large HR lesions are induced by several of the hybrids on tomato, indicating an alteration to the extent of the HR. Future genetic work could help to identify the components of host-specificity in these interactions.

Partial resistance

Partial resistance to *Phytophthora infestans* occurs commonly in wild *Solanum* species[27]. Cytological examination of plants infected by *P. infestans* reveals HR-like necrotic reactions and, on numerous occasions, late or trailing HR are observed (Fig. 4). Interestingly, a similar phenotype is observed in transgenic *Arabidopsis* plants homozygous for the *R* gene *RPP1-WsB* following inoculation with *Peronospora parasitica*[11]. These plants show partial resistance to *P. parasitica*, as illustrated by a trail of HR cells adjoining the invading hyphae. This suggests that in some cases, weak *R* gene–*Avr* gene interactions or gene–dosage effects could result in ineffective HR reactions, resulting in partial resistance phenotypes.

Partial resistance to two races of *P. infestans* was found to segregate in a cross between non-inbred diploid potato lines. Quantitative trait loci (QTLs) contributing to resistance to late blight have been identified[28]. Two of these loci correspond to regions of the genome that contain clusters of known *R* genes and *R* gene analogs[29], raising the possibility that these QTLs might represent genes homologous to typical *R* genes. Molecular cloning of the sequences determining the QTLs for late blight resistance should help to explain the molecular basis of partial resistance to *P. infestans*.

Resistance to Pythium

Pythium species are abundant in water and soil habitats. In contrast to many *Phytophthora*, and all downy mildew species, *Pythium* are not host-specific and can cause minor infections on numerous plant species. In most cases, *Pythium* causes limited infection and is restricted to the meristematic tips, epidermis, cortex of roots, and fruits[30]. A severe host response to *Pythium* infections occurs when the pathogen moves deeper into plant tissue and reaches the vascular system, resulting in severe wilting. Thus, most mature plants are partially resistant to *Pythium* and the infection is restricted to peripheral or immature tissue. This resistance does not appear to directly involve the HR, but instead defense responses mediated by physical barriers and the plant hormones jasmonate and ethylene. *Arabidopsis* mutants deficient or insensitive to jasmonate are heavily colonized by the normally minor pathogens *Pythium mastophorum* and *Pythium irregulare*[30,31]. Similarly, transgenic tobacco plants exhibiting ethylene sensitivity following transformation with the *Arabidopsis* mutant gene *etr1-1* were more susceptible to *Pythium sylvaticum*[32]. This jasmonate and ethylene-mediated defense system could form the basis of the ubiquitous partial resistance of plants to these common oomycetes.

Interestingly the jasmonate pathway, which mediates resistance to *Pythium*, appears to act independently of the salicylic acid pathway[33], which is activated during and following the HR (Refs 2,34). In contrast to treatments with salicylic acid, treatment of *Arabidopsis* plants with methyl-jasmonate does not result in resistance to *Peronspora parasitica*[33]. In addition, the jasmonate-insensitive *Arabidopsis* mutant *coi1* does not show enhanced susceptibility to *P. parasitica*[33]. These results suggest that the HR and HR-related pathways are more important in resistance against host-specific biotrophic pathogens, such as the downy mildews, than in resistance against non-specific pathogens, such as *Pythium*.

A general role for the hypersensitive response

The HR is associated with all known forms of genetic resistance to *Phytophthora* and downy mildew oomycetes. There is an emerging body of evidence that suggests that *R* gene receptors triggered by pathogen elicitors might mediate nonhost resistance and partial resistance phenotypes. This should lead to a reassessment of the potential usefulness in the field of resistance reactions mediated by *R* genes and involving the HR. Even though *R* genes are thought to be ineffective in the field over long periods of time, there are plausible hypotheses that suggest that these genes could mediate durable resistance. For example, an arsenal of *R* genes recognizing a number of unrelated *Avr* targets would be difficult to overcome as the pathogen would require multiple independent mutations to become virulent[3,35]. This model of genes-for-genes interactions is sufficient to explain nonhost resistance of *Nicotiana* to *Phytophthora*,

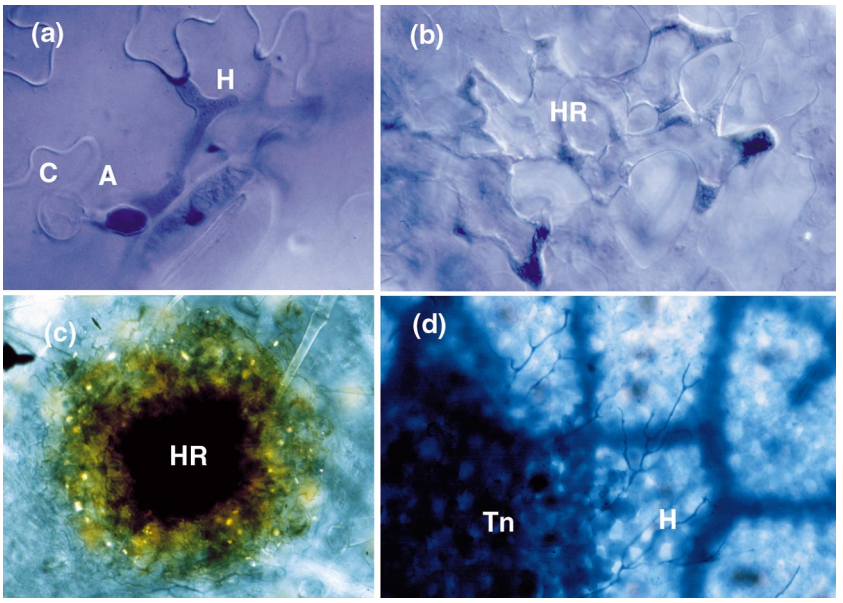

Fig. 4. Cytology of *Phytophthora infestans* and *Solanum* host plant interactions. Hyphae and reacting plant cells are visualized by trypan blue staining (a, b, d), and phenolic compounds are visualized as brown spots in aniline blue stained tissue (c) with DIC optics. (a) Penetrated plant cells of a susceptible potato cultivar 'Bintje' do not show a visible plant response and pathogen hyphae expand through the plant tissue (1000×). (b) In potato cultivar 'Ehud' carrying the R1 resistance gene, a few mesophyll cells beneath the penetration site have collapsed following the induction of the HR (640×). (c) In the partially resistant cultivar 'Robijn', several mesophyll cells are involved in the HR before the pathogen is restricted (200×). (d) Containment of hyphae in HR lesions is not always achieved in partially resistant plants, such as *S. arnezii* × *hondelmannii*. In some infection sites, the expanding hyphae are followed by a trailing necrosis (200×). Abbreviations: A, appressorium; C, cyst; H, hypha; HR, hypersensitive response; Tn, trailing necrosis.

a system in which multiple elicitor signals have been identified in the pathogen[21,25,36,37]. Alternatively, a durable *R* gene could recognize an *Avr* gene that is essential to the pathogen[3,38,39]. Targeting the pathogen's 'Achilles heel' is expected to lead to durable resistance because mutations in the dual *Avr*–virulence gene would probably result in a severe fitness penalty for the pathogen. In the tomato fungal pathogen *Cladosporium fulvum*, the application of this concept led to the identification of a tomato *R* gene targeted against ECP2, the most important virulence factor of this organism[39]. Widespread cultivation of tomato lines harboring *R-Ecp2* would help to determine the long-term resistance of this genotype, and the future potential of the strategy.

It is possible that the ability of pathogens to evolve new races, which is the basis of the lack of durability of genetic resistance, is linked to epidemiological events. For example, plants that exhibit partial resistance might not impose sufficient selection pressure to allow novel virulent races to dominate populations of the pathogen[40]. In this case, partial resistance could prove durable regardless of whether it is mediated by *R* genes or by other mechanisms.

Nonhost resistance genes from Arabidopsis?

An untapped source of nonhost resistance genes might be the model plant *Arabidopsis*. Resources for genetic and genomic analyses are well developed for *Arabidopsis* and the entire genome is scheduled to be sequenced by the year 2000 (Ref. 41). *Arabidopsis* is resistant to economically important oomycetes, such as *P. infestans and P. sojae*. Following inoculation of *Arabidopsis* leaves with *Phytophthora* zoospores, a typical HR response is observed (E. Huitema and S. Kamoun, unpublished). *Arabidopsis* genes, perhaps homologs of known *R* genes that direct this nonhost resistance might occur. As transfer of disease resistance genes between different plant species has been successful in some cases[42,43], the potential exists to isolate resistance genes from *Arabidopsis* and transfer them to potato or soybean to engineer nonhost resistance to *Phytophthora* in these crops.

Future prospects

Many of the components that define the molecular basis of resistance and host-specificity in interactions between oomycetes and plants remain unknown. However, oomycete research is entering an exciting phase. Recent technical developments, such as routine DNA transformation[44], genetic manipulation using gene silencing[45] and the development of detailed genetic maps[46], will facilitate cloning and allow functional analysis of numerous candidate genes involved in oomycete interactions with plants. Map-based cloning of *Avr* genes from *P. infestans* and *P. sojae* is in progress. The isolation of *Avr* genes from downy mildews is more challenging because of the biotrophic nature of these organisms. However, biochemical-screening approaches, such as the identification of pathogen molecules that interact with plant receptors, might prove fruitful. Viral systems for the expression of *Avr* or elicitor genes in plants[39,47,48], should facilitate the identification of elicitor activity and the dissection of genetically complex resistance processes, such as the nonhost resistance of *Nicotiana* to *Phytophthora*. Unraveling the nature of oomycete *Avr* and elicitor molecules, and their role in the various types of resistance, will aid in understanding the molecular basis of race evolution and defining sustainable strategies for engineering durable genetic resistance.

A remaining challenge is to identify the resistance genes involved in nonhost or partial resistance to economically important oomycetes, such as *P. infestans* and *P. sojae*. With our improved understanding of the molecular nature of *R* genes, new methods, such as PCR-based approaches to isolate analogs of *R* genes from resistant plants, in combination with reverse genetics and complementation into the host crop, should facilitate the cloning and identification of novel *R* genes[42].

Acknowledgements

Our thanks to Lauren Farr for preparing Fig. 3, Anne Dorrance, David Francis and Tea Meulia for helpful comments and suggestions on the manuscript, and the Fyto cantine for promoting scientific interaction.

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