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Authors: Micali, Cristina, Göllner, Katharina, Humphry, Matt, Consonni, Chiara, and Panstruga, Ralph

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The Powdery Mildew Disease of Arabidopsis: A Paradigm for the Interaction between Plants and Biotrophic Fungi

Cristina Micali,^a Katharina Göllner,^{a,b} Matt Humphry,^a Chiara Consonni,^a and Ralph Panstruga^{a,1}

^a Max-Planck Institute for Plant Breeding Research, Department of Plant-Microbe Interactions, Carl-von-Linné-Weg 10, 50829 Köln, Germany

^b Present address: University of Aachen, Department for Biology III, Worringer Weg 1, 52056 Aachen, Germany

¹ Address correspondence to panstrug@mpiz-koeln.mpg.de

The powdery mildew diseases, caused by fungal species of the Erysiphales, have an important economic impact on a variety of plant species and have driven basic and applied research efforts in the field of phytopathology for many years. Although the first taxonomic reports on the Erysiphales date back to the 1850's, advances into the molecular biology of these fungal species have been hampered by their obligate biotrophic nature and difficulties associated with their cultivation and genetic manipulation in the laboratory. The discovery in the 1990's of a few species of powdery mildew fungi that cause disease on Arabidopsis has opened a new chapter in this research field. The great advantages of working with a model plant species have translated into remarkable progress in our understanding of these complex pathogens and their interaction with the plant host. Herein we summarize advances in the study of Arabidopsis-powdery mildew interactions and discuss their implications for the general field of plant pathology. We provide an overview of the life cycle of the pathogens on Arabidopsis and describe the structural and functional changes that occur during infection in the host and fungus in compatible and incompatible interactions, with special emphasis on defense signaling, resistance pathways, and compatibility factors. Finally, we discuss the future of powdery mildew research in anticipation of the sequencing of multiple powdery mildew genomes. The cumulative body of knowledge on powdery mildews of Arabidopsis provides a valuable tool for the study and understanding of disease associated with many other obligate biotrophic pathogen species.

INTRODUCTION

From the 1943 first proposal of Arabidopsis as a genetic model organism to the publication of its entire genome sequence in 2000 by the Arabidopsis Genome Initiative, this small mustard plant has been the source of a large body of biological information on many topics, some highlighted within this book, including the realm of plant pathology (see Meyerowitz, 2001 for a retrospective of Arabidopsis biology).

Heralded by Friedrich Laibach as a great genetic tool (see Leonelli, 2007 for a brief history of Arabidopsis research), due to its small genome, its relatively short generation time, high fecundity and ease of mutagenesis, Arabidopsis has been used extensively for the past 20 years to unravel basic plant defense response mechanisms that reach beyond the plant biology boundaries (e.g. Ratcliff et al., 1997; Felix et al., 1999; Robatzek et al., 2006; Navarro et al., 2006; Shen et al., 2007). The recent identification of common resistance genes and basic defense-related pathways among cereals and Arabidopsis (Collins et al., 2003; Consonni et al., 2006; Jensen et al., 2007; Shen et al., 2007) further reinforce the value of Arabidopsis as a scientific tool for plant-microbe interaction studies.

The scientific progress made on Arabidopsis pathology research has gained momentum in the past few years. In particular,

the study of obligate biotrophic and hemibiotrophic pathogens such as powdery mildews (ascomycetes), downy mildews (oomycetes) and bacteria has significantly contributed to our current knowledge about the molecular basis of basal and isolate-specific defense mechanisms. The discovery and functional characterization of bacterial and oomycete pathogen effectors also brought us closer to a general understanding of their disease-causing mechanisms. In this review, we summarize the scientific progress that has been made in the study of powdery mildew diseases in Arabidopsis and discuss the features of this pathosystem(s) that make it the prototype for the study and understanding of biotrophic fungi-plant interactions in general.

The Magic Roundabout: Life cycle of powdery mildews on Arabidopsis

The causal agents of powdery mildew diseases encompass a diverse range of pathogenic species under the broad umbrella of the order Erysiphales, phylum of Ascomycota (see Braun et al., 2002 for more details). Worldwide, approximately 500 powdery mildew species are able to colonize about 10,000 distinct plant species (Takamatsu, 2004). The disease is characterized by the

appearance of white powder-like fungal growth, which consists of the mycelium and spore carriers (conidiophores), on the surface of infected plant organs (predominantly leaves, Figure 1A). Powdery mildew is particularly prevalent in temperate and humid climates where it frequently causes significant yield losses and reductions in product quality in agricultural settings. Among the economically important plant species susceptible to powdery mildew are cereals (e.g. wheat and barley), members of the Solanaceae (e.g. tomato), Cucurbitaceae (e.g. squash), grapevine, and ornamental plants (e.g. roses), (Adam and Somerville, 1996). Although natural and induced resistance to the powdery mildew disease has been known and extensively studied in cereals such as barley (Jørgensen, 1994), it is with the relatively recent identification of fungal species pathogenic on *Arabidopsis thaliana* that conceptual models of plant resistance and host compatibility are beginning to emerge.

Erysiphe cruciferarum (Koch and Slusarenko, 1990), *Golovinomyces* (syn. *Erysiphe*) *cichoracearum* (Adam and Somerville, 1996) and *Golovinomyces* (syn. *Erysiphe*) *orontii* (Plotnikova et al., 1998) are powdery mildews of cucurbits and crucifers that are able to infect *Arabidopsis* (Table 1). In addition, the less-extensively characterized tomato powdery mildew pathogen *Oidium neolycopersici* can successfully reproduce on *Arabidopsis* (Bai et al., 2008; Ellis and Turner, 2001; Jones et al., 2001; Göllner et al., 2008; Whipps et al., 1998; Xiao et al., 2001; Table 1). Although all aforementioned species can colonize *Arabidopsis* under controlled laboratory conditions, the fungal species range, frequency and intensity of infections in natural *Arabidopsis* habitats has, to our knowledge, not been studied. Preliminary observations suggest that powdery mildew does not appear to represent a particularly

prevalent disease of *Arabidopsis* in natural settings (K. Schmid, personal communication). Initial surveys of resistance and susceptibility to various powdery mildew isolates were performed on a broad range of *Arabidopsis* accessions collected throughout the world (Adam et al., 1999). However, more in-depth pathology and genetic studies involved a defined number of *Arabidopsis* ecotypes and mutants and are summarized below.

In laboratory conditions, fungal infections are performed by brushing, touching or shaking infected material onto *Arabidopsis* leaves. Within 1 or 2 hours, a conidium that has landed on a leaf will imbibe and germinate, producing a primary germ tube that differentiates at its terminus a specialized infection structure, the appressorium (Figure 2, 3 and 4A). The appressorium defines the site at which the fungal pathogen attempts to breach the underlying cell wall. A mixture of enzymatic activities and pressure from the penetration peg (2 to 4 MPa in the grass powdery mildew *Blumeria graminis*; reviewed in Tucker and Talbot, 2001) acting on the epidermal cell pave the way for plant cell invasion. Penetration attempts are typically accompanied on the host side by the production of cell wall appositions (CWA, also termed papillae), which are thought to represent a physical and chemical blockade deployed to arrest infection (see discussion below). Successful penetration results in host plasma membrane invagination to accommodate the primary feeding structure of the fungus, the haustorium (Figure 5, reviewed in O'Connell and Panstruga, 2006). In biotrophic pathogens haustoria are believed to be responsible for the uptake of sugars and amino acids from the plant to the fungal mycelium (Hahn et al., 1997; Voegelé et al., 2001) and are thought to actively deliver proteins (effectors) to suppress plant immune responses as is the case for rust fungi (Dodds et

Table 1. Distinguishing anatomical and developmental features of four powdery mildew species pathogenic on *Arabidopsis*^a.

	<i>G. cichoracearum</i> (UCSC1)	<i>G. orontii</i> (MGH)	<i>E. cruciferarum</i> (UEA1)	<i>O. neolycopersici</i>
Conidial size and appearance	26 to 33 µm long 16 to 19 µm wide Smooth surface	29 to 35 µm long 15 to 19 µm wide Mostly smooth surface	38 to 46 µm long 13 to 16 µm wide Wart-like projections	23 to 45 µm long 13 to 20 µm wide Ribbon-like projections
Number of conidia per conidiophore	3 to 5	7 to 20	1 to 2	Rarely more than one and up to 3 ^c
Appressoria	Unilobed	Unilobed	Multilobed	Multilobed
Hauatoria	Ellipsoidal	Spherical	Ovoid, elongated	Spherical, sac-like ^c
Hyphal branch angles	45 to 90 degrees	90 degrees	Less than 45 degrees	90 degrees ^c
Alternate hosts	Asteraceae, Cucurbitaceae	Brassicaceae, Solanaceae, Cucurbitaceae	Brassicaceae	Cucurbitaceae, Solanaceae
Conidium germination	1 to 2 hpi ^b	1 to 2 hpi	N/A	3 to 5 hpi ^c
Appressorium formation	6 to 10 hpi	~5 hpi	N/A	6 to 8 hpi ^c
Hauatorium formation	10 to 14 hpi	14 to 16 hpi (D. Meyer, personal communication)	N/A	N/A
Conidiophore formation	4 dpi ^b	5 dpi	5 to 6 dpi	6 dpi ^c

^a Information was obtained from personal communications with D. Meyer as well as from the following publications: Adam and Somerville, 1996; Plotnikova et al., 1998; Adam et al., 1999; Vogel and Somerville, 2002.

^b hpi, hours post-inoculation; dpi, days post-inoculation; N/A: not available.

^c phenotype observed on tomato (Whipps et al., 1998; Jones et al., 2001)

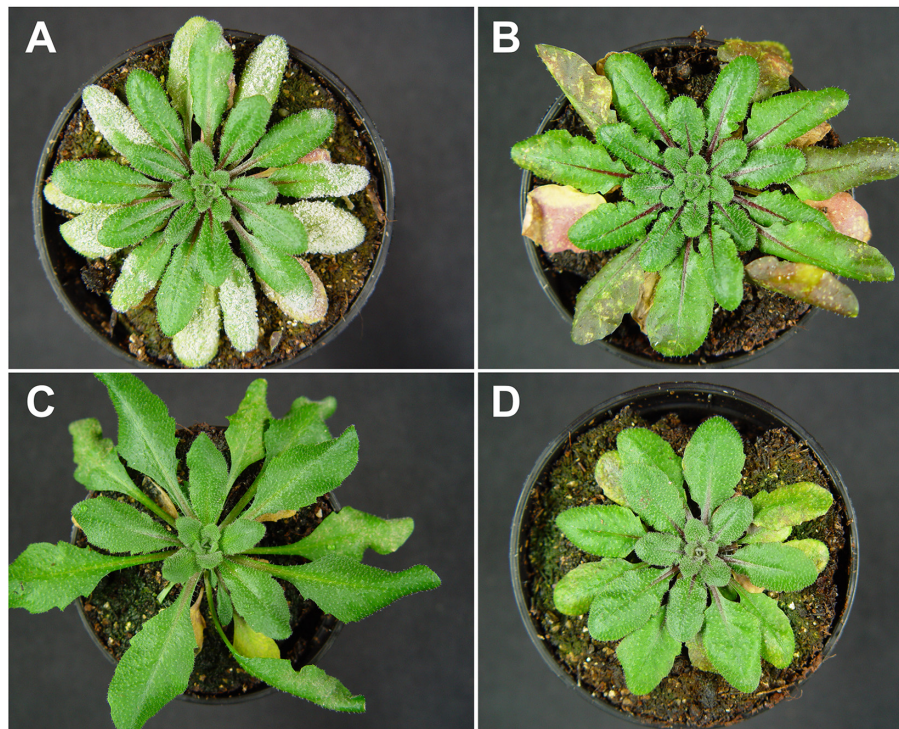


Figure 1. Macroscopic infection phenotypes of susceptible and resistant Arabidopsis lines.

Rosette leaves of 5-6 week old *A. thaliana* ecotypes Col-0 (A), Do-0 (B), and Sorbo (C) as well as the powdery mildew resistant mutant *pmr6-3* (D) at 13 days post-inoculation with *G. orontii*. Completion of the asexual powdery mildew life cycle is evidenced by the occurrence of abundant sporulation (white powder) on inoculated rosette leaves of the susceptible accession, Col-0. Younger leaves without disease symptoms emerged after inoculation with fungal conidiospores. Note the difference in appearance of infected leaves of resistant accessions Do-0 and Sorbo. Resistance in both accessions is assumed to be governed by *RPW8* (Göllner et al., 2008).

al., 2004; O'Connell and Panstruga, 2006). Interestingly, powdery mildew fungi do not invade deeper plant tissues, such as mesophyll cells, but rather limit their growth to the epidermal layer. It has been suggested that the lack of or lower photosynthetic activity of this plant cell layer makes it a powerful nutrient sink that is efficiently exploited by the powdery mildew pathogens (Zeyen et al., 2002). Subsequent to haustorial establishment, secondary hyphal proliferation occurs exclusively on the surface of the leaf or stem (Figure 4B and C). Along the hyphae, new appressoria can form and penetrate epidermal cells and further develop secondary haustoria (Figure 3). Conidiation (the formation and release of asexual spores) completes the vegetative life cycle of the pathogen (Figure 4D).

The better-studied powdery mildew species on Arabidopsis, namely *G. cichoracearum*, *G. orontii* and *E. cruciferarum*, exhibit different infection intensities that are subject to environmental conditions such as temperature, humidity and light intensity (see Table 1). *G. cichoracearum* displays abundant conidiation visible to the naked eye, starting at 7 days post-inoculation (dpi), whereas *G. orontii* requires 10 days for full conidiation and *E. cruciferarum* sporulates little on Arabidopsis (Vogel and Somerville, 2002). The variability in infection phenotypes correlates with the phylogenetic relationship of the three species (the more virulent species *G. cichoracearum* and *G. orontii* being closely related to each other

and each being more distantly related to *E. cruciferarum*; Adam et al., 1999) and is likely indicative of the level of adaptation of each fungus to Arabidopsis. In this sense, the study of the three different powdery mildew species provides a large body of information on the molecular pathways that control this interaction.

The Battleground: Structural and functional aspects of the fungal-plant interface

The intimate interaction established between the plant host and obligate biotrophic fungi such as powdery mildews testifies to the complex cellular processes deployed by both host and pathogen to establish the interface between the two living organisms. The plant cell modifies its architecture and metabolism in response to the invading fungal haustorium to support growth of the fungal colony. Conversely, the fungus adjusts its development and morphology to occupy this niche. Studies into the cellular and sub-cellular structures of the plant-pathogen interface provide valuable information regarding the establishment and maintenance of this fragile interaction (reviewed in O'Connell and Panstruga, 2006).

Among the first critical stages in the infection process of a variety of fungal species is the formation, after germination, of the appressorium and penetration peg. In Arabidopsis and other plant

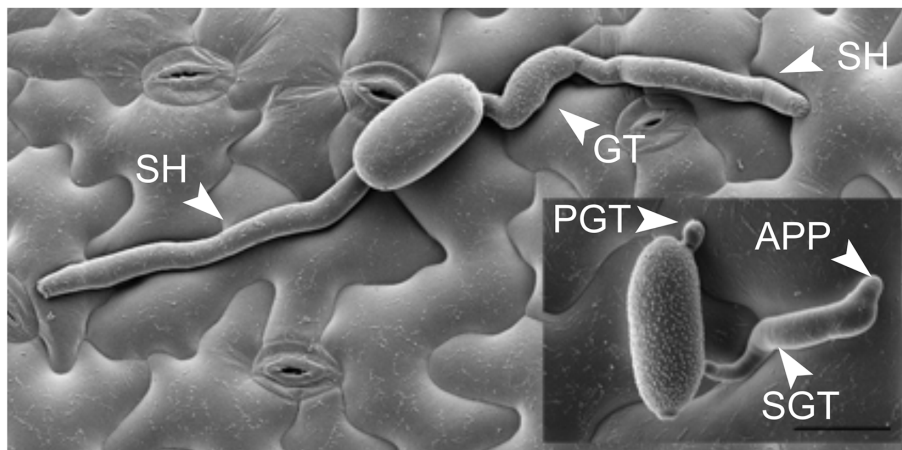


Figure 2. Host and non-host powdery mildew interactions in Arabidopsis.

Scanning electron micrographs of Arabidopsis leaf surface carrying germinated spores of adapted *G. orontii* (large image) and non-adapted *B. graminis* f. sp. *hordei* at 48 hours post-inoculation. Note that *Bgh* forms a primary (**PGT**) and a secondary germ tube (**SGT**), the latter of which differentiates into an appressorium (**APP**), while *G. orontii* produces only one germ tube (**GT**). In the case of *Bgh*, infection is arrested at this stage in approximately 95% of the cases. In contrast, *G. orontii* has already formed secondary hyphae (**SH**) indicating successful host cell penetration and haustorium formation (Photo courtesy of D. Meyer). Scale bar: 20 μ m.

species, attacked cells react to penetration attempts through the formation of CWAs (Figure 6), which – despite sparse experimental evidence supporting this view – are commonly thought to provide both physical cell wall reinforcements as well as a chemical anti-microbial blockade against the invading pathogen (reviewed in Hardham et al., 2007 and Hückelhoven, 2007). Papillae are formed within a few hours after fungal penetration attempts in response to adapted and non-adapted pathogens. Remarkably, physical damage (by needle puncture, for example) can also induce the formation of papilla-like structures, which suggests that it is the pathogen-triggered wounding of plant cells that prompts the formation of CWAs (Aist, 1976). However, detailed analysis of the structures formed in response to non-biotic, mechanical wounds revealed that they are distinct in their composition and likely in their function from fungus-induced CWAs (Russo and Bushnell, 1989). In addition, no papilla formation was detected in response to mechanical (needle) stimulation of parsley suspension culture cells, despite detection of other responses associated with pathogen recognition such as reactive oxygen intermediates (ROI) production and induction of several elicitor-response genes (Gus-Meyer et al., 1998). Although there is no absolute association between papilla formation and resistance to fungal penetration, delayed formation of CWAs is correlated with enhanced fungal infection (Assaad et al., 2004). CWAs are composed of an apparently amorphous mixture of cellulose, pectin, callose, lignins, phenolics, silicon, H_2O_2 and derivatives as well as dedicated *de novo*-synthesized antimicrobial metabolites (phytoalexins) and fungal enzyme inhibitors (Figure 6). Some of these compounds are delivered within secretory vesicles while others are synthesized on the spot by cell wall-resident enzymes (reviewed in Hückelhoven, 2007). Each component of the CWA likely plays a role in defense. Structural components such as pectin, callose and cellulose are thought to provide physical reinforcement to the plant

cell wall at the site of attack (Zeyen et al., 2002). In addition, released moieties of these carbohydrate polymers as well as enzymes involved in their synthesis have potent signaling capabilities and are thought to be involved in the modulation of downstream defense responses (see discussion below). For example, callose synthase GSL5/PMR4 protein (and/or callose itself) appears to be a negative regulator of SA-dependent defense responses and mutations in this gene render Arabidopsis resistant to *G. orontii* and *G. cichoracearum* (Jacobs et al., 2003; Nishimura et al., 2003).

Silicon (Si) is another component found in papillae (Figure 6) that was long thought to provide structural reinforcement to the cell wall (Zeyen et al., 2002). More recently, a comparative transcriptome analysis of Arabidopsis plants either supplied with or lacking Si, revealed that silicon modulates gene expression in a pathogen-dependent manner (Fauteux et al., 2006). Specifically, it appears to dampen general stress responses associated with pathogen infection and partially restores expression of genes encoding components of primary metabolism to normal conditions without affecting the expression of defense-related genes. Reduction of biotic stress responses results in reduced powdery mildew density and conidiation on leaves, effects that had been historically reported for a variety of other plant species treated with Si (Ghanmi et al., 2004).

To complete defense at the cell wall, pathogen-induced antimicrobial compounds (phytoalexins) are actively delivered to the site of fungal contact. Components of the basal defense machinery such as the PEN2 glycosyl hydrolase (associated with peroxisomes; Figure 6) and the plasma membrane-resident PEN3 ABC transporter (Figure 6) are thought to cooperate and generate toxic anti-microbial compounds that are pumped at the site of attack (Lipka et al., 2005; Stein et al., 2006; see below).

The delivery of cell wall components and anti-microbial compounds at CWAs is thought to occur at least in part in membrane-

bound vesicles that move along tracks of actin microfilaments (Figure 6). This view is supported by the observation of massive cytoskeletal re-organization of plant cells upon pathogen attack. Reminiscent of findings in other plant-powdery mildew interactions (Kobayashi et al., 1997a; Opalski et al., 2005) fluorescence microscopy of GFP-tagged Arabidopsis cytoskeletal proteins revealed a rapid concentration of actin arrays towards the site of attack by the non-adapted fungus *B. graminis* f. sp. *hordei*. This rearrangement was accompanied by a mobilization of the nucleus and endoplasmic reticulum to the site of the emergent penetration peg and later towards the developing haustorium (Takemoto et al., 2006). Golgi-derived bodies circulate and make frequent stops below the incipient penetration peg, consistent with the hypothesis that the plant protein synthesis and secretory machinery is actively recruited to the emerging infection structures (Hardham et al., 2007). Mutations in *PEN1*, originally identified as a component of powdery mildew non-host resistance, did not affect actin re-organization upon challenge with the non-adapted barley powdery mildew fungus (Takemoto et al., 2006), suggesting that this protein acts downstream of actin re-organization. However, in barley cells, chemical and genetic interference with actin polymerization significantly affects basal defense and blocks at least partially non-host resistance against inappropriate powdery mildews

(Kobayashi et al., 1997a and b; Miklis et al., 2007). The scenario is similar in Arabidopsis (Yun et al., 2003) and suggests an important functional as well as structural role for cytoskeletal components in plant defense responses (reviewed in Schmidt and Panstruga, 2008).

It is interesting to note that plant cytoskeleton and organelle responses documented for powdery mildew infections are strikingly similar to those observed during infection of several plant species with beneficial arbuscular mycorrhizal (AM) fungi (Strack et al., 2003). In this case, the plant cell guides the formation of intracellular arbuscules (analogous in structure and function to haustoria) through the formation of microtubule tracks and by re-organization of the actin network. In tomato, inhibition of microfilament formation interferes with the proper development of the fungus on root tissue (Timonen et al., 2006).

In pathogenic powdery mildew-plant interactions, components of both fungal and plant origin are implicated in the formation of the haustorium. Post-penetration, the plant plasma membrane invaginates and the haustorium starts to develop, initially as a bud, then as a relatively smooth globular body and finally matures into an intricate, highly convoluted and branched structure (Koh et al., 2005; Figure 5). The haustorium is a unicellular structure shielded from the plant environment by its own plasma membrane, cell wall,

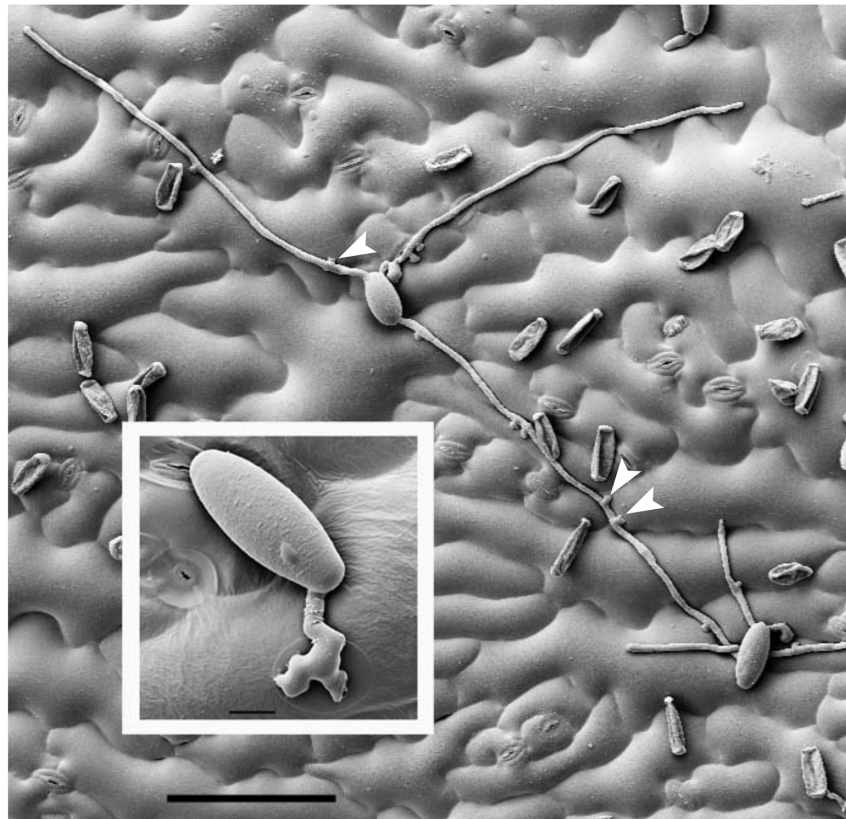


Figure 3. *O. neolycopersici* growing on Arabidopsis Col-0 at four days after inoculation.

Notice the lobate appressoria (arrowheads) that form at regular intervals along the secondary hyphae. The disease index on Col-0 is usually 2.6 (approximately 30% leaf coverage at 15 days post-inoculation; Bai et al., 2008). Scale bar: 10 µm (inset), 100 µm (large picture).

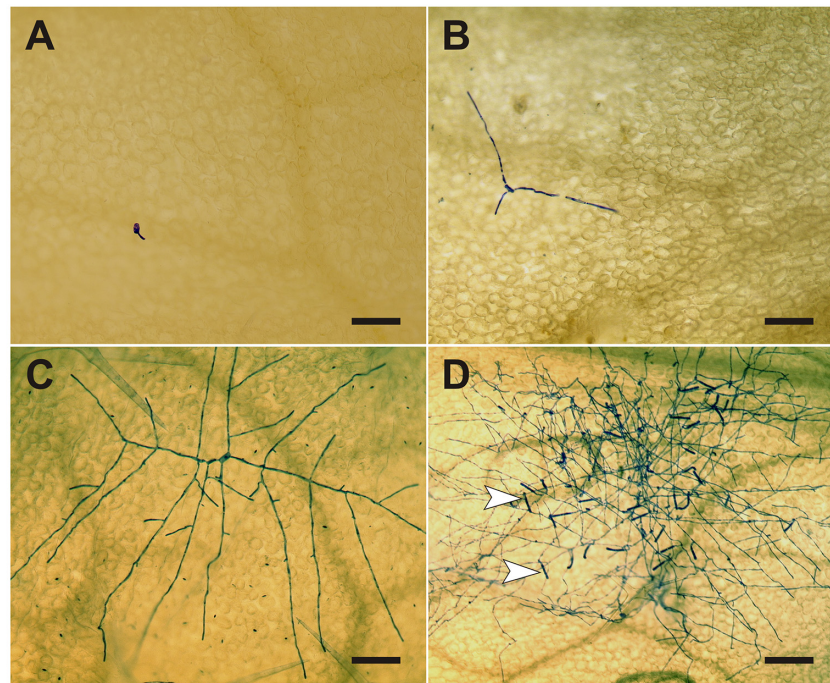


Figure 4. Microscopic analysis of the development of a powdery mildew colony.

The micrographs show the expansion of a *G. orontii* colony on the surface of a Col-0 rosette leaf. The series of events starts with a germinated spore at 24 hours post-inoculation (**A**) (see also Figure 2 for further details on spore germination) and continues with initial hyphal elongation (following successful establishment of the first haustorium inside a host cell) at 48 hours post-inoculation (**B**). Subsequently, a multi-branched mycelium develops (**C**; photo taken at 63 hours post-inoculation) and the appearance of numerous conidiophores (arrowheads) from a fully expanded fungal colony from 5 days post-inoculation onwards completes the asexual life cycle (**D**). Fungal structures were highlighted by Coomassie Blue staining of cleared leaf samples. Scale bar: 100 μ m (**A-C**), 200 μ m (**D**).

extrahaustorial matrix (an amorphous environment separating plant and fungal structures) and extrahaustorial membrane (EHM, a unique interface between the host and the pathogen, thought to be composed of a modified plant plasma membrane; Bracker, 1968). In studies of *G. cichoracearum* haustoria on Arabidopsis, fluorescently labeled host plasma membrane markers spread as far as the two haustorial neckbands that separate fungal from plant structures. Below the neckbands, the EHM has a distinct architecture and function from the plant and fungal membranes (Koh et al., 2005). ATPase and other enzymatic activities normally found at the plant plasma membrane are lacking in the EHM (Spencer-Phillips and Gay, 1981). The EHM enveloping haustoria of the pea powdery mildew, *Erysiphe pisi*, is twice as thick as normal host plasma membrane, is highly convoluted in healthy haustorial complexes and is resistant to detergent treatments (Gil and Gay, 1977). The biogenesis and molecular composition of EHMs covering the haustoria of biotrophic pathogens represents indeed one of the major mysteries of plant-powdery mildew interactions. Under optimal conditions, the life-span and transport capacity of a single haustorium appears to be sufficient to allow the fungus to complete its life cycle (Shirasu et al., 1999). However, defense responses deployed by the host can interfere with optimal haustorium development and function. In Arabidopsis cells infected with *G. orontii*, for example, mature haustoria are frequently encased (partially or fully) in what

appears to be an extension of the papillary structure, characterized by presence of callose (D. Meyer, P. Schulze-Lefert, R. O'Connell and C. Micali, unpublished data). These encasements, when complete, appear to crush haustorial bodies and may restrict passage of nutrients to the fungus and pathogen effectors to the host. As such they may represent one of the several layers of resistance to powdery mildew infection that are discussed in more detail below.

Déjà vu: RPW8-mediated defense as a recurrent theme in natural powdery mildew resistance

Efforts in dissecting resistance to powdery mildews in Arabidopsis have exploited the natural variation in resistance phenotypes among several hundred accessions collected worldwide (Adam and Somerville, 1996; Adam et al., 1999; Göllner et al., 2008). In most accessions analyzed to date resistance is either polygenic, based on the atypical resistance (*R*) gene *RESISTANCE TO POWDERY MILDEW 8* (*RPW8*), or on combinations thereof, with *RPW8* representing the major Quantitative Trait Locus (Adam and Somerville, 1996; Xiao et al., 1997; Adam et al., 1999; Schiff et al., 2001; Wilson et al., 2001; Orgil et al., 2007; Göllner et al., 2008; Figure 1A-C, Figure 7). In general, more accessions are resistant to *E. cruciferarum* (76%) than to *G. cichoracearum* (63%) (Adam

et al., 1999), while out of 64 accessions tested in an independent study, only 26% were resistant to *G. orontii* (Göllner et al., 2008). These numbers may reflect the degree of adaptation that each of these powdery mildew species possesses to cope with the variations of the antifungal defense repertoire that is common in natural Arabidopsis populations. Notably, the reference ecotype Col-0 was found to be susceptible to all four powdery mildew fungi known to successfully colonize *A. thaliana* (Xiao et al., 1997; Plotnikova et al., 1998; Adam et al., 1999).

RPW1, *RPW2*, *RPW4* and *RPW5* were described as semi-dominant resistance loci and localized to chromosomes II, III, IV and V, respectively (Adam and Somerville, 1996). Additional *RPW* genes, including *RPW6* through *RPW13* were later identified (Xiao et al., 1997; Adam et al., 1999; Wilson et al., 2001). In depth analysis of the genetic basis underlying natural resistance repeatedly pointed to locus *RPW8* as a key player (found in accessions Co-3, Do-0, Ei-4, Ei-5, Kas-1, Ms-0, Nok-3, Shahdara and Wa-1; Wilson et al., 2001; Schiff et al., 2001; Xiao et al., 2001; Göllner et al., 2008). In Ms-0, the best-studied accession exhibiting *RPW8*-mediated resistance, the *RPW8* locus comprises two naturally polymorphic and dominant genes, *RPW8.1* and *RPW8.2*, which control resistance to a broad range of powdery mildew pathogens (Xiao et al., 2001). This scenario is in contrast to the situation with the majority of other *R* genes, which generally confer isolate-specific resistance (reviewed in Martin et al., 2003). In addition to the functional *RPW8* copies, the Ms-0 locus contains the sequence-related paralogs *HR1*, *HR2* and *HR3*, which have been shown not to contribute to resistance (Xiao et al., 2001). Two basic Arabidopsis haplotypes have been identified at the *RPW8* locus based on the presence/absence of *RPW8.1* and *RPW8.2*: one comprises both *RPW8.1* and *RPW8.2* and the other, found in susceptible ecotypes, contains *HR4* in replacement of *RPW8.1* and *RPW8.2* (Xiao et al., 2001; Xiao et al., 2004).

The *RPW8.1* and *RPW8.2* proteins share 45% identity at the amino acid level and lack the typical nucleotide-binding site (NBS) and leucine-rich repeat (LRR) motifs found in most *R* proteins (Martin et al., 2003). Instead, they carry a predicted coiled-coil

(CC) domain and an N-terminal transmembrane (TM) helix that is assumed to localize *RPW8* to endomembranes (Wang et al., 2007; Figure 6). However, as in the case of most *R* genes, *RPW8*-mediated resistance is associated with the expression of pathogenesis-related (*PR*) genes and triggers a hypersensitive response (HR; evidenced by whole cell callose deposition, H_2O_2 accumulation and cell death) in response to pathogen attack (Xiao et al., 2001; Xiao et al., 2003; Xiao et al., 2005; Göllner et al., 2008; Figure 7). Signaling in *RPW8*-mediated resistance has been proposed to occur through a feed back amplification loop in the salicylic acid (SA) pathway and requires the classical components *PHYTOALEXIN DEFICIENT 4* (*PAD4*), *ENHANCED DISEASE SUSCEPTIBILITY 1* (*EDS1*), *EDS5* and *NONEXPRESSOR OF PATHOGENESIS-RELATED PROTEIN 1* (*NPR1*) (Figure 6). Resistance conferred by *RPW8* is however independent of the ethylene (ET) and jasmonic acid (JA)-dependent signaling pathways, since mutations in *CORONATINE INSENSITIVE 1* (*COI1*) and *ETHYLENE INSENSITIVE 2* (*EIN2*) do not compromise *RPW8*-mediated resistance (Xiao et al., 2005). In addition to protection from powdery mildew fungi, *RPW8* conveys resistance to oomycetes (*Hyaloperonospora parasitica*, the causal agent of the Arabidopsis downy mildew disease) and the cauliflower mosaic virus, but not to bacteria (*Pseudomonas syringae*), suggesting that this protein is a component of a larger signaling conduit leading to broad-spectrum resistance to biotrophs, rather than a *bona fide R* gene (Wang et al., 2007). Since the pathways controlling resistance against biotrophic and necrotrophic pathogens appear often to be antagonistic (Feys and Parker, 2000; Glazebrook, 2005; Gupta et al., 2000; Ton et al., 2002), it is not surprising that *RPW8* expression also leads to enhanced susceptibility to necrotrophic fungi such as *Alternaria* and *Botrytis* species (Wang et al., 2007). In this respect, Arabidopsis is confronted with the same dilemma as other plant species: enhanced protection against one type of pathogen might open the door for another. Consequently, occurrence of *RPW8* is associated with both fitness benefits and costs, depending on the presence or absence of the concerned pathogens (Orgil et al., 2007).

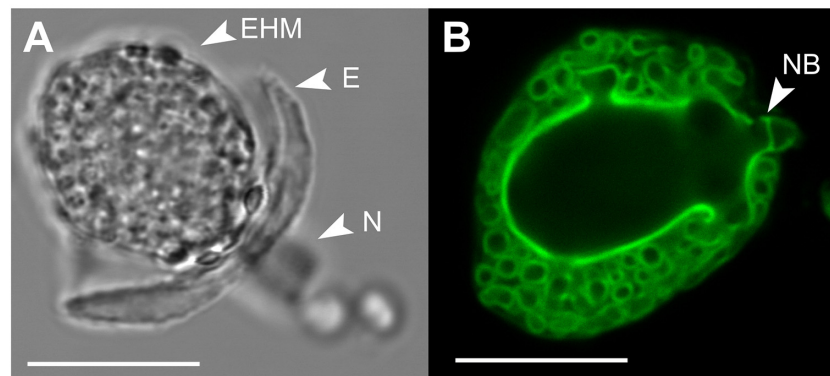


Figure 5. Haustorial complexes of *G. orontii*.

Phase contrast (**A**) and epifluorescence (**B**) micrographs of *G. orontii* haustoria isolated from Arabidopsis leaves. Notice the highly convoluted and complex folding of the haustorial cell surface providing a large area for nutrient uptake from and effector delivery into the host. Haustoria were labeled with wheat germ agglutinin-FITC. EHM: extrahaustorial membrane, E: encasement, N: haustorial neck, NB: neck band. Scale bars: 20 μ m.

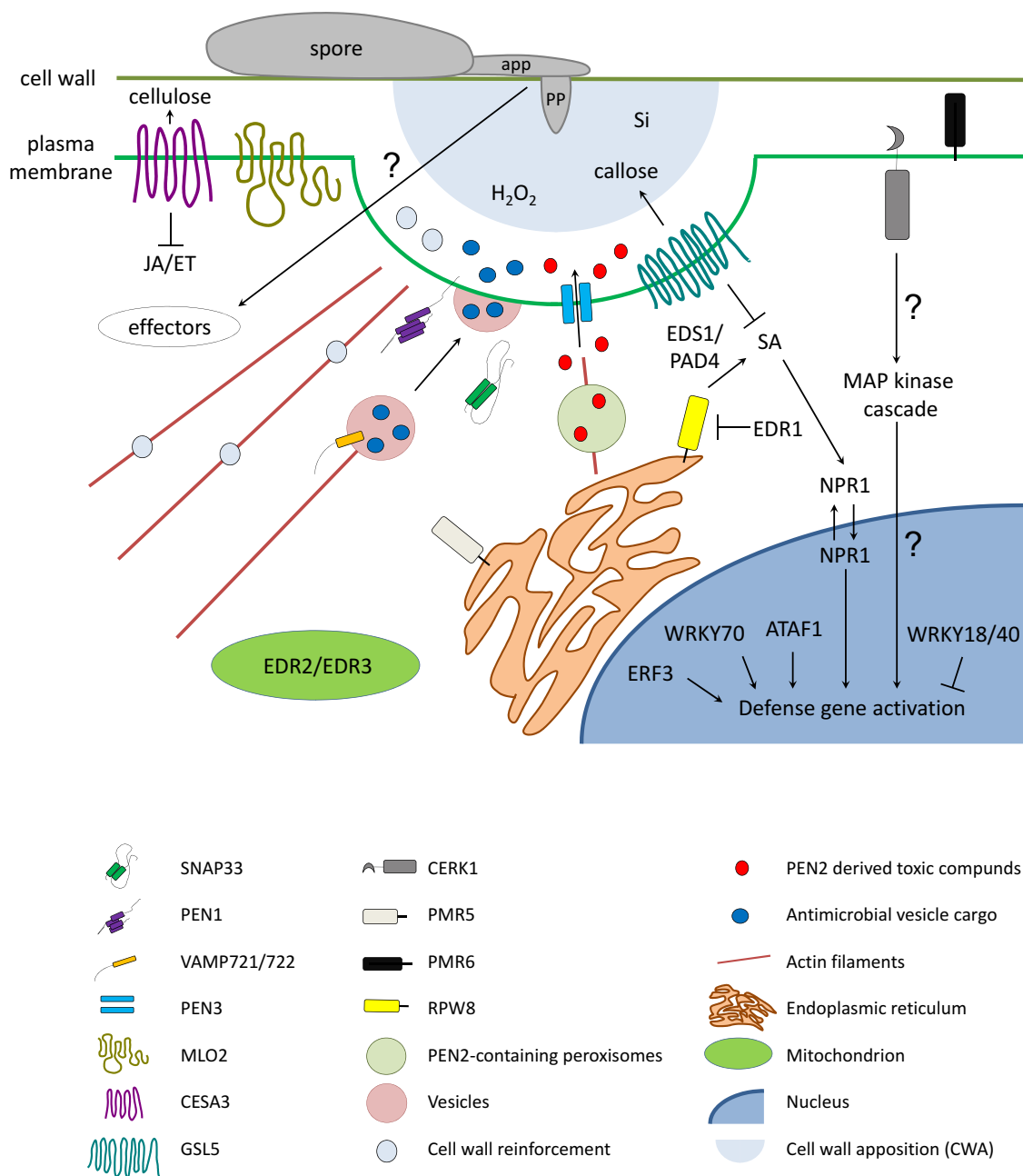


Figure 6. Schematic diagram illustrating genetically-anchored components in Arabidopsis powdery mildew susceptibility/resistance.

The figure depicts a section of a host cell attacked by a powdery mildew germing. Components coded by shape and color are explained in the legend below the scheme. app: appressorium, pp: penetration peg, Si: silicon. Question marks indicate presumed links/activities. For further details, see main text

Despite in-depth searches into Arabidopsis natural isolates from diverse geographical locations, no true race-specific resistance genes against powdery mildew fungi have been identified yet (Göllner et al., 2008). This is in stark contrast to other plant species such as barley (Halterman et al., 2001), grapevine (Barker et al., 2005) and tomato (Bai et al., 2005; Li et al., 2007), where in each case multiple *R* genes recognizing specific fungal avirulence determi-

nants exist. This striking observation suggests that the Arabidopsis-powdery mildew pathosystem might have developed relatively recently and has not had time to mature the classical *Avr/R* gene pairs observed in other pathosystems. Alternatively, it is possible that Arabidopsis is not the primary host of these powdery mildew species in nature (Schulze-Lefert and Vogel, 2000). Finally, the emergence of *RPW8*-based broad spectrum resistance in Arabidopsis may have

eliminated the evolutionary driving force for the acquisition of prototypical *R* genes conferring race-specific resistance. This possibility underscores the importance of the *RPW8* locus as a main component of defense against powdery mildews in Arabidopsis (Xiao et al., 2004; Orgil et al., 2007; Göllner et al., 2008).

Non-host Defenses: Trespassers will be shot! Survivors will be shot again!

Non-host resistance has been defined as the capacity of a particular plant species to resist infection by all genetic variants of a pathogen that normally infect other host species (Thordal-Christensen, 2003). Recent in-depth analysis of genes initially identified as “non-host” defense components suggests that plants deploy a similar arsenal in response to both adapted and non-adapted invaders. The intensity and rapidity of the defense response appear to be essential in determining whether a particular microbe will successfully colonize the plant or be blocked in its attempts.

In Arabidopsis, resistance to non-adapted powdery mildews such as *Blumeria graminis* f. sp. *hordei* (*Bgh*; pathogenic on barley) and *Erysiphe pisi* (pathogenic on pea) is readily detectable at the penetration stage, by the arrest of approximately 80 to 90% of host cell entry attempts. Rare cases of haustorium formation are usually accompanied by callose encasement and often hypersensitive death of the attacked epidermal cell, which prevents any further fungal development (Collins et al., 2003; Assaad et al., 2004; Lipka et al., 2005; Stein et al., 2006). In forward genetic screens, four *penetration* (*pen*) mutants impaired in pre-invasion defenses have been identified, indicating that the respective wild type genes (*PEN1* through *PEN4*) are essential for non-host resistance to *Bgh* and *E. pisi* (Collins et al., 2003; Lipka et al., 2005; Stein et al., 2006; M. Lim and S. Somerville, unpublished data). All four mutants show enhanced penetration and haustorium formation by the two non-host powdery mildew species, yet fail to support further fungal development and sporulation, suggesting that additional defense responses downstream of entry control are at play.

PEN1 encodes a NSF (*N*-ethylmaleimide-sensitive factor) attachment protein receptor (SNARE) domain-containing and plasma-membrane resident syntaxin (Collins et al., 2003). Fluorophore-tagged versions of *PEN1* have been shown to focally accumulate beneath papillae at sites of attempted fungal penetration (Assaad et al., 2004; Bhat et al., 2005). The *PEN1* protein associates via the adaptor protein SNAP33 to Vesicle Associated Membrane Proteins (VAMP), preferentially VAMP721 and VAMP722, to form ternary SNARE complexes (Kwon et al., 2008a; Figure 6). In eukaryotes, ternary SNARE complexes mediate membrane fusion events between vesicles and target membranes (reviewed in Lipka et al., 2007). In the context of antifungal defense, the association of *PEN1*, SNAP33 and VAMP721/722 is believed to tether secretory vesicles to the plasma membrane and eventually force the release of vesicle cargo to the outside of the infected cell (Kwon et al., 2008a). Although the nature of the vesicles and the contents of the cargo are currently unknown, one can not help but compare the action of *PEN1* to that of other syntaxins involved in cell-mediated resistance and inflammatory responses in mammalian systems (Skula et al., 2000). In this well-studied system, immune cells such as cytotoxic T cells and Natural Killer cells can deliver suicide

orders such as the release of GranzymeB-packaged vesicles, to virus-infected cells. By analogy to these mammalian defense systems, *PEN1* is postulated to mediate the release of anti-microbial and possibly cell-wall reinforcing compounds at the site of fungal attack that spare the plant cell from cell death (Kwon et al., 2008b). Delivery of anti-microbial and cell-wall components within specialized vesicles supposedly depend on intact cytoskeleton tracks (see discussion above and Figure 6).

Similarly, the *PEN2* and *PEN3* proteins also contribute to penetration resistance at the cell periphery. *PEN2* shows sequence similarity to glycosyl hydrolases and *PEN3* is a predicted ATP binding cassette (ABC) transporter (Lipka et al., 2005; Stein et al., 2006). *PEN2* was recently shown to possess unexpected myrosinase activity *in vitro*, processing indole glucosinolates into apparently novel toxic products that may act to block further fungal progression (P. Bednarek, personal communication; Figure 6). *PEN3* is thought to cooperate with *PEN2* in pumping out these toxic compounds at the site of fungal penetration (Lipka et al., 2005; Stein et al., 2006). In accordance with this hypothesis, functional *PEN3*-GFP localizes to the plasma membrane and accumulates at the site of *Bgh* penetration (Figure 6). Beyond fungal penetration, the activities of *PEN2* and *PEN3* are thought to further play a role in resistance subsequent to invasion, by poisoning the fungal haustorium with toxic products delivered to the extrahaustorial matrix (Stein et al., 2006). In contrast to *pen1* mutants, which show no dramatic alterations in response to appropriate powdery mildews, *pen2* is hyper-susceptible to the adapted powdery mildews *G. orontii* and *G. cichoracearum* (Lipka et al., 2005). In addition strong chlorosis symptoms were observed on *pen3* after inoculation with the adapted powdery mildew species, *G. cichoracearum* (Stein et al., 2006). This chlorosis phenotype is proposed to be the result of high levels of toxic *PEN2*-derived products, which accumulate in response to repeated epidermal penetration by *G. cichoracearum* in the absence of *PEN3* (Stein et al., 2006). It is notable that the requirements for non-host resistance appear to strongly depend on the nature of the attacking pathogen, since the *PEN1* syntaxin is functionally dispensable for effective pre-invasion (penetration) resistance in non-host interactions with different *Colletotrichum* species (Shimada et al., 2006). Similarly, *pen2* and *pen3* but not *pen1* mutants showed enhanced susceptibility to the inappropriate hemibiotrophic oomycete pathogen *Phytophthora infestans* and the necrotrophic fungus *Plectosphaerella cucumerina*, suggesting that the two former components of non-host defense play a wider role in preventing pathogen attack than the latter (Lipka et al., 2005; Stein et al., 2006).

In addition to pre-invasion resistance controlled by *PEN* genes, post-invasive defenses restrict pathogen growth after the formation of the primary haustorium. The effects of post-penetration defenses were revealed by the removal, through mutation, of penetration resistance associated with *PEN* genes (Lipka et al., 2005). Genes encoding the defense components PAD4, EDS1 and SAG101 (SENESCENCE ASSOCIATED GENE 101; Lipka et al., 2005; Stein et al., 2006) are involved in the establishment of basal defense during compatible interactions and the execution of isolate-specific resistance conferred by a subset of *R* genes (Parker et al., 1996; Feys et al., 2005). In the double mutants *pen2 pad4* and *pen2 eds1*, the non-adapted fungus *Bgh* was able to develop secondary hyphae while in the triple mutant *pen2 pad4 sag101*,

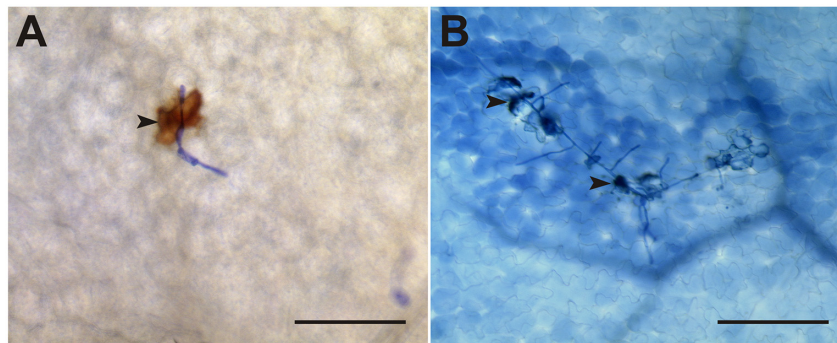


Figure 7. Typical cytological features of *RPW8*-mediated powdery mildew resistance in ecotype Ms-0.

Whole-cell hydrogen peroxide (H_2O_2) accumulation in a *G. orontii*-attacked leaf epidermal cell of the Ms-0 ecotype (A), which is known to express *RPW8*-based powdery mildew resistance (Xiao et al., 2001). H_2O_2 accumulation is highlighted as a brownish 3,3-diaminobenzidine (DAB) precipitate (Thordal-Christensen et al., 1997) inside the challenged cell (arrowhead). Trailing necrosis of *G. orontii*-challenged leaf epidermal cells highlighted by Trypan-blue staining (B). Exemplary dead cells are highlighted by arrowheads. Scale bars: 100 μm

microcolonies were formed and the pathogen was able to complete its life cycle, effectively abolishing non-host resistance in this interaction (Lipka et al., 2005). In addition, triple mutants exhibited full susceptibility to another non-adapted pathogen, *E. pisi*, allowing sporulation comparable to the interaction between wild-type plants and an adapted powdery mildew fungus such as *G. orontii* (Lipka et al., 2005).

Taken together, cumulative mutations in all layers of the non-host defense machinery can transform a non-adapted powdery mildew fungus into a full-fledged pathogen, suggesting that it is largely the ability or inability to overcome species-specific defense barriers that determines the success or failure of a microbe in a given plant-pathogen interaction. Conversely, as outlined below, mutations in so-called compatibility genes can partially or completely close the door to adapted fungi.

Passing on the Message: Defense signaling in Arabidopsis-powdery mildew interactions

It is currently widely accepted (although exceptions exist, see below) that defense signaling in response to biotrophic pathogens typically converges on a pathway controlled by salicylic acid (Glazebrook, 2005). In contrast, defense pathways controlled by JA and ET are overall antagonistic to the SA pathway and are in general known to govern resistance to necrotrophs. Early studies revealed a collection of SA pathway genes involved in basal defense, including *EDS1*, *PAD4*, and *NPR1*. Individuals carrying mutations in these genes allow enhanced growth of the compatible powdery mildew pathogens *G. cichoracearum* and *G. orontii* (Reuber et al., 1998; Glazebrook, 2005), demonstrating the importance of these SA signaling components in limiting growth of powdery mildews on Arabidopsis.

NPR1 and its homologues are major convergence points for SA and JA signaling. NPR1 is a positive regulator of SA signaling and controls basal defense to a variety of pathogens including powdery mildews. Under non-challenged conditions NPR1 exists as cytoplasmic oligomers. Upon increase in SA levels triggered by

pathogen attack, it monomerises and shuttles to the nucleus where it interacts directly with TGA transcription factors and activates *PR* genes and genes encoding WRKY transcription factors responsible for plant defense and cell death (reviewed in Loake and Grant, 2007; Figure 6). The NPR1 homologue NPR4 appears to have a similar role in basal defense. T-DNA insertion mutants in *NPR4* are compromised in their resistance to *G. cichoracearum* (Liu et al., 2005). NPR4 shares 36% amino acid identity to NPR1, its transcript is induced upon SA treatment and it mediates both SA- and JA-dependent gene induction, in a parallel but distinct pathway from NPR1.

In addition to SA signaling, the JA and ET signaling pathways can also contribute to powdery mildew resistance. Although these pathways do not appear to be induced in compatible powdery mildew infections (Reuber et al., 1998; Zimmerli et al., 2004; Glazebrook, 2005), mutants in *CESA3* (*cev1*), encoding a plasma membrane-resident cellulose synthase (Figure 6), produce JA and ET constitutively, have elevated stress response gene expression and are resistant to *G. cichoracearum* (Ellis et al., 2002a and b). Induction of JA responsive genes can also be reproduced by treatment of wild type plants with cellulose synthesis inhibitors, suggesting a role for plant cell wall signaling in general defense responses. However, the artificial means used to induce JA signaling in this mutant and the fact that JA-dependent defense responses are not typically triggered by compatible powdery mildew species (or may actively be suppressed) argues against an authentic role of JA and ET in resistance against these fungal pathogens under natural conditions.

The Right Stuff: Arabidopsis-powdery mildew compatibility factors

The biotrophic lifestyle of powdery mildew fungi dictates that they infect plants and establish colonies in a “quiet” manner, so as not to arouse the defense mechanisms of the host (Panstruga, 2003). They likely also usurp host infrastructure for transport of nutrients and building blocks and coerce the host cell into accommodating

their impressive haustorial feeding structures (Figure 5, Mendgen and Hahn, 2002; Schulze-Lefert and Panstruga, 2003). Specific host genes and/or proteins termed compatibility or susceptibility factors are believed to be essential for successful pathogenesis by a given microbe, and a lack of these factors is predicted to result in resistance to an otherwise virulent pathogen (Vogel and Somerville, 2000; Panstruga, 2003). To isolate compatibility factors, two independent genetic screens were performed in the late 1990s and identified many new components that paint an ever more complex picture of Arabidopsis cellular mechanisms of defense.

A hallmark of constitutive defense is the transcriptional activation of *PR* genes such as *PR1* (reviewed in Loake and Grant, 2007). In an attempt to identify novel elements of resistance, three powdery mildew (*G. cichoracearum*) resistant mutants that do not constitutively express *PR1* were isolated in the lab of R. Innes and named *enhanced disease resistance (edr)* 1, *edr2* and *edr3* (Frye and Innes, 1998; Frye et al., 2001; Tang and Innes, 2002; Tang et al., 2005a and b; Tang et al., 2006). All three mutants display late-onset of resistance (5 to 8 days post-inoculation) that is characterized by accelerated cell death in mesophyll cells leading to large necrotic lesions and limited or absent conidiation of the pathogen. Resistance in all cases is SA-dependent and JA-independent.

EDR1 encodes a CTR1-like protein kinase and negative regulator of disease resistance (Frye et al., 2001). Presence of *EDR1* limits the transcriptional amplification of *RPW8.1* and reduces *RPW8*-conditioned host cell death in response to pathogen attack (Xiao et al., 2005; Figure 6). *EDR2* encodes a mitochondrial protein (Figure 6) with a pleckstrin homology domain and a steroidogenic acute regulatory protein-related lipid transfer (START) motif that are each indicative of a role in lipid binding and signaling. Both *EDR1* and *EDR2* function in a common pathway since double mutants display resistance phenotypes identical to the respective single mutant plants (Tang et al., 2005a). In addition, both mutants display enhanced senescence in response to ethylene. In contrast, *EDR3* appears to function in an independent pathway from *EDR1* and *EDR2* and the corresponding mutant does not display an early senescence phenotype. Like *EDR2*, *EDR3* localizes at least in part to mitochondria and encodes a dynamin-like protein with an N-terminal GTPase domain and a C-terminal GTPase effector region (Tang et al., 2006; Figure 6). In mammals such proteins are responsible for membrane tubulation and vesicle pinching and regulate mitochondrial dynamics associated with apoptosis (programmed cell death; Tang et al., 2006). The characterization of *edr* mutants suggests a link between SA-mediated resistance, mitochondrial function and programmed cell death and further stresses the broad parallels that exist between animal and plant immune responses (Ausubel, 2005). Indeed, a central feature of defense responses in mammalian systems is the ability to undergo apoptosis in response to pathogen (or non-self) detection (Hiscott et al., 2006). Often the apoptotic program is either initiated or amplified in mitochondria and components of the mitochondrial apoptosome are absolutely required for completion of programmed cell death (Keeble and Gilmore, 2007).

In an independent screen performed by Vogel and Somerville to recover loss-of-susceptibility to *G. cichoracearum* mutants in Arabidopsis, the *powdery mildew resistant (pmr)* mutants *pmr1* to *pmr6* were isolated and to date four of them have been cloned

(Vogel and Somerville, 2000; Vogel et al., 2002; Jacobs et al., 2003; Nishimura et al., 2003; Vogel et al., 2004; Consonni et al., 2006; Figure 1D). *PMR2* is allelic to *MLO2* (see also below), *PMR4* (synonyms *CALS12* and *GSL5*) encodes a wound- and pathogen-associated callose synthase, *PMR5* belongs to a large family of plant-specific genes of unknown function and *PMR6* encodes a glycosyl-phosphatidyl-inositol (GPI)-anchored pectate-lyase-like protein (Vogel et al., 2002; Jacobs et al., 2003; Nishimura et al., 2003; Vogel et al., 2004; Consonni et al., 2006). In *pmr4*, *pmr5* and *pmr6* mutants resistance is entirely established post penetration (M. Humphry, unpublished data) and results in reduced colony size and conidiophore formation in interactions with both *G. cichoracearum* and *G. orontii*. The *PMR* genes cloned to date are involved in different cellular activities, underscoring the diversity of plant biological processes that are required for successful powdery mildew pathogenesis.

PMR4 controls callose synthesis at cell wall appositions (papillae) that form beneath infection and wound sites and that are believed to provide a physical barrier to fungal penetration (Aist and Bushnell, 1991; Figure 6). It therefore came as a surprise that a loss-of-function in a callose synthase renders a plant more resistant to powdery mildew infection (Jacobs et al., 2003; Nishimura et al., 2003). A comparative analysis of genes that are differentially expressed in wild-type and *pmr4* plants upon infection with *G. cichoracearum* revealed that resistance to powdery mildews is likely the result of constitutive activation of the SA signaling pathway that is further enhanced upon pathogen attack (Nishimura et al., 2003). Mutations in genes encoding components of the salicylic acid signaling pathway indeed abolished *pmr4*-based resistance without restoring callose deposition at papillae. Callose and/or callose-synthase-based signaling was shown to activate basal defense responses that are effective against a variety of pathogens including *G. orontii* and *H. parasitica* (Jacobs et al., 2003; Nishimura et al., 2003). In this sense, *PMR4* is likely less a fungal-specific compatibility molecule and more a general basal defense switch located at the cell wall that is effective against a broad range of pathogens.

Two additional *pmr* mutants stress the potential importance of cell wall integrity surveillance in resistance mechanisms. *PMR6* encodes a putative pectate lyase with proposed pectin-degrading activity localized at the cell wall. The *pmr6* mutant displays an increased pectin and uronic acid content in the cell wall and exhibits a stunted phenotype (Vogel et al., 2002). In *pmr5*, similar changes in cell wall components have been reported. *PMR5* codes for a member of a large family of plant-specific proteins of unknown function that is likely targeted to the endoplasmic reticulum/secretory pathway (Figure 6). Although the exact mechanism leading to powdery mildew resistance is unknown, it is independent of SA, ET and JA signaling, since mutations in any of the known defense pathways have no effect on *pmr5*- or *pmr6*-based resistance. However, *pmr5/6* double mutants show further increased resistance compared to the respective single mutants, indicating that the two genes likely control parallel and independent defense responses. Furthermore, the fact that *pmr5* and *pmr6* are resistant to *G. cichoracearum* and *G. orontii*, but fully susceptible to unrelated pathogens such as virulent strains of either *P. syringae* or *H. parasitica*, suggests that these two proteins, in contrast to the *PMR4* callose synthase gene, may in fact be true powdery mildew-specific compatibility factors (Vogel and Somerville, 2000; Vogel et al., 2002 and 2004).

MLO proteins: A league of their own

Isolated in the same genetic screen as genes *PMR4*, *PMR5* and *PMR6*, *PMR2* encoding *MLO2* (*MILDEW LOCUS O*) has an essential role in the establishment of compatibility with the powdery mildew species *G. cichoracearum* and *G. orontii*. Together with the phylogenetically closely related paralogs *MLO6* and *MLO12*, which act in concert with *MLO2* in partial functional redundancy (Consonni et al., 2006), *MLO2* controls entry of powdery mildew fungi in Arabidopsis epidermal cells (Figure 8). In this respect, *MLO2*, *MLO6* and *MLO12* and the barley homologue - and first member of this protein family to be identified - *Mlo* (Panstruga, 2005), represent the prototype for molecules that mediate compatibility between powdery mildews and their plant hosts. Loss of particular MLO protein(s) in barley, tomato and Arabidopsis render these plant hosts immune to powdery mildew attack (Bai et al., 2008). The conserved function of MLO proteins in plant defense predates the divergence of dicots and monocots and underscores the importance of this protein family in the establishment of compatible plant-powdery mildew interactions (Consonni et al., 2006). MLO proteins are integral membrane proteins with seven transmembrane domains (Figure 6) that have so far only been identified in plants (Devoto et al., 2003). In Arabidopsis they are encoded by a family of 15 genes and appear to have diverse functions in addition to plant defense. However, only the three closely-related members *MLO2*, *MLO6* and *MLO12* seem to play a role in powdery mildew compatibility.

Consistent with previous findings in barley (Jarosch et al., 1999; Kumar et al., 2001), *mlo2 mlo6* double and *mlo2 mlo6 mlo12* triple mutants show enhanced susceptibility to the necrotrophic pathogens *Alternaria alternata* and *A. brassicicola* and the hemibiotrophic oomycete *Phytophthora infestans*, indicating that MLO proteins modulate the infection process of pathogens with diverse lifestyles (Consonni et al., 2006). Barley MLO and MLO2 from Arabidopsis each interact via a conserved peptide domain in their cytoplasmic carboxyl terminus with the Ca^{2+} sensor calmodulin (Kim et al., 2002; Bhat et al., 2005) and are thought to regulate defense responses against powdery mildews via PEN1 (ROR2 in barley)-dependent mechanisms at the cell periphery (Collins et al., 2003; Schulze-Lefert, 2004; Panstruga, 2005). Similar to non-host resistance, *mlo*-mediated resistance in *A. thaliana* does not depend on the JA/ET or SA signaling pathways (Collins et al., 2003; Lipka et al., 2005; Stein et al., 2006; Consonni et al., 2006). The physical proximity of MLO to the PEN1-dependent non-host defense machinery at the sites of fungal attack (Bhat et al., 2005), the recently observed transcriptional co-expression of these genes in Arabidopsis (M. Humphry, unpublished data) and the genetic and cytological similarities between *mlo*-based and non-host resistance (Humphry et al., 2006) point to a tight mechanistic link between MLO and the basal defense apparatus. The fact that presence of MLO is absolutely required by powdery mildew fungi to successfully infect host plants suggests that these pathogens possibly exploit MLO function(s) to suppress basal defense responses (Panstruga, 2005).

Gene Switches: Transcription factors and gene regulation involved in defense against powdery mildews

In plants, recognition of microbial attack and/or pathogen entry and initiation of defense responses results in a dramatic re-pro-

gramming of gene expression (Schenk et al., 2000; Zimmerli et al., 2004). Whether mediated by direct interaction between a pathogen receptor and transcription factors (Shen et al., 2007) or, as more often observed in animal systems, by a complex signal transduction cascade (mediated by MAP kinases; Asai et al., 2002), the complete activation of defense responses relies in part on the activity of so-called WRKY transcriptional regulators (reviewed in Eulgem and Somssich, 2007).

In Arabidopsis, the WRKY family is composed of 72 expressed members displaying various degrees of functional redundancy with respect to the diverse biological roles they are involved in, including plant defense. *WRKY70* for example, is transcriptionally induced by SA signaling and mediates basal resistance to a variety of pathogens including *G. cichoracearum* (Li et al., 2006; Wang et al., 2006; Ülker et al., 2007; Figure 6). In contrast, *WRKY18* and *WRKY40* act as negative regulators of basal defense against *G. orontii* (Figure 6) and double mutants in these genes are fully resistant to fungal attack (Shen et al., 2007). In the analogous interaction of the monocot barley with its cognate powdery mildew pathogen, *Bgh*, *WRKY18* and 40 counterparts *WRKY1* and *WRKY2* were shown to interact with the CC domain of MLA immune receptors (Shen et al., 2007). Under normal (pathogen-free) conditions, *WRKY1* and *WRKY2* are proposed to suppress the transcription of genes involved in basal defense. Upon pathogen challenge and activation by a matching fungal avirulence protein, the MLA receptor is re-localized to the nucleus where it recruits *WRKY1* and *WRKY2* away from the promoters of defense genes. As expected, silencing of these WRKY transcription factors results in enhanced basal defense against *Bgh* (Shen et al., 2007; Eeckey et al., 2004).

In addition to WRKY transcription factors, the NAC transcription factors, barley NAC6 and its Arabidopsis homolog ATAF1, were recently identified as positive regulators of transcription involved in early defense against powdery mildews. Silencing (barley) or knock out (Arabidopsis) of the respective gene resulted in decreased penetration resistance upon inoculation with *Bgh* while overexpression (in barley) resulted in increased resistance (Figure 6). These findings suggest a conserved contribution of NAC transcription factors in pre-haustorial defense (Jensen et al., 2007).

A member of another group of transcription factors, the wheat Ethylene Response Factor ERF3, has been also suggested to act as a positive regulator of early defense against powdery mildews (Zhang et al., 2007; Figure 6). *ERF3* expression is induced by pathogen challenge (*Bgh*) and the gene product operates as a GCC box-binding transcriptional activator of SA signaling genes (Zhang et al., 2007). Similarly, heterologous overexpression of other members of this family from tomato in Arabidopsis resulted in enhanced resistance to the adapted powdery mildew, *G. orontii*, further corroborating their role as positive regulators of transcription in pathogen defense (Gu et al., 2002).

The Ups and Downs of Gene Expression: Transcriptional changes in response to powdery mildew attack

The broad range of transcriptional changes that occur in Arabidopsis during powdery mildew infection (Zimmerli et al., 2004; Fabro et al., 2008) reflect both defense responses mounted by the plant as well as possible manipulation of the host by the fun-

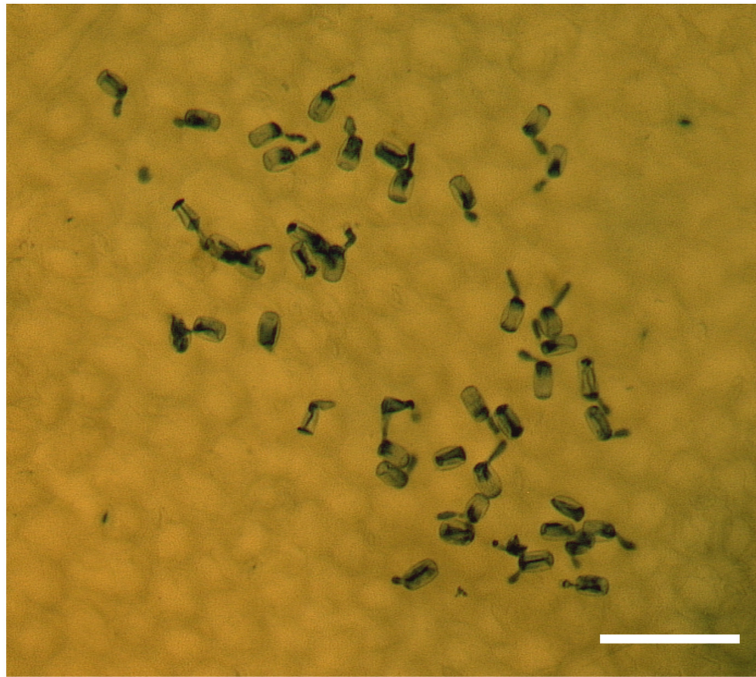


Figure 8. Resistance in Arabidopsis *mlo2 mlo6 mlo12* triple mutants is characterized by complete failure of successful host cell invasion.

The micrograph shows attempted penetration of numerous *G. orontii* sporelings at 48 hours post-inoculation on a highly resistant *mlo2 mlo6 mlo12* triple mutant in the genetic background of otherwise susceptible Col-0 (Consonni et al., 2006). Note the aborted fungal entry evidenced by a lack of secondary hyphae compared to the situation in a Col-0 wild type plant (Figure 4B). Scale bar: 100 μ m.

gal pathogen. With the sequencing of the Arabidopsis genome and availability of novel technologies for transcript profiling (oligonucleotide-based microarray chips) it has been possible to peek into the gene expression changes that occur during the infection process. Several dedicated websites such as Genevestigator (<https://www.genevestigator.ethz.ch/>) and ATGenExpress (<http://www.arabidopsis.org/info/expression/ATGenExpress.jsp>) provide publicly available collections of microarray data on Arabidopsis challenged with a variety of pathogens including powdery mildews, which represent a largely unexplored treasure of information. However, the spatial resolution of microarray data is limiting, since most microarray experiments are performed on whole leaf samples and as such only provide a gross overview about changes in transcript abundance in pathogen-challenged leaf tissue. Since powdery mildews exclusively colonize the epidermal layer of the leaf, many tissue-specific transcriptional changes are likely to be masked by proportionately larger amounts of mesophyll transcripts. Even within the epidermis, attacked cells and successfully colonized cells each differ in their transcript profile from non-attacked cells (Gjetting et al., 2004 and 2007). Owing to these limitations, expression levels of numerous genes in infected host cells might be considerably underestimated. Employment of techniques that allow transcript profiling of powdery mildew-challenged Arabidopsis leaves at cellular resolution, e.g. based on RNA extraction via microcapillaries or by laser microdissection (Kehr et al., 2003), is thus urgently required to refine the currently existing data sets.

A previous study analyzing transcriptional changes in Arabidopsis compared the response observed in host (*G. cichoracearum*) and non-host interactions (*Bgh*; Zimmerli et al., 2004) at 8, 18 and 24 hours post-inoculation. Surprisingly, many of the differentially regulated genes displayed a similar response in both host and non-host combinations. However, in the non-host interaction, the response was more rapid and of greater amplitude than in the compatible interaction, supporting the hypothesis that a common defense machinery is activated upon attack by adapted and non-adapted pathogens and reinforcing the notion that adapted pathogens are able to partially suppress basal defense in their host species.

Among the genes that exhibit lower transcript abundance after pathogen challenge, a majority encode proteins that are involved in photosynthesis, metabolism, transport and transcription/translation. Consistent with these functions, half of the gene products are either known or predicted to be chloroplast residents. This observation corroborates further studies indicating that Arabidopsis suffers up to 30% reduction in the gain of dry weight following *Bgh* infections (Zimmerli et al., 2004). This decrease is more modest in compatible infections with *G. cichoracearum*. An inverse relationship between defense responses and plant growth has been also observed in interactions between cereals and powdery mildews and underscores the metabolic costs associated with activation of defense pathways (Swarbrick et al., 2006; Wright et al., 1995a and b). Intriguingly, a recent microarray analysis of the compatible

interaction between Arabidopsis and *G. cichoracearum*, revealed that host photosynthesis is likely stimulated by the fungus, through the induction of genes involved in chlorophyll binding and chlorophyll a oxygenase (Fabro et al., 2008). Though it is conceivable that an increase in photosynthetic rate is required, as the metabolic demands of the infected epidermal tissue increase, these findings are somewhat contradictory to those obtained in the study of Zimmerli et al. (2004). Manipulation of the host metabolism by the fungal parasite thus likely involves up- as well as downregulation of photosynthetic genes.

However, many gene transcripts related to defense responses accumulate upon both host and non-host powdery mildew attack (e.g. transcripts encoding glycosyl hydrolases and β -1,3-glucanase). Consistently, many of the respective genes contain in their up-stream promoter region the *cis*-regulatory element OCS, which is known to be responsive to auxin, SA and hydrogen peroxide. Transcripts specifically accumulating during non-host interactions encode defensins and derive from genes that are regulated by JA and ethylene. SA signaling therefore does not appear to play an important role in non-host defense against *Bgh*. Alternatively, SA- controlled genes may only become activated once the penetration defenses have failed.

In a separate experiment, analysis of the transcriptional response of Arabidopsis leaves to chitin (the main fungal cell wall polysaccharide) and chitin derivatives identified several genes involved in defense responses (Ramonell et al., 2002). Genes encoding plant-derived chitinases exhibit higher transcript accumulation upon pathogen challenge compared to control conditions and chitin oligomers obtained as fungal cell wall degradation products constitute potent signaling molecules responsible for induced resistance to *G. cichoracearum*. This resistance response appears to be activated through signaling routes that are distinct from the SA, JA and ET pathways (Ramonell et al., 2002). Genes encoding PR5, two WRKY transcription factors and several disease resistance proteins belonging to the TIR-NB-LRR family were induced upon chitin treatment (Ramonell et al., 2005). Genes with reduced transcript abundance included *ETR2*, encoding a transmembrane protein kinase with a LRR domain, the defensin *PDF2.5*, *RAR1* (encoding a protein with two zinc-finger-like domains that is required for the accumulation of many R proteins) and several other genes coding for zinc-finger proteins. To functionally validate the microarray experiments, T-DNA insertion mutants within seven of the differentially expressed genes were tested for susceptibility to *G. cichoracearum*. Three of the seven mutants, encoding a putative RING zinc-finger and two putative disease resistance proteins, displayed enhanced susceptibility to the pathogen, further reinforcing the role of chitin sensing and signaling in plant defense responses (Ramonell et al., 2005).

The critical role played by chitin perception in plant defense responses was recently strengthened by the cloning of the presumptive Arabidopsis chitin (co-)receptor *LysM Receptor-Like Kinase1* gene (*LysM RLK1* or *CERK1*) by two independent groups (Miya et al., 2007; Wan et al., 2008). The gene codes for a plasma membrane-resident protein with a single transmembrane domain, three extracellular LysM domains and a cytoplasmic serine/threonine kinase domain (Figure 6). Mutations in this gene abolish virtually all changes in gene transcription normally observed upon chitin perception by the plant, without affecting other elicitor perception such as flagellin sensing, suggesting that the protein is

part of the chitin receptor complex (Wan et al., 2008). It is conceivable that in analogy to the FLS2 receptor kinase, which is responsible for flagellin-triggered signaling (Asai et al., 2002), LysM RLK1/CERK feeds into MAP kinase signaling and defense gene activation (Figure 6). Interestingly, although loss of *LysM RLK1* caused enhanced susceptibility to the host fungus *G. cichoracearum* at the post-penetration stage (Wan et al., 2008), it did not affect the plant response to the adapted hemibiotrophic fungus *Colletotrichum higginsianum* and resulted in only a marginal increase in susceptibility to the non-adapted necrotrophic fungus *Alternaria brassicicola*. These observations suggest that pathogen perception by the plant is microbe-specific and implies the existence of more elicitor-specific receptors yet to be discovered.

In addition to genes involved in defense responses, genes that are induced because they are likely required for pathogen growth have also been identified (Fotopoulos et al., 2003). The observation that Arabidopsis leaves infected with *G. cichoracearum* have an enhanced sugar uptake compared to non-infected leaves prompted an investigation of sugar transporter expression upon powdery mildew challenge. *G. cichoracearum* induces expression of *STP4*, encoding a glucose transporter as well as *β fruct1*, coding for a cell wall invertase, in several cell types of the leaf (most notably the epidermis and vascular bundle) irrespective of whether they are penetrated by the fungus or not. This transcriptional induction is sustained for up to 6 days post-inoculation and is not reproducible in a non-host interaction with *Bgh*. A similar role for sugar transporters in fungal development was also found in the interaction between the rust fungus *Uromyces fabae* and broad bean (*Vicia faba*). However, in this case, the hexose transporter is of fungal origin and resides in the haustorial membrane (Voegelé et al., 2001), suggesting that exchange of nutrients at the plant/biotroph interface requires transport facilitators on both sides. It is not surprising that sugars, and therefore sugar biosynthesis and transport, would be important for fungal growth and development and enhanced by successful fungal pathogens. The mechanisms leading to this genetic and physiological manipulation remain an enigma. However, new efforts into powdery mildew studies promise to lift the veil on the mystery.

Through the Looking Glass: Powdery mildew biology

A large body of knowledge on plant compatibility and resistance to powdery mildews has considerably advanced our understanding of these diseases. However, our lack of information about many functional aspects of the biology of powdery mildew fungi has created a plant-centric view of this pathosystem. At the present time, we obtain biological information about the fungus predominantly by indirectly looking in the reflection provided by Arabidopsis research. Although the image of this “mirror” is valuable it may sometimes be skewed and it certainly is incomplete. The difficulties hampering direct powdery mildew research stem mainly from their obligate biotrophic lifestyle. The fungi can not be maintained on artificial media and their vegetative spores, at least in the case of the four species pathogenic on Arabidopsis, can not be stored frozen or lyophilized (see long-term storage methods for some powdery mildew species reported in Bardin et al., 2007). Although spores germinate on artificial hydrophobic substrates, growth does not progress beyond the formation of an appressorium. In addi-

tion to these hurdles that prevent any forward genetic screens for pathogenicity mutants, reproducible genetic manipulation of these pathogens is not feasible at present.

Despite these difficulties, genomic and transcript analysis methods have recently been used to crack the code of powdery mildew genes and provide a glimpse into their biology. Several expressed sequence tags (ESTs) and microarray analyses have been performed on *Bgh* (Both et al., 2005a and b) and the genome of this cereal pathogen has been sequenced and is currently being annotated by a scientific consortium in the U.K. (P. Spanu, S. Gurr, N. Talbot, J. Brown, C. Ridout and co-workers, personal communication; see also the BluGen database at <http://www.blugen.org/>). Several thousand ESTs and data from one development-specific microarray analysis of *Bgh* transcripts are publicly accessible (<http://cogeme.ex.ac.uk/index.html>; Soanes and Talbot, 2006; Soanes et al., 2002; Both et al., 2005a). In addition, the genomes of *G. orontii* and *E. pisi* are currently being sequenced by next generation high-throughput DNA sequencing techniques (pyrosequencing) at the Max-Planck Institute for Plant Breeding Research (C. Micali, S. Noir, M. Benjdia, K. Stüber, P. Schulze-Lefert and R. Panstruga, unpublished data). This effort should provide a starting point to the exploration of powdery mildew biology. Among the first cloned genes from a powdery mildew species that is able to colonize *A. thaliana*, a putative ATPase transporter gene (*PMA1*) from *G. cichoracearum* was shown to be induced starting at 3 days and until 6 days post-inoculation on Arabidopsis leaves (Fotopoulos et al., 2006). The complete lack of expression of the gene at 1 day post-inoculation may suggest its selective expression in haustoria, which are not abundant at that early infection stage. A similar induction of a plasma membrane H⁺ ATPase reported for the barley pathogen *Bgh* further supports a role for ATPase pumps in the establishment of a proton potential that can drive the transport of sugars and other nutrients to the fungal haustorium (Both et al., 2005a).

In addition to genes involved in basic fungal housekeeping functions such as nutrition and development, genes that play a direct role in pathogenicity begin to emerge, as more and more fungal pathogen genomes and transcriptomes are being analyzed. The isolation and characterization of bacterial, fungal and oomycete effector and avirulence protein coding genes has opened a new chapter in plant-microbe interactions and has reshaped the way we think about disease and disease resistance (see Bent and Mackie, 2007 for a review of the subject). Although no genes directly involved in virulence have so far been identified in any of the powdery mildew fungi colonizing Arabidopsis, more than 25 avirulence genes and their cognate host *R* genes are known for *Bgh*.

Recently, the isolation and characterization of the first avirulence genes, *AVR_{k1}* and *AVR_{a10}*, from *Bgh* has provided an exciting starting point for further research in the field (Ridout et al., 2006). *AVR_{k1}* and its paralogue *AVR_{a10}* are tightly-linked avirulence genes and encode proteins recognized by the barley resistance genes *ML_{k1}* and *ML_{a10}*, respectively. Using conventional AFLP marker segregation in two crosses between virulent and avirulent *Bgh* strains, the two genes were mapped within a 7.5 kb. interval interspersed with several repetitive sequences. *AVR_{k1}* is a 422 amino acid protein with no homology to any known proteins in the databases. A premature stop codon at amino acid 14 in this protein renders it undetectable by the *ML_{k1}* R protein and is responsible for

virulence of certain *Bgh* strains on *ML_{k1}* plants. Overexpression of either *AVR_{k1}* or *AVR_{a10}* in barley epidermal cells causes cell death that is dependent on the presence of the cognate R protein, *ML_{k1}* or *ML_{a10}*, respectively. In addition, overexpression of the same genes enhances penetration by *Bgh* in the absence of the cognate R protein, indicating a role for *AVR_{k1}* and *AVR_{a10}* in disease establishment. *AVR_{k1}* and *AVR_{a10}* appear to be part of a large gene family, with at least five additional expressed paralogs (based on a survey of the current *Bgh* EST database) and more than 30 genomic copies. The close proximity of the genes to retrotransposon sequences suggests a possible mechanism of gene amplification and genome-wide dissemination. In addition, the multicopy nature of *AVR_{k1}* and *AVR_{a10}* provides the possibility for mutation and escape from host detection, without the evolutionary cost associated with the loss of a virulence gene.

Do *AVR_{k1}* and *AVR_{a10}* represent typical effector/avirulence protein encoding genes in powdery mildew species? Preliminary analysis suggests the existence of *AVR_{k1}*-like sequences in the genomes of *E. pisi* and *G. orontii*, also nested within or in close proximity to retrotransposable elements (C. Micali and R. Panstruga, unpublished results). Whether these sequences are transcribed and encode *bona fide* genes, and whether these genes play a role in pathogenesis are among the many questions that remain to be answered. Based on our current knowledge of effector-encoding genes from other fungal and oomycete pathogens, there appears to be no prototypical protein effector structure. For example, a canonical N-terminal signal peptide for passage through the secretory pathway, a hallmark of nearly all characterized fungal effectors (Bent and Mackie, 2007), is lacking in *AVR_{k1}*, *AVR_{a10}* and its *Bgh*, *E. pisi* and *G. orontii* homologues.

The genetic and molecular study of powdery mildew fungi is still in its infancy. The contribution from genome sequencing efforts will greatly enhance our understanding of these fungi. In the case of powdery mildew fungi, a comparative analysis of the genomes of *Bgh*, *E. pisi* and *G. orontii*, will provide a precious glimpse into their virulence arsenal. In addition, ultrastructural and biochemical studies of the haustoria will likely provide valuable information about the nutrient uptake and host manipulation strategies of these pathogens. Further studies on the lifestyle, sexual reproduction and population structure of powdery mildew species in nature will help to bridge the gap in knowledge we currently have about these fungi and their interaction and disease-causing mechanisms in plants.

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