Complex Interactions between Fungal Avirulence Genes and Their Corresponding Plant Resistance Genes and Consequences for Disease Resistance Management

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INTRODUCTION

During infection, pathogens secrete an arsenal of molecules, collectively called effectors, key elements of pathogenesis which modulate innate immunity of the plant and facilitate infection. Some of these effectors can be recognized directly or indirectly by resistance (R) proteins from the plant and are then called avirulence (AVR) proteins. Recognition of a pathogen AVR protein triggers a set of immune responses grouped under the term hypersensitive response and results in resistance of the plant. R—AVR gene interactions are frequently exploited in the field to control diseases. Recently, the availability of fungal genomes has accelerated the identification of AVR genes in plant pathogenic fungi, including in fungi infecting agronomically important crops. While single AVR genes recognized by their corresponding R gene were identified, more and more complex interactions between AVR and R genes are reported (e.g., AVR genes recognized by several R genes, R genes recognizing several AVR genes in distinct organisms, one AVR gene suppressing recognition of another AVR gene by its corresponding R gene, two cooperating R genes both necessary to recognize an AVR gene). These complex interactions were particularly reported in pathosystems showing a long co-evolution with their host plant but could also result from the way agronomic crops were obtained and improved (e.g., through interspecific hybridization or introgression of resistance genes from wild related species into cultivated crops). In this review, we describe some complex R—AVR interactions between plants and fungi that were recently reported and discuss their implications for AVR gene evolution and R gene management.

Keywords: avirulence genes, resistance genes, fungal effectors, resistance management, virulence factors
Effectors-Triggered Immunity (ETI), frequently leading to a rapid localized cell death termed the hypersensitive response (HR) (Jones and Dangl, 2006). Under the selection pressure exerted by R genes, pathogens can become virulent through evolution of their AVR gene repertoire. Mechanisms leading to virulence include complete deletion, inactivation, or down-regulation of the AVR gene, or point mutations allowing recognition to be evaded while maintaining the virulence function of the AVR protein (Jones and Dangl, 2006; Guttman et al., 2014). One class of R proteins corresponds to cell surface LRR-containing R proteins that are anchored to the plasma membrane via a transmembrane (TM) domain and sometimes include an intracellular kinase domain (Receptor-Like Proteins, RLP/Receptor like Kinases, RLK; Yang et al., 2012). The major class of identified R proteins however corresponds to intracellular nucleotide-binding and leucine-rich repeat receptors (NLR). NLR are multi-domain proteins containing a C-terminal leucine-rich repeat (LRR) domain, a central nucleotide-binding (NB) domain and a N-terminal domain often composed of a Toll/interleukin-1 receptor (TIR) or a coiled-coil (CC) domain (Takken and Govers, 2012). Their multi-domain structure allows R proteins to simultaneously recognize AVR proteins and trigger plant defense reactions. Four models of AVR recognition by R proteins have been proposed and found to co-exist. In the elicitor-receptor model, the R protein directly recognizes its corresponding AVR protein and triggers defense responses (Keen, 1990; Jia et al., 2000; Dodds et al., 2006; Catanzariti et al., 2010; Steinbrenner et al., 2015). In the guard model, the interaction between R and AVR proteins is indirect: the R protein detects modifications of an effector’s host target protein, called a “guardee” (Dangl and Jones, 2001). In the decoy model, the R protein detects modifications in a plant protein (called a “decoy”) that mimics the effector target and “traps” the AVR protein (van der Hoorn and Kamoun, 2008). Finally, in the recently proposed integrated decoy model, non-canonical domains mimicking the effector target are integrated into NLRs and play the role of “decoy” (Cesari et al., 2014a; Le Roux et al., 2015; Sarris et al., 2015).

Fungi are the most devastating pathogens of plants, including crops of major economic importance (Fisher et al., 2012). Genetic control is widely used to limit disease development, mainly through the use of major plant R genes recognizing fungal AVR genes. However, as more and more R and AVR genes are cloned and their molecular interactions are characterized, an increasing number of complex R—AVR gene interactions have been identified (Table 1). Such complex R—AVR gene interactions potentially result from long co-evolution between plants and pathogens and also from the way agronomic crops were obtained and improved, e.g., through interspecific hybridization or introgression of R genes from wild related species. In this review, we highlight some complex R—AVR gene interactions and discuss how they allow plants to expand pathogen recognition, how pathogens circumvent those plant resistances, and how complex interactions could be managed to improve crop disease resistance.

AVIRULENCE GENES RECOGNIZED BY SEVERAL RESISTANCE GENES

AVR genes recognized by several R genes were reported in the pathosystem Leptosphaeria maculans/油菜 rape. L. maculans is a hemibiotrophic ascomycete responsible for stem canker (Blackleg) of oilseed rape (Brassica napus) and is mainly controlled using specific R genes often combined with quantitative resistance. To date, 7 AVR genes from L. maculans have been cloned and all are located in repeat-rich, gene-poor genomic regions (Rouxel and Balesdent, 2017).

AvrLm1 is recognized by two R genes, Rlm1 and LepR3. The two R genes are located on different chromosomes and are thus expected to encode different R proteins, although direct evidence is missing to date since only LepR3 has been cloned (through map-based cloning; Larkan et al., 2013). AvrLm1 is located as a solo gene in the middle of a 269 kb repeat-rich region. Rlm1 resistance was deployed in the 1990s and overcome in only 3 years (Rouxel et al., 2003). The main mechanism leading to virulence toward Rlm1 was a large deletion of AvrLm1 and its surrounding region (Gout et al., 2007), supporting a limited role of AvrLm1 in fungal fitness which is cultivar-dependent (Huang et al., 2010). More recently, AvrLm1 was reported to be recognized by the R protein LepR3, a RLP (Larkan et al., 2013). LepR3 resistance was rapidly overcome in parts of Australia soon after its introduction (Sprague et al., 2006) as a consequence of the previous use of Rlm1 cultivars and the deletion of AvrLm1 in a high proportion of Australian L. maculans isolates (Gout et al., 2007).

AvrLm4-7 is also recognized by two R genes, namely Rlm4 and Rlm7. It is unclear whether Rlm4 and Rlm7, which are clustered in the same linkage group but not cloned, are two different genes or two alleles of the same gene (Delourme et al., 2004). In the field, Rlm4 resistance has been extensively used since the 1970s but is now largely overcome (Rouxel and Balesdent, 2017). The switch to virulence against Rlm4 was due to a single non-synonymous mutation which does not modify the overall 3-D structure of AvrLm4-7 (Blondeau et al., 2015) and does not affect recognition by Rlm7 (Par Lange et al., 2009). Rlm7 resistance was deployed in 2004 and then used extensively (e.g., Rlm7 cultivars comprised 50–70% of the French oilseed crop in 2013; Balesdent et al., 2015). However, the evolution of French L. maculans populations toward virulence against Rlm7 was a long process (4% of virulent isolates in 2010, 19% in 2013). The first molecular events leading to virulence toward Rlm7 mainly corresponded to drastic events (deletion, accumulation of mutations) and also to three amino acid changes without major modification of protein structure (Daverdin et al., 2012; Blondeau et al., 2015). The durability of Rlm7 resistance may reflect the importance of AvrLm4-7 for fungal fitness and aggressiveness (Huang et al., 2006) but also the introduction of Rlm7 into cultivars with high levels of quantitative resistance (Balesdent et al., 2015) and the antagonistic role of AvrLm4-7 on the AvrLm3/Rlm3 interaction (see section An avirulence gene suppressing recognition of another avirulence gene below). In contrast to the AvrLm1/Rlm1–LepR3 interaction, the
TABLE 1 | Characteristics of fungal avirulence genes and plant resistance genes involved in complex interactions.

| Type of interaction | Resistance (R) gene (R protein nature, plant species) | Use in the fields (durability) | Avirulence (AVR) gene (fungal species) | Interaction R/AVR | Involvement in fungal virulence | Main molecular mechanisms leading to virulence | References |
|---------------------|------------------------------------------------------|-------------------------------|----------------------------------------|-----------------|-------------------------------|---------------------------------------------|------------|
| AVR gene recognized by several R genes | Rlm1 (nd, *Brassica napus*) | In the 1990s (overcome in 3 years) | AvrLm1 (*Leptosphaeria maculans*) | nd | Low (cultivar dependent) | Large deletion (AvrLm1 and surrounding genomic region) | Rouxel et al., 2003; Gout et al., 2006, 2007; Sprague et al., 2006; Huang et al., 2010; Larkan et al., 2013 |
| | LepR3 (RLP, *B. napus*) | In 2000 in Australia (overcome in 2 years) | | | | | |
| AVR gene recognized by several R genes | Rlm4 (nd, *B. napus*) | Since the 1970's (1999?) | AvrLm4-7 (*L. maculans*) | nd | High | One point mutation (no major change of the protein structure) | Huang et al., 2006; Parlange et al., 2009; Daverdin et al., 2012; Baclesdent et al., 2015; Blondeau et al., 2015 |
| | Rlm7 (nd, *B. napus*) | Since 2005 (beginning of overcome in 2013) | AvrLm4-7 (*L. maculans*) | nd | High | Inactivating events (deletions, accumulation of mutations/three point mutations (no major change of the protein structure) | |
| AVR gene recognized by two “cooperating” R genes | Pik-1 and Pik-2 (NLR, *Oryza sativa*) | Serial deployment (nd) | AVR-Pik (*Magnaporthe oryzae*) | Direct with the HMA domain of Pik-1 | nd | Point mutations at the interfacing surface involved in Pik/AVR-Pik physical interaction | Yoshida et al., 2009; Kanazaki et al., 2012; Zhai et al., 2014; Macbool et al., 2015 |
| AVR gene recognized by two “cooperating” R genes | RGA4 and RGA5 (also called Pi-CO39, NLR, *O. sativa*) | nd (overcome) | AVR1-CO39 (*M. oryzae*) | Direct with the HMA domain of RGA5 | nd | Deletion | Farman et al., 2002; Okuyama et al., 2011; Cesari et al., 2013; de Guillen et al., 2015; Ortiz et al., 2017 |
| | | | | | | | |
| AVR gene suppressing recognition of another AVR gene | I-2 (NLR, *Solanum lycopersicum*) | In the 1960s (efficient 20 years in combination with I) | AvrR2 (*Fusarium oxysporum* f.sp. *lycopersicium*) | Essential for full virulence | Suppression of I-2-mediated recognition by Avr1/Point mutations in AvrR2 (maintaining effector function) | | Rep et al., 2005; Houterman et al., 2008, 2009; Catanzanii et al., 2015 |
| | I-3 (RLK, *S. lycopersicum*) | In the 1980s (nd) | AvrK3 (*F. oxysporum* f.sp. *lycopersicium*) | Essential for full virulence | Suppression of I-3-mediated recognition by Avr1 | | |
| AVR gene suppressing recognition of another AVR gene | Rlm3 (nd, *B. napus*) | nd | AvrLm3 (*L. maculans*) | nd (conserved in *L. maculans* isolates) | Suppression of Rlm3-mediated recognition by AvrLm4-7 | | Plissonneau et al., 2016, 2017 |

(Continued)
Houterman et al., 2013). Recently, Cesari et al., 2013 found that binding of AVR-Pia to the RATX1 domain of $R_{GA5}$ increases the overall effector binding affinity of $R_{GA5}$ (called the RATX1/HMA domain) resembling a heavy metal-associated (HMA) domain protein from *Saccharomyces cerevisiae*, thought to function as an integrated decoy domain (Cesari et al., 2013, 2014b; Kroj et al., 2016). The Pik locus is also composed of two head-to-head genes separated by a non-coding intergenic region and a HMA domain is present in Pik-1, in this case between the CC and NB domains (Yoshida et al., 2009; Kanzaki et al., 2012). A physical interaction has been demonstrated between AVR-Pik and the HMA domain of Pik-1 (Zhai et al., 2014). Both AVR-Pik and the HMA domain of Pik-1 exhibit amino acid polymorphisms between pathogen isolates and rice cultivars (Yoshida et al., 2009; Kanzaki et al., 2012), located at the interface between Pik-1 and AVR-Pik, mediating their physical interaction and recognition (Maqbool et al., 2015). In *M. oryzae* isolate collections, most are virulent toward *Pia* and *Pi-CO39* and have lost *AVR-Pia* and *AVR1-CO39* (Farman et al., 2002; Cesari et al., 2013). Three isolates virulent toward *Pia* were found to carry an *AVR-Pia* allele with a SNP leading to a non-synonymous substitution, which abolishes interaction with *RGA5* and subsequent recognition (Cesari et al., 2013). Recently, Ortiz et al. (2017) found that binding of *AVR-Pia* to the RATX1 domain of *RGA5* involved hydrophobic interactions and that *AVR-Pia* also interacted with other, as yet undefined, regions of *RGA5*, increasing the overall effector binding affinity of *RGA5* and allowing *AVR-Pia* recognition and plant defense induction despite the accumulation of point mutations in *Avr-Pia* and moderate affinity to RATX1. This work highlights the advantage

### AVIRULENCE GENES RECOGNIZED BY TWO “COOPERATING” RESISTANCE GENES

*AVR* genes recognized by two distinct *R* genes that are both necessary for recognition were reported in the *Magnaporthe oryzae*/rice pathosystem. *M. oryzae*, the causal agent of rice blast, is mostly controlled using resistant rice cultivars harboring major *R* genes. Seven *M. oryzae* *AVR* genes have been cloned (Liu et al., 2013). Interestingly, four of those *AVR* genes (*AVR-Pik*, *AVR-Pii*, *AVR1-CO39*, and *AVR-Pia*) are involved in complex interactions, in that two “cooperating” *R* genes are necessary to recognize each *AVR* (respectively *Pik-1/Pik-2, Pii-1/Pii-2*, and *RGA4/RGA5*; Okuyama et al., 2011; Kanzaki et al., 2012; Cesari et al., 2013; Takagi et al., 2013).

Okuyama et al. (2011) showed that *AVR-Pia* is recognized by two head-to-head *R* genes, *RGA4* and *RGA5*, both being required for resistance. These *R* genes also recognize another *M. oryzae* *AVR* gene, *AVR1-CO39* (Cesari et al., 2013). In this pair of *R* proteins, *RGA4* acts as constitutively active disease resistance and cell death inducer and is repressed by *RGA5* in absence of the pathogen. Direct binding of *AVR-Pia* or *AVR1-CO39* to *RGA5* leads to *RGA4* de-repression and activation of immune signal transduction (Cesari et al., 2014b). Effector binding to *RGA5* occurs in a non-canonical C-terminal domain of *RGA5* (called the RATX1/HMA domain) resembling a heavy metal-associated (HMA) domain protein from *Saccharomyces cerevisiae*, thought to function as an integrated decoy domain (Cesari et al., 2013, 2014b; Kroj et al., 2016). The *Pik* locus is also composed of two head-to-head genes separated by a non-coding intergenic region and a HMA domain is present in *Pik-1*, in this case between the CC and NB domains (Yoshida et al., 2009; Kanzaki et al., 2012). A physical interaction has been demonstrated between *AVR-Pik* and the HMA domain of Pik-1 (Zhai et al., 2014). Both AVR-Pik and the HMA domain of Pik-1 exhibit amino acid polymorphisms between pathogen isolates and rice cultivars (Yoshida et al., 2009; Kanzaki et al., 2012), located at the interface between Pik-1 and AVR-Pik, mediating their physical interaction and recognition (Maqbool et al., 2015). In *M. oryzae* isolate collections, most are virulent toward *Pia* and *Pi-CO39* and have lost *AVR-Pia* and *AVR1-CO39* (Farman et al., 2002; Cesari et al., 2013). Three isolates virulent toward *Pia* were found to carry an *AVR-Pia* allele with a SNP leading to a non-synonymous substitution, which abolishes interaction with *RGA5* and subsequent recognition (Cesari et al., 2013). Recently, Ortiz et al. (2017) found that binding of *AVR-Pia* to the RATX1 domain of *RGA5* involved hydrophobic interactions and that *AVR-Pia* also interacted with other, as yet undefined, regions of *RGA5*, increasing the overall effector binding affinity of *RGA5* and allowing *AVR-Pia* recognition and plant defense induction despite the accumulation of point mutations in *Avr-Pia* and moderate affinity to RATX1. This work highlights the advantage

### TABLE 1 | Continued

| Type of interaction | Resistance (R) gene (R protein nature, plant species) | Use in the fields (durability) | Main molecular mechanisms leading to virulence | Interaction R/AVR | Involvement in fungal pathogenesis | Resistance (R protein nature, plant species) | Essential for full virulence | Essential for host cell death | Essential for susceptibility to host cell death |
|---------------------|-----------------------------------------------|-------------------------------|-----------------------------------------------|------------------|---------------------------------|-----------------------------------------------|---------------------------|---------------------------|-------------------------------------------|
| Bipartite AVR gene recognized by one *R* gene | *AVR2 (F.oxysporum f.sp. lycopersicium)* | In the 1960s (efficient in combination with other *R* genes) | Point mutations in *AVR2* maintaining effector function | Direct | Essential for full virulence | *SIX5 (F. oxysporum f.sp. lycopersicium)* | Essential for full virulence | Essential for host cell death | Essential for susceptibility to host cell death |
| Multiple AVR genes recognized by several *R* genes in distinct organisms | *Avr2 (Cladosporium fulvum)* | In the 1990s (difficult to identify *R* genes) | Essential for full virulence | Direct | Essential for host cell death | *Gr-VAP1 (Globodera rostochiensis)* | Indirect | Essential for host cell death | nd |
| nd | nd | nd | nd | nd | nd | nd | nd | nd | nd |

**Note:** The late breakdown time does not reflect durability of *Rlm4* since it has been used discontinuously.
of integrating the decoy domain into the NLR, instead of having the decoy as an independent molecule. Indeed, even if physical interactions between R and AVR proteins favor diversification at the interfacing surfaces, the high resilience of RGA4/RGA5-mediated AVR-Pia recognition to reduction of AVR-Pia-RATX1 interaction strength limits the pathogen’s ability to circumvent host recognition. The next step forward would be to fuse other effector targets to NLRs as integrated domains to test whether this can confer increased recognition specificity. These effector targets could themselves be engineered in order to be targeted by a larger panel of effectors and pathogens, such as PBS1 from *A. thaliana*, which cleavage by the bacterial protease AvrPphB is detected by the R protein RPS5, and in which substitution of AvrPphB cleavage site with cleavage sites from other effector proteases extended the recognition specificity of RPS5 to other pathogens (Kim et al., 2016).

**AN AVIRULENCE GENE SUPPRESSING RECOGNITION OF ANOTHER AVIRULENCE GENE**

Among the proposed roles of pathogen effectors is the suppression of ETI in order to circumvent plant defenses (Jones and Dangl, 2006). In some cases, an effector, which suppresses the AVR activity of another effector, can itself be recognized by an *R* gene, thus allowing mechanistic-based strategies to genetically control plant diseases. Two such cases of *AVR* genes hiding another *AVR* gene have been reported in *L. maculans* and *F. oxysporum*.

*L. maculans* avirulence gene *AvrLm3* is recognized by *Rlm3*. This recognition is suppressed in presence of *AvrLm4-7* which is itself recognized by *Rlm4* and *Rlm7*. Indeed, silencing of *AvrLm4-7* in an isolate virulent toward *Rlm3* allowed recognition by *Rlm3*, and the complementation of an isolate avirulent toward *Rlm3* with *AvrLm4-7* conferred virulence on *Rlm3* cultivars (Plissonneau et al., 2016), confirming the ability of *AvrLm4-7* to suppress *AvrLm3/Rlm3*-mediated resistance and the presence of *AvrLm3* in *L. maculans* populations. *AvrLm3* was recently identified and is located in a telomeric region of the *L. maculans* genome (Plissonneau et al., 2016). The conservation of *AvrLm3* despite its telomeric location suggests an involvement of *AvrLm3* in fungal fitness (Plissonneau et al., 2017). It seems that the main mechanism to acquire virulence toward *Rlm3* was not the deletion of *AvrLm3* but rather the production of an effector, *AvrLm4-7*, that conceals *AvrLm3*.

*Fusarium oxysporum* f.sp. *lycopersici* (*Fol*) is a common soil fungus infecting tomato. Several *Fol* *AVR* genes were identified, including *AVR1* (recognized by *R* genes *I* and *I-1*), *AVR2* (recognized by *I-2*) and *AVR3* (recognized by *I-3*; Rep et al., 2005; Houterman et al., 2008, 2009). *AVR1* is involved in the suppression of *I-3* and *I-2*-mediated recognition of *AVR3* and *AVR2* respectively. Deletion of *AVR1* in an isolate virulent toward *I-2* and *I-3* allowed recognition by *I-3* and *I-2* plants, and the complementation of isolates avirulent toward *I-3* or *I-2* with *AVR1* conferred virulence on *I-3* and *I-2* tomato plants. *AVR3* and *AVR2* were shown to be essential for full virulence of *Fol* on tomato. In agreement, *AVR3* and *AVR2* are never deleted in *Fol* isolates, and no SNP preventing recognition by *I-3* has been identified, while three SNPs preventing recognition by *I-2* without altering virulence of the corresponding isolates were reported (Lievens et al., 2009). In contrast, *AVR1* has no major effect on *Fol* virulence, suggesting that its role is mainly restricted to suppressing *I-2* and *I-3*-mediated recognition (Houterman et al., 2008).

Such interactions offer great opportunities for the genetic control of plant diseases. In tomato, the combination of *I-1* and *I-2*/I-3 may lead to a durable resistance toward *Fol*, since one *R* gene will be effective against an *AVR* gene important for fungal virulence (*AVR3* or *AVR2*) and another against the suppressor of *I-3*/I-2-mediated resistance. The combination of *Rlm7* and *Rlm3* against *L. maculans* could also increase the durability of the two *R* genes in oilseed rape. It is now important to determine whether pyramiding or alternating deployment is the best strategy. Pyramiding the two *R* genes will exert a strong selection pressure on fungal isolates, which could lead to the emergence of isolates virulent toward both resistances. Alternating two resistances in the field combined with a surveillance of *Fol* and *L. maculans* populations would allow counter-selection of virulent isolates.

**A BIPARTITE AVIRULENCE GENE NECESSARY FOR RECOGNITION BY ONE RESISTANCE GENE**

So far, only a single case of bipartite *AVR* gene/*R* gene interaction has been reported. In *Fol*, *AVR2*, which triggers *I-2*-mediated recognition and is required for full virulence on susceptible tomato (Houterman et al., 2009), shares its promoter region with *SIX5*, which also encodes a protein secreted in tomato xylem sap. Ma et al. (2015) recently reported that *SIX5* is also required to trigger *I-2*-mediated recognition. Thus, deletion of *SIX5* allows *Fol* to escape *I-2*-mediated resistance, while reintroduction of *SIX5* restores avirulence toward *I-2*, showing that *AVR2* and *SIX5* are both necessary to induce *I-2*-mediated resistance. *Avr2* and *SIX5* physically interact, suggesting that *I-2* recognizes the *Avr2*/*SIX5* complex. Similar to *AVR2*, *SIX5* is also present in all *Fol* isolates, and is required for full virulence on tomato (Ma et al., 2015). It is unlikely that specific resistances involved in such bipartite *AVR* gene/*R* gene interactions are more durable, since deletion or point mutation of only one of the *AVR* genes is sufficient to escape recognition by the corresponding *R* gene. Indeed, while no polymorphism was observed in the *SIX5* sequence of isolates virulent toward *I-2*, three point mutations causing single amino acid changes were observed in *AVR2*, allowing *Fol* strains to escape *I-2*-mediated recognition without altering virulence.

**RESISTANCE GENES RECOGNIZING SEVERAL AVIRULENCE GENES IN DISTINCT ORGANISMS**

It has been hypothesized that pathogen effectors target a common set of plant proteins and that plants have evolved...
surveillance systems to recognize multiple AVR genes sharing the same plant target (Mukhtar et al., 2011). Several R genes able to recognize distinct pathogens have been reported, which potentially decreases the need for chemical interventions and opens the path to broad-spectrum disease control. A notable example is Cj2 from tomato, which confers resistance to both the fungal pathogen Cladosporium fulvum and the nematode Globodera rostochiensis (Rooney et al., 2005; Lozano-Torres et al., 2012).

Several apoplastic effectors of oomycetes, fungi, bacteria and nematodes were reported to target papain-like cysteine proteases (PLCP; Kaschani et al., 2010; Lozano-Torres et al., 2012). Avr2, from the tomato leaf mold agent C. fulvum, targets the tomato PLCP Rcr3 and inhibits its activity. Its effector activity on Rcr3 is indirectly recognized by the tomato R gene Cj2, according to the guard model (Rooney et al., 2005). Cys protease activity profiling showed that Avr2 inhibited multiple extracellular Cys proteases, including Rcr3 and its close relative Pip1, and it was proposed by van der Hoorn and Kamoun (2008) that Pip1 was the operative target of Avr2 and Rcr3 acted as a decoy. Silencing of Avr2 significantly decreased C. fulvum virulence on tomato (van Esse et al., 2008). Interestingly, Rcr3 is also targeted by effectors from other pathogens. For example, for an effector of the nematode G. rostochiensis, Gr-VAP1, physically interacts with Rcr3 and triggers a Cj2-dependent hypersensitive response in tomato (Lozano-Torres et al., 2012). Broad-spectrum resistances exert a strong selection pressure on pathogen populations, potentially leading to them being rapidly overcome. Indeed, even though Avr2 was demonstrated to be important for virulence, isolates of C. fulvum virulent toward Cj2 were rapidly reported (Luderer et al., 2002). However, Cj2 is still effective as a result of pyramiding with other specific R genes in tomato crops (de Wit, 2016).

**CONCLUDING REMARKS**

While complex interactions between bacterial AVR genes and plant R genes have been previously discovered and well-studied (Cui et al., 2009; Khan et al., 2016), the characterization of plant/fungal interactions are emerging and show some similarities (cooperating R genes, R genes recognizing distinct pathogens, AVR gene suppressing recognition of another AVR gene) but also specificities (bipartite AVR gene). Among the R genes displaying complex interaction with AVR genes, some of the most promising are those conferring broad-spectrum resistances since they guard key components of plant immunity and, as such, target essential effectors. Even if they exert a strong selection pressure on pathogen populations, they may remain effective through pyramiding with other specific or quantitative R genes. Another promising strategy to manage durable resistances would be to target antagonistic interactions between AVR genes and to combine the corresponding R genes in the same cultivars through pyramiding or to sequentially use the R genes in rotation. Although antagonistic interactions between AVR genes have only been reported twice in plant-fungi pathosystems, they are probably more widely distributed than suspected. Indeed, in cereal powdery mildews it has been suggested that pairs of AVR genes and suppressors of AVR gene recognition could form the basis of specificity (Bourras et al., 2015, 2016).

**AUTHORS CONTRIBUTIONS**

Both authors reviewed literature, contributed to writing the manuscript, and approved it for publication.

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