Plant disease resistance genes: recent insights and potential applications

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Plant disease resistance genes (*R* genes) encode proteins that detect pathogens. *R* genes have been used in resistance breeding programs for decades, with varying degrees of success. Recent molecular research on *R* proteins and downstream signal transduction networks has provided exciting insights, which will enhance the use of *R* genes for disease control. Definition of conserved structural motifs in R proteins has facilitated the cloning of useful *R* genes, including several that are functional in multiple crop species and/or provide resistance to a relatively wide range of pathogens. Numerous signal transduction components in the defense network have been defined, and several are being exploited as switches by which resistance can be activated against diverse pathogens.

Despite substantial advances in plant disease control strategies, our global food supply is still threatened by a multitude of pathogens and pests [1–3]. Plant diseases can dramatically reduce crop yield and the impact of disease outbreaks is particularly acute in developing nations. Pesticides provide effective protection but their applicability can be compromised by adverse environmental effects and by the emergence of resistant pathogen strains. Chemical controls are often beyond the means of farmers in developing nations. For these reasons, much effort has been invested towards understanding innate resistance mechanisms in plants. Plants can activate a very effective arsenal of inducible defense responses, comprised of genetically programmed suicide of infected cells (the hypersensitive response, HR), as well as tissue reinforcement and antibiotic production at the site of infection [4]. These local responses can, in turn, trigger a long lasting systemic response (systemic acquired resistance, SAR) that primes the plant for resistance against a broad spectrum of pathogens [5,6].

This multicomponent response requires a substantial commitment of cellular resources, including extensive genetic reprogramming and metabolic re-allocation [7]. Thus, defenses are kept under tight genetic control and are activated only if the plant detects a prospective invader. Plants do not have the benefit of a circulating antibody system so plant cells autonomously maintain constant vigilance against pathogens by expressing large arrays of '*R* genes' (R, resistance) [8–10]. *R* genes encode putative receptors that respond to the products of '*Avr* genes' (Avr, avirulence) expressed by the pathogen during infection (Box 1, Fig. 1). In many cases, a single *R* gene can provide complete resistance to one or more strains of particular pathogen, when transferred to a previously susceptible plant of the same species. For this reason, *R* genes have been used in conventional resistance breeding programs for decades [11]. The strong phenotypes and natural variability at *R* loci have also been exploited by molecular geneticists to clone the *R* genes and investigate their molecular modes of action.

R gene-mediated resistance has several attractive features for disease control. When induced in a timely manner, the concerted responses can efficiently halt pathogen growth with minimal collateral damage to the plant. No input is required from the farmer and there are no adverse environmental effects. Unfortunately, *R* genes are often quickly defeated by co-evolving pathogens [11]. Many *R* genes recognize only a limited number of pathogen strains and therefore do not provide broad-spectrum resistance. Furthermore, introgression of R genes into elite cultivars by conventional breeding is a lengthy process. However, recent molecular-level insights into the function of R proteins and downstream signal transduction pathways might provide strategies to remedy these deficiencies. We highlight recent advances in basic understanding of *R* gene-dependent resistance and discuss

Box 1. Virulence genes and avirulence genes: what is in a name…?

Although the term 'resistance gene' suggests an obvious function, the term 'avirulence gene' can be somewhat confusing: why would a pathogen express a gene that triggers host resistance? This term was coined by H. H. Flor, during his pioneering classical genetic studies of the flax-flax rust interaction that led to the gene-for-gene hypothesis [56]. Flor observed that *R* genes respond specifically to the direct or indirect products of cognate genes in the pathogen (depicted in Fig. 1), which he dubbed avirulence genes. In this context, the term avirulence gene is appropriate because expression of the *Avr* gene product does indeed confer lack of virulence upon the pathogen. More recent molecular genetic studies with cloned *Avr* genes (unavailable in Flor's time) have shown that many *Avr* genes promote virulence in hosts that do not express the corresponding *R* gene (Fig. 1a). This suggests an evolutionary tug of war in which the pathogen evolves virulence genes, and the plant in turn evolves *R* genes that recognize virulence proteins (or their targets) as signals of invasion (Fig. 1b,c). Thus, a virulence protein can become an avirulence protein if an R protein in the host recognizes it.

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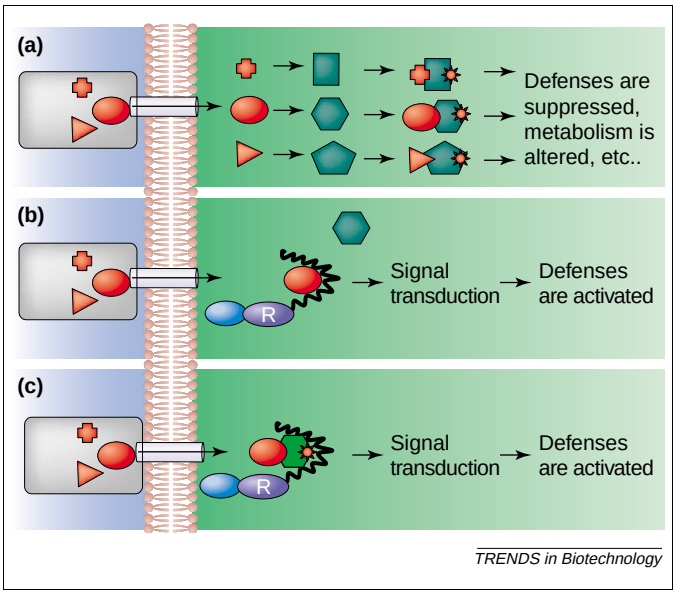

Fig. 1. Interactions between pathogen Avr proteins and plant R proteins. A hypothetical pathogen (grey) has attached to a plant cell and is expressing a suite of virulence proteins (red). These proteins are translocated into plant cells via Type III secretion (bacteria) [52] or other unknown mechanisms (fungi and oomycetes). Once inside, they target host proteins (green) that control defense responses, metabolism or other plant process that affect pathogen virulence (note that virulence proteins could also be targeted towards extracellular proteins). (a) In this panel, the plant cell does not express an R protein that is capable of recognizing any virulence protein. Thus, the plant cannot detect the pathogen efficiently and defenses are, at best, only weakly induced. Disease then results from the collective action of the virulence proteins. (b) This panel depicts the classic receptor–elicitor hypothesis, in which an R protein directly binds a virulence protein. This recognition event activates a complex signal transduction network, which in turn triggers defense responses. (c) This panel depicts the guard hypothesis, in which an R protein (guard) detects a modified host protein (guardee, red star), perhaps as a complex with the 'attacking' virulence protein.

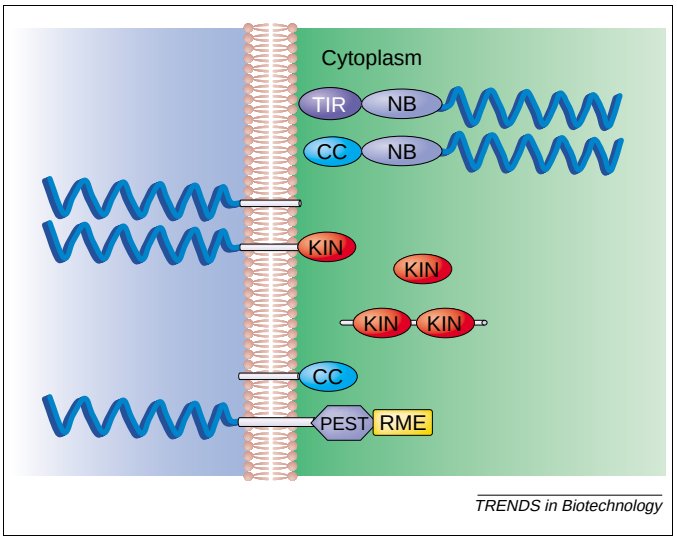

Fig. 2. Major families of R proteins. The majority of R proteins contain tandem leucine-rich repeats (LRRs, depicted in blue), which have a major role in recognition specificity [10]. Members of the most widely represented R protein family (NB-LRR) also contain a nucleotide-binding site and a region of similarity to proteins that regulate programmed cell death in metazoans [8]. NB-LRR proteins are likely localized in the cytoplasm, perhaps as peripheral membrane proteins. Some NB-LRR proteins contain a TIR domain with homology to the metazoan superfamily of Toll-like innate immunity receptors. Other NB-LRR proteins contain a putative coiled-coil domain (CC) at the N-terminus. The eLRR protein family consists of extracytoplasmic leucine-rich repeats, anchored to a transmembrane domain. The LRR-kinase superfamily consists of an eLRR fused to a cytoplasmic serine-threonine kinase domain (KIN). One resistance protein (tomato Pto) is a Ser-Thr kinase, without LRRs, and another (maize Rpg1) contains two kinase domains. The *Arabidopsis* RPW8 protein contains a membrane anchor, fused to a putative coiled-coil domain (CC). The tomato Ve1 and Ve2 proteins contain putative extracellular LRRs, along with a PEST domain for protein degradation (found only in Ve2, and not Ve1), and short proteins motifs that might target the protein for receptor-mediated endocytosis (RME).

initial steps and future prospects for using this knowledge base to enhance natural resistance mechanisms in crops.

Conserved motifs in *R* gene products

Dozens of *R* genes, against many different pathogens, have now been cloned from a variety of plants. These genes encode proteins that can be grouped into several superfamilies, based on protein domains that are described in Figure 2. The vast majority of genes cloned so far belong to the NB-LRR, eLRR, or LRR-Kinase superfamilies [8–10]. These superfamilies were initially identified in tomato, tobacco and *Arabidopsis* by map-based cloning or transposon tagging. The requisite infrastructure for these cloning techniques is not available for many crops, nor for their wild relatives, which can be valuable sources of 'new' resistance genes. However, resistance gene analogs (RGAs) can now be easily identified by sequence similarity: certain functional domains (e.g. the NB domains and core residues of the LRRs) are highly conserved even among distantly related *R* genes, and genomic studies have revealed that the NB-LRR, eLRR, and LRR-Kinase superfamilies are ubiquitous in plants [12]. Thus, RGAs can be cloned by PCR-based approaches and/or by using genomic information and then genetically mapped. If an RGA maps to a previously defined resistance locus its functionality can be tested. This is usually done by determining whether the candidate gene confers resistance when expressed as a transgene in a line that is ordinarily susceptible to disease. This step is often the most problematic in crops that are difficult to transform, particularly because resistance loci are often comprised of complex multicopy clusters of genes [13], which must be sorted through individually. However, this 'positional candidate' approach for *R* gene cloning will become easier as plant genomics initiatives advance and transformation protocols are further streamlined. Thus, it is becoming practical to clone *R* genes from a variety of crops or their wild relatives and to rapidly transfer them into elite cultivars [14], this is a major technological advance from conventional breeding programs.

Prospects for durable resistance

Although it is now easier to identify and deploy useful *R* genes, the problem of durability remains. Many *R* genes lack durability because they can be defeated by a single loss-of-function mutation in the corresponding *Avr* gene (thereby rendering the pathogen 'invisible'). Because individual *Avr* genes often make only incremental contributions to virulence, pathogens can afford to alter or discard an *Avr* gene with little or no fitness penalty [15]. Traditional breeding strategies have used *R* genes 'one at time' in crop monocultures. Such homogeneous host populations exert strong selection for mutation of the relevant *Avr* gene, and then become extremely vulnerable to the emergent pathogen. As an alternative to single-gene deployment, multiple *R* genes ('pyramids') can be bred into individual plant lines [11]. In principle, these pyramids

require the pathogen to accumulate mutations in multiple *Avr* genes to escape detection. This is unlikely to occur if the mutations have a strong cumulative effect on virulence. Another approach is to sow a mixture of lines, each expressing a different *R* gene(s), in the same plot. A susceptible line can be included in the mixture, to reduce the selection pressure for mutations in *Avr* genes [16]. A multiline protocol was tested in a recent study, with striking success [17]. Pyramiding and multiline deployment have not been widely used, owing to the time required for breeding assortments of *R* genes into elite cultivars. However, these strategies will become much more practical as the approaches described earlier are further developed.

There are also prospects for transgenic use of single *R* genes that have previously been proven durable. For example, the pepper gene *Bs2* has provided long-standing resistance against bacterial spot disease, caused by the bacterium *Xanthomonas campestris*. *Bs2* has been cloned from pepper and shown to encode a NB-LRR protein [18]. *X. campestris* is also a significant pathogen of tomato and a pepper *Bs2* transgene works effectively in tomato against *X. campestris*. Recently cloned *R* genes with potential use against fungal pathogens include the barley *Rpg1* gene [19,20] and the tomato *Ve*1 and *Ve*2 genes [21]. *Rpg1* has provided remarkably durable resistance to stem rust for decades while *Ve*1 and *Ve*2 target *Verticillium* species that cause wilt in many different crops. The *Ve* genes can provide resistance to different *Verticillium* species and are functional in potato when expressed as transgenes. The *Rpg1* and *Ve* genes are also interesting from a basic research standpoint because they have novel structural features that distinguish them from previously characterized *R* genes (Fig. 2). It will be particularly interesting to determine whether these genes can be used as prototypes to identify additional *R* genes by sequence similarity.

Additional useful genes might be unearthed through investigations of so-called 'non-host resistance' [22]. This term refers to interactions in which all varieties of a plant species are resistant to all strains of a particular pathogen species (as opposed to intraspecific variability, which is observed for *R* gene-mediated resistance). Because non-host resistance is not genetically variable, this trait has not been amenable to classical genetic analyses. However, experimental tools now available in model plants (e.g. large-scale forward and reverse genetic screens) have made non-host resistance more accessible to genetic dissection. For example, *Arabidopsis* and tobacco are uniformly resistant to many microbes that plague crops (e.g. *Phythophthora infestans*, which caused the Irish potato famine) [23]. Recently, it has been shown that certain signal transduction components are used in *R* gene resistance and for some non-host resistances [24,25]. Thus, it might be possible to identify effective resistance genes against crop pathogens from model species and transfer them into crops. It will be of great interest to determine whether non-host resistance results from natural pyramiding of *R* genes, and/or from use of *R* genes that recognize virulence factors that are essential for the pathogen to cause disease. Note that non-host resistance might result from several mechanisms [22] and it is possible that genetic dissection of non-host resistance will provide unanticipated tools for engineered resistance.

Efforts to transfer *R* genes from model species to crops, or between distantly related crops, could be hampered by a phenomenon termed 'restricted taxonomic functionality' (RTF) [18]. *Bs2* and several *R* genes from tomato can function as transgenes within related species from the same family [13] (e.g. tobacco, potato and pepper, which belong to the *Solanaceae*). However, *Bs2* does not function in *Arabidopsis*, nor does the *Arabidopsis RPS2* resistance gene function in tomato [18]. The molecular basis of RTF is unknown but might reflect an inability of the R protein to interact with signal transduction components that have diverged in the heterologous host [26]. It remains to be seen whether RTF is a general attribute of *R* genes. A recent report suggests that it will indeed be possible to transfer certain *R* genes between distantly related species: the *Arabidopsis RPW8* gene provides broad-spectrum resistance to powdery mildew in *Arabidopsis* and in tobacco [27] (and has a novel structure, Fig. 2). A solution to the RTF problem might be developed as we gain a deeper understanding of *R* gene signaling. Even if this problem proves intractable for 'wide transfers', it should be noted that increasing the breadth of potential resistance sources even by a few genera or species would significantly affect resistance strategies, as exemplified by *Bs2* and the *Ve* genes.

The guard hypothesis

The simplest version of the classical receptor-elictor model predicts a direct interaction between the R protein and the corresponding Avr protein (Fig. 1b). However, intense efforts with numerous sets of R and Avr proteins have revealed only two direct interactions [28,29]. The lack of demonstrable R-Avr interactions led to the formulation of the 'guard hypothesis' by Van der Biezen and Jones [30] (Fig. 1c). This model predicts that R proteins activate resistance when they interact with another plant protein (a guardee) that is targeted and modified by the pathogen in its quest to create a favorable environment. Resistance is triggered when the R protein detects an attempt to attack its guardee, which might not necessarily involve direct interaction between the R and Avr proteins. Compelling evidence for this model was recently reported for an *Arabidopsis* R protein [31] and other putative guard-guardee interactions are being investigated [32,33].

It remains to be seen whether guarding or direct Avr binding is the prevalent mode of R protein action; but if generalized, the guard model represents a significant shift in our view of how R proteins undertake surveillance. Rather than acting as passive security guards that idly wait for specific signals from an invader, R proteins might actively and continuously monitor key physiological processes that are targeted by pathogens. It will be of great interest to define the complete complement of guardees that are targeted by different pathogens and to determine how many different virulence factors converge upon the same targets. For example, one would predict that defense response regulators would be popular targets for manipulation by many types of pathogens.

The guard hypothesis also has implications for engineering resistance. For example, RTF might reflect the

divergence or absence of an appropriate guardee, rather than the inability of the R protein to interact with downstream signaling components in a heterologous host. If true, then transgenic transfer of guard–guardee pairs might extend the range of *R* gene functionality. As the molecular basis of the interactions between pathogen virulence proteins and their host targets becomes clear, it might also be possible to alter guardees so that they cannot be modified by the corresponding virulence factor. This approach carries the obvious challenge of designing a modification that prevents attack while retaining the guardee's endogenous function. However, this could be a fruitful avenue towards cost-free 'passive' resistance, particularly if it is possible to identify guardees that have major roles in disease establishment.

Increasing the breadth of resistance

Many *R* genes have a narrow range of resistance, often to only one or a few strains of a single pathogen species (although some *R* genes do provide a wider spectrum, as noted above). Figure 3 illustrates an alternative strategy for engineering broad-spectrum resistance, based on coordinate expression of an *R* gene and a corresponding *Avr* transgene, controlled by a pathogen-inducible promoter [34]. This tactic enables induction of defense by multiple pathogens without pyramiding numerous *R* transgenes. Furthermore, this system might circumvent the loss of durability commonly observed with *R* genes because the *Avr* gene is not under selective pressure for mutation.

One crucial aspect of this strategy lies in selecting the right promoter to drive the *Avr* gene. An ideal promoter would respond rapidly to a wide variety of pathogens and thereby provide broad-spectrum resistance. The promoter must be inactive under disease free conditions to ensure that the plant does not sustain collateral damage from spurious defense responses triggered by leaky expression of the Avr transgene. Datasets from microarray experiments will aid in the identification of useful promoters. In a different approach, synthetic promoters were engineered by combining *cis* regulatory elements that had been previously

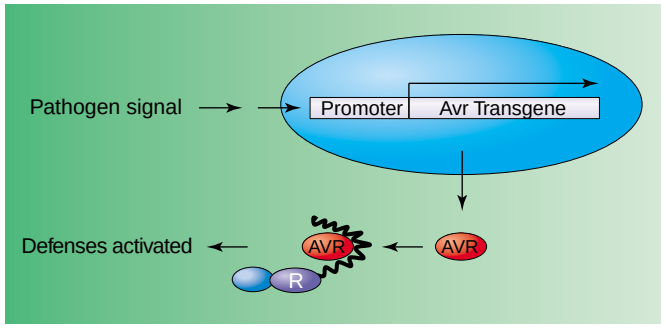

Fig. 3. Strategy for engineering broad-spectrum resistance by induction of Avr/R transgene combinations. A pathogen *Avr* gene is expressed in plant cells as a transgene, under the control of a plant promoter that is induced by a range of pathogens. A corresponding *R* gene (either endogenous or a transgene) is also expressed. Upon pathogen attack, the pathogen-responsive promoter is activated, the *Avr* gene is expressed, and the Avr protein interacts with the R protein to induce the HR and other defense responses. Note that this system can be activated by any pathogen (or spurious stimulus) that is capable of activating the promoter of the *Avr* gene.

associated with defense [35]. Some synthetic configurations were strongly induced by pathogens, while remaining quiescent under disease free conditions. These promoters might prove to be important tools for engineering R/Avr resistance as well as for other strategies, such as localized expression of antimicrobial proteins [36].

Broad-spectrum resistance might also be achieved through manipulation of defense signaling components that act downstream of pathogen recognition. A plethora of defense signals has been identified using genetic, biochemical and physiological approaches [37,38]. Key players in the network include reactive oxygen intermediates (ROIs), nitric oxide (NO), the phenolic salicylic acid (SA), the hormones ethylene and jasmonic acid, and several proteins with presumed or demonstrable regulatory roles. In principle, each component of the signaling network represents a potential switch for activating the defense arsenal. This approach could provide broad-spectrum resistance, if based on master regulators that activate the entire arsenal of defense responses. This approach is likely to be durable: A gain-of-function mutation (e.g. a suppressor of downstream signals) in the pathogen would probably be required to subvert a multicomponent resistance. However, care must be taken to design modifications that are free of undesired side effects, such as reduced stature, which are typically observed in mutants that constitutively express defenses.

With these considerations in mind, the *Arabidopsis NPR1* gene has emerged as a good candidate to provide broad-spectrum resistance. *NPR1* appears to regulate defense gene transcription, through a mode of action described in Figure 4. Recent studies demonstrated that enhanced resistance to diverse pathogens is provided by overexpression of *NPR1* in *Arabidopsis* [39,40] and rice [41], indicating functionality across a wide taxonomic range. Significantly, this resistance is achieved without a substantial yield penalty. This is probably because the *NPR1* transgenic plants do not express defenses constitutively; rather, they appear to be 'primed' to respond to pathogens that would not trigger a timely response in wild-type plants. Transgenic rice plants expressing *NPR1* are currently being tested under field conditions (pers. commun. from Z. He and X. Dong).

As an alternative to transgenic approaches, naturally occurring, defense-inducing compounds could be directly applied to crops [2]. For example, a synthetic analog of SA is being marketed as a foliar spray to control pathogens by inducing systemic acquired resistance in crops [42]. A pathogen's own weapon is used against it in a second approach: A protein called Harpin, which regulates Type III secretion of virulence factors in pathogenic bacteria, can also induce SAR when applied as a spray [2].

Most of the strategies discussed above induce the HR, resulting in programmed cell death (PCD) around the infection site. PCD is obviously an effective defense against 'biotrophic' pathogens that parasitize living plant cells. However, many important fungal pathogens use a 'necrotrophic' approach, in which they obtain nutrients by killing plants cells. It is not clear that HR-based strategies will be useful against nectrotrophs. Indeed, some necrotrophs exploit endogenous plant PCD pathways

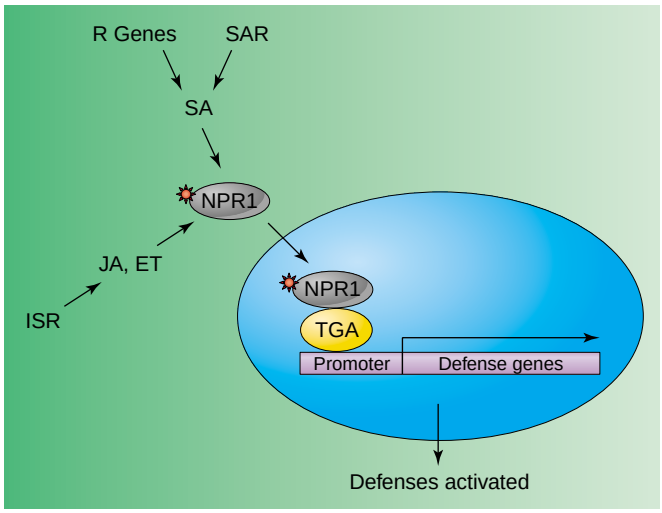

Fig. 4. Regulation of defense gene expression by NPR1. NPR1 has an important role in 'local' resistance triggered by some *R* genes, as well as two types of systemic resistance: Systemic acquired resistance (SAR), which is induced by nectrotizing pathogens on foliar tissue and which acts through salicylic acid (SA); and induced systemic resistance (ISR), which is induced by soil-dwelling bacteria and acts through jasmonic acid (JA) and ethylene (ET) [5]. These cascades trigger an as-yet unknown posttranslational modification of NPR1 (depicted by a red star). NPR1 then translocates from the cytoplasm to the nucleus [53]. Once inside the nucleus, NPR1 interacts with TGA transcription factors, and perhaps other proteins, to regulate transcription of defense-associated genes [54,55].

and might therefore thrive on plants with an increased propensity for the HR [43–46]. However, recent studies demonstrated that resistance to necrotrophs can be provided by transgenes encoding antiapoptotic proteins from mammals [47,48]. These transgenes apparently interfere with activation of PCD in the host. Anti-apoptotic genes might be very useful tools against necrotrophs for which natural sources of genetic resistance are rare.

Conclusions and future prospects

Although many exciting insights have emerged from recent research on plant defense signaling, our overall understanding of the process is still fragmentary. For example, we still know very little about the structural basis of pathogen recognition. In fact, we are less sure than before about what R proteins actually recognize (Avr proteins, modified guardees, or complexes that include both?). Furthermore, many gaps remain in our models of the defense signal transduction network and these must be bridged before we can design truly rational strategies to activate the network. Nevertheless, useful applications are already being developed from our relatively limited knowledge base and others will undoubtedly follow as our level of basic understanding grows. In the short term, we expect that additional useful *R* genes will be cloned and that models of resistance signaling developed in *Arabidopsis* will continue to be evaluated for applicability in crops [49]. We also anticipate the application of functional genomic tools to disease resistance [50], which will greatly accelerate the pace of discovery and provide new insights into interactions between defense signaling and other plant processes [51]. In the longer term, a detailed understanding of the structural basis of recognition will enable us to approach the holy grail of designing R proteins that recognize essential virulence factors (or important guardees).

We emphasize that the problem of disease resistance is being addressed on many fronts – this review covers only a subset of the exciting approaches being explored [2]. Given the diversity of strategies that pathogens use and their ability to rapidly adapt, it would be rash to predict the development of a magic bullet for durable, broad-spectrum resistance. However, it is reasonable to expect a forthcoming array of sophisticated weapons that will provide effective protection in certain contexts, when judiciously integrated with other control measures.

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