MOLECULAR PLANT PATHOLOGY (2003) **4**(6), 517–530 DOI: 10.1046/J.1364-3703.2003.00198.X

Review

Deciphering host resistance and pathogen virulence: the *Arabidopsis*/*Pseudomonas* interaction as a model

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SUMMARY

The last decade has witnessed steady progress in deciphering the molecular basis of plant disease resistance and pathogen virulence. Although contributions have been made using many different plant and pathogen species, studies of the interactions between *Arabidopsis thaliana* and *Pseudomonas syringae* have yielded a particularly significant body of information. The present review focuses on recent findings regarding *R* gene products and the guard hypothesis, RAR1/SGT1 and other examples where protein processing activity is implicated in disease resistance or susceptibility, the use of microarray expression profiling to generate information and experimental leads, and important molecular- and genome-level discoveries regarding *P. syringae* effectors that mediate bacterial virulence. The development of the *Arabidopsis*–*Pseudomonas* model system is also reviewed briefly, and we close with a discussion of characteristics to consider when selecting other pathosystems as experimentally tractable models for future research.

INTRODUCTION

The molecular mechanisms of pathogen virulence and host resistance are inherently interesting subjects for investigation, but a better understanding of these phenomena should also allow the design of molecular strategies to improve disease resistance (Bent and Yu, 1999; Dangl and Jones, 2001; Lucas, 1998). Plant disease incidence can be reduced by appropriate cultivation practices and by the use of pesticides, but use of disease-resistant cultivars remains the most inexpensive and safe method for disease control. Disease resistant crop varieties have typically been generated by traditional breeding, accessing resistance present in related domesticated or wild germplasm (Simmonds and Smartt, 1999). Unfortunately, this process is time consuming, and undesirable traits are often brought along with the disease resistance trait, especially in the case of multigenically inherited resistance. Disease resistance based on single race-specific resistance (*R*) genes has been highly effective in blocking diseases in many crop species. However, this type of resistance often becomes ineffective as members of the pathogen population emerge that avoid recognition by the plant immune system, requiring the introduction of new resistance traits. In addition, resistance against a given pathogen race or species cannot always be found in the available germplasm, and in many clonally propagated crops any plant breeding is minimally feasible. Against these challenges, work on the molecular basis of plant disease resistance takes on added interest. For example, *R* genes can now be introduced into crop species by genetic transformation to convert a disease susceptible plant to resistant.

The present review discusses recent findings in molecular plant pathology research, and focuses on the interaction between *Arabidopsis thaliana* and *Pseudomonas syringae* bacteria as a vehicle for this type of research. Discoveries are highlighted regarding *R*-gene-mediated recognition of pathogen avirulence gene products, the *RAR1/SGT1* system that implicates protein degradation processes in defence signalling, the use of microarray expression profiling to generate information and experimental leads, and molecular mechanisms of bacterial virulence. The development of the *Arabidopsis-Pseudomonas* model system is also reviewed briefly, and the review closes by discussing characteristics to consider for those interested in developing other experimentally tractable pathosystems for future research.

Establishing the *Arabidopsis-Pseudomonas* experimental system

Work on any biological system benefits from a broad base of prior knowledge and research tools. Fifteen years ago there were no publications about *Arabidopsis*–pathogen interactions other than brief accounts that certain microbial species had been observed on *Arabidopsis*. However, plant-pathogenic *Pseudomonas* bacteria

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(under shifting taxonomic names) had received extensive study as economically important agricultural pests (Schroth *et al.*, 1991), and *Arabidopsis* seemed poised to become a heavily studied plant (Meyerowitz and Somerville, 1994; Meyerowitz, 1987). Molecular-level studies of *Pseudomonas syringae* on other plant hosts had yielded knowledge of toxin production, the *hrp* genes that control bacterial virulence and avirulence via Type III secretion systems, and the first pathogen avirulence genes ever to be cloned and molecularly characterized (Alfano and Collmer, 1996). Importantly, and in contrast to most fungal pathogens, *Pseudomonas syringae* was amenable to molecular genetic manipulations such as gene introduction, transposon mutagenesis and targeted gene replacement. *Arabidopsis* seemed to offer opportunities not only because of its small size, rapid generation time and amenability to mutational studies, but also because of a coalescence of molecular genetic researchers prepared to develop tools and methodologies.

Establishment of an *Arabidopsis-Pseudomonas* experimental system had to start with the identification and/or adoption of workable plant growth, pathogen inoculation and disease scoring methods, virulent and avirulent pathogen strains, and resistant and susceptible host lines (Debener *et al.*, 1991; Dong *et al.*, 1991; Whalen *et al.*, 1991). Some *P. syringae* pv. *tomato* and pv. *maculicola* strains are virulent on some *Arabidopsis* ecotypes; typical disease symptoms are shown in Fig. 1. With the study of bacterial pathogenesis well underway using other plant species, much early *Arabidopsis-Pseudomonas* work was focused on host resistance. The avirulence genes *avrRpt2* and *avrRpm1* were cloned and characterized in large part to establish isogenic pathogen strains whose elicitation of *Arabidopsis* resistance could be attributed to a single pathogen *avr* gene (Debener *et al.*, 1991; Dong *et al.*, 1991; Whalen *et al.*, 1991). PR (pathogenesis-related) gene expression associated with resistant and susceptible *Arabidopsis* responses was initially defined (Davis and Ausubel, 1989; Dong *et al.*, 1991; Uknes *et al.*, 1992). Separately, it was discovered that *avrRpt2* and *avrRpm1* also convert *P. syringae* pathogens of pea, bean or soybean to avirulence on those host species, and that the soybean-associated *avrB* is 'recognized' by *Arabidopsis* (Dangl *et al.*, 1992; Innes *et al.*, 1993; Whalen *et al.*, 1991). These findings echoed earlier work (Whalen *et al.*, 1988) and suggested substantial conservation of pathogen recognition mechanisms between crop plants and the experimentally tractable *Arabidopsis*.

The molecular description of a plant *R* gene was a primary goal in molecular plant–microbe interaction research a decade ago, and the isolation of *RPS2* and *RPM1* helped to define the very widespread NB-LRR class of *R* genes that encode proteins with a putative nucleotide binding site and leucine-rich repeats (Hammond-Kosack and Jones, 1997; Michelmore, 2000). It is instructive that the first round of successes in *R* gene isolation occurred not only using *Arabidopsis*/*Pseudomonas*, but also tomato, tobacco and flax. Map-based cloning and transposon tagging approaches were both successful.

Another important element of pathosystem establishment was the identification of other bacterial, fungal and viral pathogens that attack the same host genotype (Crute *et al.*, 1994). Substantial benefit in dissecting host responses has accrued in particular from studies of *Arabidopsis* and *Peronospora parasitica*, the oomycete downy mildew pathogen, and *Arabidopsis* work will also continue to benefit from study of many other pathogens such as *Erysiphe, Botrytis, Alternaria, Ralstonia*, *Xanthomonas*, Turnip crinkle virus and Tobacco etch virus. Each pathogen helps to identify novel elements of host susceptibility and resistance, and the focus on a single host allows discoveries made with one pathogen to be tested and extended using the range of pathogens.

DISSECTING PLANT DEFENCE SIGNAL TRANSDUCTION

While biochemical characterizations of defence processes have progressed using a variety of plant species, one of the strongest contributions of *Arabidopsis* research has been in using genetics to identify the proteins and pathways that mediate defence signal transduction. A set of related themes have become established:

1 The majority of *R* genes encode NB-LRR proteins that confer capacity for specific recognition of pathogens that express a corresponding *avr* gene.

2 Many *Arabidopsis R* genes require *EDS1* or *NDR1*, but not both, to activate defences. Other genes (such as *NPR1/NIM1*, or *PBS1, PBS2* and *PBS3*, among others) also contribute uniquely to the defences activated by some but not all *R* genes.

3 Salicylic acid and NPR1/NIM1 are central mediators of plant defence responses against many, but not all pathogens. A number of other genes have been identified that modulate salicylate-based signalling and/or systemic acquired resistance.

4 The interrelated ethylene and jasmonic acid signal transduction pathways mediate defence responses to some pathogens, but play a minor role in most *R/avr*-mediated defences. The ethylene/jasmonate and salicylate-mediated pathways can compete against each other or contribute additively in promoting different plant defences.

5 *Arabidopsis* mutants with altered programmed cell death have been identified. Study of these mutants or the encoded gene products (such as LSD1, DND1 or ACD5) are helping to reveal the contributions of hypersensitive response (HR) to disease resistance, and how HR cell death is controlled.

6 Many mutations induce constitutive broad-spectrum defence to some degree. This is often associated with reduced plant size and/or seed production. The direct role of these mutationally identified gene products in normal defence signal transduction, if any, is unclear.

7 There is some overlap between the genes and pathways that control responses of *Arabidopsis* to pathogens and those that control responses to ozone, wounding and other stresses.

The above themes have been reviewed extensively elsewhere (Beers and McDowell, 2001; Chen *et al.*, 2002; Dangl and Jones, 2001; Dong, 2001; Feys and Parker, 2000; Glazebrook, 2001; Lam *et al.*, 2001; Mahalingam *et al.*, 2003; Rao and Davis, 2001).

Work on these subjects is by no means complete. Genes that mediate reactive oxygen and nitric oxide responses are being characterized (Hancock *et al.*, 2002; Huang *et al.*, 2002). MAP kinase pathways are being defined and connected to host resistance (Jonak *et al.*, 2002). Second-generation screens for genetic suppressors or yeast two-hybrid interactors are now identifying additional plant proteins that influence many aspects of defence signal transduction (e.g. Fan and Dong, 2002; Kachroo *et al.*, 2001; Kim and Delaney, 2002; Mackey *et al.*, 2002). An important trend is to move toward cell biological and biochemical studies of the *Arabidopsis* proteins and processes identified through genetics-based whole-plant work (e.g. Azevedo *et al.*, 2002; Kinkema *et al.*, 2000; Mackey *et al.*, 2002; Spoel *et al.*, 2003). The *Arabidopsis*/*Pseudomonas* pathosystem is playing a supporting role or a central role in many new discoveries, and the cases discussed below serve as noteworthy examples.

THE GUARD HYPOTHESIS FORCES A CHANGE OF THINKING

The initial recognition event mediated by functionally matched *R* and *avr* genes has attracted attention for decades, with the prevailing hypothesis being that the *R* gene protein product directly interacts with the corresponding *avr* gene product. However, this hypothesis is now being modified. Most *R* genes encode LRR-containing proteins, yet these R proteins have been shown to directly interact with an Avr protein in only two examples (the rice blast resistance protein Pi-ta and Avr-Pita from *Magnaporthe grisea*, and RRS1-R/PopP2 of *Arabidopsis* and *Ralstonia solanacearum* (Jia *et al.*, 2000; Deslandes *et al.*, 2003). Experiments in many other laboratories with other LRR-class R proteins have failed to detect direct R–Avr interactions, but have noted other interactions. For example, the responsiveness of tomato to the *P. syringae avrPto* gene product requires two R proteins, one of which is the NB-LRR protein Prf, the other being the Pto protein kinase. Pto interacts physically with AvrPto (Scofield *et al.*, 1996; Tang *et al.*, 1996), while there is no evidence that Prf interacts. These types of negative and positive findings, from a variety of systems, prompted the formulation of the 'guard hypothesis', whereby the LRR R protein monitors the status of one or more other host proteins (Bonas and Lahaye, 2002; Dangl and Jones, 2001; Holt *et al.*, 2003; Van der Biezen and Jones, 1998). In place of the strong and direct LRR/Avr protein–protein interactions postulated in earlier models, *R*-encoded LRR proteins may instead more commonly detect physical alterations of a plant protein that are caused by the pathogen Avr protein. The term 'guard' acknowledges the concept that Avr proteins are often virulence factors that attack host cellular machinery (discussed below), with the R protein alerting the cell to this attack and calling forth a broad-scale counterattack against the pathogen.

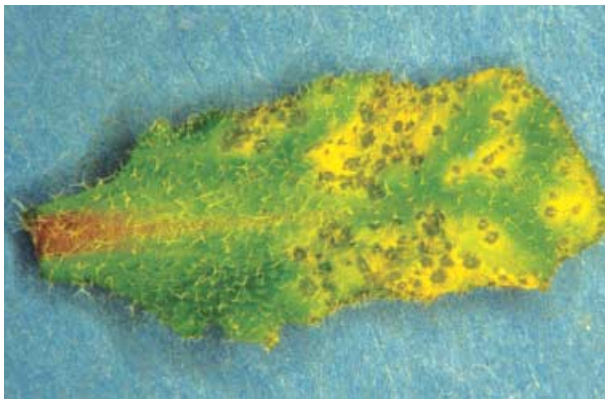

Fig. 1 Typical symptoms exhibited by an *Arabidopsis* leaf infected by *Pseudomonas syringae* pv. *tomato* strain DC3000. Water-soaked areas of collapsed tissue form and are surrounded by chlorotic tissue 3–5 days after initial infection. (Photo courtesy of B. Kunkel.)

The guard hypothesis is finding strong support in recent studies of *Arabidopsis–Pseudomonas* interactions. Mackey *et al.* (2002) initially identified RIN4 (RPM1-interacting protein) as an *Arabidopsis* protein that physically interacted with *P. syringae* AvrB in a yeast two-hybrid screen. In immunoprecipitation studies, RIN4 was shown to physically interact with AvrB and the sequence-unrelated avirulence factor AvrRpm1 that are each recognized by RPM1. RIN4 is essential to RPM1-dependent defences, as a reduction in RIN4 levels inhibits the restriction of pathogen growth and the HR in response to bacteria that express *avrRpm1* or *avrB*. Phosphorylation of RIN4 was induced by AvrRpm1 and AvrB, independent of the presence of RPM1. Mackey *et al.* (2002) proposed a model in which RIN4 is the direct binding target of AvrRpm1 and AvrB, and the phosphorylation of RIN4 induced by these pathogen effector proteins is perceived by RPM1, causing defence activation. An updated model of this interaction is presented in Fig. 2.

In two additional exciting papers, Mackey *et al.* (2003) and Axtell and Staskawicz (2003) have explored the relationship between RIN4, RPS2 and AvrRpt2. Some type of mechanistic connection between RPS2 and RPM1 action had been suspected for years, following the observation that expression of AvrRpt2 blocked host responsiveness to AvrRpm1 (Ritter and Dangl, 1996; see also Reuber and Ausubel, 1996). In recent work, RPS2 was shown to physically interact with RIN4 (Fig. 2). Furthermore, it was found that AvrRpt2 induces RIN4 disappearance (Axtell and Staskawicz, 2003; Mackey *et al.*, 2003). Over-expression of *RIN4* blocks the detection of AvrRpt2 by RPS2, while under-expression of *RIN4* or over-expression of *RPS2* causes constitutive defence activation and cell death in *RPS2*$^+$ plants independent of AvrRpt2.

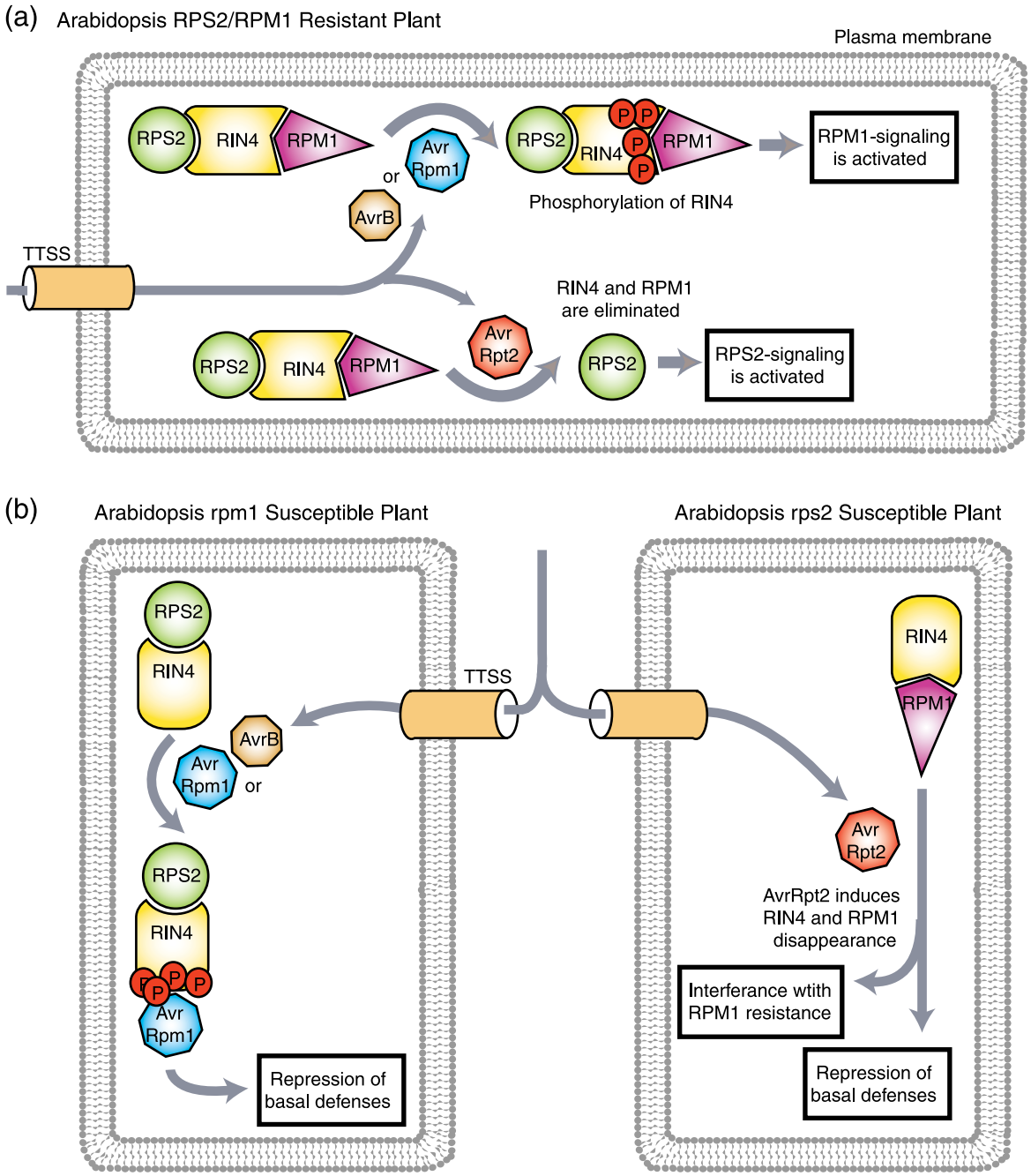

Fig. 2 Model for indirect recognition of avirulence effectors by RPM1 and RPS2, and aspects of the virulence activity of these effectors in susceptible plants. Adapted from Mackey *et al.* (2002), Mackey *et al.* (2003) and Axtell *et al.* (2003). (a) Resistant *Arabidopsis* plant expressing the resistance genes *RPM1* and *RPS2*. Avirulence effectors are delivered by bacteria to the plant cytoplasm through a type III secretion system (TTSS). When AvrRpm1 or AvrB are delivered they target the host protein RIN4 and lead to its phosphorylation. RPM1, which guards RIN4, detects this modification and activates *RPM1*-dependent defences. When AvrRpt2 is delivered, RIN4 is also targeted but is now eliminated. This is recognized by the guard RPS2 which triggers *RPS2*-signalling to activate defences. (b) Susceptible *rpm1*$^{-}$ and *rps2*$^{-}$ plants. On the left panel, when AvrRpm1 or AvrB are delivered into susceptible a *rpm1* plant, they target RIN4, resulting in its phosphorylation. This modification is postulated to enhance the activity of RIN4 as a negative regulator of basal defences. On the right panel, in *rps2*$^{-}$ plants, AvrRpt2 inhibits *RPM1*-mediated defences by indirectly causing degradation of RPM1. The AvrRpm1, AvrB and AvrRpt2 effectors may also enhance virulence due to impacts on other plant targets.

A quantitative titration of RPS2 by RIN4 was suggested, with RPS2 active in defence elicitation if it is free of RIN4. Absence or presence of AvrRpt2 is apparently detected by RPS2 indirectly, via the presence or absence of RIN4.

The mediating role that RIN4 plays in pathogen virulence and avirulence is remarkable, and may even suggest an evolutionary chain of events. AvrRpm1 and AvrRpt2 have been shown to contribute to the virulence of *P. syringae* on susceptible hosts, and a blocking effect of AvrRpt2 on AvrRpm1-elicited avirulence in *RPM1*$^+$ hosts has been documented (Chen *et al.*, 2000; Ritter and Dangl, 1995, 1996). In plants lacking RPM1, AvrRpm1- or AvrB-mediated phosphorylation of RIN4 presumably reduces plant defences (or enhances susceptibility), although this has not been shown. RPM1 may have evolved to detect this RIN4 phosphorylation and activate defences. AvrRpt2 may have subsequently evolved to remove RIN4 and thereby prevent RPM1 from detecting the *P. syringae* that express AvrRpm1 or AvrB. But then the presence of RPS2 allowed the plant to detect the disappearance of RIN4. By adding *RPS2* to the *RPM1*$^+$ genotype, either phosphorylation or disappearance of RIN4 is detected and the plant sustains resistance to the *P. syringae* that target RIN4. Areas for future research include investigating the functions of RIN4 protein in plant responses to virulent pathogens, and investigating the other pathogen effectors and host proteins that engage the RIN4 protein complex.

More about the guard hypothesis is emerging from studies of a separate *Arabidopsis–Pseudomonas* interaction. In a story that echoes *Pto/Prf/avrPto* findings, *Arabidopsis* recognition of *P. syringae* that express the AvrPphB has been shown to require not only the NB-LRR protein RPS5, but also PBS1, which encodes a protein kinase (Swiderski and Innes, 2001; Warren *et al.*, 1999). PBS1 is substantially divergent from Pto. Last year, Shao *et al.* reported that AvrPphB carries cysteine protease activity (Shao *et al.*, 2002). As the present review went to press, it was reported that the AvrPphB protease cleaves PBS1, and that this cleavage is required for RPS5-mediated resistance (Shao *et al.*, 2003). This series of papers provides another excellent example of the molecular mechanisms that can account for Avr protein function and *R* gene-mediated resistance. Because *pbs1* null mutants are susceptible to *P. syringae* that express AvrPphB, and because PBS1 kinase activity is required for RPS5 resistance but not for cleavage by AvrPphB, it is suggested that RPS5 detects AvrPphB indirectly, due to the changes in PBS1 that are caused by AvrPphB. If Avr proteins are often detected due to their virulence function rather than their direct structural features, this has significant ramifications for the evolution, range of specificity and functional durability of *R* genes (Shao *et al.*, 2003).

In separate work, the LRR domains of RPS2 and RPS5 have been implicated in interactions with other host proteins that mediate downstream defence signalling (Banerjee *et al.*, 2001; Warren *et al.*, 1998). For future studies it will be important to investigate what R proteins do after the guarded protein has been attacked, i.e. to investigate the host proteins that RPS2, RPS5, RPM1 and other R proteins engage after activation by avirulent pathogen.

GENOMICS AND *R* GENE BIOLOGY

Plant NB-LRR proteins have to date been associated only with disease resistance, and in animals they have roles in immune function and programmed cell death (Dangl and Jones, 2001; Inohara and Nunez, 2003). The genomes of *Arabidopsis* and rice have been completely sequenced, offering a chance to analyse *R*-gene-like sequences as a group. *Arabidopsis* encodes 149 NB-LRR proteins that apparently form a key 'front end' of the plant immune system (Table 1; http://niblrrs.ucdavis.edu). Of these, 92 encode TIR-NB-LRR proteins and 51 encode CC-NB-LRR proteins (TIR = 'Toll/Interleukin Receptor' similarity; CC = coiled-coil). Intriguingly, an additional 53 genes encode apparently truncated TIR and TIR-NB genes that need to be examined for a potential defence-regulating function (Table 1; Meyers *et al.*, 2002). Studies of large *R* gene sets, in one genome or between alleles from different *Arabidopsis* genomes, has revealed that detectably different selective pressures have been exerted on different types of

Table 1 Number of occurrences of NB-LRR *R* gene-like genes in the *Arabidopsis* genome, including putative truncated homologues that do not encode an LRR domain (from Meyers *et al.*, 2002).

Predicted protein domains[a]	Letter code	Occurrences[b]
CC-NBS-LRR	CNL	51
NBS_{CC}-LRR	NL	4
TIR-NBS-LRR	TNL	83
NBS_{TIR}-LRR	NL	2
TIR-NBS-LRR-X	TNLX	5
TIR-NBS-TIR-NBS-LRR	TNTNL	2
TIR-TIR-NBS-LRR	TTNL	2
Total with LRRs		149
TIR-NBS	TN	21
TIR-X	TX	30
X-TIR-NBS-X	XTNX	2
CC-NBS	CN	4
CC-NBS-X	CNX	1
CC (related to CNL)	C	1
NBS_{CC}	N	1
Total without LRRs		58

[a]CC: coiled coil; TIR: 'Toll/Interleukin Receptor' similarity; NBS: nucleotide binding site; LRR: leucine-rich repeat; NBS_{CC} or NBS_{TIR}: an NBS closely resembling NBS frequently associated with CC-NBS-LRR or TIR-NBS-LRR proteins, respectively; X: other substantial domains (such as WRKY domain); CNL: CC domains of CC-NBS-LRR proteins.

[b]Number of genes in the *Arabidopsis* genome that encode a protein of this type, as determined using bioinformatic methods by Meyers *et al.* (2002).

Arabidopsis R genes and on different domains within single *R* genes (Mauricio *et al.*, 2003; McDowell *et al.*, 1998; Palomino *et al.*, 2002; Tian *et al.*, 2002, 2003).

It is also intriguing that rice, a model for most grain crops, carries over 600 NB-LRR genes, yet none encode TIR-NB-LRR proteins (Bai *et al.*, 2002). The molecular mechanisms engaged by R proteins that carry TIR domains may follow notably distinct paradigms from those of CC-NB-LRR proteins such as RPS2, RPM1 and RPS5 that were discussed above. For example, the *Arabidopsis* resistance gene *RPS4* which detects *P. syringae* that express *avrRps4* encodes a TIR-NB-LRR, and is functionally dependent on *EDS1* (a lipase) rather than *NDR1* (an apparent glycosylphosphatidylinositol (GPI)-anchored protein) (Aarts *et al.*, 1998). Further distinct mechanisms of pathogen detection and defence activation may be revealed through study of *RRS1-R* (resistance to *Ralstonia solanacearum*); this gene encodes a rare example of a TIR-NB-LRR that carries a WRKY transcription activating domain at its C-terminus (Deslandes *et al.*, 2002, 2003).

Distinct host species can sometimes recognize expression of the same *P. syringae avr* gene. Ashfield, Innes and colleagues have preliminarily reported isolation of *Rpg1-b*, the *R* gene from soybean that confers recognition of *P. syringae* that express *avrB*. Soybean Rpg1 and *Arabidopsis* RPM1 encode notably different (non-orthologous) CC-NB-LRR proteins (Ashfield *et al.*, 1995). Comparisons to reveal what is common or divergent in this recognition of the identical pathogen effector protein between distantly related species should further define the molecular basis of *R*/*avr* function. It may also illuminate the agronomically very relevant question of why *R* genes often do not function when transformed into taxonomically distant plant species.

RAR1 AND SGT1: PROTEIN DEGRADATION MODULATES DEFENCE?

A separate, important new development concerns the role of RAR1 and SGT1 in plant defence signalling pathways. Like the emergence of the guard hypothesis from studies of both tomato and *Arabidopsis*, credit for this RAR1/SGT1 story must go to barley and *Nicotiana* research as much as to *Arabidopsis*. Rar1 was first identified in barley mutational studies as a gene 'required for *Mla*–mediated resistance' (Torp and Jorgensen, 1986), and map-based cloning revealed that the protein carries a zinc-binding CHORD domain (Shirasu *et al.*, 1999). *Arabidopsis RAR1* was independently identified and cloned following mutational studies of resistance against *P. syringae* and *Peronospora* (Muskett *et al.*, 2002; Tornero *et al.*, 2002). In barley and *Arabidopsis*, some but not all *R* genes show RAR1-dependence (Muskett *et al.*, 2002; Shen *et al.*, 2003; Tornero *et al.*, 2002). Metazoan CHORD-containing proteins similar to RAR1 carry a second domain that is found, separately, in yeast SGT1. Plant SGT1s were identified from *Arabidopsis* in mutational studies of disease resistance, as well as in yeast two-hybrid screens of *Arabidopsis* cDNAs for proteins that interact with barley Rar1 (Austin *et al.*, 2002; Azevedo *et al.*, 2002; Tor *et al.*, 2002). SGT1 has been clearly implicated in some but not all *R* gene-initiated defence pathways (Austin *et al.*, 2002; Azevedo *et al.*, 2002; Shen *et al.*, 2003; Tor *et al.*, 2002). Important studies have also been performed on Rar1 and Sgt1 of tobacco, which were identified by homology and by interaction cloning and studied following inactivation by virus-induced gene silencing (Liu *et al.*, 2002b,c; Peart *et al.*, 2002).

A molecular function for plant SGT1s was suggested by the homology with yeast SGT1, which is known to associate with SCF ubiquitin ligase complexes through interaction with SKP1 (Kitagawa *et al.*, 1999). Yeast SGT1 is required for at least some forms of SCF-mediated protein ubiquitination (Kitagawa *et al.*, 1999). *Arabidopsis SGT1a* and *SGT1b* both rescue yeast *sgt1* mutants (Azevedo *et al.*, 2002). Figure 3 provides a diagram of a generic SCF-type E3 ubiquitin protein ligase complex. These complexes foster the ubiquitination of target proteins, which marks the target protein for degradation by the 26S proteasome (Vierstra, 2003). Intriguingly, the *Arabidopsis* genome contains 694 potential proteins that carry the Skp interaction domain known as an

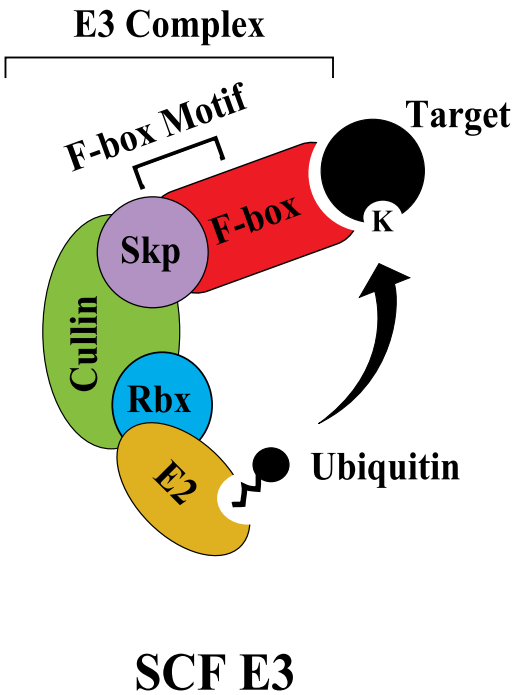

Fig. 3 A Skp-Cullin-F-box (SCF)-type ubiquitin ligase complex. The covalent attachment of one or a chain of ubiquitins to the target protein (at 'K', a lysine residue) marks the target for degradation by the 26S proteasome. This process can play key regulatory roles in plant signal transduction (Vierstra, 2003). The *Arabidopsis* genome encodes 19 putative Skp proteins and 694 candidate F-box proteins, suggesting the high level of specificity possible in this process. (Figure courtesy of J. Gagne.)

F-box (Gagne *et al*., 2002). These F-box proteins also carry one or more additional protein–protein interaction domains that apparently determine interaction with specific proteins that are then targeted for degradation. The huge diversity of F-box proteins apparently allows the organism substantial specificity in targeting particular proteins to be degraded at any given time (Vierstra, 2003; Gagne *et al*., 2002). Barley and *Nicotiana benthamiana* Sgt1 associate with the corresponding homologues of SKP1, CUL1 as well as with COP9 signalasome components (Azevedo *et al*., 2002; Liu *et al*., 2002c). Hence, as for plant photomorphogenesis, auxin-responsive signal transduction and other plant responses (Vierstra, 2003), ubiquitin-dependent regulated protein degradation processes are now implicated in plant defence signalling.

Protein degradation may fit into plant signal transduction in different ways that are not mutually exclusive. The most common hypotheses postulate a negative regulator of defences that is active downstream of some *R* gene products, and which is degraded due to RAR1/SGT1 activity to allow defence activation. However, SCF E3 ubiquitin ligases may also directly activate proteins (Pickart, 2001). There is some evidence that barley SGT1 can exist in two distinct complexes, associated with either RAR1 or with SCF ubiquitin ligases/COP9 signalosome components (Azevedo *et al*., 2002). The target defence signal transduction proteins that are ubiquitinated by this system remain to be identified. It is also possible that RAR1 and SGT1 act as co-chaperone or assembly factors that assist the formation of a diverse range of multiprotein complexes, and that impacts of RAR1/SGT1 on defence signalling occur entirely independent of ubiquitin-mediated phenomena.

Other findings draw attention to protein degradation. RPM1 is known to be degraded coincidently with the hypersensitive response (Boyes *et al*., 1998). Protease activity has been identified in bacterial Avr proteins and in plant genes required for defence (Kruger *et al*., 2002; Orth *et al*., 2000; Shao *et al*., 2002). Identified F-box proteins that very likely mediate protein degradation include *Arabidopsis* COI1 and SON1. *Arabidopsis coi1* mutants are insensitive to the *P. syringae* toxin coronatine and are deficient in jasmonic acid signal transduction (Devoto *et al*., 2002; Kloek *et al*., 2001; Xie *et al*., 1998). The *Arabidopsis son1* mutant suppresses *npr1*/*nim1* mutations and generates salicylate-independent resistance (Kim and Delaney, 2002). The mechanisms and roles of protein processing events in defence signal transduction are likely to be important topics in the coming years.

EXPRESSION PROFILING YIELDS NEW LEADS

Large-scale expression profiling, in which the abundance of thousands of mRNA species are simultaneously monitored using microarray technologies, has opened a number of new avenues for the study of plant–pathogen interactions. Due to the advanced state of *Arabidopsis* structural genomics, *Arabidopsis* has been in a lead role with this relatively new and imperfect technology. Maleck *et al*. (2000) pioneered the use of this technology for *Arabidopsis* in a study of 14 different SAR-related treatments, including samples taken 44 h after inoculation with *P. syringae*. They identified sets of similarly regulated genes, and determined the degree of overall similarity of the plant response to the different treatments. The previously known W-box promoter motif was found to be over-represented upstream of genes coinduced with *PR-1*. Scheideler *et al*. (2002) monitored over 13 000 genes at four time points during the response to *P. syringae* that express *avrRpt2*, and focused on the notable shift from housekeeping functions to defence metabolism. Schenk *et al*. (2000) studied responses to *Alternaria brassicicola*, salicylic acid, jasmonic acid and ethylene. They identified, most prominently, an unexpected degree of similarity in the genes regulated by salicylate and jasmonate treatments. Glazebrook *et al*. (2003) have appreciably extended these two studies in recent work examining *Arabidopsis* mutants and treatments that impact SA and JA signalling. Overlaps in plant responses to stress have also been noted in other studies (Mahalingam *et al*., 2003; Reymond *et al*., 2000).

More recently, Tao *et al*. (2003) compared responses to *P. syringae* that lack any recognized *avr* gene to the responses to *P. syringae* that express *avrRpt2* or *avrB*. Through global similarity comparisons of profiles, they noted that these plant defence responses are somewhat similar, showing quantitative rather than qualitative differences. The strong response to avirulent pathogens was more robust (reproducibly detectable) than the response to virulent pathogen. Dong *et al*. (2003) found that 49 of 72 apparent WRKY-like genes in *Arabidopsis* exhibited defence-associated regulation, and suggested extensive transcriptional activation and repression of WRKY gene expression by its own superfamily of transcription factors. In a broader study, Cheong *et al*. (2002) monitored 402 putative transcription factor genes, using activation or repression after a stress treatment as preliminary evidence implicating any given transcription factor in the associated plant response. de Torres *et al*. (2003) correlated the expression profiles for a small set of transcripts with other plant responses such as changes in host $[Ca^{2+}]_{cyt}$ and leaf collapse during the response to *P. syringae* that express *avrRpm1*. They extended in admirable detail the observation that basal plant responses occurring in the first 2 h after infection with *P. syringae* arise independent of Type III secretion. *RPM1*-mediated responses were not detectable for 3 h, yet early stages of leaf collapse arose within 2 h. In our own unpublished work comparing responses to five different isogenic *P. syringae* strains (expressing *avrRpt2, avrRpm1, avrPphB, avrRps4*, or no *avr* gene), we have explored methods of identifying a limited set of specific genes that serve as robust indicators of certain *R/avr* interactions (Wan *et al*. unpublished). A novel candidate promoter element upstream of

many *R/avr*-regulated genes was also identified. Unfortunately, our work also presents evidence that a significant number of false positive genes are identified in many expression profiling studies.

In the above studies, dozens of new genes were added to the list of pathogenesis-related genes, and many are legitimate additions. Some of these new pathogenesis-related genes encode products with identifiable similarity to transcription factors, protein kinases or other known proteins, while others represent genes of unknown function, but all of these genes are relevant candidates for further study with respect to plant disease resistance and susceptibility. Expression profiling of *Arabidopsis*–pathogen interactions is likely to foster even more progress as researchers move to whole-genome chips, work on similar technical platforms, reduce rates of false-negatives and false-positives in data sets, replicate aspects of each other's studies, share complete data sets and use identical gene-naming systems that facilitate a comparison of results between labs. Many mutants, time-points, pathogen/plant genotype combinations, pharmacological inhibitors, spatial locations and other treatments remain to be profiled, and we can expect many intriguing hypotheses to emerge (Wan *et al.*, 2002).

PATHOGEN BIOLOGY: MECHANISTIC AND GENOMIC VIEWS OF PESKINESS

Important discoveries regarding bacterial virulence mechanisms have emerged in the last few years. As for the preceding topics, discoveries have been made using many pathogen and plant species, but the *Arabidopsis-Pseudomonas* pathosystem has been (and likely will remain) a major contributor.

The dual role of avirulence gene products in pathogen virulence and avirulence has already been discussed above. The discovery in the mid-1990s that *hrp* genes encode an apparent Type III secretion system implicated this system in bacterial virulence and avirulence, and suggested close mechanistic parallels between bacterial pathogens of plants and animals (Alfano and Collmer, 1996). Subsequent studies have demonstrated that the *P. syringae* Type III secretion system forms pili that actively secrete effector proteins (Hu *et al.*, 2001; Jin and He, 2001; Jin *et al.*, 2001), and that Avr/Vir effector proteins are active inside plant cells, often as processed proteins that have been cleaved, myristoylated or otherwise modified (e.g. Casper-Lindley *et al.*, 2002; Chen *et al.*, 2000; Gopalan *et al.*, 1996; Leister *et al.*, 1996; Mudgett and Staskawicz, 1999; Nimchuk *et al.*, 2000). Importantly, other pioneering studies indicated that at least some bacterial effectors actively suppress plant defence responses (e.g. Brown *et al.*, 1995; Jackson *et al.*, 1999; Tsiamis *et al.*, 2000).

More recently, substantial progress has been realized in assigning specific molecular functions or more precise impacts on the host to *P. syringae* Type III-secreted effectors. Cysteine protease activity was first observed by Orth *et al.* (2000) in a study that included the *Xanthomonas campestris* pv. *vesicatoria* effector AvrBsT. An important study of *P. syringae* AvrPphB and *Yersinia* YopT revealed that these two proteins exhibit cysteine protease activity that is required for autoproteolytic processing, cleavage of host targets, and/or (in plants) functional elicitation of the HR in resistant genotypes (Shao *et al.*, 2002; see also Shao *et al.*, 2003). *P. syringae* AvrPtoB is now known to suppress host programmed cell death (Abramovitch *et al.*, 2003). HopPtoD2 is a tyrosine phosphatase that suppresses the HR and other host defence reactions (Bretz *et al.*, 2003; Espinosa *et al.*, 2003). In *Arabidopsis*, AvrPto suppresses cell wall-based defences such as callose deposition (Hauck *et al.*, 2003). The impacts of AvrRpm1 and AvrRpt2 on *Arabidopsis* RIN4, RPM1 and RPS2 were discussed above. Clearly, the study of *P. syringae* effectors is blossoming as we learn more about their biochemical activities, host targets, suppression of host defences, and the ways in which their roles in virulence and avirulence can vary based on host genotype.

A number of strategies are being applied to discover more if not all secreted effector proteins and pathogenesis proteins. Following the completion of the genome sequence of *P. syringae* pv. *tomato* strain DC3000, complex bioinformatic approaches were used to identify genes that contain an identifiable 'hrp box', a *cis*-acting transcription regulatory element found upstream of genes whose expression is activated by hrpR/S-hrpL systems during growth on plants (Fouts *et al.*, 2002; Zwiesler-Vollick *et al.*, 2002). Secreted proteins are being directly isolated and identified, and the conserved secretion-targeting signal used as a further tool to search the *P. syringae* genome sequence (Petnicki-Ocwieja *et al.*, 2002). Separately, a transposon-tagging strategy that fused the HR-eliciting segment of avrRpt2 to anonymous proteins was used, with an HR bioassay on *Arabidopsis* expressing RPS2, to identify 13 proteins that encode Type III secretion targeting signals (Guttman *et al.*, 2002). Bioinformatic analysis then allowed the prediction of additional effectors. An IVET-based approach was used to identify bacterial genes that are expressed during growth in *Arabidopsis* and not in culture (Boch *et al.*, 2002). In that study, over 500 promoter fusions were isolated, and sequence analysis of 79 fusions revealed known and potential virulence genes, including *hrp/hrc*, *avr* and coronatine biosynthetic genes, as well as metabolic genes which were presumably important for adaptation to growth in plant tissue and several genes with unknown function that may encode novel virulence factors. Priorities for future research will include the identification of the plant targets (such as RIN4) and functional mechanisms (such as cysteine protease activity) through which these bacterial effector proteins function. A very high priority will be to study the molecular mechanisms that allow plant-pathogenic bacteria to complete other aspects of their disease cycle such as leaf or root surface colonization, seed invasion, or movement into the plant interior.

DEFINING HOST RANGE

The basis of host specificity among *Pseudomonas syringae* bacteria is of particular interest, for both conceptual and practical reasons. *P. syringae* pathovar designations group bacteria according to the limited set of plant species upon which a given strain can cause disease. Through the efforts of many researchers, some of whom were cited above, a generalized scenario can be advanced. The basic pathogenicity of bacteria such as *P. syringae* on plants has apparently long-since been matched by broad-spectrum plant resistance mechanisms that prevent disease. Specific bacterial pathovars achieve virulence on certain hosts by expressing unique sets of effector proteins that overcome basal defences in a host-species-specific manner, in some cases by active suppression or interruption of host defence activation. But then, in certain genotypes of the host species, *R* gene products are present that recognize these key effector proteins and activate very strong host defences, reasserting resistance. Broadly conserved *R* genes may also make important contributions to the basal defence of non-host species against bacterial pathovars that do not infect any plants of that species.

The evidence for the above is too substantial to cover further in the present review (see also Greenberg and Vinatzer, 2003; Staskawicz *et al*., 2001). However, one additional project deserves highlighting. *Arabidopsis nho1* mutants had been identified that fail to carry out non-host resistance (Lu *et al*., 2001), and the NHO1 gene has now been cloned and further characterized (Kang *et al*., 2003). *P. syringae* pathogens of bean and tobacco induce NHO1 gene expression, but virulent *P. syringae* pv. *tomato* strain DC3000 suppresses NHO1 expression. This suppression requires COI1. Transgenic over-expression of NHO1 blocks the virulence of DC3000. Activation of *R/avr*-mediated signalling overcomes the suppression of NHO1 expression by DC3000 in wild-type plants, and confers resistance. In this very significant paper (Kang *et al*., 2003), NHO1 was also reported to encode a glycerol kinase. Associations with lipid-mediated signalling, as for EDS1, NDR1, SSI2 and DIR1, are advanced as one possible basis for the activation of host defences via NHO1.

USE OF THE WEED ELICITS NOVEL APPROACHES TO BACTERIA–HOST INTERACTIONS

Arabidopsis is a naturally occurring weed rather than an intensively bred crop species, and this opens up a uniquely powerful opportunity to study disease resistance and host-pathogen biology in native plant populations. As was mentioned briefly above, papers examining *RPS2* and *RPM1* across multiple ecotypes have provided evidence for stable maintenance and balancing selection of some *R* genes, in contrast to the divergent selection at sites encoding solvent-exposed LRR residues that has been observed for other *R* genes including *RPP8* of *Arabidopsis* (Mauricio *et al*., 2003; McDowell *et al*., 1998; Tian *et al*., 2002, 2003). Naturally occurring *P. syringae* and *Pseudomonas viridiflava* pathogens of *Arabidopsis* have recently been reported and are ripe for analysis (Jakob *et al*., 2002); naturally occurring isolates of *Peronospora parasitica* have been studied for years but this pathogen has been less amenable to molecular genetic analysis.

Additional approaches have emerged from *Arabidopsis*-*Pseudomonas* systems. Rahme, Ausubel and colleagues demonstrated an important concept when they showed that molecular mechanisms of bacterial pathogenesis on mammals could be studied directly by assays of virulence on *Arabidopsis* or *Caenorhabditis elegans* (Hendrickson *et al*. 2001; Rahme *et al*., 1995; Rahme *et al*., 1997). Pathogenesis assays on mammalian hosts are expensive and at times unpleasant, and a number of *Pseudomonas aeruginosa* virulence factors have now been identified through studies using these alternative hosts. Separately, the rhizosphere colonizer *Pseudomonas chlororaphis* is now being studied using *Arabidopsis* (Schmidt-Eisenlohr and Baron, 2003; Schmidt-Eisenlohr *et al*., 2003). *Arabidopsis* is also poised to serve as a useful species for the study of host contributions to bacterial colonization of leaf surfaces or seed coats—important stages in the disease cycle of many bacterial pathogens.

ATTRIBUTES OF MODEL SYSTEMS

The impressive progress made using *Arabidopsis* and *Pseudomonas syringae* to define mechanisms of plant defence and bacterial virulence can be attributed to the synergism of facile molecular genetic tools, in particular the relative ease of studying genes defined by mutations, and the interest of multiple laboratories who frequently share reagents and pre-publication results. The availability of molecular genetic tools and a substantial cooperative community of researchers go hand-in-hand, and have repeatedly been key attributes of model experimental organisms.

What specific attributes should be sought in other plant species that might be adopted as desirable models for experimental progress? In any molecular genetic model system, one desires low barriers to cloning genes, carrying out molecular genetic complementation, and obtaining directed gene knockouts. Ease of genetic transformation can be crucial. A completely sequenced genome opens up impressive new approaches to the study of an organism and changes the pace and method by which many routine experiments are done. Large databases of expressed sequence tags are a useful substitute presently available for many plant species. Additional resources that are important include genetic maps densely populated with molecular markers and bacterial artificial chromosome libraries that have been end-sequenced and arranged into contigs, as these facilitate map-based cloning of genes known only by phenotype. Transient *in planta* gene assays via agroinfiltration can facilitate impressive progress, as

witnessed recently in studies of Solanacae (e.g. Bouarab *et al.*, 2002; Moffett *et al.*, 2002; Tang *et al.*, 1996). *Nicotiana benthamiana* is a valuable model because relatively reliable virus-induced gene silencing is available (Baulcombe, 1999; but see also Liu *et al.*, 2002a, b). Gene silencing via transformation with dsRNA-generating constructs is very important and may be a more robust technology than VIGS, but often requires the generation of stably transformed plant lines (Wang and Waterhouse, 2002). In *Arabidopsis*, the sequence-indexed gene knockout collections now available for reverse-genetic analysis (e.g. J. Ecker and colleagues, Salk Institute, La Jolla, CA; http://signal.salk.edu/cgi-bin/tdnaexpress) are having a huge positive impact on research progress. Large populations of T-DNA-tagged or transposon-tagged lines can also be invaluable for gene cloning following forward genetic screens, especially with modifications such as enhancer-trap or activation-tag transposons (Parinov and Sundaresan, 2000). Expression profiling is a powerful tool, and standardized resources and technical platforms for expression profiling are desirable within the research community for a given plant species (Wan *et al.*, 2002). Between or even within the plant species being considered for intensive research, genotypes can be chosen to favour ease of transformation, rapid generation time, small plant size, diploidy, ease of genetic crosses and ease of seed harvest. These and other attributes have also been discussed by others (Bouche and Bouchez, 2001; Chory *et al.*, 2000; Holtorf *et al.*, 2002; Meyerowitz and Somerville, 1994; Somerville and Somerville, 1999).

The list of desirable resources for pathogens is in many respects very similar to the above (Petnicki-Ocwieja *et al.*, 2002; Xu and Xue, 2002; Yoder and Turgeon, 2001), and *P. syringae* research has prospered because of its tractability and popularity as a study system. Many viruses and bacteria can be experimentally facile subjects, but it will remain important that substantial financial resources and actively growing pools of colleagues, knowledge and tools stay focused on a limited set of pathogen species. For fungi and oomycetes, particularly desirable attributes of an experimental organism include their relative genetic stability over time, ease of culture independent of the host, tractability for reverse genetic studies such as targeted gene disruption, and amenability to classical genetic analysis.

A separate desirability index for plants or pathogens can be established based on economic relevance, both absolute and relative to the option of developing other taxonomically related species as models. As mentioned above, the use of multiple pathogen species to study susceptibility and resistance in a single host species can be quite productive. In all cases, as study of an organism becomes more extensive it becomes important to have stable funding for genetic and molecular genetic stock centres and for bioinformatics curation.

Many crop plants have deep genetic resources, and molecular genetic resources are being developed for some of these species. Improved molecular genetic tools are also becoming increasingly available for many fungal and oomycete pathogens, and most (but not all) viruses are highly tractable. Hence opportunities are now emerging for increased research progress in many pathosystems. Agricultural research has both benefited and suffered from the division of labour across so many different experimental systems, especially given the relatively small pool of scientists and funding available to pursue this research. The advantage of diverse study systems, in addition to the obvious need for some study of all relevant food, fibre and horticultural crops, is that unique biological mechanisms are constantly discovered. However, the danger remains of an effort spread too thin. Benefits will accrue if a substantial proportion of plant–microbe interactions researchers continue to form, build, and welcome new researchers into communities that focus on a limited set of experimental organisms.

ACKNOWLEDGEMENTS

We apologize to those whose work was not directly cited or discussed in the present limited review. B.F.Q. is grateful to Dr R. Caldas for his support. Work by A.F.B. is funded by USDA-NRI, USDA-Hatch, NSF-Plant Genome and DOE-Energy Biosciences.

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