BACTERIAL AVIRULENCE GENES

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ABSTRACT

Although more than 30 bacterial avirulence genes have been cloned and characterized, the function of the gene products in the elicitation of resistance is unknown in all cases but one. The product of avrD from Pseudomonas syringae pv. glycinea likely functions indirectly to elicit resistance in soybean, that is, evidence suggests the gene product is an enzyme involved in elicitor production. In most if not all cases, bacterial avirulence gene function is dependent on interactions with the hypersensitive response and pathogenicity (hrp) genes. Many hrp genes are similar to genes involved in delivery of pathogenicity factors in mammalian bacterial pathogens. Thus, analogies between mammalian and plant pathogens may provide needed clues to elucidate how virulence gene products control induction of resistance.

The gene-for-gene relationship... opens up new approaches to studies of the origin of new races... and the nature of resistance.

HH Flor (42)

INTRODUCTION

Over 50 years have passed since Flor's careful analysis of the genetics of both the host plant and pathogen led him to propose the “gene-for-gene” hypothesis to describe the genetic basis for elicitation of resistance (41–43). In its simplest form, the hypothesis predicts that resistance (or incompatibility) is governed by the interaction of single dominant host genes for resistance (R genes) and the corresponding pathogen genes for avirulence (avr). In the years since the model was proposed, outstanding progress toward understanding the molecular basis for resistance has been made on two fronts, the identification and cloning of the...
avr and R genes and the characterization of the cellular defensive responses that are induced after recognition. Induced plant defensive responses include enhanced production of active oxygen species, phytoalexin biosynthesis, cell wall reinforcement, the release of hydrolytic enzymes or other inhibitory proteins, and the hypersensitive response (HR), a rapid cell death that is proposed to be comparable to programmed cell death in other eukaryotes [for review, (4, 36, 47, 49, 78)]. The physical analysis of avr genes in concert with analysis of R genes has focused attention on a limited number of models for the recognition and elicitation of resistance. Thus, some 50 years after Flor provided a genetic model for induction of resistance, we are on the verge of describing in molecular terms how the products of the avr and R genes interact to elicit resistance. Several excellent reviews have been published that detail the characteristics of the avr and R genes that have been cloned (31, 34, 88, 98, 128). In this review, we highlight key features of bacterial avr genes and their products that are relevant to host specificity, describe other bacterial genes essential to the function of avr genes, and summarize models of how avr and R genes interact to elicit resistance.

AVIRULENCE GENES AND RACE-SPECIFICITY

Over 30 avirulence genes have been cloned from bacterial plant pathogens (Table 1). Prior to cloning, the existence of the genes was inferred by the differences in interactions (compatible or incompatible) of individual pathogen strains with a host plant. The genes are detected in members of a single pathogen species or pathovar by inoculation to sets of host differentials (host plant lines or cultivars with different resistance genes). An individual pathogen strain may have multiple avirulence genes, and the combination of avr genes within a particular strain specifies the physiologic race of the strain (125). Thus, the avr genes impose race-specificity on a pathogen that is otherwise compatible in association with a given plant species. For example, avrA, the first avirulence gene characterized, was cloned from a race 6 strain of the soybean pathogen Pseudomonas syringae pv. glycinea and, when transferred to other races of P. syringae pv. glycinea, conferred the ability to elicit a resistant response only on cultivars of soybean with the Rpg2 gene for resistance (127).

Within a species or pathovar, avirulence genes hypothetically are the most recent genetic variations in the evolutionary adaptation process between the host and pathogen. However, plant pathogenic bacteria generally exist as complexes of related species or pathovars that are adapted to different plant species. As a consequence, avirulence genes may be involved in the recognition of related pathogens in nonhost plant species. This second type of avirulence gene, sometimes referred to as a heterologous avirulence gene, has been identified after inter-pathovar or inter-species transfer of the gene. The first heterologous avr
gene identified, *avrRxv*, was cloned from the pepper pathogen *Xanthomonas campestris* pv. *vesicatoria*. When introduced into a strain from the pathovar that is pathogenic to bean (*X. campestris* pv. *phaseoli*), *avrRxv* conferred the ability to elicit resistance in bean in a race/cultivar-specific manner (146). Interestingly, *avrRxv* is rather broadly recognized and not only conferred avirulence to *X. campestris* pv. *phaseoli* for particular bean cultivars, but also resulted in the induction of resistance by several *X. campestris* pathovars on their normally susceptible hosts (pv. *glycines* on soybean, pv. *vignicola* on cowpea, pv. *holcicola* on corn, pv. *alfalae* on alfalfa, and pv. *malvacearum* on cotton). When introduced into *P. syringae* pv. *glycinea*, four heterologous avirulence genes from *P. syringae* pv. *tomato* (*avrD*, *avrE*, *avrPto*, and *avrRpt2*) were identified based on recognition by soybean (77, 83, 94, 116). Although originally identified in pathovar *glycinea*, functional homologs of *avrA* were found in *P. syringae* pv. *tomato*, qualifying this gene as a heterologous gene (83). Additional heterologous bacterial *avr* genes include the *avrPpiA* gene from *P. syringae* pv. *pisi*, which alters the virulence of *P. syringae* pv. *phaseolicola* to bean and *P. syringae* pv. *maculicola* to Arabidopsis (32), two genes *avrPphB* and *avrPphD* from *P. syringae* pv. *phaseolicola*, which confer avirulence to *P. syringae* pv. *pisi* on pea (39, 150), and *pthA* (for pathogenicity) from *X. citri*, which functions as an avirulence gene in *X. campestris* pvvs. *alfalae* and *phaseoli* (131).

Although heterologous *avr* genes were identified by interspecific screening and have been proposed to contribute to the host range of a pathogen, none of the heterologous genes in bacteria has been proven to be lone determinants of host range (83, 147). Inactivation of *pthA* in *X. citri* resulted in loss of the ability to elicit a HR on bean but did not extend the host range of *X. citri* to bean (131). Mutations in *avrRxv* did not change *X. campestris* pv. *vesicatoria* into a pathogen of bean (146). Inactivation of an avirulence gene from *P. solanacearum* rendered the strain incapable of eliciting the HR on tobacco but did not enable the strain to induce disease symptoms (23). In the latter two cases, mutant strains inactivated in heterologous avirulence genes enabled the strains to multiply to higher populations on nonhost plants suggesting that multiple avirulence gene/resistance gene interactions might be contributing to host range. One study has addressed this possibility (94). This study utilized four heterologous avirulence genes *avrA*, *avrD*, *avrE*, and *avrPto*, which were identified on the basis of elicitation of the HR in soybean cultivars when introduced into *P. syringae* pv. *glycinea*. A strain of *P. syringae* pv. *tomato* with mutations in each of these four genes remained nonpathogenic to soybean (94). Although additional avirulence genes may be acting to condition this nonhost resistance, another group of genes required for pathogenicity to different plant species may be involved. These genes, called host species-specificity or *hsn*
genes, in fact, have been described in several bacterial/plant systems (95, 102, 131, 140). Thus, whether heterologous genes contribute to restrictions in host range remains unclear.

STRUCTURAL FEATURES OF AVIRULENCE GENES

In general, structural analyses of bacterial avirulence genes have not provided insight into the function of the genes or the gene products. The general conclusions from the studies are that (a) sequence analysis reveals relatively little similarity among the various avirulence genes or to other sequences in the databases; (b) the genes generally encode a single open reading frame (ORF, monocistronic); and (c) the predicted products of the avirulence genes do not have recognizable motifs, such as those characteristic of kinase activity or export signals. Note that the majority of avirulence genes upon which these conclusions have been based were from pathovars of \( P. \) syringae, and, therefore, generalities drawn from these examples may reflect the attributes and strategies of this genus.

Sequence Relationships

Functional homologs to bacterial avirulence genes that have the same host specificity are found in different pathovars of a pathogen species. Functional alleles have been described for the \( P. \) syringae pv. glycinea genes \( \text{avrA} \) [in \( P. \) syringae pv. tomato (83)] and \( \text{avrC} \) [\( \text{avrPphC} \) from \( P. \) syringae pv. phaseolicola (160)], the \( P. \) syringae pv. tomato gene \( \text{avrD} \) [from \( P. \) syringae pv. lachrymans and phaseolicola (157)], and the \( P. \) syringae pv. pisi gene \( \text{avrPpiA} \) [\( \text{avrRpm1} \) from \( P. \) syringae pv. maculicola (32)] (Table 1). Sequence similarity also exists between a few avirulence genes with different specificities. The deduced proteins of the \( \text{avrB} \) and \( \text{avrC} \) genes from \( P. \) syringae pv. glycinea, for example, share 42% amino acid identity (134). The only example of sequence similarity from avirulence genes in different bacterial genera is provided by \( \text{avrBs1} \) from \( X. \) campestris pv. vesicatoria and \( \text{avrA} \) from \( P. \) syringae pv. glycinea, which share 47% sequence identity in their carboxy terminal regions (117). Although a single case, this may be indicative of other common structural features among the \( \text{avr} \) genes that are yet unrecognized. Finally, in only one documented case has a bacterial avirulence gene demonstrated sequence similarity with genes from bacteria that are not plant pathogens. The \( X. \) campestris pv. vesicatoria gene \( \text{avrRxv} \) shows similarity to the \( \text{yopJ} \) gene of \( Yersinia \) pseudotuberculosis [(Figure 1), (46)]. This relationship is particularly interesting, because the \( \text{yopJ} \) product is secreted and components of the \( Yersinia \) YOP secretion pathway are related to the \( \text{hrp} \) pathway, as is discussed below (120).

The case of the \( \text{avrBs3} \) gene family from \( Xanthomonas \) species is quite different from other avirulence genes in that members of this family have been found
A VIRULENCE GENES

in a number of pathovars. The *avrBs3* gene, which was cloned from the pepper and tomato pathogen, *X. campestris pv. vesicatoria* (17), was the first-identified member of this large gene family, which is widely distributed in several *Xanthomonas* pathovars (13, 17, 21, 33, 57, 131, 155). Some pathovars contain multiple copies of related homologs (17, 33, 57, 131, 155); *X. oryzae pv. oryzae* and *X. oryzae pv. oryzicola* may be extreme examples, possessing upwards of 12 to 14 copies (57). The gene family members are highly conserved and encode proteins with 90–97% amino acid sequence identity (15). Not all homologs possess avirulence activity. The members of the family are found exclusively in xanthomonads, but not all avirulence genes from xanthomonads are *avrBs3* homologs; *avrRxv*, *avrBs1*, and *avrBs2* from *X. campestris pv. vesicatoria* share no apparent sequence similarity with *avrBs3* (Table 1).

The structure of genes within the *avrBs3* family is remarkable. The central domain of these genes contains a series of 102 bp, directly repeated DNA sequences (13, 17, 21, 33, 57, 131) (Figure 2). Each *avrBs3*-homolog may contain different numbers of the 102-bp repeat (Figure 2). For example, the *avrBs3*, *avrBs3*-2, and *pta* genes contain 17.5 copies (13, 17, 131); *avrXa10* contains 15.5 copies (57); and *avrB6* contains 13.5 copies (33). Minor differences occur within 102-bp repeats of a given gene, and most of the differences are located within a variable two-codon region (codons 12 and 13, Figure 2b) (13, 17, 21, 33, 57, 131). Although different gene family members have some of the same two-codon combinations in the variable regions of their 102-bp repeats, the order in which they are arranged in each gene is different (Figure 2b).
Table 1  Bacterial avirulence genes

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Avirulence gene</th>
<th>Alleles or related gene (+/− avirulence activity)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas syringae pv. glycinea</td>
<td>avrA</td>
<td>Allele from <em>P. syringae</em> pv. <em>tomato</em> (+)</td>
<td>83, 106, 127</td>
</tr>
<tr>
<td></td>
<td>(avrPgyA1.Rpg2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>avrB</td>
<td>Sequence similarity to <em>avrC</em></td>
<td>63, 64, 99, 126</td>
</tr>
<tr>
<td></td>
<td>(avrPgyB1.Rpg1)</td>
<td></td>
<td>133, 134, 141</td>
</tr>
<tr>
<td></td>
<td>avrC</td>
<td><em>avrPphC</em> from <em>P. syringae</em> pv. <em>phaseolica</em> (+); similarity to <em>avrB</em></td>
<td>126, 133, 134, 160</td>
</tr>
<tr>
<td></td>
<td>(avrPgyC1.Rpg3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas syringae pv. tomato</td>
<td>avrD</td>
<td>Alleles from <em>P. syringae</em> pv. <em>glycinea</em> (−), <em>lachrymans</em> 1 (+), <em>lachrymans</em> 2 (+)</td>
<td>73, 76, 77, 82–84, 157–159</td>
</tr>
<tr>
<td></td>
<td>(avrPtoA1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>avrE</td>
<td></td>
<td>73, 94</td>
</tr>
<tr>
<td></td>
<td>(avrPtoE1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>avrPto (avrPtoC1)</td>
<td></td>
<td>116, 119, 162</td>
</tr>
<tr>
<td></td>
<td>avrRpt2 (avrPtoB1)</td>
<td></td>
<td>37, 64, 86, 145</td>
</tr>
<tr>
<td></td>
<td>avrBs1</td>
<td>Similarity to <em>avrA</em> from <em>P. syringae</em> pv. <em>glycinea</em></td>
<td>71, 117, 129</td>
</tr>
<tr>
<td></td>
<td>avrBs2</td>
<td>Functional homologs in <em>X. campestris</em> pv. <em>alfalfa</em>, <em>malvacearum</em>, <em>vignicola</em>, <em>vitiens</em>, <em>campestris</em>, &amp; <em>phaseolii</em>, <em>X. oryzae</em> pv. <em>oryzae</em>?</td>
<td>72, 101, 105</td>
</tr>
<tr>
<td></td>
<td>avrBs3</td>
<td>Related to genes from <em>X. campestris</em> pv. <em>vesicatoria</em>, <em>X. oryzae</em> pv. <em>oryzae</em>, <em>X. campestris</em> pv. <em>malvacearum</em>, <em>X. citri</em></td>
<td>13, 17, 20, 80</td>
</tr>
<tr>
<td></td>
<td>avrBsT</td>
<td></td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>avrBsP</td>
<td><em>avrBs3</em> homolog</td>
<td>13, 21</td>
</tr>
<tr>
<td></td>
<td>(avrBs3-2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthomonas campestris pv. malvacearum</td>
<td>avrB4</td>
<td><em>avrBs3</em> homolog</td>
<td>33, 152</td>
</tr>
<tr>
<td></td>
<td>avrB6</td>
<td><em>avrBs3</em> homolog</td>
<td>33, 152</td>
</tr>
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</table>
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## Table 1 (continued)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Genes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas syringae</em> pv. <em>pisi</em></td>
<td>avrPpiA ((avrPpiA1.R2)) (\text{avrRPM1 (avrPmaA1RPM1)}) (\text{from P. syringae pv. maculicola 1 (+); maculicola 2 (+)})</td>
<td>32, 35, 39, 114, 138</td>
</tr>
<tr>
<td></td>
<td>avrPpi3 ((avrPpiB.R3))</td>
<td>8, 27</td>
</tr>
<tr>
<td></td>
<td>avrRpo4</td>
<td>55</td>
</tr>
<tr>
<td><em>Pseudomonas syringae</em> pv. <em>phaseolicola</em></td>
<td>avrPph1 ((avrPphA1.R1))</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>avrPphB ((avrPph3.R3))</td>
<td>No hybridizing sequences in \text{virulent races} 39</td>
</tr>
<tr>
<td></td>
<td>avrPphC</td>
<td>Homolog of \text{avrC} 160</td>
</tr>
<tr>
<td></td>
<td>avrPphE ((avrPph2.R2))</td>
<td>Hybridizes to \text{virulent races} 66, 96</td>
</tr>
<tr>
<td></td>
<td>avrPphD</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>avrA</td>
<td>23</td>
</tr>
<tr>
<td><em>Pseudomonas solanacearum</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Xanthomonas campestris</em> pv. <em>vesicatoria</em></td>
<td>avrRxv</td>
<td>146, 147</td>
</tr>
<tr>
<td></td>
<td>avrB7</td>
<td>\text{avrBs3 homolog} 33, 152</td>
</tr>
<tr>
<td></td>
<td>avrB101</td>
<td>\text{avrBs3 homolog} 33, 152</td>
</tr>
<tr>
<td></td>
<td>avrBln</td>
<td>\text{avrBs3 homolog} 33, 152</td>
</tr>
<tr>
<td></td>
<td>avrB102</td>
<td>\text{avrBs3 homolog} 33, 152</td>
</tr>
<tr>
<td></td>
<td>avrBn</td>
<td>\text{avrBs3 homolog} 155</td>
</tr>
<tr>
<td><em>Xanthomonas campestris</em> pv. <em>citri</em></td>
<td>pthA</td>
<td>\text{avrBs3 homolog} 130, 131, 153, 155</td>
</tr>
<tr>
<td><em>Xanthomonas campestris</em> pv. <em>raphani</em></td>
<td>avrXca</td>
<td>108</td>
</tr>
<tr>
<td><em>Xanthomonas oryzae</em> pv. <em>oryzae</em></td>
<td>avrXa7</td>
<td>\text{avrBs3 homolog} 24, 57</td>
</tr>
<tr>
<td></td>
<td>avrXa10</td>
<td>\text{avrBs3 homolog} 57</td>
</tr>
<tr>
<td></td>
<td>avrXa5</td>
<td>\text{avrBs3 homolog} 57</td>
</tr>
</tbody>
</table>

1The first plant (\text{R gene, where known}) is the plant on which the avirulence gene was identified. Others also exhibit a resistant response in interactions with the avirulence gene.

2Based on DNA sequence data, in most cases.
Organization of Avirulence Genes

The majority of avirulence genes are monocistronic or the activity is dependent on the product of a single open reading frame (ORF) of an operon. Genes \textit{avrC} (133) and \textit{avrD} (82), for example, are encoded by the first ORF of two and five ORF operons, respectively. None of the other ORFs was required for avirulence activity. Two possible exceptions to the single ORF rule have been reported. The activities of \textit{avrE} (93) of \textit{P. syringae pv. tomato} and \textit{avrPphD} (150) from \textit{P. syringae pv. phaseolicola} appear to require two ORFs. Many avirulence genes are bounded by repetitive elements (13, 33, 73, 126, 131). Several are located on plasmids [for review, see Tables 1 & 2 in reference (31)], such as the six avirulence genes of the \textit{avrBs3} family in \textit{X. campestris pv. malvacearum} (33).

The \textit{avrB} gene is postulated to have been derived from outside the \textit{P. syringae} group since the codon usage does not reflect the GC content of the genome (133). All of the latter observations are consistent with the hypothesis that many \textit{avr} genes share a history of recent mobility and reflect genetic variation in the evolution for host/pathogen interactions.

AVIRULENCE GENE FUNCTION

The most perplexing aspect of bacterial avirulence genes has been the deciphering of their physiological or biochemical function in the elicitation of resistance. Either the product of the \textit{avr} gene(Avr) must function itself as an elicitor or it may modify some other protein or metabolite to produce an elicitor. In the case of an enzymatic mode-of-action, activity may occur within the bacterium, within the plant cell, or in the extracellular spaces. Sequence analysis shows
that the predicted protein products of all bacterial \textit{avr} genes are hydrophilic and do not contain a signal peptide sequence, suggesting an intracellular or indirect role. Furthermore, with the exception of the elicitors directed by \textit{avrD} from \textit{P. syringae pv. syringae}, no race-specific elicitors have been isolated from phytopathogenic bacteria or from their culture supernatants. Thus, \textit{avrD}, as described below, provides the only known example for a possible intracellular, enzymatic function for the Avr protein. Despite the inability to detect gene products extracellularly, analyses of structure-function relationships of other \textit{avr} genes, particularly the \textit{avrBs3} family, are suggestive of an extrabacterial role for the Avr protein, and models must incorporate this possibility. Indeed, recent evidence regarding \textit{avr} gene function lends further credence to the possibility that some \textit{avr} gene products are secreted and act in some form as the elicitors of resistance. Promise for resolving the perplexities of \textit{avr} function is apparent in parallels drawn from mechanisms for virulence of animal pathogenic bacteria (26).

\textbf{Molecular Analysis of Resistance Genes}

The structures of a number of recently cloned resistance genes provide important clues for the role of the \textit{avr} genes in resistance [for review, see (98, 128)]. Deduced amino acid sequences of the six resistance genes cloned thus far demonstrate that the proteins have features indicative of roles in signal recognition and transduction. The \textit{Pto} gene from tomato encodes a serine-threonine kinase (STK, (92, 99)), suggesting a role in protein phosphorylation. \textit{Cf9}, also from tomato (68), \textit{N} from tobacco (148), \textit{RPS2} from \textit{Arabidopsis} (10, 104), and \textit{Lb} from flax (87) contain a leucine-rich repeat (LRR) domain suggestive of ligand binding or direct protein-protein interactions (85). Interestingly, the recently cloned \textit{Xa21} gene from rice contains both the STK and LRR domains (124). Only \textit{Cf9} (68) and \textit{Xa21} (124) appear to have transmembrane domains. While \textit{Lb} contains sequences consistent with attachment to the membrane (87), the other \textit{R} gene products appear to be cytoplasmic (99, 148). \textit{RPS2}, \textit{N}, and \textit{Lb} share significant homology and contain putative nucleotide-binding sequences. The structures and locations of the \textit{R} gene products suggest that these molecules, either directly or as part of a protein complex, probably bind to a pathogen-derived elicitor molecule or detect the binding of the elicitor to a common receptor.

\textbf{Models for Avirulence Gene Function}

Of the several types of models proposed in the past, models incorporating elicitor/receptor interactions have predominated (1, 44, 74, 88, 128). The evidence emerging from studies of pathogen \textit{avr} and host \textit{R} genes is consistent with elicitor/receptor models. In the simplest model, the primary \textit{avr} gene
Figure 3 Models for avirulence gene function in the elicitation of plant defense responses. In Model 1, the avr gene product (Avr) is the elicitor. The elicitor is exported from the cell via the Hrp apparatus and interacts directly with the plant receptor, which is likely the product of the corresponding resistance gene. In Model 2, Avr directs the synthesis of or modifies a metabolite or protein, which is the race-specific elicitor. In both Models 1 and 2, the receptor may span in the plant cell membrane, or may be cytoplasmic. In Model 3, Avr is the elicitor, but it is directly delivered to the cytoplasm of the plant cell via an attachment between the bacterial and plant cell, possibly containing Hrp proteins.

The product is the elicitor or ligand (Model 1, Figure 3). The paradigm for this model is the peptide coded by the Avr9 gene from the fungal pathogen Cladosporium fulvum. Although the evidence is suggestive, as discussed below, no bacterial avr gene product has been directly demonstrated to fit this model. In Model 2, the product of the avr gene directs the synthesis of, or modifies, a race-specific elicitor; that is, the Avr protein has an enzymatic function. Only one example exists thus far for this scenario. The product avrD gene from the bacterial pathogen P. syringae pv. tomato directs the extracellular accumulation of low molecular weight acyl glycosides, called syringolides 1 and 2, that are sufficient
to trigger the HR (77, 103, 123). No examples, fungal or bacterial, exist yet for Model 3, which proposes the transfer of a proteinaceous elicitor or enzyme (avr gene product) into the plant cell and is based on analogy with the strategies of some bacterial mammalian pathogens (26). A variation of the elicitor/receptor model is that the elicitor (either a protein or a metabolite) may be a toxin-like compound, and binding by the receptor may direct the toxin to a site for insertion into the cell membrane or site of inhibition (or activation) of a host enzyme (not shown).

**Avirulence Gene Product Functions Enzymatically: avrD**

Keen and coworkers (77) postulated that the product of the avrD gene from the bacterial pathogen *P. syringae* pv. *tomato* is an enzyme that directs the synthesis of elicitor-active compound(s); this interaction is represented in Model 2. The expressed protein does not elicit the HR in soybean cultivars with the corresponding resistance gene Rpg4 (77, 82, 84). Instead, expression of avrD leads to the accumulation of low molecular weight acyl glycosides, called syringolides 1 and 2, in the culture supernate that are sufficient to trigger the HR (77, 103, 123). Active elicitors can be produced after expression of avrD in *Escherichia coli*, indicating that the precursors and, thus, the biochemical pathway are common to both bacterial genera. Where (intra- or extracellularly) the interaction between the syringolides and their putative receptor occurs has not been determined. Based on the proposed synthetic scheme for syringolides, avrD likely encodes a protein that catalyzes the condensation of xylulose with a β-keto acid (either β-hydroxydecanoic acid or β-hydroxyoctanoic acid) to form the syringolides (103, 123, 159). The syringolides are intriguing molecules, not only because they elicit the plant HR in hosts with only the Rpg4 gene, but also because they are similar in structure to signal molecules from other organisms, for example, butanolides produced by *Streptomyces* (which induce sporulation and antibiotic production (11)), the lactone autoinducers from *Vibrio* spp. (5, 22), *Agrobacterium tumefaciens* (161), *Erwinia carotovora* (40), and *P. aeruginosa* (109), and endogenous jasmonic acid and related signal molecules of plants (51). The analogies in the structures of these molecules and their roles as signal molecules indicate that their modes of action (what they interact with and how) might be similar.

**Avirulence Gene Products as Elicitors**

Examples where the avr gene product appears to interact directly with a host component (Model 1) are available thus far only from viral and fungal pathogens. Single amino acid substitutions in the coat protein of the Tobacco Mosaic Virus (TMV) resulted in virus that caused the induction of a localized HR in tobacco carrying the *N'* gene (28, 81). All mutants caused systemic, mosaic symptoms
(wild-type) on the susceptible (n') genotype, suggesting the coat protein serves not only as a structural protein, but also as a host gene–specific elicitor of the HR. The second example, the Avr9 gene, cloned from the fungal pathogen C. fulvum, encodes an extracellular peptide that, once processed, induces the HR in tomato plants carrying the resistance gene Cf9 (136, 137). Since the putative Cf9 protein contains sequences consistent with a transmembrane domain, this interaction may occur at the cell surface (68). Other cases of fungal proteins thought to mediate avirulence are the elicitors from Phytophthora spp. [for review, see (113)], NIP1 from Rhychosporium secalis (52, 79), and the product of the PWL2 gene from Magnaporthe grisea (132).

The large number of bacterial avr genes and the lack of sequence identity to the ever-expanding sequence data bases together argue against an enzymatic role for many of the gene products. Structural features of some bacterial avr genes also suggest that the gene product may directly function in avirulence. Exchange of domains between two Pseudomonas avr genes related by sequence, avrB and avrC, revealed that avirulence specificity was determined by the central region (134). Similar types of experiments between members of the avrBs3 family also indicated that cultivar specificity resides within the central domain (17, 56, 152). The central portion of these genes harbors the 102-bp repeats with their two-codon variable region (Figure 2); the requirement for this repeated region suggests a physical role for the protein, rather than an enzymatic role. Herbers et al (54) and Bonas et al (13) demonstrated that the number of repeats present in the avrBs3 homolog is not sufficient by itself to dictate specificity; the organization or number of specific repeats (i.e. with particular variable regions) is likely responsible for cultivar specificity. Random deletion of 102-bp repeats from avrBs3 created mutations with different numbers of repeats (54).

Some, but not all, deletions abolished avrBs3 activity when tested on pepper with Bs3, indicating that the number of repeats was not by itself critical for activity. However, other deletions of the same number of repeats, although different specific repeats, retained avirulence activity. A very interesting finding was that some deletions created new specificities to tomato and pepper, thereby uncovering unknown resistance genes in both hosts (54). Similar results were reported for pthA, an avrBs3-member from X. citri (153, 155).

Deletion of the carboxy terminus of the protein encoded by avrBsP, a homolog of avrBs3 from a X. campestris pv. vesicatoria strain pathogenic on pepper and avirulent on tomato (21), does not affect avirulence activity; deletion of that portion of the protein from avrBs3 results in a loss of activity (13, 17). The avrBsP gene has the same amino terminal region as avrBs3 but, as originally cloned, only six copies of the 102-bp repeat sequence and none of the carboxy terminal region. The avrBsP gene apparently was isolated as a
truncated version of *avrBs3-2*, which was subsequently cloned and shown to have 17.5 copies of the repeat. The *avrBs3-2* gene, like *avrBsP*, confers the ability to induce the HR in tomato but not pepper (13). Like *avrBsP*, *avrBs3-2* can be reduced to only three repeats while retaining avirulence activity (13, 17).

Although the above structure-function studies suggested that the Avr proteins could function directly in avirulence, other data do not support a direct role. In all reported cases, when concentrated proteins synthesized from avirulence genes expressed from their own promoters or over-expressed from lacZ or T7 promoters in *E. coli* or in the pathogen were introduced into plants, they did not elicit the HR (77, 119, 133, 154, 156). The location of the Avr proteins is not consistent with a role as an extracellular elicitor that would have to interact with a host receptor. The products from *avrBs3* (from *X. campestris pv. vesicatoria*) and *avrXa10* (from *X. oryzae pv. oryzae*) have been shown by biochemical fractionation and immunoelectron microscopy experiments to be located mainly in the cytoplasm of the bacterial cells (20, 80, 156). In both cases, the avirulence genes were overexpressed to increase the amount of detectable antigen. Younget al (156) used not only epitope-tagged *avrXa10* for specific detection of the gene product with monoclonal antibodies, but also a polyclonal antibody that was shown to bind to the repeat domain of the protein. Thus, even if only portions of the repeat domain were exported, the peptides should have been detected in either concentrated culture filtrates or by immunolabeling of infected plant tissues.

The evidence that bacterial avirulence gene products do not function outside the bacterial cell, although compelling, remains inconclusive. As described in the next section, bacterial proteins can be exported through alternate secretion pathways without the need for signal sequences (120), and some exported proteins, such as α-hemolysins, require *in vivo* modification for activity (61, 139). Thus, the avirulence gene products may not have been detected outside the bacterial cells because they are: (a) modified such that they are not recognized by the antibodies; (b) rapidly degraded by host proteases, as found for some harpins (143); or (c) exported in very low amounts and/or at very specific times during infection. Additionally, testing for elicitor activity by infusion of plant tissue may not mimic presentation of the Avr protein in vivo. Avr protein may be introduced by some mechanism directly into the plant cells (Model 3). Precedence for direct introduction to eukaryotic cells can be found in secretory systems of animal pathogens. *Yersinia pseudotuberculosis* exports the cytotoxic product of the *yopE* gene directly to HeLa cells during infection of the cells with bacteria (118). The export mechanism of the *yopE* cytotoxin is related to the *hsp* secretory apparatus, which is required for *avr* gene activity [discussed below, (38, 48, 58, 59, 120)].
An intriguing recent report by Yang & Gabriel (154) provides evidence that avirulence genes contain sequence motifs that function inside plant cells. They identified sequences resembling three nuclear localization signals (NLSs, see Figure 2) in the carboxy-terminal regions of the predicted proteins of all sequenced members of the \textit{avrBs3}-family. When introduced into onion cells, \(\beta\)-glucuronidase translational fusions with DNA encoding the C-terminal regions of two \textit{avrBs3} homologs (\textit{avrb6} and \textit{pthA}) were transiently expressed, and GUS activity was detected specifically in the nuclei of transformed cells. Mutations in the NLS sequences of \textit{avrBs3} disrupted avirulence activity (U Bonas, personal communication). The \textit{avrBs3}-homologs also contained heptad repeats similar to leucine zippers. Leucine zippers and leucine-rich repeats may serve as sites for protein-protein interactions (67). One possible model from these data is that the avirulence gene product is delivered to the plant cell, where it could interact directly with resistance gene products. The presence of NLSs in a bacterial gene does not prove that they function in nature to localize the bacterial protein to the plant nucleus. In fact, deletion of the region encoding most of the C-terminus (including the NLSs) from one \textit{avrBs3}-homolog, \textit{avrBs3}-2, did not affect avirulence activity (13). Although not conclusive, these intriguing findings may require that we revisit our view with regard to avirulence gene product location and function.

\textbf{Interaction of \textit{avr} and \textit{hrp} Genes}

Insight into avirulence gene function is coming from studies of a second group of genes referred to as the \textit{hypersensitivity reaction/pathogenicity (hrp; pronounced as “harp”) genes} ([91, 107]; for review, (12, 25, 149)]. The \textit{hrp} genes were originally identified as mutations that caused the loss of a strain’s ability to elicit an HR on nonhost plants (generally tobacco was used) and loss of pathogenicity (ability to colonize and initiate disease symptoms) on host plants. Most \textit{hrp} genes have been identified as part of large gene clusters (2, 9, 16, 60, 91). The conserved nature of the \textit{hrp} genes from a variety of plant pathogens, the similarities to gene clusters from other bacteria (38, 48), and the biochemical evidence from \textit{E. amylovora} and pathovars of \textit{P. syringae} (53, 144) support the concept that the \textit{hrp} genes encode the components of a supramolecular type III secretory apparatus. Six proteins, whose synthesis and secretion are directed by \textit{hrp} gene clusters, have been identified from \textit{E. amylovora} (142), \textit{P. syringae pv. glycinea} (111), \textit{P. syringae pv. tomato} (111), \textit{E. chrysanthemi} (7), \textit{P. syringae pv. syringae} (53), and \textit{P. solanacearum} (3). When purified and injected into appropriate plant tissues, the proteins elicited responses consistent with the HR. The first five proteins have been given the generic name harpin after the \textit{hrpN} gene of \textit{E. amylovora}. The elicitor from \textit{P. solanacearum} is the product of the \textit{popA} gene. Harpin-like elicitors are generally considered to be
nonrace-specific elicitors since their activity was not cultivar specific. However, one of the proteins, the product of the popA gene, has harpin-like function only on certain lines of petunia—a property strikingly similar to race-specific elicitors (3). Note that harpins or PopA have not been shown to elicit the HR in vivo, and mutations affecting only the specific ORFs in question did not eliminate the HR on the plants that reacted to purified protein (3, 110). Either other elicitors are produced or the proteins do not elicit the HR in vivo.

The activities of all bacterial avirulence genes examined are dependent on functional hrp genes. Strains with mutations in hrp genes cannot elicit their normal avirulence gene-mediated, race-specific interactions with host plants (63, 73, 77, 80, 119). In some cases, the lack of race-specific resistance in hrp mutants was thought to be explained by apparent coordinate regulation of avr and hrp genes. Expression of hrp genes has been shown to be regulated by nutrient conditions (63), osmolyte concentrations (63, 112), and plant-inducing factors (69, 90, 112, 121). All avr genes from P. syringae pathovars either have features consistent with coordinate regulation or are coordinately regulated with the hrp genes (64, 119, 121a). The promoters of many of the avirulence genes from P. syringae pathovars have elements that suggest the genes are responsive to the hrp regulatory factors. A number of genes, including avrD, avrB, avrPto, avrRpt2, are induced upon expression of the transcriptional regulator loci hrpS and hrpL (63, 64, 119, 121a). The gene hrpS is a member of the two-component regulatory gene family (50). The hrpL gene that is regulated by hrpS encodes an alternate sigma factor and can activate hrp promoters in the absence of hrpS, if constitutively expressed (62, 151). In the absence of the regulatory genes, most avr genes would not be induced. However, despite the inducibility of many avr genes, the lack of avr gene induction does not appear to provide an adequate explanation for the dependence of avirulence activity on Hrp activity. Even in the case of avrD, avirulence activity is lost in bacterial strains with mutations in genes for the hrp secretory apparatus as well as mutations in the transcriptional regulatory genes (73). The avrBs3 gene is expressed independent of hrp function, although five of six known hrp genes were required for induction of an HR (80).

Another explanation for hrp dependence of avr function is that secretion of race-specific elicitor is independent of hrp activity, but the elicitor was not present or secreted in sufficient quantity due to insufficient bacterial growth. In planta bacterial growth is often severely depressed by hrp mutations. Although not examined and, therefore, not ruled out in most cases, several experiments indicate that insufficient growth is not responsible for hrp-dependence. P. syringae pv. glycinea containing avrB, when cultured under hrp-inducing conditions, remained competent for eliciting an HR on soybean containing
the appropriate R-gene despite treatment with transcription-inhibitory concentrations of rifampicin (63). Since the rifampicin prevented the bacteria from multiplying upon inoculation, adequate numbers of bacteria for induction of the HR were apparently introduced at the time of inoculation and further growth of the bacteria was not necessary (63). The findings of Kamoun & Kado (69) are relevant to the growth hypothesis. They attempted to complement in planta the growth of a hrp-deficient strain with a hrp-proficient strain and found that hrp-deficient strains of X. campestris pv. campestris grew to the same level as did hrp-proficient strains when coinoculated. Therefore, hrp-deficient strains can grow in planta and provide hrp functions extracellularly for hrp-deficient strains. However, when a hrp-deficient strain with avrXa10, which is phenotypically suppressed in hrp-deficient strains, was coinoculated with hrp-proficient bacteria lacking avrXa10 into rice containing the R-gene Xa10, no elicitation of resistance occurred (W Zhu & F White, personal communication). Theavr-containing strain grew to population levels comparable to wild-type. This experiment also argues against a third explanation, that the race-specific HR is dependent on at least two signals from the bacterium, one of which is hrp-dependent and the other avr-dependent. The evidence indicates that avr and hrp genes are required in the same bacterial cell for elicitor activity.

Reconstitution of the hrp secretory apparatus in E. coli provides a valuable tool for directly analyzing the relationship of hrp and avr gene functions. The hrp cluster from Erwinia was the first to be shown to function in E. coli, and E. coli containing the hrp cluster will elicit the HR on tobacco (9). However, no avirulence genes have been identified in Erwinia. The hrp region from P. syringae pv. syringae also functions in E. coli, if the hrpL gene is expressed constitutively (62, 110), and has permitted tests for race-specific elicitor activity when a variety of avr genes are expressed concomitantly with the hrp cluster (110). Race-specific resistance responses on soybean plants with the appropriate corresponding R gene were detected with avrB, avrA, avrPto, avrRpt2, avrRpm1, and avrPph3 when the genes were expressed with the hrp genes in E. coli (110). Curiously, elicitor activity was enhanced but not dependent on a functional hrpZ gene, which encodes the P. syringae pv. syringae homolog of harpin (110).

Evidence, therefore, is mounting for a role of the hrp secretory apparatus in the secretion of avr proteins. Consistent with this role is the lack of a typical secretory peptide in proteins secreted by type III systems (120) and the structural relationship of YopJ (46), a protein secreted by Y. pseudotuberculosis, with the putative protein product of avrRxv (147). Further comparisons with other bacterial systems are providing a wealth of experimental directions and may help explain confounding features that have prevented the identification of
extracellular elicitors (45, 120). Proteins secreted by Yersinia species (Yops), for example, are only detected in Ca\(^{++}\)-depleted media [reviewed in (26)]. However, the secretion into the media may be due to interference with the normal secretory controls. Evidence exists that cell-to-cell contact and the proper conditions for yop gene expression are required in vivo for Yops secretion; low Ca\(^{++}\) conditions may cause the release of the contact sensor, which is the product of the yopN locus (118). Mutations in yopN also cause release of proteins into the culture media upon inducing conditions. In vivo, a number of the Yop proteins appear to be targeted for injection directly into the animal cells upon contact. Thus, many Avr and other potentially hrp-secreted proteins may not be secreted into the culture medium without plant cell contact and are therefore not easily detected in hrp-inducing media. If the Avr protein must be in the host cytoplasm to function, then assays based on the infusion of purified Avr protein may not be successful.

**ROLE OF AVIRULENCE GENES IN PATHOGENICITY**

Because inactivation of avr genes in pathogens in several cases does not attenuate the pathogen’s ability to colonize and cause symptoms on the host plant (94, 97), and no enzymatic or physiological function can be ascribed to most avirulence gene products, avr genes generally were not thought to be critical for the survival of the pathogen (44, 75). However, increasing evidence implicates avr genes in roles other than race-specificity. An understanding of these functions will contribute to our understanding of the evolution of avirulence and pathogenicity. Further drawing on the parallels with animal pathogenic bacteria, Avr proteins may be transported directly into the plant cells, where their intended targets are plant cellular processes involved in resistance. Jakobek & Lindgren (65) have reported the expression of defense-related genes after challenge of the plants with hrp-deficient bacteria. Similarly, Brown et al (19) have observed the apparent inhibition of papillae formation by hrp-proficient bacteria.

The first such evidence that avirulence genes serve additional functions in the pathogen was reported by Kearney & Staskawicz (72). They found that strains of *X. campestris* pv. *vesicatoria* containing an inactivated avrBs2 gene were less aggressive to a susceptible cultivar of pepper than was the wild-type strain (72). Sequences related to avrBs2 occur in all strains of *X. campestris* pv. *vesicatoria* and in many other pathovars of *X. campestris* and *X. oryzae* (72, 101, 105). Mutants in avrBs2-homologs in *X. campestris* pv. *alfalfa* also were reduced in their ability to multiply in alfalfa plants (72). Therefore, avrBs2 appears to be essential for the growth of the pathogen in these hosts.

The pthA gene, which functions as an avirulence gene on bean and cotton (when present in *X. campestris* pv. *phaseoli* and *malvacearum*, respectively),
originally was identified as a gene for pathogenicity in *X. citri* and is required for induction of Asiatic citrus canker symptoms and colonization of citrus (130). Similarly, *X. campestris* pv. *malvacearum* containing avrb6 induced more water-soaking on the host cotton than did strains without avrb6. Yang and coworkers (155) demonstrated that combinations of avrBs3-homologs in *X. campestris* pv. *malvacearum* contributed additively to the ability of the pathogen to cause watersoaking on cotton. A mutant in which seven of the ten gene homologs had been inactivated did not cause symptoms on cotton. Interestingly, the rate of growth of the mutant bacteria in planta was identical to the wild-type strain, but over 1000-fold fewer bacteria were released to the leaf surface than the wild-type strain. This suggests that pathogenicity on cotton requires multiple members of the avrBs3 gene family, but in planta growth does not. Other avirulence genes that function in aggressiveness or fitness to host plants are the avrE and avrA genes from *P. syringae* pv. *tomato* (94), avrRpm1 from *P. syringae* pv. *maculicola* (114), *pthA* gene from *X. citri* (130), and avrXa7 from *X. oryzae* pv. *oryzae* (24).

**EVOLUTION OF AVIRULENCE GENES**

In plant/pathogen systems, evolution of a pathogen population is directed toward avoiding recognition and induction of resistance by the host plants. Avoidance may result from the masking of elicitation of resistance by production of aggressiveness factors. Pectic enzyme production by *Erwinia chrysanthemi* masks expression of the HR (6). Alternatively, lack of recognition may be due to modification or absence of the avirulence gene in virulent races. Races of *P. syringae* pv. *glycinea* virulent to soybean with RPg2, for example, do not contain DNA that hybridizes with avrA gene and are not recognized by the RPg2 resistance gene (127). Alternatively, as in the cases of avrD alleles in *P. syringae* pv. *glycinea*, DNA that hybridizes to the avirulence genes is present, but the alleles do not confer avirulence activity due to minor changes in the sequences (158). More radical changes can involve insertions by mobile DNA elements. Transposition of an insertion element into the avrB51 locus in strains of the bacterial spot pathogen of pepper (*X. campestris* pv. *vesicatoria*) inactivated the gene and the strains became virulent to pepper with Bs1 (29, 71).

In multigene families of avirulence genes such as the avrBs3 family, the existence of many copies within a strain may provide opportunities for intragenic or intergenic recombination, thereby accounting for divergence between the copies (89). New host specificities of the avrBs3 homolog from *X. campestris* pv. *vesicatoria* were created in vitro by changing the number of 102-bp repetitive sequences (13, 54, 152). Recent evidence indicates that similar reassortment can occur by recombination in vivo. Recombinants of *pthA* from *X. citri*, an avrBs3 homolog with both avirulence and aggressiveness functions, were
selected with the aide of a marker, an nptI-sac cartridge, that had been inserted into one of the 102-bp repeats of the gene (153). The pthA recombinants obtained had more or fewer copies of the 102-bp repeat; in assays on plants, mutants were identified that had gained or lost avirulence function. Thus, in this assay, intragenic recombination generated new avr-pth genes.

FUTURE DIRECTIONS

Research in bacterial avirulence genes has revealed the close dependence of avirulence gene function and the secretory apparatus that is encoded by the hrp genes and required for bacterial pathogenicity. The association suggests that pathogenicity and/or in planta survival factors, which are secreted upon growth in the plant and, perhaps, are dependent on direct bacterial/plant cell contact, may provide key signals for recognition of bacterial pathogens by the host plants. Although there appears to be no a priori reason for avirulence genes to be involved in pathogenicity, all of the known bacterial avirulence genes have some connection with pathogenicity (i.e. either direct effects on pathogenicity or indirectly through induction in planta). Presumably the bacteria are attempting to alter normal plant cell metabolism or responses to infection. It would appear that plants can turn the tables on the pathogen and use the very factors the pathogen targets to the host as a means to recognize and resist the pathogen. In the near future, with advances in the analysis of avirulence proteins, we will likely learn how each avirulence gene product functions in resistance. Even in the case of avrD, the possibility exists that the gene product functions in the plant cell. In the cases where the avirulence gene products function in pathogenicity, future research will be directed at understanding the targets of the pathogenicity factors in or on the plant cell. The recognition process between avirulence gene products or enzymatic metabolites and the resistance genes of plants also remains uncharacterized. Despite the complexity of the systems involved and the resultant confounding of avirulence gene function, much progress can be expected in the next few years. Deviations from the classic gene-for-gene interaction (e.g. 32, 33, 64, 73, 93, 96) have been identified, and further nuances can be anticipated. However, the “gene-for-gene” model may come remarkably close to describing at the molecular level the process of resistance signaling. Understanding the process for recognition in both race-specific and nonhost interactions will likely lead to improved strategies for disease resistance.

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