### 掲載内容

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<td>誌名</td>
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</tr>
<tr>
<td>ISSN</td>
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<td>著者</td>
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<td>掲載ページ</td>
<td>p. 61-110</td>
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<td>発行年月</td>
<td>1997年3月</td>
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農林水産省 農林水産技術会議事務局筑波産学連携支援センター
Tsukuba Business-Academia Cooperation Support Center, Agriculture, Forestry and Fisheries Research Council Secretariat
Evolution of Host-Pathogen Relationships III
Evolution of Pathogen-Genotype Specific Resistance and Host Range

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(Received May 8, 1996)

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Synopsis

After the evolution of the basic pathogenicity system, specific host-pathogen relationship originated by the evolution of specific resistance genes in the host plant. The time is considered after formation of vascular bundle in plants, because the gene-for-gene relationship is observed only on leaves in many cases and on stems in a few cases. It is considered that the gene-for-gene relationship originated in each family or each genus independently, because different genes exist among most families, and even among many genera. There are some genera and species which do not show gene-for-gene relationships. At least, wild species have many specific resistance genes which are not included in cultivated plants. This suggests that specific resistance genes originated in early stage of development of each family or genus.

Key words: Avirulence, Evolution, Gene-for-gene relationship, Specific resistance

Introduction

In the previous papers (Kiyosawa and Nomura 1997a, b), the origin of pathogens, basic pathogenicity and hrp with increase of mainly nonspecific and minor genic resistance for this period was discussed. Here, we will mention

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later stage of evolution of the host-pathogen relationship.

**Gene-for-gene relationship**

Disease resistance in crop plants was introduced from wild plants in many crops: rust resistance in wheat, barley and oats, powdery mildew resistance in wheat and barley, and late blight resistance in potato. This indicates that many disease resistance genes are included in wild plants (Kiyosawa 1981). This does not always indicate that wild plants have resistance genes more than cultivated plants, because most tests were carried out with fungus strains isolated from cultivated plants, although it can not be denied.

It can be concluded that at least, there are many genes in wild plants which are not included in cultivated plants. Of these genes, many are of a specific nature. These facts suggest that specific resistance genes originated before these host plants were domesticated.

Cultivation of crops advanced through following processes: collective cultivation of a single plant in a limited area, fertilization, weeding and release of a small number of improved varieties developed by breeding. All of these processes are favourable for disease development. Selection of an excellent plant by most efficient farming producer and improvement by breeder protected the plants from the diseases, but these resistant varieties were soon broken down by occurrence of virulent races by mutation and/or selective reproduction of virulent races. Also at present, such cycles are being repeated. A few years after release of new resistant varieties, if the varieties have specific resistance genes, the resistance is broken down. There are some evidence which acquisition of virulence by pathogens for varieties having specific resistance genes accompany decrease of fitness of pathogens (Kiyosawa 1986, Kiyosawa et al. 1991, 1994, 1997a, b). Therefore, for virulence genes produced under the pressure of resistant varieties accompany the cost, frequencies of virulent races tend to approach an equilibrium, if the frequencies of host genotypes do not change (Kiyosawa 1995). Even if the frequencies of host genotypes change, frequencies of host genotypes and pathogen genotypes trend to approach to around a limited cycle, when resistance genes have a cost (Leonard 1994).

Genes controlling pathogenicity are divided into two groups: general (non-specific) and specific genes. The general pathogenicity genes are represented by the *hrp* genes and genes controlling toxin production. Also, specific pathogenicity genes are divided into two groups: positively and negatively regulating genes. The former is considered to be related to acquisition of basic pathogenicity, and the latter is called avirulence gene and is associated with the gene-for-gene relationship. According to Ilo et al. (1989), the gene-for-gene relationship is found in 30 crop and pathogen combinations. In Table 1, 59
Table 1. The number of resistance genes designated and crop-pathogen combinations in which gene-for-gene relationships are known.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Host</th>
<th>The number of resistance genes designated</th>
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<td><strong>MYXOMYCOTA</strong></td>
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<td><em>Plasmodiophora brassicae</em></td>
<td><em>Brassica oleracea</em></td>
<td>Cabbage</td>
<td>2, (1), [2] pb&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>MASTIGOMYCOTINA</td>
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<tr>
<td><em>Albugo candida</em></td>
<td><em>Brassica napus</em></td>
<td>Rape</td>
<td>3, Ac7&lt;sup&gt;1&lt;/sup&gt;</td>
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<td><em>Bremia lactucae</em></td>
<td><em>Lactuca sativa</em></td>
<td>Lettuce</td>
<td>14, {4}{2}{3}, R</td>
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<td><em>Peronosclerospora sorghi</em></td>
<td><em>Sorghum bicolor</em></td>
<td>Sorghum</td>
<td>16, (7){3}, Dm</td>
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<td><em>Peronospora farinosa f. sp. spinaciae</em> (=<em>effusa</em>)</td>
<td><em>Spinacea oleracea</em></td>
<td>Spinach</td>
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<td><em>magnaporthea tripholorum</em></td>
<td><em>Glycine max</em></td>
<td>Soybean</td>
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<tr>
<td><em>Phytophthora fragariae</em></td>
<td><em>Medicago sativa</em></td>
<td>Alfalfa</td>
<td>2, <em>Rpm</em></td>
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<td><em>infestans</em></td>
<td><em>Fragaria × ananassa</em></td>
<td>Strawberry</td>
<td></td>
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<tr>
<td><em>megasperma f. sp. medigenis</em></td>
<td><em>Solanum tuberosum</em></td>
<td>Potato</td>
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<tr>
<td><em>sojae</em></td>
<td><em>Medicago sativa</em></td>
<td>Alfalfa</td>
<td>6, <em>Pm</em></td>
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<tr>
<td>(=<em>P. m. f. sp. glycinea</em>)</td>
<td><em>Glycine max</em></td>
<td>Soybean</td>
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<tr>
<td><em>Phyllosticta halstedi</em></td>
<td><em>Helianthus annuus</em></td>
<td>Sunflower</td>
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<td><em>Pseudoperonospora cubensis</em></td>
<td><em>Cucumis melo</em></td>
<td>Muskmeleon</td>
<td>5, <em>Pc</em></td>
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<td>DEUTEROMYCOTINA</td>
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<td><em>Alternaria alternata</em> f. sp. lycopersici</td>
<td><em>Alternaria</em></td>
<td><em>Lycopersicon esculentum</em></td>
<td>Tomato</td>
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<sup>1</sup> pb: pathogenicity band.
(Table 1. Continued)

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<td><em>triticina</em></td>
<td>stem canker</td>
<td>Wheat</td>
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<td>Ascochyta rabiei</td>
<td>Leaf blight</td>
<td>Triticum aestivum</td>
<td>* 4, Arc</td>
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<td><em>faba</em></td>
<td>Ascochyta blight</td>
<td>Cicer arietinum</td>
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<tr>
<td><em>sojina</em></td>
<td>Brown spot</td>
<td>Vicia faba</td>
<td>* 7, Af</td>
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<td><em>oryzae</em></td>
<td>Frogeye leafspot</td>
<td>Glycine max</td>
<td>* 2, Rcs</td>
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<td><em>Cladosporium fulvum</em></td>
<td>Narrow brown leaf spot</td>
<td>Oryza sativa</td>
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<tr>
<td><em>Colletotrichum graminicola</em></td>
<td>Leaf mold</td>
<td>Lycopersicon esculentum</td>
<td>* 11, (3), Cf</td>
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<td><em>lindemthianum</em></td>
<td>Anthracose</td>
<td>Sorghum bicolor</td>
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<td><em>oribiculare</em></td>
<td>Anthracose</td>
<td>Phasolus vulgaris</td>
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<tr>
<td><em>Fusarium oxysporum f. sp.</em></td>
<td>Anthracose</td>
<td>Cucumis sativus</td>
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<tr>
<td><em>ciceris</em></td>
<td></td>
<td>Cicer arietinum</td>
<td>* 2, b</td>
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<td><em>lentil</em></td>
<td></td>
<td>Lens calinaris</td>
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<td>Cucumis melo</td>
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<td>Gossypium hirsutum barbadense</td>
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<td><em>Helminthosporium</em></td>
<td>Southern leaf blight</td>
<td>Zea mays</td>
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<td>(= <em>Exserohilum turcicum</em>)</td>
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<td>(= <em>Setosphaeria turcica</em>)</td>
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<td>(= <em>Tricnomegasphaeria turcica</em>)</td>
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<td>Glycine max</td>
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<td><em>Pyricularia oryzae</em></td>
<td>Blast</td>
<td>Oryza sativa</td>
<td>* 16, [11], (5) (2), <em>Pi</em></td>
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References:
- Kulshrestha and Rao 1976
- Dey and Singh 1993, Jan and Wiese 1991
- Rashid et al. 1991a, b
- Probst et al. 1965, Ross 1968
- Sah and Rush 1988
- Lindhout et al. 1989
- Lenhardt et al. 1972
- Kanwar et al. 1980
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- Tu 1988
- WasiIwa et al. 1993
- Upadhyaya et al. 1983, Jiménez-Díaz 1989
- Kamboj et al. 1990
- Zink and Thomas 1990
- Armstrong and Armstrong 1980
- Carson 1995
- Willmot and Nickell 1989
- Kiyosawa 1989
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<td></td>
<td>Ali et al. 1976</td>
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<td>Rasmussen and Rogers 1963</td>
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<td>Wells and Skoropad 1963</td>
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<td>Abadassi et al. 1987</td>
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<td>Forbes et al. 1964</td>
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<td><strong>7</strong>, <strong>2</strong>, <em>Pa</em></td>
<td>Quresh et al. 1993</td>
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<td>Rust</td>
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<td>recondita</td>
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<td><strong>38</strong>, (4) <strong>3</strong> (3) (2), <em>Lr</em></td>
<td>Storey and Howland 1967</td>
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<td>sorghii</td>
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<td><strong>10</strong>, [4], (7), <em>Rpl</em></td>
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<td><strong>18</strong>, [14], (2) (2), <em>Yr</em></td>
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<td>Rice</td>
<td>★ 21, (2), Xa</td>
</tr>
<tr>
<td></td>
<td>Capsicum annuum</td>
<td>Pepper</td>
<td>3, Bs</td>
</tr>
<tr>
<td></td>
<td>Vigna unguiculata</td>
<td>Cowpea</td>
<td>5, Bp</td>
</tr>
<tr>
<td></td>
<td>Bacterial spot</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial pustule</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: The number of genes identified, [the number of loci], (the number of multiple alleles), (the number of loci in a linkage group)
b: Race number.
c: The last one of serial numbers given to resistance genes.
★: Host-pathogen combination in which gene-for-gene relationship is known.
☆: The presence of RS/SR pattern suggests the gene-for-gene relationship, but additional evidences are necessary.
combinations are shown in a range of pathogenic fungi and bacteria, with the numbers of resistance genes and loci designated in the hosts and their linkage relationships.

The gene-for-gene relationship is determined by specific interaction of a resistance gene in the host and an avirulence gene in the pathogen. Only when a pathogen with an avirulence gene contacts with a host having the corresponding resistance gene, a resistant reaction (hypersensitive response) is induced. In other words, both the resistance gene and avirulence gene are necessary to induce hypersensitive reaction. This system (Table 2) shows a reaction pattern different from the pattern shown in Table 1 in a previous paper (Kiyosawa and Nomura 1997a). This leads to the question which was earlier in evolution, resistance or avirulence.

Table 2. Host-pathogen relationship in gene-for-gene system.

<table>
<thead>
<tr>
<th>Host\Pathogen</th>
<th>Avirulent</th>
<th>Virulent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Susceptible</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

The basic pathogenicity model proposed by Heath (1987, 1991) predicts that a gene-for-gene interaction evolves as a response to selection pressure on the host after basic pathogenicity is attained by the pathogen via the production of pathogenicity factors (de Wit 1992). After development of basic pathogenicity, specific resistance genes were developed. Verderevsky (1959) and Heath (1987) mentioned a similar opinion. They thought that specific resistance evolved after general resistance developed. Before development of specific resistances, potential avirulence genes had already developed in the pathogens. At least part of avirulence genes would play some roles, for example, in the absorption of some substances. However, the role is not essential for fungal life, because mutants of avirulence genes still have the ability to attack resistant plants having corresponding resistance genes. The facts that mutation of avirulence genes leads to a decrease of fitness in the fungus strain (van der Plank 1968, Kiyosawa et al. 1993) support this consideration.

Gene-for-gene relationships are mainly observed in foliar diseases. In these diseases, specific resistance genes expressed in parenchyma of the leaves. In Phytophthora infestans (Tomiyama et al. 1968, Curtler 1984), and Phytophthora megasperma (Rennie et al. 1992), the expression of specific resistance genes is observed also in the stem. Xanthomonas campestris (Kamoun et al. 1992) and X. oryzae (= campestris) (Horino and Yamada 1982) induce specific resistance in vascular bundle of leaf of cabbage and rice, respectively. Specific resistances
to *Pyricularia oryzae (= Magnaporthe grisea, rice blast) are not expressed in rice root (Ishii 1978). These indicate that avirulence genes developed greatly after the stems and leaves of plants originated.

1. Genetics of specific resistance

(1) *Pseudomonas*

Innes et al. (1993a) found a new resistance gene in *Arabidopsis*. This gene was named as *RPS3*. *RPS3* was mapped to chromosome 3 and ≤ 1 cM from another resistance gene, *RPM1*. The genes *RPS3* and *RPG1* found by Keen and Buzzell (1991) both confer *avrB*-specific disease resistance; may be same.

(2) Crown rust

Many resistance genes have been found: more than 75 (*Pc* gene) in oat to *Puccinia coronata f. avenae* (crown rust). The last 40 of these genes, derived primarily from *Avena sterilis*, have been described since 1964. In only one instance, a potentially new gene from *A. sterilis*, has been recognized as a previously identified gene (Martens and Dyck 1989, Rooney et al. 1994).

(3) Powdery mildew

Many powdery mildew (*Erysiphe graminis f. sp. hordei*) resistance genes in barley follow the gene-for-gene relationship. Of them, 28 alleles map to the *Mla* locus on the short arm of chromosome 5. Different *Mla* alleles show characteristic, macroscopic infection types (ITs), ranging from ITs 0 to 4 (Boyd et al. 1995).

(4) Downy mildew

Most attention in lettuce breeding has been devoted to developing cultivars resistant to downy mildew, caused by the Oomycete pathogen, *Bremia lactucae* (Crute 1987, 1992). There are at least 15 well-characterized dominant genes for resistance to downy mildew (*Dm*. Johnson et al. 1978, Farrara et al. 1987, Maisonneuve et al. 1994). Each *Dm* gene is matched by specific avirulence gene in the pathogen in a gene-for-gene interaction (Crute and Johnson 1976, Ilott et al. 1989) (Witsenboer et al. 1995).

Disease resistance genes in lettuce are organized in several distinct clusters. Three major clusters have been identified so far (Johnson et al. 1978, Hulbert and Michelmore 1985, Farrara et al. 1987, Kesseli et al. 1994). Genes for resistance to several parasites are present in two of the clusters (Witsenboer et al. 1995).

The largest cluster contains at least eight *Dm* genes (Farrara et al. 1987) plus a gene for root-aphid resistance (Crute and Dunn 1980); this cluster spans a genetic distance of 20cM and a physical distance of at least 6 Mb (P.
Anderson, R. Kesseli, and R. Michelmore, unpublished). Several additional R-factors have been mapped to this cluster (Bonnier et al. 1994) (Witsenboer et al. 1995).

The second largest cluster contains at least two *Dm* genes (see below), together with *Tu*, providing resistance against turnip mosaic virus (Zink et al. 1973), and *ptr*, conferring resistance to *Plasmopara lactucae-radicis* root downy mildew (Vandemark et al. 1992). This cluster spans over 6.4 cM (Hulbert and Michelmore 1985, Robbins et al. 1994, Kesseli et al. 1993). R17, a new resistance factor is also loosely linked to this cluster (Maisonuneuve et al. 1994) (Witsenboer et al. 1995). The third cluster contains three downy mildew resistance genes *Dm4, Dm7* and *Dm11* (Hulbert and Michelmore 1985). Not all resistance genes have been mapped to clusters; linkage to other resistance genes has not been shown for *Dm13, Ant1* (resistance to *Microdochium panationiana* (O. Ochoa and R. Michelmore, unpublished) and *cor* (resistance to *Rhizomonas suberifaciens*, Brown and Michelmore 1988, Kesseli et al. 1994) (Witsenboer et al. 1995). Witsenboer et al. (1995) indicated that *Dm5* and *Dm8* are the same genes. This cluster of resistance genes spans 6.4 cM, with *Dm10* 1.2 cM from *Dm8* (Witsenboer et al. 1995).

2. Genetics of avirulence

(1) *Pseudomonas*

In pseudomonads with a narrow host range, genetical studies have been concentrated in *Pseudomonas syringae* in which many pathovars and many races in the pathovars have been found. In them, avirulence (*avr*) genes comprises loci which determine pathogen-genotype (race) specificity.

Recent characterization of strains of *Pseudomonas syringae* pv. phaseolicola based on their virulence towards *Phaseolus* genotypes has demonstrated the existence of gene-for-gene interactions based, in theory, on the presence of five genes for avirulence (*A1*—*5*) in *P.s.* pv. phaseolicola which match five genes for resistance (*R1*—*5*) in bean (Jenner et al. 1991, Teverson 1991, Taylor et al. 1989). Resistance is expressed by the hypersensitive reaction (HR), at inoculation sites in leaves and pods (Harper et al. 1987, Jenner et al. 1991). The HR resulting from the *R3/A3* interaction occurs more rapidly and is associated with more distinct browning than is observed with other resistance genes (Mansfield et al. 1994).

The avirulence gene matching the *R2* gene for resistance to halo-blight disease in *Phaseolus* was characterized. The predicted 41 kDa *AvrPphE* protein is hydrophilic, has no features that indicated function, and no similarity to other protein sequences. The promoter region of *avrPphE* contains a “harp box” motif. The gene was expressed more strongly in minimal than in nutrient-rich media. Homologs of *avrPphE* were detected in strains represent-
ing eight races of *P. s. pv. phaseolicola* including those virulent on cultivar with the *R2* resistance gene, and in *P. s. pv. tabaci* but not in *P. cichorii* or *P. s. pv. coronafaciens*, glycinea, maculicola, pisi or syringae. Disruption of *avrPphE* prevented induction of the HR but did not appear to affect basic pathogenicity (Mansfield et al. 1994).

Molecular cloning of avirulence genes *avrPphA* *R1* and *avrPphB* *R3* (named as proposed by Vivian and Mansfield 1993) which match resistance genes *R1* and *R3*, respectively, has confirmed part of the gene-for-gene relationship proposed in bean halo-blight disease (Hitchin et al. 1989, Jenner et al. 1991, Taylor et al. 1989). Additional *avr* genes cloned from *P. s. pv. phaseolicola* *avrPphC* and *avrPphD* determine ability to cause the HR on certain cultivars of the non-host plants soybean and pea, respectively (Yucel et al. 1994a, b, Wood et al. 1994). Both of the non-host *avr* genes are located on an 150 kb plasmid.

Avirulence genes *avrB* in *P. s. pv. glycinea* and *avrD, avrE, avrPto*, and *avrRpt2* from *P. s. pv. tomato* have been found to be regulated by loci which are homologous to *hrpS* and *hrpL* from *P. s. pv. phaseolicola* (Huynh et al. 1989, Innes et al. 1993b, Salmeron and Staskawicz 1993, Shen and Keen 1993, Lorang and Keen 1995). Conserved regions (so-called “harp boxes”) associated with regulation by *hrp* genes, have been located within promoters of several *avr* genes from pathovars of *P. syringae* (Jenner et al. 1991, Dangl et al. 1992, Innes et al. 1993b). In *P. s. pv. tomato*, *avrE* is physically linked to *hrpRS* at the right border of the *hrp* cluster (Lorang and Keen 1995).

Transposon mutagenesis and DNA sequencing showed that *avrPphE* was linked to *hrpY*, a *hrp* locus identified at the left end of the *hrp* gene cluster. Sequence analysis showed that the region linked to *avrPphE* was very similar to DNA containing *hrp* genes from *P. s. pv. syringae* including *hrpI*, *hrpL*, and *hrpK* (Mansfield et al. 1994).

Avirulence gene D (*avrD*) cloned from *Pseudomonas syringae* pv. *tomato* (Kobayashi et al. 1990a, b) caused *P. s. pv. glycinea* race (*R4*) to elicit the hypersensitive response (HR) on soybean cultivars containing the resistance gene, *Rpg4* (Keen and Buzzell 1991). *Escherichia coli* and other gram-negative bacteria expressing *avrD* produce a cultivar-specific elicitor of the soybean HR, identified as two novel acyl glycosides called syringolides (Keen et al. 1990, Midland et al. 1993, Smith et al. 1993). The 311 amino acid protein encoded by *avrD* is thought to have an enzymatic activity that converts normal bacterial metabolites into the HR-inducing syringolides (Yucel et al. 1994a).

Some other pathovars, including *P. s. pv. glycinea*, harbor DNA sequences with considerable similarity to *avrD* (Kobayashi et al. 1990a). The *avrD* allele from *P. s. pv. glycinea* encodes a protein that has 86% amino acid identity with the *avrD* protein from *P. s. pv. tomato* yet does not confer the avirulent phenotype. Several amino acid substitutions throughout the length of the *P. s.*
pv. glycinea protein distinguished it from that of P. s. pv. tomato (Kobayashi et al. 1990a), yet it directed the production of extremely small quantities of elicitor when overexpressed in E. coli (Keen et al. 1990). The amino acid substitutions in the P. s. pv. glycinea protein may therefore impair enzymatic activity required to produce the elicitor and/or reduce protein stability. Studies of recombinant genes (Kobayashi et al. 1990b) indicated that the carboxyl terminus of the avrD protein influences protein stability, but the specific amino acids required for the avirulence phenotype were not identified (Yucel et al. 1994a).

In order to define the amino acids and regions of AvrD necessary for the avirulence phenotype, Yucel et al. (1994a) surveyed several P. syringae pathovars for the occurrence of avrD genes and cloned and characterized three new avrD from P. s. pvs. phaseolicola and lachrymans. These avrD genes occurred on indigenous plasmids in both pathovars, like the allele originally cloned from P. s. pv. tomato, P. s. pv. lachrymans was unique in that it carried two different alleles on plasmids of different sizes. These alleles were cloned on 5.6- or 3.8-kb HindIII fragments that are conserved in several other P. syringae pathovars. Surprisingly, the two avrD alleles from P. s. pv. lachrymans were the most divergent of those compared, with only 85% amino acid identity. Allele I from P. s. pv. lachrymans was 95% identical to avrD from P. s. pv. tomato but less similar to the other three avrD genes. These two alleles were accordingly called homology class I. The avrD gene from P. s. pv. phaseolicola and allele 2 from P. s. pv. lachrymans were 97% and 98% identical, respectively, at the amino acid level with the nonfunctional P. s. pv. glycinea allele. These three alleles were therefore grouped into homology class II. Comparison of these alleles permitted the identification of four amino acid substitutions, unique to the P. s. pv. glycinea allele at positions 19, 245, 280, and 304 (Yucel et al. 1994a).

The avrD allele in Pseudomonas syringae pv. glycinea is nonfunctional. This allele is highly homologous to active class II avrD alleles but has five unique amino acid substitutions. Three of these five amino acid changes were shown to be absolutely required for restoration of avrD activity to the P. s. pv. glycinea allele by oligonucleotide site-directed mutagenesis. They were cysteine 19 to arginine, alanine 280 to valine, and leucine 304 to serine. In addition, changing leucine 301 to phenylalanine was required for high activity. However, alteration of the leucine at position 245 of the P. s. pv. glycinea allele to serine present in the active alleles, did not affect avrD activity (Yucel and Keen 1994).

The finding that the newly characterized class II avrD alleles yielded different products from class I alleles is of considerable significance. The results support previous interpretation (Yucel and Keen 1994) that the avrD protein products likely have enzymatic functions that lead to the elicitor-active syringolides as well as structurally related compounds of lesser activity. Some
of the products produced by the newly characterized class II \textit{avrD} alleles appear to arise exclusively from $\beta$-hydroxyoctanoic acid, but the corresponding products from $\beta$-hydroxydecanoic acid could not be detected. This indicates that the putative enzymatic functions of the two classes of \textit{avrD} proteins discriminate against fatty acid derivatives differing in length by two carbon atoms. Thus, the utilization by class I \textit{avrD} alleles of only $\beta$-hydroxyoctanoic acid and $\beta$-hydroxydecanoic acids is unlike normal biosynthetic enzymes of the malonyl CoA fatty acid biosynthetic pathway, which recognize intermediates irrespective of their chain length. However, the class II \textit{avrD} alleles appear to have an even more stringent substrate requirement, since they recognize the $\beta$-hydroxyoctanoic acid but not the $\beta$-hydroxydecanoic acid precursor (Yucel et al. 1994b).

(2) \textit{Xanthomonas}

In \textit{Xanthomonas campestris} pv. oryzae causing bacterial leaf blight to rice, two genes, \textit{avrBs3} and \textit{avrBsP}, from \textit{X. campestris} pv. vesicatoria contain a 102-bp sequence in the coding region; this sequence is repeated 17.5 and six times, respectively. The close similarity between the two genes, with the exception of rearrangements in the repeat structure, as well as the requirement of the repetitive region for avirulence activity of \textit{avrBsP}, has led to the suggestion that the repeat domain controls, in part, the specificity of avirulence activity (Hopkins et al. 1992).

Two avirulence genes in \textit{Xanthomonas oryzae} pv. oryzae, \textit{avrXa7} and \textit{avrXa10}, which correspond to resistance genes \textit{Xa-7} and \textit{Xa-10}, respectively, in rice were identified and partially characterized from the hybridizing clones. \textit{BamHI} fragments that are homologous to \textit{avrBs3} in \textit{Xanthomonas campestris} pv. vesicatoria and correspond to \textit{avrXa7} and \textit{avrXa10} contain a different number of copies of a 102-bp direct repeat (Hopkins et al. 1992).

\textit{Xanthomonas campestris} pv. vesicatoria is the causative agent of bacterial spot disease of pepper (\textit{Capsicum annuum}) and tomato (\textit{Lycopersicon esculentum}). In the compatible interaction, the bacteria multiply to a high density in the intercellular spaces of leaves causing water-soaked lesions that later become necrotic, whereas in an incompatible interaction the HR is induced, leading to restriction of bacterial growth (Bonas et al. 1993).

The avirulence gene \textit{avrBs3} from \textit{X. c.} vesicatoria specifies incompatibility in the pepper cultivar ECW-30R. This gene is particularly interesting because its internal part consists of a tandemly repeated, nearly identical motif of 102 bp, present in 17.5 copies (Bonas et al. 1989). The repeat units determine the specificity of the avirulence gene and new alleles that differ in specificity with respect to the plant genotype can be found (Herbers et al. 1992). Furthermore, the presence of homologous sequences in some, but not all, strains of \textit{X.}}
c. vesicatoria and in other pathovars of *Xanthomonas* is intriguing (Bonas et al. 1989, Canteros et al. 1991, Knoop et al. 1991, Swarup et al. 1992). Recently, the characterization of an *avrBs3*-homologous gene from *X. c. vesicatoria*, *avrBsp*, has been reported (Canteros et al. 1991). The *avrBsP* gene is present on a 1.7 kb fragment and confers avirulence activity towards tomato (Bonas et al. 1993).

Based on DNA homology to the avirulence *avrBs3*, which induces the resistance response on pepper, Bonas et al. (1993) isolated another avirulence gene from *X. c. vesicatoria*, designated *avrBs3*-2. This gene differs in specificity from *avrBs3* in inducing the hypersensitive response on tomato but not on pepper. Sequence analysis of the *virBs3*-2 gene revealed a high degree of conservation: the 3480 bp open reading frame contains an internal region of 17.5 nearly identical 102 bp repeat units that differ in their order from those present in the *avrBs3* gene. The coding region is 97% identical to *avrBs3* and expresses constitutively a 122 KDa protein, this representing a natural allele of this gene. The previously isolated 1.7 kb *avrBsP* gene from *X. c. vesicatoria* is 100% identical to the corresponding *avrBs3*-2 sequence, indicating that these genes might be identical (Bonas et al. 1993).

A striking feature of the *avrBs3*-2 sequences was found outside of the gene: *avrBs3*-2 is flanked by nearly perfect inverted repeats (IR-L and IR-R) (Fig. 1), each 62 bp long. These IR are also present in the *avrBs3* sequence, based on partial sequencing (Bonas et al. 1989); their possible significance, however, became more evident. Interesting, the IR-L is also present upstream of the *pthA* gene (*pathogenicity gene*) from *X. citri*, which seems to be homologous to *avrBs3*-2 (Swarup et al. 1992); there is no sequence information on the right IR sequences in the *avrBs3*-2 and the *avrBs3* genes are identical, with the exception of one nucleotide in the IR-L. No additional DNA fragments homologous to the IR were found to be genetically linked to the *avrBs3* to *avrBs3*-2 gene (Bonas et al. 1993).

![Fig. 1. Nearly perfect inverted repeats (IR-L and IR-R) in flanking region of avirulence gene *avrBs3*-2 in *Xanthomonas vesicatoria* (Bonas et al. 1989).](image)

Several plant resistance genes (*Bs1, Bs2, Bs3*) have been genetically characterized from pepper (*Capsicum annumum*) that determine resistance to particular races of the pathogen carrying specific avirulence genes. For example, pepper plants carrying the resistance locus *Bs3* are resistant to *Xanthomonas campestris* pv. vesicatoria strain expressing the avirulence gene *avrBs3*. 
Nucleotide sequence analysis of the *avrBs3* gene revealed that the internal portion of the predicted protein product consists of a nearly identical 34 amino acid repeat unit, present in 17.5 copies. Herbers et al. (1992) found that the repetitive region of the *avrBs3* gene determines race specificity and that deletions of repeat units generate new avirulence specificities and unmask undiscovered resistance genes in hosts, pepper and tomato. Race-specificity is determined by repetitive motifs (Herbers et al. 1992).

(3) *Cladosporium*

Van den Ackerveken et al. (1992) clearly demonstrated that the avirulence gene *avr9* is responsible for pathogen-genotype specificity on tomato genotype *Cf9* and fully support the gene-for-gene theory. The *avr9* gene is the first fungal avirulence gene to be cloned. The gene encodes a precursor protein of 63 amino acids and is interrupted by a short 59 bp intron. The mature *avr9* elicitor peptide of 26 amino acids is located at the C-terminus of the precursor protein. A putative TATA-box (TATAAGT) is located 40 bp upstream of the main transcription start. The 5' upstream region contains two imperfect repeats of 61 bp that are 77% identical. The 3' untranscribed region contains eight direct repeats of 17 bp (CGCATCGACTGCCGG) (Van den Ackerveken et al. 1992).

The avirulence gene *avr9* of the fungal tomato pathogen *Cladosporium fulvum* encodes a race-specific peptide elicitor that induces the hypersensitive response in tomato plants carrying the complementary resistance gene *Cf9*. The *avr9* gene is not expressed under optimal growth conditions in vitro, but is highly expressed when the fungus grows inside the tomato leaf. The induced expression of *avr9* is possibly mediated by a positive acting nitrogen regulatory protein, homologous to the *Neurospora crassa* NIT2 protein, which induces the expression of many genes under conditions of nitrogen limitation. Detailed *avr9* promoter analysis will reveal whether the nitrogen responsive elements in the promoter are indeed responsible for the high expression of *avr9* in *C. fulvum* growing in planta (Van den Ackerveken et al. 1994).

3. **Identity and similarity between resistance genes**

To date, seven resistance genes were cloned and characterized: *Hm1* in maize to *Helminthosporium maydis* (= *Cochlioborus carbonum*) (Johal and Briggs 1992), *Pto* in tomato to *Pseudomonas syringae* pv. tomato carrying *avrPto* (Martin et al. 1993), *Cf9* in tomato to *Cladosporium fulvum* (Jones et al. 1994), *N* in tobacco to tobacco mosaic virus (Whitham et al. 1994), *RPS2* in *Arabidopsis thaliana* to *Pseudomonas syringae* (Bent et al. 1994). *RPM1* (= *RPM3*) in *Arabidopsis thaliana* to *Pseudomonas syringae* (Grant et al. 1995), and *L5* in flax to *Melampsora lini* (Grant et al. 1995).
**Pseudomonas**

*Arabidopsis thaliana* **RPM1** gene enables dual specificity to pathogens expressing either of two unrelated *Pseudomonas syringae* avr genes. Despite this function, **RPM1** encodes a protein sharing molecular features with recently occurring, disease-susceptible *Arabidopsis* accessions (Grant et al. 1995).


**RPM1** was identified in *A. thaliana* accession Col-O as conferring resistance to *P. syringae* isolates expressing the avrRmp1 gene (Dangl 1993, Debener et al. 1991). Functional homologs of **RPM1** exist in pea, bean and soybean (Dangl et al. 1992). Resistance in *A. thaliana* to the *P. syringae* avrB gene also mapped to the **RPM1** interval (initially termed RPS3) (Innes et al. 1993a), and genetic analysis of *A. thaliana* mutants have suggested that **RPM1** conferred resistance to *P. syringae* expressing either avrRpml or avrB (Bisgrove et al. 1994). Because the sequences of avrB and avrRpml are unrelated (Dangl et al. 1992, Tamaki et al. 1988), **RPM1** appears to determine a dual specificity. The data show **RPM1** is confined to a 5 kb region and that this region allows recognition of *P. syringae* expressing either avrRpml or avrB (Grant et al. 1995).

The **RPM1** ORF contains features found in the predicted polypeptide sequence of other R genes (Martin et al. 1993, Bent 1994, Mindrinos et al. 1994, Whithan et al. 1994, Ellis, et al. 1995, Dangl 1995): a potential six-heptad amphipathic leucine zipper (positions 10 to 51), two motifs of a nucleotide binding site (NBS; positions 200 to 208 and 279 to 288) (Saraste et al. 1990), and 14 imperfect leucine-rich repeats (LRRs) from position 553 (Kobe and Dalesnohofer 1993). These features most closely resemble those of the *A. thaliana* RPS2 gene (23% identity and 51% similarity), which confers resistance to *P. syringae* expressing avrRpt2 (Bent 1994, Mindrinos et al. 1994). In addition to the NBS and LRRs, three other sequence blocks are shared with RPS2, the *tobacco N* gene, and the *flax L* gene: a potential kinase 3a site of the NBS (position 307 to 319), a hydrophobic stretch (positions 373-395) potentially involved in membrane association, and a short domain from positions 431 to 438 (aligned in Fig. 2). Three potential N-glycosylation sites were found at positions 54, 610, and 917 (Fig. 2) (Grant et al. 1995).

Bisgrove et al. (1994) identified mutations in four rpm1 loss-of-function alleles. A nucleotide deletion in codon 818 causes a frame shift and termination
after 11 amino acids in rps3-1, which suggests a functional requirement for the COOH-terminus of RPM1, including the final three LRR repeat units. The leucine to phenylalanine change in rps3-2 introduces a bulky aromatic side chain that may alter juxtaposition of the kinase 2 and kinase 3a domains in the NBS. A glycine to glutamic acid exchange in rps3-4 introduces a charge and may disrupt the α-helical structure of an LRR unit (Kobe and Dahlenhofer 1993, 1994, 1995). Finally, rps3-3 is a nonsense mutation resulting in termination at codon 87 (Grant et al. 1995).

Two similarly sized transcripts are produced, as observed for RPS2 (Mindrinos et al. 1994) and the tomato Cf-9 gene (Jones et al. 1994). In contrast, six naturally occurring accessions of A. thaliana that are susceptible to infection with P. syringae expressing avrRpm1 or avrB lack RPM1. This is unusual because common features of the R locus structure are multigene families and the presence of a homolog or homologs at the corresponding position in susceptible plants (Flor 1971, Keen 1990, Dangl 1992, Martin 1993, Bent 1994, Mindrinos et al. 1994, Whitham et al. 1994, Jones et al. 1994, Ellis et al. 1995, Dangl 1995). RPM1 may be recently evolved or may have been lost in A. thaliana accessions through genomic instability at RPM1. A DNA probe extending upstream from the RPM1 ORF (probe 3) detected a band of weaker relative intensity in the rpm1-null accessions that was roughly 200 bp larger than the corresponding band in RPM1 accessions. All six rpm1-null accessions
contained the same size band, which suggests that a single event has introduced or deleted RPM1 from this locus. Low-stringency hybridization revealed one strongly hybridizing and several weakly hybridizing bands that may represent RPM1-related sequences elsewhere in the A. thaliana genome (Grant et al. 1995).

Whether RPM1, or any R gene product directly interacts with the corresponding avr-dependent signal is unknown. The signal produced by P. syringae strains expressing either avrRpm1 or avrB could be structurally similar, and the dual specificity of RPM1 could reflect a single, or overlapping, binding site. The lack of mutants separating these two specificities seems to argue that the A. thaliana RPM1 molecule does not possess two avr-signal binding sites. However, genetic analyses of soybean cultivars reveal allelic R specificities recognizing P. syringae expressing avrRpm1 or avrB or both (Innes and Ashfield unpublished). The evolution of R genes determining multiple specificities may be one way of reducing the absolute number of R genes required to meet these demands (Grant et al. 1995).

Innes et al. (1993a) suggested the homology between two resistance genes to Pseudomonas syringae in Arabidopsis and soybean. The avrB avirulence gene was transferred from the soybean pathogen Pseudomonas syringae pv. glycinea into a P. syringae pv. tomato strain that is virulent to Arabidopsis. Of 53 ecotypes examined, 45 were resistant to a P. syringae pv. tomato strain carrying avrB, and eight were susceptible. The inheritance of this resistance was analyzed using a cross of resistant ecotype and susceptible ecotype. For both pathogen strains with and without avrB, cosegregation was obtained.

4. Identity and similarity between avirulence genes

(1) Pseudomonas

The avirulence gene D (avrD) from Pseudomonas syringae pv. tomato comprises the first open reading frame (ORF) of a putative operon consisting of at least five tandem ORFs. The promoter of the avrD operon was localized to a 150-bp DNA fragment occurring 5' to the avrD gene by using the Tn7-lux and gus reporter systems. The avrD promoter in P. syringae pv. tomato and P. syringae pv. glycinea was poorly expressed when bacteria were grown in complex culture media but was activated during bacterial growth in plants. The timing and level of induction were similar in virulent and avirulent plant-pathogen interactions. Two transcription initiation sites 87 and 41 nucleotides upstream from the translational start site were found. Only the -41 transcriptional start site was identified in bacteria grown in soybean leaves. A σ44 promoter consensus sequence (GG-10 bp-GC) occurred 14 bp upstream of the -41 transcriptional start, and 3' deletions into this region completely abolished promoter activity. Expression from the avrD promoter also required the hrp regulatory genes, hrpS and hrpL. Deletions from the 5'
end of the promoter region and base substitution analyses also identified two upstream elements important for expression. Sequence comparison of these elements with other cloned avirulence genes revealed the presence of a conserved consensus sequence (GGAACC-N15/16-CCAC) in the promoters of nine different avirulence genes from P. syringae pathovars. Compared pathovars are P. s. pathovar tomato (avrD), glycinea (avrA, avrB, avrC), tomato (avrPto, avrRpt2), pisi (avrPpi1), maculicola (avrRpm1), and phaseolicola (avrPph3) (Shen and Keen 1993).

Ronald et al. (1992) cloned an avirulence gene, designated avrPto, from Pseudomonas syringae pv. tomato race 0. It was shown that strains with sequences homologous to avrPto are included in P. syringae pv. maculicola 795 and 4981. P. syringae pv. phaseolicola, P. syringae pv. pisi, and P. syringae pv. coronafaciens, which are radish, bean, pea, and oat pathogens. P. syringae pv. maculicola strains 4326 and 2744, which cause disease on 76R, lack homology to avrPto, as do P. syringae pv. glycinea, P. syringae pv. lachrymans, P. syringae pv. tabaci, and P. solanacearum, which are pathogens of soybeans, cucurbits, tobacco, and solanaceous plants, respectively.

The avrRpt2 locus from Pseudomonas syringae pv. tomato causes virulent strains of P. syringae to be avirulent on some, but not all, lines of Arabidopsis thaliana and Glycine max (soybean). The DNA sequence of the avrRpt2 locus was determined and the avrRpt2 gene was identified as a 768-bp open reading frame encoding a putative 28.2-kDa protein. Further evidence that this open reading frame encodes AvrRpt2 was provided. The avrRpt2 gene also has avirulence activity in P. syringae pathovars of Phaseolus vulgaris (common bean), suggesting that disease resistance genes specific to avrRpt2 are functionally conserved among diverse plant species. The predicted AvrRpt2 protein is hydrophilic and contains no obvious membrane-spanning domain or export signal sequence, and there was no significant similarity of AvrRpt2 to sequences in the GenBank, EMBL, or Swiss PIR data bases. A comparison of the avrRpt2 DNA sequence to nine other P. syringae avirulence genes revealed a highly conserved sequence, GGAACCNA-N14-CCANNA, upstream of the translation initiation codon. This motif is located 6 to 8 nucleotides upstream of the transcription start site in all four P. syringae avirulence genes for which a transcription start site has been determined, suggesting a role as a binding site for a novel form of RNA polymerase. Regulation of avrRpt2 was similar to other P. syringae avirulence genes; expression was high in minimal medium and low in rich medium and depended on the hrpRS locus and as additional locus at the opposite end of the hrp cluster of P. syringae pv. tomato (Innes et al. 1993b).

The avrPto avirulence gene from Pseudomonas syringae pv. tomato (Pst) race 0 governs race-specific resistance to bacterial speck disease in tomato
cultivars containing the \( Pto \) resistance gene. The \( \text{avrPto} \) gene encodes 0.7 and 0.75 kb mRNAs whose predicted translation product is a mostly hydrophilic 164 amino acid protein of 18.3 kDa that reveals no homology to protein sequences in GenBank of EMBL databases. Highest expression of \( \text{avrPto} \) in cell culture is observed in minimal media containing sugars and sugar alcohols as carbon sources and lowest expression in minimal media containing tricarboxylic acid intermediates and in complex media. Transcription of \( \text{avrPto} \) requires the \( hrpSR \) pathogenicity function, but is independent of other \( \text{Pst} \) \( h\beta \) genes. A region of the \( \text{avrPto} \) promoter shows homology to \( hrp \) box sequences upstream of the \( \text{P. syringae} \) genes that required the \( hrpSR \) locus for expression, and both avirulence activity and \( \text{avrPto} \) locus for expression, and both avirulence activity and \( \text{avrPto} \) mRNA accumulation are abolished by deletions extending into this region. The \( \text{avrPto} \) transcription start site maps 31 nucleotides downstream of the \( hrp \) box motif (Salmeron and Staskawicz 1993).

A region of high similarity to sequences upstream of other \( \text{P. syringae} \) avirulence genes occurs between nucleotides \(-37\) and \(-31\) (Table 3). The sequence, TGGAACC, is found upstream of the \( \text{P. syringae} \) pv. phaseolicola avirulence gene \( \text{avrPph3} \) gene (Jenner et al. 1991), the \( \text{P. s. pv. glycinea} \) \( \text{avrB} \) and \( \text{avrC} \) genes (Tamaki et al. 1988), and the \( \text{P. s. pv. tomato} \) genes \( \text{avrD} \) (Kobayashi et al. 1990a) and \( \text{avrRp} \) (Innes et al. 1993b). The sequence fits the consensus \( hrp \) box motif, TG(A/C)AANC, found upstream of four \( \text{P. s. pv. phaseolicola} \) \( hrp \) operons which require the \( hrpSR \) locus for expression (Fellay et al. 1991). Sequences with similarity to the consensus \(-24/-12\) elements, which in many bacteria utilize the \( \sigma^{34} \) transcription factor for activation (Thöny and Hennecke 1989), are also found centered at \(-36/-24\) and \(-4/+10\),

<table>
<thead>
<tr>
<th>Gene</th>
<th>Upstream boundary</th>
<th>Sequence</th>
<th>Downstream boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{avrPto} )</td>
<td>(-68)</td>
<td>TGGAACC</td>
<td>(-62)</td>
</tr>
<tr>
<td>( \text{avrPph3} )</td>
<td>(-99)</td>
<td>TGGAACC</td>
<td>(-93)</td>
</tr>
<tr>
<td>( \text{avrB} )</td>
<td>(-133)</td>
<td>TGGAACC</td>
<td>(-127)</td>
</tr>
<tr>
<td>( \text{avrC} )</td>
<td>(-252)</td>
<td>TGGAACC</td>
<td>(-246)</td>
</tr>
<tr>
<td>( \text{avrD} )</td>
<td>(-123)</td>
<td>TGGAACC</td>
<td>(-117)</td>
</tr>
<tr>
<td>( \text{avrRp} )</td>
<td>(-41)</td>
<td>TGGAACC</td>
<td>(-35)</td>
</tr>
<tr>
<td>( \text{hrp} )</td>
<td>(-59)</td>
<td>GGGAACC</td>
<td>(-53)</td>
</tr>
</tbody>
</table>

(Salmeron and Staskawicz 1993)
although the location of the *avrPto* transcription start site described below argues against their functioning as $-24/-12$ sequences in the *avrPto* promoter (Salmeron and Staskawicz 1993).

A putative ribosome binding site (Shine and Dalgarno 1974) occurs 9 nucleotides upstream of the predicted ORF1 initiator codon, between nucleotides 18-23. Hydropathy analysis predicts the AvrPto protein to be mostly hydrophilic, although the first six amino acids are hydrophobic. Comparison of the predicted amino acid sequence of the AvrPto protein to GenBank and EMBL databases has revealed no homology to other known protein sequences (Salmeron and Staskawicz 1993).

In recent studies (Grant et al. 1995), a resistance gene in *Arabidopsis* (*RPM1*) induces avirulent reactions to two avirulence genes in two strains of *Pseudomonas syringae* (avirulence to *Arabidopsis* and avirulence to pea, respectively). Bisgrove et al. (1994) also found that two avirulence genes (*avrB* and *avrRpm1*) in *Pseudomonas syringae* strains showed hypersensitive reaction to one resistance gene *RPS3* (*=RPM1*) in the *Arabidopsis thaliana* lines.

(2) Xanthomonas

DNA sequences related to *avrBs3* from *X. c. pv. vesicatoria* were detected in seven additional pathovars of *X. campestris* that cause disease on diverse dicots. Recently, homologs of *avrBs3* from *X. c. pv. malvacearum* and *X. c. pv. citri* were shown to have avirulence activity. Although avirulence activity has yet to be demonstrated for many of the *Xanthomonas* pathovars with sequences homologous to *avrBs3*, the presence of *avrBs3* homologs with avirulence function in several pathovars implies that a common resistance mechanism may be operating in dicots and monocots (Hopkins et al. 1992).

The DNA sequence of *avrXa10* is nearly identical to *avrBs3*. Hopkins et al. (1992) suggested that *avrXa7* and *avrXa10* are members of an avirulence gene family from xanthomonads that control the elicitation of resistance in monocot (rice) and dicots (pepper, tomato and cotton).

DNA from *Xanthomonas campestris* pv. *vesicatoria*, a pathogen of tomato plants, and *P. fluorescens*, a saprophyte, also lack homology to the probe. These results demonstrate that *avrPto* is present in a wide variety of pathogens but not in strains that cause disease on the *Pto* tomato cultivar 76R (Ronald et al. 1992)

**Distribution of resistance genes on chromosomes**

Many resistance genes have been found in crop plants as shown in Table 1. Although it is not always said that all of these genes are of specific nature, many of them seem to be in the gene-for-gene relationship. Many of these genes were introduced from wild plants through breeding. For example, 20 of 50
genes found to control resistance to stem rust in wheat were introduced from *Triticum turgidum* (Sr2, Sr9d, Sr9e, Sr9g, Sr13, Sr14, Sr17), *T. monococcum* (Sr21, Sr22, Sr35), *Agropyron clonatum* (Sr24, Sr25, Sr26), *Secale cereale* (Sr27, Sr31), *T. speltoides* (Sr32), *T. tauschii* (Sr33), *T. comosum* (Sr35), and *T. timopheevi* (Sr36, Sr37) (Roelfs 1988). These results do not always indicate that wild related species have a larger number of resistance genes than cultivated plants, because it is considered that fungus strains collected from the cultivated varieties have adapted to the cultivated varieties for a long time. It can be, however, considered that many resistance genes which are not found in cultivated varieties are present in wild related plants. This indicates that many resistance genes evolved in wild plants.

As mentioned above, many resistance genes are being introduced from wild species. These resistances were broken down in many cases within a few years after varieties with these resistance genes were released to the farmers (Kiysawa 1989), demonstrating the presence of gene-for-gene relationships between genes in a host species/pathogen combination. Recent studies are accumulating evidences that the gene-for-gene relationships are found between genes in different formae speciales in fungi (Tosa and Sakai 1991) and in different pathovars in bacteria (Kobayashi et al. 1989) and genes in hosts. Recent works indicate that there are same or similar resistance genes in distantly related species: pea and bean and *Arabidopsis* (Dangl et al. 1992), and soybean and tomato (Kobayashi et al. 1989).

Localizations of resistance genes in hosts as a whole indicate that resistance genes do not distribute uniformly in chromosomes, and many multiple resistance alleles are frequently found in a locus (Table 1). For example, a number of stem rust resistance genes are either identical or very closely linked to resistance genes for wheat leaf or stripe rust resistance, e.g. Sr9g-Yr7, Sr15-Lr20, Sr24-Lr24, Sr25-Lr19, Sr31-Lr26-Yr9 (Roelfs 1988), Rpp9-Rpld in *Zea mays* to *Puccinia polysora* and *Puccinia sorghi* and *Pa4-Mla* in barley to rust and powdery mildew (Roane 1973).


A similar phenomenon has been found in resistance of tomato to *Pseudomonas syringae* pv. tomato and sensitivity to the insecticide Fenthion.
The resistance is conferred by a single gene, *Pto*, and closely linked with the latter (Carland and Staskawicz 1993). Leaves of tomato cultivars that contain the *Pto* bacterial resistance locus develop small necrotic lesions within 24 hr after exposure to Fenthion. *Pto* is one member of a multigene family that is clustered within a 400 kb region on chromosome 5. Another member of this gene family, termed *Fen*, is responsible for sensitivity to Fenthion. The *Fen* protein shares 80% identity (87% similarity) with *Pto* but does not confer resistance to *Pseudomonas syringae* pv. tomato. These results suggest that *Pto* and *Fen* participate in the same signal transduction pathway (Martin et al. 1994).

It cannot be said that all of the genes in Table 1 are of race-specific nature. Most of them, however, seem to be race-specific. Accordingly, avirulence genes in the number corresponding to the number of resistance genes are considered to be involved in the respective pathogen according to the gene-for-gene theory.

**Evolution**

On bacterial avirulence genes, Ritter and Dangl (1995) described as follows. Several puzzling enigmas exist regarding bacterial avirulence genes. Since they have a negative effect on pathogen fitness on hosts capable of recognizing their activity, why do *avr* genes persist in bacterial populations? Though *avr* genes probably serve a positive function at some stage in the bacterial life strategy, clear roles as virulence or pathogenicity factors have been ascribed to only a minority (Kearney and Staskawicz 1990, Swarup et al. 1991, Swarup et al. 1992, Lorang et al. 1994). Are they structural triggers of plant resistance, or are they enzymes whose products elicit plant resistance response? This question has been satisfactorily addressed only for the *avrD* gene from *P. syringae* pv. tomato, whose expression leads to the production of a low molecular weight syringolide which acts as a specific trigger of resistance on appropriate plant genotypes (Keen et al. 1990, Midland et al. 1993). What is the mechanism of *avr* gene action, and is it fundamentally tied to pathogenesis in ways not yet recongized? In this regard, one could imagine that *avr*-gene function is required during epiphytic bacterial growth or early in the shift to pathogenesis (Ritter and Dangl 1995).

On the problem of the presence of avirulence gene in pathogens, Kiyosawa and Nomura (1995) mentioned as follows. Avirulence genes had a role probably including uptake of nutrients before occurrence of resistance genes corresponding to the avirulence genes in the host. The function of these avirulence genes was not so important in the life strategy of the pathogens, because the pathogens keep sufficient fitness at least on resistant varieties after mutation to virulence. Lorang et al. (1994) indicated that the avirulence genes, *avrA* and *avrE* in *Pseudomonas syringae* pv. tomato PT23 play a role in virulence on
tomato plants, when inoculated host line has no corresponding resistance genes, $PtoA$ and $PtoE$. Similar phenomenon was found by $avrRpm1$ gene of *Pseudomonas syringae* pv. maculicola for virulence on *Arabidopsis* (Ritter and Dangl 1995).

The following scenario for the evolution of plant disease resistance has been proposed (Pryor 1987). The evolutionary ground state is considered to be a compatible interaction in which a pathogen has evolved to be virulent on a particular host plant. Selection favors the evolution and spread of host individual that specifically recognize the pathogen and resist infection. For example, a receptor that evolved to activate defense responses to pathogens in general may be modified so that it specifically recognizes a particular pathogen product (an avirulence gene product). The pathogen responds by losing the avirulence gene by mutation. This phenomenon is absolutely essential for the survival of obligate parasites. The host is now susceptible, and again selection is brought to bear on new host $R$ gene specificities. Consequently, the evolution of gene-for-gene interactions can be seen as a continuing step-by-step or move-counter-move process, whose consequence in plant populations is a diversity of $R$ genes in different individuals of avirulence genes in different pathogen races.

The existing diversity of $R$ genes is the product of an evolutionary process that appears to have proceeded along two major branches. On one branch, exemplified by the $M$ rust resistance locus in flax, tandem array of related $R$ genes with different specificities are found in the plant genome (Ellis et al. 1995). The other evolutionary branch is exemplified by the flax $L$ rust resistance locus, the specificities at this locus behave genetically as alleles of a single gene, and different specificities existing in heterozygotes cannot be recombined (Ellis et al. 1995). The cloning of the $L^a$ allele of this locus supports the classical genetic interpretation of a simple $L$ locus but has also provided some surprises (Lawrence et al. 1995). The genes at the genetically complex $M$ locus are related in sequence to the un-linked $L$ gene, with 70 to 90% nucleotide identity. The $M$ locus appears to have evolved by local duplication and divergence from an $L$-like $R$ gene progenitor, whereas the $L$ locus appears to have evolved as a multiple allelic series, with only a single $L$ specificity capable of existing in a homozygote. The contrasting evolution of two such closely related genes may be the results of a rare duplication event that occurred only at the $M$ locus and then provided the opportunity for rapid amplification by unequal crossing over. Similarly, molecular analyses of the TMV resistance locus $N$ in tobacco and of the $Cf-9$ locus in tomato have revealed a clustered gene family (Jones et al. 1994, Whitham et al. 1994, Staskawicz et al. 1995).

In multiple allelic series in blast resistance of rice, two types have been observed: one is stair-type (Tables 4 and 5) and other is cross-type (Table 6). This suggests that the stair-type is made from the tandem amplification of an
Table 4. Reaction of Pi-k locus (Stair type).

<table>
<thead>
<tr>
<th>Rice variety</th>
<th>Gene</th>
<th>Fungus strain (genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Aichi Asahi</td>
<td>Pi-k+</td>
<td>S</td>
</tr>
<tr>
<td>Shin 2</td>
<td>Pi-k*</td>
<td>MR</td>
</tr>
<tr>
<td>K 60</td>
<td>Pi-kp</td>
<td>R</td>
</tr>
<tr>
<td>Kusabue</td>
<td>Pi-k</td>
<td>R</td>
</tr>
<tr>
<td>Tsuyuake</td>
<td>Pi-kr</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 5. Reaction of Pi-ta locus (Stair type).

<table>
<thead>
<tr>
<th>Rice variety</th>
<th>Gene</th>
<th>Fungus strain (Genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Aichi Asahi</td>
<td>+</td>
<td>S</td>
</tr>
<tr>
<td>K 1</td>
<td>Pi-ta</td>
<td>R</td>
</tr>
<tr>
<td>Pi No. 4</td>
<td>Pi-ta2</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 6. Reaction of Pi-z locus (Cross type).

<table>
<thead>
<tr>
<th>Rice variety</th>
<th>Gene</th>
<th>Fungus strain (Genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Aichi Asahi</td>
<td>+</td>
<td>S</td>
</tr>
<tr>
<td>Fukunishiki</td>
<td>Pi-z</td>
<td>R</td>
</tr>
<tr>
<td>Toride 1</td>
<td>Pi-z1</td>
<td>S</td>
</tr>
</tbody>
</table>

original allele and individual repetitive sequences has the same function with additive effect, although molecular analysis is lacking.

*R* genes specifically distinguish isolates of a single pathogen species. The multiple resistance specificities encoded by the 13 alleles of the cloned *L* gene of flax provide an opportunity to study the molecular basis of this specificity. Three alleles, *L*2, *L*6, and *L*10, have been cloned and partially characterized. Although *L*6 and *L*10 are similar, *L*2 has additional numbers of an LRR motif that occurs in the COOH-terminal region of the gene product. This region may determine ligand specificity (Staskawicz et al. 1995).

Pathogen propagules increase to vast numbers in comparison with their hosts, and consequently there is a greater opportunity for virulent pathogen races to arise than for corresponding new host resistance. Coupled with the
differences in population size, pathogen evolution from avirulence to virulence usually results from loss-of-function mutation. The corresponding gain of function (that is, resistance in the host) is unlikely to occur by simple mutation. Do plants have a mechanism to generate new R gene specificities and keep space with the evolutionary progress of pathogens? Pryor, Hulbert, Bennetzen and their colleagues have observed high-frequency loss of rust resistance in corn associated with unequal crossing over at the *Rp1* locus, and they have proposed that this shuffling of preexisting coding information may provide a means for plants to generate new specificities (Bennetzen and Hulbert 1992, Pryor and Ellis 1993). The LRR domains, which are important in receptor selectivity, may be involved in defining the recognition specificity of the pathogen (Braun et al. 1991).

Instability of the *L6* gene for rust resistance in flax is correlated with the presence of a linked Ac element (Lawrence et al. 1993).

Plasmid, insertion sequences (IS), and transposons are important players in horizontal gene transfer, the mobilization and stabilization of genetic information from one organism to another across species boundaries. Conjugative gene transfer mediated by plasmids occurs between bacteria, between bacteria and yeasts, and even between bacteria (*Agrobacterium* spp.) and plants. IS and transposons exist in the genomes of many different bacteria, including plant-associated bacteria such as *Pseudomonas, Rhizobium*, and *Agrobacterium* spp. They are frequently components of natural plasmids (Deng et al. 1995).

*Agrobacterium tumefaciens* induces the formation of tumors on plants by transferring DNA into plant cells. The transferred DNA (T-DNA) encodes enzymes responsible for the biosynthesis of plant growth regulators. Its expression in the transformed plant cells disturbs the level and balance of plant hormones, thereby leading to tumor formation. Although they are bacterial genes, they have eukaryotic-like, plant-specific regulatory signals and are expressed only in transformed plant cells. These peculiar features have lead to numerous speculations regarding their origin and evolution (Deng et al. 1995).

*A. tumefaciens* is not the only bacterium that utilizes plant growth regulators as virulence factors. The ability to produce plant hormones is widespread among soil- and plant-associated microorganisms, including species of *Pseudomonas, Xanthomonas, Erwinia, Rhizobium, Azospirillum*, and *Streptomyces*. The structural genes responsible for the biosynthesis of plant growth regulators in these microorganisms share very high sequence similarities to the T-DNA genes. The results suggest that all of these genes have a common origin. It has been proposed that the widespread distribution of genes for plant hormone biosynthesis among soil- and plant-associated bacteria results from horizontal gene transfer (Deng et al. 1995).
Discussion

Evolution of host-pathogen relationships begun when host originated in the systems that hosts are higher plants and pathogens are microbes. At that time, microbes had already differentiated into bacteria and fungi, and microbes had already acquired pathogenicity to lower plants. Therefore, pathogenicity at least to higher plants independently developed in both microbes frequently accompanying horizontal transfer of genes. These pathogenicity genes and resistance genes increased with the increase of DNA by random and tandem amplifications in bacteria and additionally by duplication of chromosomes in fungi and higher plants. This increase of DNA made it possible to change quantitatively and qualitatively pathogenicity genes and resistance genes. Recent studies demonstrated occurrence of point mutation, frame shift mutation, deletion and insertion of single bases and genes, unequal crossing-over, translocation, etc. (e.g., Joosten et al. 1994, Grant et al. 1995, Salmeron and Staskawicz 1993, Jones et al. 1994, Whitham et al. 1994, Staskawicz et al. 1995) in molecular level. Often, transposon affected the change (Lawrence et al. 1993).

Evolution of host-pathogen relationships was performed by repeating mutual acquirement of pathogenicity and of resistance. During these processes, acquirement of resistance at a high level occurred at least three times, probably more: formation of cell walls, landing of the host, and the standing-up of plants with synthesis of lignin and the formation of vascular bundle. For penetration of cell wall, synthesis of toxins and wall-degradating enzymes play an important role.

Formation of appressorium important for penetration especially in filamentous fungi originated from formation of an infection cushion, and developed to a present appressorium by increasing penetrating ability of single hypha. The first evolution of appressorium occurred on roots.

Some pathogenic fungi and bacteria enter into host plant through natural pores, wounds and others by way of penetration peg from appressorium.

Elongation of fungal hypha in plants at first was performed intracellularly and then the elongation of the hypha was inhibited by development of resistance in the host and/or by development of inhibitor (negative regulatory system) in the pathogen. Thus, hyphae of which growth was inhibited in the host plants formed haustoria in the cells of the host in one hand and developed in intercellular hypha (many biotrophic fungi) or hypha running on the host surface on the other hand (powdery mildew).

In bacteria, pathogenicity is controlled by many genes which form cluster. This indicates that many genes are required for development of pathogenicity. Two-component regulatory systems in ancestral bacteria before development
of pathogenicity and ancestral bodies of present \textit{hrp} genes were used for acquirement of basic pathogenicity. At that time, basic pathogenicity was developed in various bacteria by maintaining a conserved region of DNA sequence, and by adaptively changing its flanking region.

On the other hand, in leguminous plants approximately 30 plant genes have been identified as concerning to the nodulation (Nap et al. 1989). This suggests that occurrence of about 30 genes in the host plant was required for development of symbiosis.

After development of basic pathogenicity, specific resistance genes evolved in some plants. In this case, specific resistance genes evolved as genes corresponding to avirulence genes which were already present. These avirulence genes probably played a role in survival of the pathogens. Although the function was not greatly significant for survival of the pathogen, at least a part of their functions would be absorption of some substance: mutants (virulent strains) of the avirulence genes still maintain high reproductivity especially on resistant varieties.

The symptoms of diseases on the host are determined by interactions between pathogen pathogenicity and host resistance. Evolution of host-pathogen relationship proceeded, as shown in Fig.3. ① The first entrance of potential pathogen occurred through wound or on weakened plants. ② Acquirement of basic pathogenicity in the pathogen. ③ Increase of pathogenicity in the pathogen. ④ Increase of resistance in the host and/or decrease of pathogenicity in the pathogen. ⑤ Evolution of specific resistance genes and expression of interaction between the resistance genes in the host and the avirulence genes in the pathogen. ⑥ Mutation of avirulence genes to virulence.

At present, the frequencies of virulence genes are largely changing due to the frequencies of resistance genes, but if the frequencies of host genotypes do not change, the frequencies of virulence genes approach to an equilibrium in relatively quick spead (Kiyosawa 1995). Even if frequencies of resistance genotypes do not artificially change by selection of varieties by farmer, the frequencies of pathogen genotypes approach around an equilibrium point [limit cycles of Leonald (1994)] for the cost of resistance in natural conditions.

Summary

After the evolution of the basic pathogenicity, increase or decrease in pathogenicity of pathogens and in resistance of hosts occurred during evolution of host-pathogen relationships. Specific host-pathogen relationship orginated by the evolution of specific resistance genes in the host plant. The time is considered after formation of vascular bundle in plants, because the gene-for-gene relationship is observed only on leaves in many cases and on stems in a few cases. It is considered that the gene-for-gene relationship originated in
Fig. 3. Process of evolution of host-pathogen relationship.

1. Infection to wound or weaken plants; 2. Acquisition of pathogenicity by production of toxins, etc.; 3. Increase of pathogenicity; 4. Increase of resistance and/or decrease of pathogenicity; 5. Expression of avirulence genes by evolution of specific resistance genes; 6. Susceptibility by mutation of avirulence genes.

Each family or each genus independently, because different genes exist among most families, and even among many genera. There are some genera and species which do not show gene-for-gene relationships. At least, wild species have many specific resistance genes which are not included in cultivated plants. This suggests that specific resistance genes originated in early stage of development of each family or genus. Advances of molecular genetics made it possible to write a scenario on evolution of host-pathogen relationships based on structure of resistance and avirulence genes.

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和文摘要

宿主—病原菌関係の進化 III
宿主特異的抵抗性の進化

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宿主・病原菌関係の進化の初期に，病原性優位，抵抗性優位と交互に変化している間に生じた抵抗性は主として非特異的真性および圃場抵抗性であった。特異的抵抗性抵抗性は比較的後期に生じた，少なくとも維管束が生じた後と考えられる。維管束の形成は病原菌を空中に押し上げるのに重要な役割を果たした。葉の形成におよんでこの型の抵抗性遺伝子は急速に増えた，この抵抗性は病原菌中に特異的に対応する非病原性遺伝子が存在して初めて可能になる。したがって，特異的抵抗性遺伝子が生じたときに非病原性遺伝子は生じていたものと考えられる。選択的利益がないと生存し難いので，非病原性遺伝子産物は菌にとって亜分吸収などに多少の役割をもっていたと考えられる。非病原性遺伝子が突然変異を起こしても病原性をもつので少なくともその機能は菌の生存にとって本質的なものではない。

各作物の起源となっている近縁野生種は栽培種の持たない多数の抵抗性遺伝子を持っている。このことは，特異的抵抗性遺伝子はその属の発生初期に生じた可能性が高いことを示している。

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