T cells have been directly involved in disease induction? Also, the distinction between T_H1 and T_H2-like T cells is less clear in humans than in mice; a substantial number of human myelin basic protein–specific T cells have a T_H0 phenotype, and the minority have a T_H1 phenotype (9). Thus, further definition of these populations in the marmoset will be necessary before the findings of Genain *et al.* can be fully understood. The investigators report changes in IL-10, but the cytokine most consistently associated with a T_H2-like phenotype in humans, IL-4, was not examined. Thus, it is possible that in the marmoset a T cell subset intermediate between T_H1 and T_H2, a T_H0 T cell, could mediate disease, as has been shown in the mouse EAE model (*10*).

The possibility that these findings are unique for MOG also needs consideration. Antibodies to other myelin antigens such as myelin basic protein or proteolipid protein, which have been the primary focus of emerging therapies, may have less influence on disease course, but even this is uncertain.

Finally, the potential of a $CD8^+$ T cell population to mediate disease must be considered: $CD8^+$ T cells specific for various myelin antigens have been found (*11*). The results of Blanas *et al.* (*2*) raise the possibility that a $CD8^+$ T cell population can be generated after oral administration of antigen and can mediate disease. But it is unclear how accurately results from a highly artificial animal model can be extrapolated to human disease. As the authors indicate, some questions remain puzzling in their model. For example, why does oral administration of antigen in animals expressing OVA on the insulin promoter fail to provoke disease?

Another area of concern is that T_H1-like T cells, although certainly linked to disease production, may be only one component of the immunological attack. Antibody can exacerbate EAE, so if a treatment only partially reduces the T_H1 response but augments the T_H2 response and increases antibody to an organ-specific autoantigen, the disease can get worse. Also, the role of $CD8^+$ T cells in autoimmune diseases is poorly defined. Although $CD4^+$ T cells may have a major role in the initial induction of many autoimmune diseases, $CD8^+$ T cells, which are cytotoxic and can secrete proinflammatory cytokines and chemokines, may also contribute to tissue damage (*10*).

Despite these reservations, these findings and others reported previously underscore the fact that the role of cytokines in immune regulation and disease is extremely complicated (see figure) and may depend on the timing of the treatment and on the dose. For example, increased concentrations of cytokines such as IL-10 at the initiation of autoimmune disease may enhance the disease process through mechanisms such as up-regulation of major histocompatability complex expression. In contrast, when IL-10 is administered after disease is initiated, the predominant effect may be to inhibit T_H1-like responses and functions. An example of these complexities is IFN-γ. Although IFN-γ is thought to be the prototypic T_H1 cytokine, IFN-γ has some protective properties in the EAE model (*12*). In contrast, administration of IFN-γ to patients with multiple sclerosis seems to increase disease (*13*).

Mechanisms of autoimmunity are more complicated than a simple T_H1-T_H2 dichotomy would suggest. More important, as we move into the clinic to treat chronic diseases with treatments that are effective in some animal models, clinicians must carefully monitor the effect of these treatments. The potential for obtaining results different from those predicted from experiments in animals or in vitro is great.

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BOTANY

A Ligand-Receptor Mechanism in Plant-Pathogen Recognition

Chris Lamb

Losses from disease limit the productivity of agricultural crops, and epidemics can have devastating consequences—a good example being the late blight destruction of the European potato crop in the mid–19th century, which caused mass starvation and precipitated a wave of emigration to North America. Many important plant diseases involve specialized interactions between pathogen and host. In 1947, Flor reported that the outcome of the interaction between flax and the flax rust fungus was determined by "corresponding" genes in the two partners, which led to the elaboration of the "gene-for-gene" hypothesis. In this scheme, a dominant resistance (*R*) gene confers resistance only to those races or strains of the pathogen expressing the corresponding dominant avirulence (*avr*) gene (*1*). This simple genetic relation, which gives a good account of many plant-pathogen interactions, suggests a physical interaction between the products of paired *R* and *avr* genes. Two reports in this issue finally provide direct evidence for such a ligand-receptor mechanism underlying plant-pathogen recognition (*2*, *3*).

Many *avr* genes have been isolated, mainly from bacteria, and recently *R* genes that respond to specific bacterial, fungal, or viral pathogens have been cloned from a variety of plants (*1*). *avr* genes encode a diverse group of proteins with few common features. In contrast, *R* genes, which mediate resistance to diverse pathogens, share common structural elements suggestive of a signal transduction function. Indeed, activation of *R* gene products induce the hypersensitive resistance response (*1*), a battery of protective mechanisms, and rapid death of challenged host cells. Thus, *Pto*, which conditions resistance of tomato to bacterial speck disease caused by the *Pseudomonas syringae* pathovar *tomato* and was the first *R* gene isolated, encodes a cytoplasmic protein–serine-threonine kinase, and other *R* genes encode proteins with leucine-rich repeats, often implicated in protein-protein interactions, and in some cases with nucleotide binding sites. Interestingly, the rice *Xa21* gene, which confers resistance to a pathogenic Xanthomonad, encodes a receptor-like kinase with a putative extracellular leucine-rich repeat and intracellular catalytic domains connected by a short transmembrane region (*4*).

Although such a protein has obvious structural attributes for interaction with signals external to the cell, it was unclear how bacterial *R* genes encoding cytoplasmic proteins might function in the recognition of extracellular pathogens. A clue came with the realization that the *Hrp* (*hypersensitive response and pathogenicity*) gene cluster in many phytopathogenic bacteria encodes proteins

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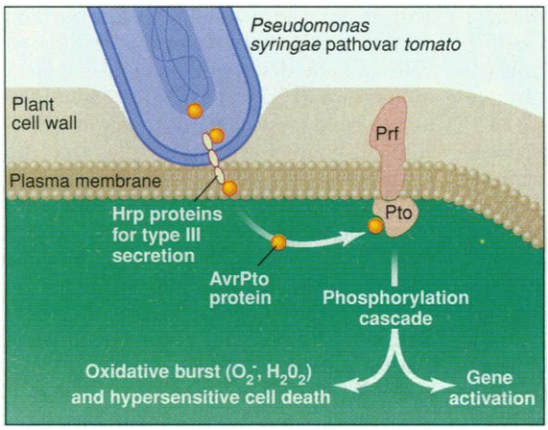

Molecular specificity. A direct interaction between products of a plant resistance gene (AvrPto) and an avirulence gene (Pto) in a pathogen accounts for the gene-for-gene specificity between plant and pest.

resembling components of the type III secretion system used by bacteria—such as *Salmonella*, *Shigella*, and *Yersinia*—for the secretion of virulence proteins into mammalian host cells (*5*, *6*). Operation of such a mechanism (see figure) would allow *avr* gene products to interact with cytoplasmic plant proteins, and in fact *avrB* from *P. syringae glycinea* induces an *R* gene–dependent resistance response when expressed as a transgene in plant cells (*7*).

Scofield *et al.* (*2*) and Tang *et al.* (*3*) report a similar effect when *avrPto* from *P. syringae tomato* is expressed in plant cells carrying *Pto*, and then take the story a decisive step further by demonstrating a direct physical interaction between the gene products with yeast two-hybrid genetic selection as an assay system (*2*, *3*). A second protein kinase, Fen, with greater than 80% sequence similarity to Pto, does not interact with the AvrPto protein. *Fen*, which is tightly linked to *Pto*, confers sensitivity to the insecticide fenthion but does not mediate resistance in response to *avrPto*. Creation of chimeric Pto-Fen proteins shows that the Fen gene product can be made competent to interact with the AvrPto ligand by substitution of a small segment of Pto involved in substrate binding, and mutations in either *avrPto* or *Pto* that render the plant-pathogen interaction biologically compatible likewise disrupt the physical interaction between the gene products. Thus, the exquisite specificity that characterizes gene-for-gene biological incompatibility in plant-pathogen interactions can also be discerned at the molecular level.

Protein kinase activity is required for the function of Pto in disease resistance, and mutations at conserved catalytic residues also block the physical interaction with the AvrPto protein. AvrPto binding might directly stimulate Pto kinase activity to trigger the phosphorylation cascade involved in activating the resistance response (see figure) (*8*). Alternatively, AvrPto might bring together two Pto molecules for cross phosphorylation. Pathway activation may also cause phosphorylation of the ligand itself. Genetic evidence indicates that *Pto* action requires a closely linked gene, *Prf*, which encodes a leucine-rich repeat protein (*9*). Although Prf does not appear to be involved in specificity, it may function as an anchor to localize the kinase (see figure). Physical interaction between Prf and Pto might create a two-component receptor system closely resembling the receptor-like protein kinase encoded by *Xa21*. It will be interesting to see which region, if any, of the *Xa21* product interacts with the corresponding AvrXa21 protein.

The isolation of bacterial genes is highly tractable, with over 30 cloned so far, and hence the use of two-hybrid selection may prove to be a powerful approach for the isolation of new *R* genes, assuming at least some function as receptors for the corresponding *avr* gene product. Two-hybrid screening should also give a quick test of the ligand-receptor mechanism in the recognition of viral and fungal pathogens for which *R* genes have been isolated.

AvrPto and Pto are both relatively small, compact proteins and hence should be amenable to structural analysis by x-ray crystallography. It would be immensely satisfying if the series of brilliant studies starting with Flor's work 50 years ago culminate in the elucidation of plant-pathogen recognition systems at the angstrom level. Such information would allow the rational design of *R* genes encoding receptors with novel recognitional specificities—powerful tools for engineering enhanced crop protection in the continuing struggle to secure food production.

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THEORETICAL BIOLOGY

Biologists Put on Mathematical Glasses

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Nothing has shaped the development of thought in physics more than Galileo's statement: "The book of Nature is written in the language of mathematics" (*1*). Physicists take it for granted that the important questions have answers that can be cast into mathematical formulas. Ever since Newton, physics and mathematics have lived in a fruitful symbiosis, with a great deal of cross-fertilization to the benefit of both disciplines. Physics, as we phrase it nowadays, is concerned mainly with the development of a comprehensive and unifying mathematical theory of Nature. The physicists are approaching this goal by experimentation, abstraction, and generalization.

Biology differs from physics in that it has an indispensable historical component. This was stressed already by Ernst Haeckel and most properly phrased by Theodosius Dobzhansky in his statement that "nothing in biology makes sense except in the light of evolution" (*2*). For this and other reasons, much of biology has traditionally described the overwhelming diversity and unique variability of the living world and has used a scientific methodology based on observation, description, and classification. Although generalization and abstraction, where feasible, was always aimed for, mathematics was usually not used in this process. For example, last century's greatest naturalist, Charles Darwin, laid down his great theory of evolution and the origin of species without making use of a single equation.

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