32. M. R. Grant *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 15843 (1998).
33. Unpublished data of authors (*39*), comparing about 2 kb of flanking sequence in 23 *A. thaliana* accessions.
34. To calculate changes in codons with more than one position substituted, current algorithms for calculating K_s and K_a assume equal rates of synonymous and replacement changes. This assumption leads to the overestimation of synonymous changes and underestimation of replacement changes when the replacement rate actually exceeds the synonymous rate (J. Comeron, M. Kreitman, unpublished results).
35. W.-H. Li, *Molecular Evolution* (Sinauer Associates, Sunderland, MA, 1997).
36. R. J. Abbott, M. F. Gomes, *Heredity* **62**, 411 (1989).
37. R. M. May, R. M. Anderson, *Proc. R. Soc. London B* **219**, 281 (1983).
38. Supplemental material is available on *Science* Online at www.sciencemag.org/cgi/content/full/292/5525/2281/DC1.
39. J. Bergelson, M. Kreitman, E. A. Stahl, D. Tian, unpublished data.
40. R. Mauricio, unpublished data.
41. We gratefully acknowledge support from the NIH to J.B. and M.K., a Packard Fellowship to J.B., and a Sloan/Department of Energy fellowship to E.A.S. K. Thornton provided computer programs.

REVIEW

Common and Contrasting Themes of Plant and Animal Diseases

Brian J. Staskawicz,[1]* Mary Beth Mudgett,[1] Jeffrey L. Dangl,[2] Jorge E. Galan[3]

Recent studies in bacterial pathogenesis reveal common and contrasting mechanisms of pathogen virulence and host resistance in plant and animal diseases. This review presents recent developments in the study of plant and animal pathogenesis, with respect to bacterial colonization and the delivery of effector proteins to the host. Furthermore, host defense responses in both plants and animals are discussed in relation to mechanisms of pathogen recognition and defense signaling. Future studies will greatly add to our understanding of the molecular events defining host-pathogen interactions.

The ability of pathogenic microorganisms to harm both animal and plant hosts has been documented since the initial demonstration in the 1870s that microbes were causal agents of disease. Since the initial discoveries by Koch (*1*) that *Bacillus anthracis* caused anthrax and by Burrill (*2*) that *Erwinia amylovora* caused fire blight in pears, our knowledge base has expanded enormously. Today, the genomes of the most important animal and plant pathogens have been or will be sequenced, and the molecular basis of pathogenicity is beginning to be deciphered. Furthermore, several model plant and animal host genomes are fully sequenced. Basic discoveries made in the post-genomic era will fuel our quest for developing new strategies for disease control.

In the past 5 years, pivotal observations have revealed that bacterial pathogens share common strategies to infect and colonize plant and animal hosts. One is the ability to deliver effector proteins into their respective host cells to mimic, suppress, or modulate host defense signaling pathways and to enhance pathogen fitness. On the host side, plants and animals have evolved sophisticated surveillance mechanisms to recognize various bacterial pathogens. Interestingly, plants recognize distinct effectors from pathogenic bacteria, whereas animals recognize conserved "molecular patterns," such as those derived from lipopolysaccharide (LPS) or peptidoglycan. The discovery that surveillance proteins in diverse hosts share common protein signatures that perform similar functions invites speculation as to how these resistance mechanisms evolved.

This rapidly expanding field is obviously a large topic, and all aspects cannot be considered here. We will mainly focus on themes of plant pathogenesis. However, when appropriate, we will discuss unique and shared strategies used by microbial pathogens to infect animal hosts. Moreover, we will compare our emerging knowledge of pathogen surveillance mechanisms used by plant and animal hosts.

Initial Interactions of Bacterial Pathogens with Host Plant Cells

The initial interactions of bacteria with their plant hosts are critical in determining the final outcome of infection. Curiously, the majority of infections do not lead to overt disease. Microorganisms are usually repelled by plant defense mechanisms. However, in some cases, interactions of microbial pathogens with their host lead to the overt harm to the presumptive host and to pathology. Factors intrinsic to both the pathogen and the plant determine the final outcome of the encounter.

The epiphytic (saprophytic) life stage of phytopathogenic bacteria often precedes entry into the host plant and the onset of pathogenicity. For example, phytopathogenic bacteria in the genera *Pseudomonas* and *Xanthomonas* can colonize leaf surfaces of plants and reach dense bacterial populations (10^7 colony-forming units per square centimeter) without causing disease. Under the appropriate environmental conditions, bacteria enter leaf mesophyll tissue through natural stomatal openings, hydothodes, or wounds, thus making their first contact with internal host cells. Phytopathogenic bacteria multiply in the intercellular spaces (apoplast) of plant cells and remain extracellular. This is in contrast to many animal bacterial pathogens that gain entry into their host cells and then multiply intracellularly.

Mechanism for Plant Cell Infection: Conservation of Type III Secretion System

To grow in the apoplast, phytopathogenic bacteria sense their environment and induce genes required for host infection. A primary locus induced in Gram-negative phytopathogenic bacteria during this phase is the *Hrp* locus (*3*). The *Hrp* locus is composed of a cluster of genes that encodes the bacterial type III machinery that is involved in the secretion and translocation of effector proteins to the plant cell. Mutations in *Hrp* genes affect both the induction of localized plant disease resistance (the hypersensitive response) and bacterial pathogenicity. This mutant phenotype and the subsequent demonstration that Hrp structural proteins and type III effectors are transcriptionally coregulated (*4*) provided important evidence that effectors not only caused disease but were the components of the pathogen recognized by the host. Although the general physiology of low sugar and low pH in the apoplast is known to induce the assembly of the Hrp type III apparatus in phytopathogenic bacteria, a specific plant-derived signal has yet to be identified.

The demonstration that phytopathogenic bacteria use genes (i.e., *Hrp*) that are remarkably similar to genes encoding the type III secretion system in animal pathogenic bacteria provided an immediate conceptual framework to explain the molecular mechanisms

[1]Department of Plant and Microbial Biology, University of California at Berkeley, Berkeley, CA 94720, USA. [2]Department of Biology and Curriculum in Genetics and Molecular Biology, University of North Carolina, Chapel Hill, NC 27599, USA. [3]Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT 06536, USA.

*To whom correspondence should addressed. E-mail: stask@nature.berkeley.edu

for pathogen infection and recognition by plants (*5*). The overall theme is that a general mechanism for bacterial pathogenesis in plants and animals involves the direct delivery of different classes of proteins to the host. These proteins, now collectively referred to as type III effectors, suppress, stimulate, interfere with, or modulate host responses to invading pathogens. We now appreciate why plant surveillance systems have evolved both surface-exposed and cytoplasmic resistance proteins to recognize phytopathogenic bacteria type III effectors targeted to the surface and the interior of the host cell. Features of type III systems in plant and animal pathogens have been substantially reviewed (*6–8*); therefore, they will not be discussed here in detail.

Bacterial-Host Surface Interactions

A common theme emerging from the study of diverse bacterial pathogens is that they interact with host cell surfaces through appendagelike structures known as pili or fimbriae, which serve as scaffolds to display or present ligands that are recognized by cognate receptors on host cells (*9*). Given the distinct features of plant and animal cells, we predict that the ligands displayed by the surface structures of pathogenic bacteria toward their respective hosts are substantially different. However, the scaffolds and/or the mechanisms of assembly of bacterial appendages are likely to share common features. For example, the plant pathogens produce an appendage-like structure that is essential for the delivery and regulation of effector proteins to the plant cell through its type III system. This pilus structure is composed of a single protein: HrpA in *Pseudomonas syringae* (*10*) and HrpY in *Ralstonia solanacearum* (*11*). A morphologically similar structure is associated with type III systems in the animal pathogens *Salmonella typhimurium* (*12*) and enteropathogenic *Escherichia coli* (*13*). The *E. coli* appendage structure is also composed of a single protein, EspA, which exhibits no sequence similarity with either HrpA or HrpY (*13*). These animal and plant pathogens thus secrete specific proteins through their type III apparatus to construct a structure that, although composed of distinct subunits, is nevertheless architecturally similar.

The plant cell wall is a unique surface structure that differentiates plant from animal cells. The plant cell wall is a thick barrier (~200 nm as compared to 8 to 10 nm for eukaryotic plasma membranes) through which bacteria must either penetrate or locally diffuse effectors to incite disease. The structural differences between the otherwise related surface appendages of plant and animal pathogenic bacteria are therefore in keeping with the marked differences between the cellular organization of plant and animal cells. It is thus remarkable that *Pseudomonas aeruginosa* strain PA14 is not only a human opportunistic pathogen but is also capable of causing disease in the plant *Arabidopsis* (*14*). This "interkingdom" pathogen has armed itself with the ability to effectively colonize the surface of both plant and animal cells and to avoid diverse host surveillance mechanisms. Future studies with this pathogen, using several host model systems, should reveal common and unique features that allow it to be a pathogen on such a wide range of eukaryotic hosts.

A vast array of structures has been characterized on the surface of animal pathogenic bacteria (*15*). These structures facilitate the colonization of different mucosal surfaces and, in many instances, determine the specific interaction of the bacterium with receptors on host cells. These recognition events often lead to the activation of signaling pathways in both the host and the pathogen that have a profound impact on the outcome of infection. For example, pathogenic *E. coli* deliver a receptor to the interior of host cells, and this receptor is then used to perceive a second pathogen-encoded molecule to initiate infection using host signaling machinery (*16*). In addition, some *E. coli* pathogens use FimH adhesin of type I fimbriae to interact with mannosylated glycoprotein receptors on the surface of mammalian cells, which leads to pro-inflammatory cytokine production in bladder infections (*17*). It remains to be determined whether plant pathogenic bacteria use similar surface structures for contact with plant cells.

Delivery of Type III Effectors into Plant Cells

Although there is extensive circumstantial evidence that phytopathogenic bacteria directly deliver effectors to plant cells, there is no direct evidence demonstrating the presence of delivered effectors inside plant cells. The strongest evidence in favor of direct delivery comes from experiments that demonstrated that the expression of various avirulence genes (from here on referred to as type III effectors) in plant cells is sufficient to induce a localized defense response in resistant plant cultivars. Additional evidence comes from the observation that the *P. syringae* AvrRpt2 effector protein is specifically cleaved at the NH_2 terminus during infection. The processing of AvrRpt2 was shown to occur in the host and to be dependent on a functional type III pathway, which suggests that proteolysis of this effector probably occurs after translocation into the host cell cytoplasm (*18*).

In contrast to phytopathogenic bacteria, there is ample direct evidence for delivery of effectors by animal pathogenic bacteria. Type III secretion–mediated protein translocation of effector proteins in host cells was first demonstrated in *Yersinia* and subsequently observed in additional animal pathogens (*6*). The mechanisms by which these proteins reach their final destination, however, remain poorly understood. With few exceptions, type III effectors from both plant and animal bacterial pathogens are structurally diverse and do not contain an obvious conserved signal peptide for export. Work carried out mostly with effectors from *Yersinia* spp. has defined two regions of type III effectors that are involved in their secretion and/or translocation into the host cell (*6*). One of these regions is located in the first ~15 amino acids and the other is contained within the first 100 amino acids. The latter serves as a binding site for customized chaperones that are required for secretion and translocation of type III effectors. In addition, the first ~15 codons of the mRNA that encodes a subset of type III effectors may also be involved in their secretion and/or translation regulation (*19*). However, this model is still debated. Additional studies are required to verify and demonstrate the universality of the proposed mechanisms of secretion in animal and plant pathogenic bacteria. It is thus conceivable that there will be unique mechanisms by which proteins are engaged by the secretion machinery. In fact, in some type III systems (such as *S. typhimurium*), the timing of host responses stimulated by specific effectors suggests an orderly delivery of each protein into the host cell (*20*). Perhaps the existence of different secretion signals operating in type III systems may provide the molecular basis for such a hierarchy of protein secretion.

Effector proteins can be secreted in vitro, in a type III–dependent manner, from phytopathogenic bacteria in the genera *Erwinia*, *Pseudomonas*, *Ralstonia*, and *Xanthomonas* (*8*). These experiments revealed that secretion signals in these bacteria are also localized to the NH_2 terminal portion of the effector proteins (*21*). The secretion signal tolerates alterations in the reading frame, which suggests an involvement of the mRNA in the secretion process (*19*). The observation that the type III secretion systems of *Xanthomonas campestris* and *E. chrysanthemi* secrete effector proteins from both plant and animal pathogens suggests some degree of ancestral conservation between type III systems (*19*, *22*). However, substantial differences are apparent. For example, although common in type III secretion systems of animal pathogens (*23*), the presence of customized chaperones for the secreted effectors in type III systems of plant pathogenic bacteria is formally lacking. Thus far, there is only one report of a type III secretion–associated gene that encodes a polypeptide with features commonly found in chaperones (*24*).

Another apparent difference between plant and animal pathogenic bacteria resides in a critical component of the supramolecular structure associated with type III systems, termed the needle complex. This structure, best characterized in the animal pathogens *Salmonella* and *Shigella*, is composed of a protein complex forming a ring base embedded in the bacterial envelope and a needlelike projection (*25*). Although homologs of the components of the base structure are present in type III systems from plant pathogenic bacteria, there are no apparent homologs of the protein subunit that makes up the needle portion (*25*). Because this component is highly conserved among animal pathogens, its absence from plant pathogenic bacteria suggests a degree of specialization in this part of the secretion apparatus. The chaperones and the needle substructure are thought to be critical for functions related to the translocation of effector proteins into host cells. Therefore, the theme emerging is that the type III secretion components that are highly conserved between plant and animal pathogenic bacteria are those involved in secretion from the bacteria.

Function of Type III Effector Proteins from Phytopathogenic Bacteria

The role of type III effectors in plant cells remains elusive. Most phytopathogenic bacterial effectors show no homology to known proteins in existing databases. Their role in virulence has been inferred from mutagenesis studies that have shown that, in the absence of these avirulence type III effector genes, there is a loss of virulence on host plants that do not contain cognate disease resistance genes (*26*). The only type III effector that shows significant homology to known proteins in a BLAST search is AvrBs2 from *X. campestris*. This protein shares homology with phosphodiesterases, which suggests that AvrBs2 may function in plants as an enzyme. AvrBs2 is found in most pathovars of *X. campestris* and is required for full pathogen fitness. Molecular studies show that *X. campestris* is evolving under selection pressure at the *avrBs2* locus to evade host recognition and to maintain larger bacterial populations in its host (*27*).

The recent application of structure prediction programs to predict the secondary structure of the YopJ family of type III effectors has provided new insight into the possible function of these proteins (*28*). The YopJ homologs can be found in plant (*Erwinia*, *Pseudomonas*, and *Xanthomonas*) and animal pathogenic bacteria (*Yersinia* and *Salmonella*) and in a plant symbiont (*Rhizobium*) (Table 1). The predicted secondary structure of some YopJ homologs is similar to the known structure of adenovirus protease (AVP), a cysteine protease. All of these effectors possess the critical residues (His, Glu, and Cys) forming the catalytic triad in the AVP cysteine protease (Table 2). Mutation of the predicted catalytic core in YopJ and AvrBsT inactivated both proteins, which suggests that these residues are critical for function. The mammalian substrates for YopJ are highly conserved ubiquitin-like molecules, namely SUMO-1 protein conjugates (*28*). The plant substrates for AvrBsT are not yet known. This work suggests that YopJ-like effectors may modulate host signaling by disrupting signal transduction events regulated by SUMO-1 post-translational modification.

Defining the molecular mechanism of the suppression of plant host defenses is a substantial challenge in the area of plant-microbe interactions. However, new evidence suggests that plant pathogen type III effectors may work in plants to suppress host defense signal transduction (*29*). Stable transgenic *Arabidopsis* plants lacking the corresponding resistance gene and expressing the *P. syringae* AvrRpt2 effector were more susceptible to *P. syringae* infection.

One theme emerging from the elucidation of the functions of several type III effector proteins is that of modulation of cellular functions by bacterial products that mimic host proteins. At the molecular level, host mimicry may take two forms. One form is characterized by the use of direct homologs of host proteins subverted for the pathogen's needs. Examples of this are the tyrosine phosphatases YopH (*30*) and SptP (*31*) from *Yersinia* and *Salmonella* and the YpkA serine-threonine kinase from *Yersinia* (*32*). The second form of mimicry is characterized by prokaryotic protein surfaces that mimic eukaryotic protein surfaces. This form of mimicry is less obvious, because it may involve proteins with no apparent sequence similarity to any known protein. We anticipate that this form of mimicry may be more widespread among type III effectors and that it may only be deciphered by the close examination afforded by crystallographic studies, as shown in the case of the guanosine triphosphatase–activating protein (GAP) domain of the *Salmonella* effector SptP (*33*). The crystal structure of SptP revealed that, although it is not obvious at the primary sequence level,

Table 1. The YopJ family of type III protein effectors is conserved in plant and animal microbial pathogens.

	Effector	Target	Effect
Animal pathogen			
S. typhimurium	AvrA	Unknown	
Yersinia spp.	YopJ/YopP	MAPK kinases, IKKβ	Inhibition of TNFα, inhibition of NFκB activation, inhibition of SUMO-1 conjugation, proapoptotic
Plant pathogen			
Erwinia amylovora	ORFB	Unknown	
P. syringae	ORF5	Unknown	
	AvrPpiG1	Unknown	Hypersensitive response
X. campestris	AvrBsT	Unknown	Hypersensitive response
	AvrRxv	Unknown	Hypersensitive response
	AvrXv4	Unknown	Hypersensitive response
Plant symbiont			
Rhizobium NGR234	Y4LO	Unknown	

Table 2. The YopJ-like effectors are proposed to be cysteine proteases. The predicted catalytic residues (His, Glu, and Cys) conserved in all protein members is shown in bold. Protein accession numbers (GenBank) are in parentheses.

(P31498)	YopJ	109	**H**FSVIDYK-HINGKTSLILF-**E**PANF---NSMGPAMLA--IRTKTAIERYQLPDCHFSMVEMDIQRSSSE**C**GIFS
(AAB83970)	AvrA	123	**H**ISVVDFR-VMDGKTSVILF-**E**PAAC---SAFGPA-LA--LRTKAALEREQLPDCYFAMVELDIQRSSSE**C**GIFS
(AAD39255)	AvrBsT	154	**H**HAAIDVR-FKDGKRTMLVI-**E**PALAYGMKDGEIKVMAGYETLGKNVQNCLGENGDMAVIQLGAQKSLFD**C**VIFS
(AAA27595)	AvrRxv	180	**H**RVAFDVRNHESGHTTIIAL-**E**PASAYN-----PDHMPGFVKMRENLTSQFGRKISFAVIEAEALKSIGG**C**VIFS
(AAG39033)	AvrXv4	155	**H**HFAVDVKHHENGASTLIVL-**E**SASAGN-----EIALPGYTKLASMLRSKFGGSARMVVIEAEAQKSLND**C**VIFA
(CAC16700)	ORF5	243	**H**HIALDIQLRYGHRPSIVGF-**E**SAPGNIIDAAEREILSAL----------GNVKIKMVGNFLQYSKTD**C**TMFA
(AAF71492)	AvrPpiGl	160	**H**HVAVDVRNHSNGQKTLIVL-**E**PITAYKDDVYPPAYLPGYPQLREEVNTRLRGNAKMSVIETDAQRSWHD**C**VIFS
(AAF71492)	ORFB	235	**H**HRVALDIQFRPGHRPSVVGY**E**SAPGNLAEHLKYGLEHGL----------R--GAKVQVVANTIQNSVRG**C**SMFA
(AAB92459)	Y4LO	123	**H**HVAADVRTRAGAAPTIIVM-**E**GANFY-------TFVASYFKLRGDSFRQLGTQAKWAFIEVGAQKSAAD**C**VMFG

this protein shares fundamental structural domains that are characteristic of eukaryotic GAPs. Therefore, despite the differences in the general architecture, the actual surface presented by SptP to its cellular targets has much in common with that of its eukaryotic counterparts.

Overall, type III effectors do not exhibit obvious sequence similarities to other proteins, despite the fact that, at least functionally, some behave like eukaryotic protein counterparts. In these cases, convergent evolution may have sculpted protein surfaces that mimic their eukaryotic "homologs." This may be the case with the LRR (leucine-rich repeat) effector proteins identified in plant (*Ralstonia*) (*6*) and animal (*Yersinia*, *Salmonella*, and *Shigella)* bacterial pathogens (*34*). One role of these LRR effector proteins might be to interfere with or modulate LRR protein receptors in the host that are involved in recognizing signals from invading pathogens.

From the bacterial perspective, there are still many unanswered questions in the fields of plant and animal pathogenesis. Several key questions remain. For instance, how many different bacterial effectors are delivered by a given pathogenic strain to its respective hosts? Is this suite of effectors different among isolates that are pathogenic on the same host species, suggesting functional redundancy at the population level? More important, what are the molecular functions of these proteins? How are these effectors detected by surveillance mechanisms in resistant hosts?

Host Surveillance Mechanisms of Plants and Animals

The host environments of plant and animal cells are vastly different and present unique challenges to invading pathogens. Because plants lack a circulatory system, each cell must be capable of responding to an invading pathogen. The genetic basis of plant resistance is often controlled by single resistance genes evolved to recognize organisms expressing specific avirulence genes. As detailed above, these generally encode type III effector proteins. This genetic interaction is the basis of the gene-for-gene hypothesis originally proposed by Flor in the 1940s (*35*). A flurry of activity in the past 8 years has resulted in the cloning and identification of plant disease resistance genes from both model and agronomically important plants (*36*). These studies reveal that several classes of proteins are involved in plant disease resistance (Fig. 1). These include Cf2, Cf4, Cf5, Cf9, Ve1, and Ve2 (*37*), transmembrane proteins containing extracellular LRRs; Xa21, a transmembrane protein containing extracellular LRRs and a cytoplasmic serine-threonine kinase; and Pto, a cytoplasmic serine-threonine kinase. However, the NB/LRR (nucleotide binding site/LRR) class of proteins is the most prevalent (*38*). This same class of proteins is capable of recognizing viruses, bacteria, fungi, nematodes, and insects. The NB/LRR class of resistance proteins can be divided into two subclasses based on conserved NH_2-terminal motifs. One class contains a coiled coil (CC) domain that contains a putative leucine zipper domain (such as RPS2 and RPM1), whereas the other class contains significant homology with the Toll/interleukin receptor (TIR) domain (such as N, L6, and RPP5, and not to be confused with the Tir protein encoded by enteropathogenic *E. coli*). The precise molecular events mediated by NB/LRR proteins, leading to pathogen recognition in plants, have not yet been established. However, NB/LRR proteins appear to be cytosolic receptors that are sometimes associated with the plasma membrane (*39*), where they may be capable of directly or indirectly perceiving pathogen effectors as they enter the plant cell. Two hybrid protein studies suggest that there may be a direct interaction between the pathogen effector and the host resistance protein (*18*), whereas other studies in plants suggest the possibility of indirect interactions mediated by a protein signaling complex with other host proteins (*40*). The molecular characterization of many NB/LRR disease resistance proteins from several plant families immediately allowed a comparison to be drawn with proteins from other organisms that contain similar motifs (*41*). The identification of the TIR domains in the N protein of tobacco and the L protein of flax suggests that plants, insects, and mammals might use proteins with similar domains to resist infection.

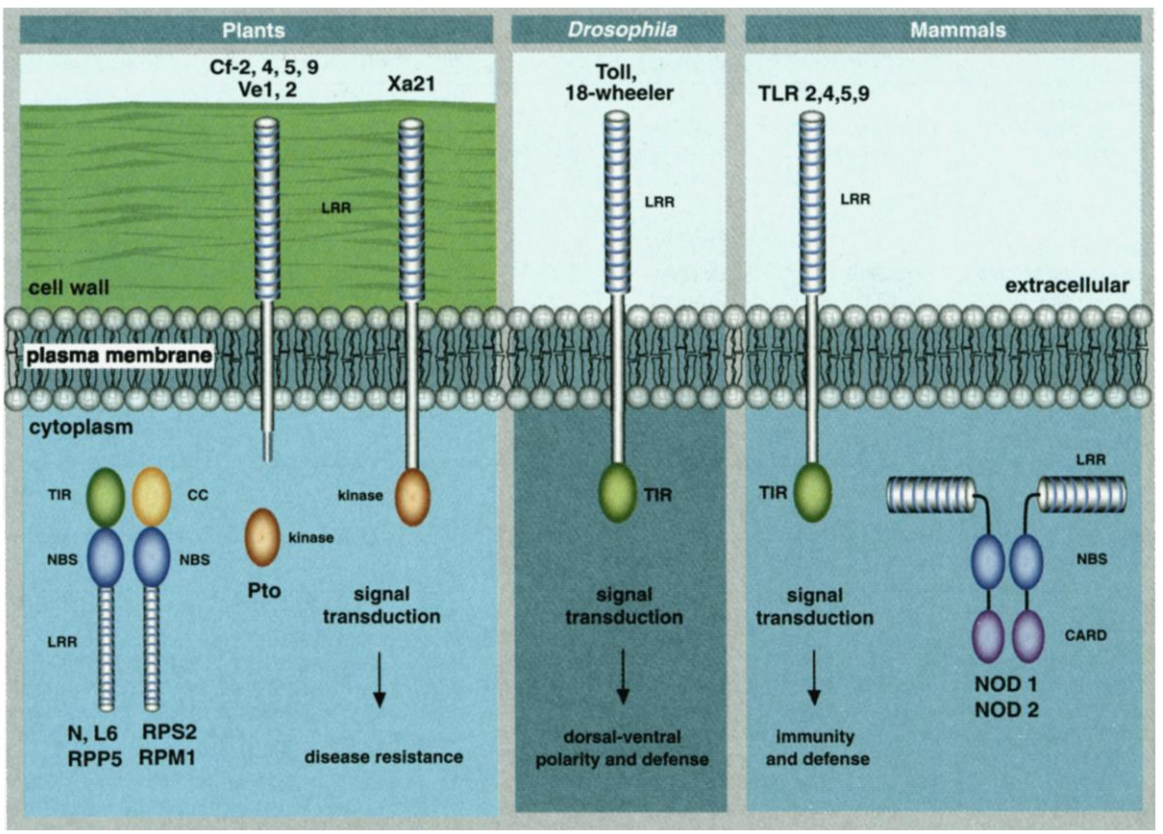

Fig. 1. Schematic diagram illustrating several proteins present in plants, *Drosophila*, and mammals that initiate signal transduction cascades after pathogen infection, which ultimately lead to disease resistance.

The demonstration that Toll receptors in both *Drosophila* and mammals play a role in innate immunity has reinforced this concept (*42*, *43*). The *Toll* family encodes transmembrane proteins containing extracellular LRRs and an intracellular motif homologous to the interleukin-1 receptor, suggesting a role in triggering signal transduction. The *Toll* pathway originally described in *Drosophila* controls the establishment of the dorsal-ventral axis in the developing embryos. However, further studies established that the *Drosophila Toll* pathways also induce the expression of antimicrobial peptides (*42*). Genetically defined components of the dorsal-ventral polarity system also function in the *Drosophilia* innate immune response, but certain steps in the signaling pathways are unique to these two very different processes. Moreover, there is some specificity in the transcriptional output of different *Toll* family members' function in the innate immune response. For example, *Toll* controls the induction of the antifungal gene *drosomycin*, whereas the *Toll* family member *18-wheeler* controls resistance to bacterial pathogens by the induction of attacin. The *Drosophila* genome project predicts that there are at least nine genes encoding Toll-like receptors. A role in innate immunity for these additional Toll-like receptors remains to be determined.

It is now well established that mammalian Toll-like receptors (TLRs) play a key role in innate immunity (*43*, *44*). For example, it has been shown that the LRR domains of TLRs are involved in the recognition of conserved pathogen components. TLR2 is involved in the recognition of bacterial lipoprotein and lipotheicoic acid, TLR4 in the recognition of LPS, TLR9 in the recognition of unmethylated DNA, and TLR5 in the recognition of flagellin. FLS2 from *Arabidopsis* uses extracellular LRRs to specifically recognize a well-conserved peptide from bacterial flagellin (*45*), and this recognition triggers typical cellular responses. The recognition of these pathogen-associated molecular patterns by the extracellular LRR motif is also involved in induced expression of cytokines that stimulate the adaptive immune response. The sequences of human and mouse genomes suggest that there are many more TLRs. The exact role these putative receptors play in innate immunity awaits further experimentation.

The extracellular TLRs are able to recognize pathogen ligands presented to the host from the outside. However, very recent studies suggest that mammalian cells also use intracellular protein receptors NOD1 and NOD2 that share homology with the NB/LRR superfamily of plant disease resistance proteins (*46*). These studies have demonstrated that NOD1 and NOD2 function as intracellular receptors for bacterial LPS and play a key role in innate immunity. The exciting discovery that the gene encoding NOD2 appears to be associated with Crohn's disease in humans has widespread implications for human health (*47*). The NOD family proteins are structurally homologous to the apoptosis regulators APAF1/CED4 and to NB/LRR disease resistance proteins. They contain an NH_2-terminal caspase recruitment domain (CARD), a central NB domain, and COOH-terminal LRRs. An examination of the human genome sequence suggests that there may be over 30 NOD gene homologs, expressing NB/LRR domains but with potentially different NH_2-terminal domains. Future research will undoubtedly be exciting as researchers begin to genetically uncover the role of intracellular NOD receptors in induction of the mammalian innate immune response.

Conclusions and Future Perspectives

The elucidation of the molecular events involved in pathogen recognition and the triggering of signal transduction events that lead to pathogen inhibition is a common goal of researchers in both the plant and animal fields. The demonstration that pathogenic bacteria that colonize such diverse host substrates contain conserved type III secretion machines is truly remarkable. However, distinct differences exist in both the proteins that make up the secretion machinery and in the types of effector proteins that are delivered to the respective host cells. The structural differences that distinguish plants and animals will most likely specify the evolution and selection of particular effectors that interfere with or modulate host function. The conservation of domains in host surveillance proteins that perform similar functions raises questions about the mechanism of their evolution. However, it remains to be shown that the biochemical mechanisms responsible for pathogen inhibition are also conserved.

A major goal in studying disease is to design new and effective methods for preventing disease. The uncovering of the precise molecular events controlling the delivery of type III effector proteins should eventually allow the design of compounds that specifically interfere with these processes without deleterious side effects in the host. One can also envision the design of novel plant resistance genes that target conserved pathogen ligands that are essential for pathogenicity. This will only become a reality once we understand the molecular basis of plant and animal diseases in sufficient detail to be able to engineer resistance proteins in a predictable fashion. The construction of transgenic plants expressing these engineered proteins may provide effective and durable disease resistance. Future research holds promise as new discoveries will continue to uncover common and contrasting mechanisms of pathogen virulence and host resistance in plant and animal disease.

References and Notes

1. R. Koch, *Beitr. Biol. Pflanz.* **2**, 277 (1876).
2. T. J. Burrill, *Trans. Ill. State Hortic. Soc.* **11**, 79 (1878).
3. J. R. Alfano, A. Collmer, *J. Bacteriol.* **179**, 5655 (1997).
4. T. V. Huynh, D. Dahlbeck, B. J. Staskawicz, *Science* **245**, 1374 (1989).
5. S. Fenselau, I. Balbo, U. Bonas, *Mol. Plant-Microbe Interact.* **5**, 390 (1992); F. Van Gijsegem, S. Genin, C. Boucher, *Trends Microbiol.* **1**, 175 (1993).
6. G. R. Cornelis, F. Van Gijsegem, *Annu. Rev. Microbiol.* **54**, 735 (2000).
7. J. E. Galan, A. Collmer, *Science* **284**, 1322 (1999).
8. S. Y. He, *Annu. Rev. Phytopathol.* **36**, 363 (1998).
9. G. E. Soto, S. J. Hultgren, *J. Bacteriol.* **181**, 1059 (1999).
10. W. Wei *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 2247 (2000).
11. F. Van Gijsegem, J. Vasse, J.-C. Camus, M. Marenda, C. Boucher, *Mol. Microbiol.* **36**, 249 (2000).
12. C. Ginocchio, S. B. Olmsted, C. L. Wells, J. E. Galán, *Cell* **76**, 717 (1994).
13. S. Knutton *et al.*, *EMBO J.* **17**, 2166 (1998).
14. J. M. Plotnikova, L. G. Rahme, F. M. Ausubel, *Plant Physiol.* **124**, 1766 (2000).
15. F. G. Sauer, M. A. Mulvey, J. D. Schilling, J. J. Martinez, S. J. Hultgren, *Curr. Opin. Microbiol.* **3**, 65 (2000).
16. B. Kenny *et al.*, *Cell* **91**, 511 (1997).
17. M. Hedlund *et al.*, *J. Infect. Dis.* **183**, S47 (2001).
18. S. Kjemtrup, Z. Nimchuk, J. L. Dangl, *Curr. Opin. Microbiol.* **3**, 73 (2000).
19. D. M. Anderson, D. E. Fouts, A. Collmer, O. Schneewind, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 12839 (1999).
20. Y. Fu, J. E. Galán, *Nature* **401**, 293 (1999).
21. M. B. Mudgett *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 13324 (2000); D. S. Guttman, J. T. Greenberg, *Mol. Plant-Microbe Interact.* **14**, 145 (2001).
22. O. Rossier, K. Wengelnik, K. Hahn, U. Bonas, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 9368 (1999).
23. P. Wattiau, S. Woestyn, G. R. Cornelis, *Mol. Microbiol.* **20**, 255 (1996).
24. S. Gaudriault, L. Malandrin, J. P. Paulin, M. A. Barny, *Mol. Microbiol.* **26**, 1057 (1997).
25. T. Kubori *et al.*, *Science* **280**, 602 (1998).
26. F. F. White, B. Yang, L. B. Johnson, *Curr. Opin. Plant Biol.* **3**, 291 (2000).
27. W. Gassmann *et al.*, *J. Bacteriol.* **182**, 7053 (2000).
28. K. Orth *et al.*, *Science* **290**, 1594 (2000).
29. Z. Y. Chen, A. P. Kloek, J. Boch, F. Katagiri, B. N. Kunkel, *Mol. Plant-Microbe Interact.* **13**, 1312 (2000).
30. J. A. Stuckey *et al.*, *Nature* **370**, 571 (1994).
31. K. Kaniga, J. Uralil, J. B. Bliska, J. E. Galan, *Mol. Microbiol.* **21**, 633 (1996).
32. E. E. Galyov, S. Hakansson, A. Forsberg, H. Wolf-Watz, *Nature* **361**, 730 (1993).
33. C. E. Stebbins, J. E. Galan, *Mol. Cell* **6**, 1449 (2000).
34. E. A. Miao *et al.*, *Mol. Microbiol.* **34**, 850 (1999).
35. H. H. Flor, *Phytopathology* **45**, 680 (1955).
36. J. Ellis, P. Dodds, T. Pryor, *Curr. Opin. Plant Biol.* **3**, 278 (2000).
37. L. M. Kawchuk *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 5945 (2001).
38. B. C. Meyers *et al.*, *Plant J.* **20**, 317 (1999).
39. D. C. Boyes, J. Nam, J. L. Dangl, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 15849 (1998).
40. R. T. Leister, F. Katagiri, *Plant J.* **22**, 345 (2000).
41. B. J. Staskawicz, F. M. Ausubel, B. J. Baker, J. G. Ellis, J. D. Jones, *Science* **268**, 661 (1995).
42. K. V. Anderson, *Curr. Opin. Immunol.* . **12**, 13 (2000).
43. R. Medzhitov, C. Janeway, *Trends Microbiol.* **8**, 452 (2000).
44. A. Aderem, R. J. Ulevitch, *Nature* **406**, 782 (2000).
45. L. Gomez-Gomez, T. Boller, *Mol. Cell* **5**, 1003 (2000).
46. N. Inohara *et al.*, *J. Biol. Chem.* **274**, 14560 (1999); Y. Ogura *et al.*, *J. Biol. Chem.* **276**, 4812 (2001).
47. Y. Ogura *et al.*, *Nature* **411**, 603 (2001); J.-P. Hugot *et al.*, *Nature* **411**, 599 (2001).

48. We gratefully acknowledge K. Anderson and M. Axtell for critical reading of the manuscript and E. Torok Clark for preparation of the figure. Work in the Staskawicz lab is supported by the U.S. Department of Energy (DOE), NSF, and Syngenta. Work in the Dangl lab is supported by grants from NSF, NIH, DOE, the U.S. Department of Agriculture, and Syngenta. Work in the Galan Lab is supported by NIH.

26 April 2001; accepted 18 May 2001