Understanding Plant Immunity as a Surveillance System to Detect Invasion

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Abstract

Various conceptual models to describe the plant immune system have been presented. The most recent paradigm to gain wide acceptance in the field is often referred to as the zigzag model, which reconciles the previously formulated gene-for-gene hypothesis with the recognition of general elicitors in a single model. This review focuses on the limitations of the current paradigm of molecular plant-microbe interactions and how it too narrowly defines the plant immune system. As such, we discuss an alternative view of plant innate immunity as a system that evolves to detect invasion. This view accommodates the range from mutualistic to parasitic symbioses that plants form with diverse organisms, as well as the spectrum of ligands that the plant immune system perceives. Finally, how this view can contribute to the current practice of resistance breeding is discussed.

"Although it is clear that ideas can provide an impetus for experiment . . . I believe that ideas, especially good ideas, can so satisfy our desire to explain what we are studying that they can inhibit our ability to explore and to understand."

- Charles A. Janeway, Jr. (*Cold Spring Harbor Symp. Quant. Biol.*, 1989, 54:1–13)

INTRODUCTION

At some point, the human population will reach Earth's carrying capacity, resulting in an inevitable food shortage. The English economist Thomas Malthus postulated this idea by contrasting our exponential growth with the linear increase in food production (94). The counterpoint is that human technological advancement will allow us to achieve more with less. In reality, both views are partially correct. Research has demonstrated a deterioration of Earth's ecosystem with respect to limited natural resources, which will exacerbate with time (149). However, countless plant breeders, agronomists, and plant pathologists sparked a green revolution, leading to a dramatic increase in agricultural productivity (76). Nevertheless, we still face the need to double crop production to meet the projected global demand of calories in 2050 (140). Research in molecular phytopathology aims to understand the plant immune system and the tools pathogens use to subvert it. As such, this research can contribute new ideas and applications to increase crop productivity and address Thomas Malthus's observation.

A number of conceptual models for the plant immune system have been described (24, 43, 69, 110, 143). The details of these models vary, but they are all grounded in the observation that plants mainly rely on an innate immune system that is largely controlled by encoded receptors that identify invasion (5, 11, 13, 111). In general, models are useful to distill and integrate empirical data to explain complex systems. Building and testing scientific models is an iterative process, and the models themselves are typically not the end of scientific quests but represent benchmarks from which to operate and generate new hypotheses. It is important to realize that (*a*) all models are generalizations and therefore incomplete, (*b*) increasing the details of a model decreases its general applicability, (*c*) multiple seemingly different models can be built to explain a phenomenon, all of which must be considered valid as long as they integrate known observations, and (*d*) all models should be continually challenged via experimentation to advance scientific knowledge.

This review highlights the role models have played in providing important conceptual advances in our understanding of the plant immune system. We aim to draw attention to the limitations of these models that narrowly define molecular plant-invader interactions and fail to integrate experimental data from diverse systems. To address these limitations, we provide a more general and inclusive conceptual view of plant immunity that we term the Invasion Model.

CONCEPTUAL ADVANCES EXPLAINING THE PLANT IMMUNE SYSTEM

In his research on the interaction between flax and the flax rust fungus in the first half of the twentieth century, Harold Flor determined that plant and pathogen genes interacted in particular combinations, providing disease resistance (43, 44). In segregating plant lines, a clear Mendelian relationship governing resistance was observed following a dominant locus segregation pattern, and allelic series could be identified that abrogated the resistance phenotype. The resulting gene-for-gene hypothesis thus proposes that a single dominant host-resistance gene (*R*) incites a phenotype of disease resistance in response to a pathogen expressing a single dominant avirulence gene (*Avr*).

A seemingly separate line of research identified so-called general elicitors from microbes that could not be used to determine race specificity or were detected by multiple plant species (31).

This was in contrast to pathogen Avrs that induced responses only on particular varieties of a host species, and these seemingly different observations were regarded as disparate phenomena. The identification and characterization of general elicitors and their corresponding receptors in vertebrate immunity helped to further refine the concept in plant immunity. Charles Janeway first postulated the importance of conserved microbial ligands for innate immunity to account for lapses in the conceptual model of vertebrate immunity (65). He reasoned that microbes possess pathogen-associated molecular patterns (PAMPs) that are recognized by host pattern recognition receptors (PRRs) as nonself (65). He anticipated that PRRs perceive microbe-derived, conserved general structural patterns that are critical for the organism and require significant changes to avoid recognition (65). The parallels between the concepts Janeway describes and the phenomena observed for general elicitors of plant immunity led to the adoption of the terms PAMP and PRR in the study of plant-microbe interactions (110). It was subsequently realized that the term PAMP is a misnomer, as it often concerns molecules present in both pathogenic and nonpathogenic microorganisms, which led to the introduction of the term MAMP (microbe-associated molecular pattern) (5). However, although the adoption of these terms and ideas helped define the plant immune system, it further divided the observations of the gene-for-gene response from the response to general elicitors.

An important conceptual advance for describing plant immunity was the inclusion of general elicitors and Avrs in a single model (24, 69), which is often referred to as the zigzag model (69). These descriptions of the plant immune system define an MTI (MAMP-triggered immunity)-ETI (effector-triggered immunity) dichotomy and separate responses to MAMPs and effectors. The zigzag model discriminates four phases of the plant immune system that determine the plant-microbe interactions manifested today. In the first phase, plants recognize MAMPs by cell surface–localized PRRs, leading to a broad-spectrum resistance against microbes termed MTI. Next, microbial-produced molecules, termed effectors, enable successful pathogens to overcome MTI, resulting in effector-triggered susceptibility (ETS). Subsequently, these effectors may be recognized by intracellular receptors (R proteins), activating ETI. In turn, the microbe may evade ETI and restore ETS, either by evasion of recognition through loss or mutation of recognized effectors or by suppression of ETI using novel effectors. The model predicts continued coevolution in which the plant restores ETI by evolving new *R* genes and the pathogen causes disease by overcoming recognition.

The most important conceptual advance of the zigzag model is that defense activation upon MAMP recognition is countered by the action of pathogen-secreted effectors, thus incorporating the seminal discovery that Avrs, as defined in the gene-for-gene model, can contribute to virulence on hosts that lack R proteins required for effector recognition (74, 136). Thus, whereas the gene-for-gene model attributes pathogen virulence to a lack of host recognition, the zigzag model prescribes virulence functions to effectors. With this, the zigzag model formally unified observations made about general elicitors and the gene-for-gene model to discriminate different layers of recognition and asserts that pathogens must subvert these layers of immunity, resulting in evolutionary pressure on both organisms to counter the other.

Typically, models are based on seminal observations from a limited number of systems. Unfortunately, nearly a decade after its introduction several misconceptions appear to be associated with the MTI-ETI dichotomy, some of which are not necessarily associated with its original description but are routinely professed at meetings, during PhD examinations, and in research articles. These misconceptions, in particular the strict separation of MTI versus ETI, and the assumptions that these layers of plant immunity are governed by separate forces, result in a narrowly defined model rather than the general view that plant immunity is a continuous system that evolves to detect invasion.

LIMITATIONS AND INCONGRUITIES IN THE MAMP-EFFECTOR DICHOTOMY

Continued research into plant-microbe interactions has identified a number of concerns about the MTI-ETI dichotomy, questioning the conceptual layout of the model in distinct phases governed by discrete responses (13, 121, 139). This concerns the ambiguous dichotomy between MAMPs and effectors, between PRRs and R proteins, and consequently between MTI and ETI, as well as the omission of endogenous damage-associated molecular patterns (DAMPs) as inducers of immune responses (13, 139). Furthermore, the model is applicable to a very particular group of symbionts, namely biotrophic (bacterial) plant pathogens, and is more difficult to apply to interactions with other symbionts, including necrotrophs, insects, and mutualists (14, 35, 47, 61). The zigzag model also does not acknowledge the number, kinetics, and combined action of multiple receptor ligands that govern these interactions. Additionally, pathogen perception and response are illustrated over an ambiguous spatial and temporal frame, obscuring the model's intention to represent evolution or a particular cellular encounter (121). The zigzag model also does not account for previous life history events of the host or invader prior to the interaction, which may influence the outcome of the interaction (63).

In the following sections, we discuss limitations that most directly address the contemporary conceptual view of plant immunity related to (*a*) the flawed application of the terms MAMPs and effectors, (*b*) the classification of MTI as a static first phase, (*c*) the classification of ETI as pathosystem-specific, and (*d*) the classification of broad-spectrum, receptor-mediated immunity as a separate form of immunity.

Evolution of the Terms Effector and MAMP, and Molecules That Defy Classification

The terminology to describe plant-microbe interactions is as diverse as the systems it encompasses, and the evolution of the lexicon has resulted in misnomers and confusion (52). Our current classification of the plant immune response according to elicitation by MAMPs or effectors requires a clear distinction between these molecules, but this is often not the case. A hindsight view suggests that the legacy of separate observations between gene-for-gene resistance and general elicitors likely accounts for their continued separation today. However, the distinction between plant immune responses based on categorizing "what" is being perceived ultimately results in an untenable dichotomy.

The gene-for-gene theory defines Avrs as molecules that allow corresponding host R proteins to recognize pathogens, defining microbial molecules from the perspective of plant recognition (45). The term Avr was often replaced by the term effector after the 1990s. Although the definition of an effector can vary across systems and researchers, an effector is generally regarded as a microbial-derived molecule that functions outside of its originator to contribute to the establishment of symbiosis (13, 70, 127). The term effector is often an improvement to the term Avr, as it refers to the primary and intrinsic function of the molecule, namely as a virulence factor.

The observations, ideas, and terminology represented by MTI were specifically established with the molecular and immunogenic characterization of flagellin and its receptor, FLAGELLIN SENSING2 (FLS2) (56, 168). However, a major complication of the current terminology is that the MAMP-effector dichotomy refers to two different, not mutually exclusive, viewpoints (**Figure 1*a***). Whereas MAMPs are defined from the viewpoint of the plant, effectors should be defined from the viewpoint of the microbe. Although the term effector is sometimes used to reflect host recognition, as in Avr, this use is inappropriate as it implies that the function of an effector is for host recognition. However, the primary effector function is to aid the invader,

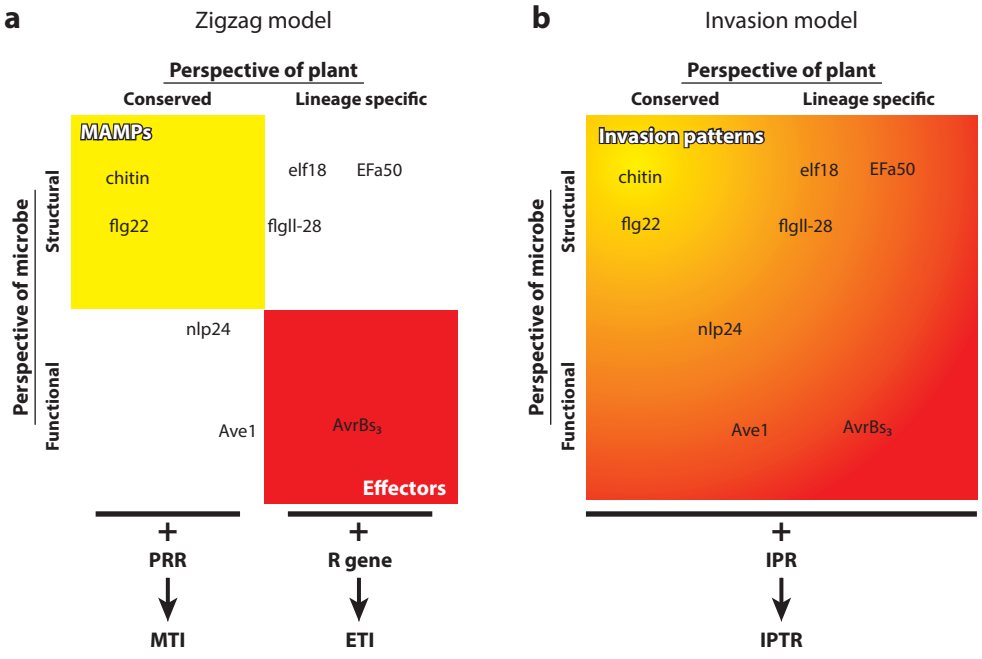

Figure 1

Comparison of the conceptual layout of the zigzag and invasion models. (*a*) The zigzag model is conceptually defined in strict terms, and plants perceive either microbe-associated molecule patterns (MAMPs; *yellow box*) through pattern recognition receptors (PRRs), leading to MAMP-triggered immunity (MTI), or effectors (*red box*) through R proteins, leading to effector-triggered immunity (ETI). The axes from either the plant or microbe perspective indicate features that most commonly define these terms. Examples of perceived molecules are shown to illustrate that some molecules defy clear classification and fall outside the colored boxes. (*b*) The invasion model is shown in a similar fashion, except that the space to define immunogenic molecules is represented as a continuum to reflect that molecules and responses occupy a spectrum with respect to any defining category. We term the ligands as invasion patterns (IPs), which are perceived by plant IP receptors (IPRs), leading to an IP-triggered response(s) [IPTR(s)]. The immunogenic molecules are equally placed in the figures to approximate their space within plant perception and microbial function.

and regardless of plant perception, the intrinsic biochemical effector function does not change within the interaction. Also, when effector catalogs encoded by symbiont genomes are defined, host recognition is not a selection criterion. Consequently, the MAMP-effector dichotomy is not meaningful when discussing host detection.

It is important to note that the term MAMP is operationally used to describe molecules that perform general fitness functions, not molecules performing specific life-history events such as those for niche adaptation (139). However, it has become increasingly apparent that many proteins defined as effectors have a more widespread occurrence, potentially qualifying them as MAMPs. The necrosis and ethylene-inducing peptide 1 (Nep1) was originally identified in culture filtrates from *Fusarium oxysporum* (7), and numerous homologs, referred to as Nep1-like proteins (NLPs), are encoded by bacteria, fungi, and oomycetes where they can positively contribute to virulence (53, 115). Recently, a conserved region of approximately 20–24 amino acids was identified on NLPs (termed nlp20 and nlp24, respectively) that serves as a potent inducer of plant immune responses (16, 114). Thus, conserved NLP effectors contain a pattern that acts as a MAMP.

Another example is BcSpl1, a cerato-platanin effector protein required for full virulence of the necrotrophic fungus *Botrytis cinerea* (49, 50). Two conserved regions within a 40–amino acid stretch of sequence that interact with each other on the protein surface are necessary and sufficient for triggering host defense, including cell death (49). The cerato-platanins constitute a widely conserved effector family encoded by diverse fungi, and the two conserved regions are present in all immunogenic cerato-platanins described (49). These and previously discussed examples (139) highlight pathogen molecules that simultaneously serve virulence functions and contain MAMP-like epitopes that are conserved across genera or even higher levels of microbial taxonomy and cannot easily be incorporated into the MTI-ETI classification.

Traditional MAMP Receptor Systems Are More Dynamic than Generally Assumed and Are Conditioned Similar to *R* genes

The strict separation of MTI and ETI results in assumptions about the evolution of immune receptors and their ligands. These include the suppositions that PRRs are old and more slowly evolving than *R* genes and are therefore more highly conserved, and that MAMPs are stable and broadly detected while effectors are variable and detected by specific hosts. However, a number of examples from well-studied systems do not support these assumptions but instead suggest that plant receptors are evolving to accurately detect invasion and, conversely, invader patterns are under pressure to avoid recognition (101, 148). This is regardless of their MTI-ETI classification.

Early experimental data clearly demonstrated that purified flagella and a specific epitope, flg22, are sufficient to elicit immune responses in tomato cells, but significant variation for flagellin perception exists across plant species (41). Likewise, flagellin and the flg22 epitope from diverse bacteria elicited varying degrees of responses (41). This led to the speculation that a then unknown "flagellin receptor represents elements of a 'non-self' perception system of plants, and that microbes adapted to grow in or on plants may have been under selection pressure to modify or lose these determinants. . ." (41, p. 273). This early insight suggested that, similar to *R* gene–mediated immunity, elicitors and their corresponding receptors impose selection on one another, potentially resulting in pathosystem-specific variation. These observations are further supported by a number of discoveries. The bacterial pathogen *Xanthomonas campestris* pv. *campestris* (Xcc) displays within-pathovar variation for *Arabidopsis* defense elicitation, which can be explained by naturally occurring variation in flagellin amino acid sequences (135). Additionally, the sequences encoding the flg22 epitope in *Ralstonia solanacearum* stain K60 and *Pseudomonas cannabina* pv. *alisalensis* (*Pcal*) strain ES4326 both contain significant sequence variation and fail to elicit immune responses in the tested plants (26, 117).

The dynamic nature of flagellin-host perception became more apparent through the discovery of microevolution in field populations of *Pseudomonas syringae* pathovars. Two striking finds were the extent of variation in the derived amino acid sequence for the flagellin-encoding *fliC* gene and the discovery of a second, 28–amino acid immunogenic region of flagellin (20). Interestingly, this region, termed flgII-28, which is C terminal to the flg22 epitope, is sufficient for the induction of defense responses in tomato, and the ancestral sequence of both flg22 and flgII-28 induced a stronger reactive oxygen burst in tomato compared with alleles encoded by current field isolates (20). The flgII-28 epitope elicits defense responses in various Solanaceae species but failed to elicit a significant response in ten plants from five additional families, indicating that sensing this epitope is a relatively recently evolved trait within the Solanaceae (26).

Posttranslational modifications have also been shown to affect flagellin perception in addition to sequence diversification. Rice responds weakly to flg22, but purified flagellin from an avirulent

strain of *Pseudomonas avenae* produces strong immune responses, including cell death, whereas flagellin from a virulent strain elicits no immune response (22). Interestingly, rice cells exposed to flagellin from virulent *P. avenae*, recombinantly produced by *Escherichia coli*, elicited strong immune responses similar to those elicited by purified flagellin from avirulent *P. avenae* (60). Flagellin from virulent *P. avenae* was shown to be glycosylated, and alanine substitution mutants in either of two glycosylated residues rendered the previously noneliciting flagellin immunogenic (60). Flagellar glycosylation, in fact, also appears to be employed by additional *Pseudomonas* species for the purpose of avoiding detection in dicots (138). An additional region of bacterial flagellin from *A. avenae* was recently reported to elicit plant defense responses in rice (73). The immunogenic epitope, termed CD2-1, is C terminal to the flg22 region, and the OsFLS2 ortholog does not mediate its recognition, suggesting a different flagellin-receptor system evolved in rice (73).

Variation for flagellin perception is also conditioned by variation in the plant receptor FLS2 (56). The *Arabidopsis thaliana* accession Ws-0 does not respond to flg22 or contain a functional FLS2 allele (9, 168), and genotypes in closely related *Arabidopsis lyrata*, *Cardamine hirsuta*, and additional Brassicaceae species do not bind the flg22 epitope (147). The tomato and *Nicotiana benthamiana* orthologs of AtFLS2 display species-specific, receptor-dependent variation for flagellin perception (123). Indeed, the recent characterization of the orthologous grape flagellin receptor VvFLS2 indicates that the flagellin encoded by a grape-adapted, plant growth–promoting rhizobacterium (PGPR), *Burkholderia phytofirmans*, elicits a weaker immune response on grape compared with flg22, which is specifically conditioned by the VvFLS2 receptor (142).

Another PRR-MAMP pair that shows signs of dynamic variation is that of the bacterial elongation factor EF-Tu and its corresponding Brassicaceae receptor, the EF-Tu receptor (EFR) (81, 167). Plants outside of the Brassicaceae do not respond to elf18 and presumably do not contain a functional homolog of EFR (13, 81). Recently, a second immunogenic epitope of EF-Tu, termed EFa50, was discovered from *P. avenae*, which elicits numerous immune responses in rice cells but not in *Arabidopsis* (51). Thus, similar to flagellin perception, independent evolution of receptors to different epitopes of EF-Tu has likely occurred, suggestive of specific host-pathogen evolution rather than general perception.

Additional receptor-ligand combinations support pathosystem-specific evolution, such as the ReMAX receptor that recognizes a currently unknown ligand from *Xanthomonas*, and the receptor appears to be limited to the Brassicaceae (67). Also, nlp24 is recognized by some Brassicaceae and distantly related lettuce but not by the more closely related plants *A. lyrata*, *Petroselinum crispum*, *N. benthamiana*, or *Solanum* spp. (16).

Taken together, these data suggest that PRRs are not generally old receptors that persist across plant families. Many of them display variation within a single species, or a relatively limited taxonomic distribution, suggestive of recent evolution. This, coupled with data suggesting the existence of independently evolved receptors for different domains of flagellin and EF-Tu, highlights the dynamic nature and distribution of PRRs and that PRR evolution is similar to the evolution of *R* genes responding to host-specific pathogens (26, 101, 148).

R-Gene Function and Evolution Are Not Confined to Host–Pathogen-Specific Interactions

Typically, *R* genes have been thought of as pathosystem-specific immune receptors. However, the nucleotide-binding site–leucine-rich repeat (NLR) immune receptor *Rxo1* of maize confers resistance to *Burkholderia andropogonis*, the causal agent of maize stripe disease, as well as to the unrelated bacterial rice pathogen *Xanthomonas oryzae* pv. *oryzicola* (163, 164). The latter is triggered following recognition of AvrRxo1, a type III effector protein of *X. oryzae* pv. *oryzicola* (164). Similarly, the

physically linked NLR pair *RRS1* and *RPS4* confers resistance to a fungal pathogen of Brassicaceae, *Colletotrichum higginsianum*, the broad-host range bacterial wilt pathogen *R. solanacearum*, and the bacterial pathogen *P. syringae* (107). In another example, the NLR immune receptor of tomato *Mi-1.2* confers resistance to phloem-feeding insects as well as root-knot nematodes (125, 152). In a screen of 171 predicted bacterial effectors from *Pseudomonas*, *Ralstonia*, and *Xanthomonas* expressed in 59 plants from four plant families, it was found that each plant responded to an average of 19 effectors. Interestingly, the necrotic response to an effector was generally not taxonomically defined (160). Taken together, these examples demonstrate that resistance conferred by NLR immune receptors is not necessarily restricted to a single pathosystem. Although some NLRs may directly perceive effectors, broadly detected effectors are likely perceived indirectly because they induce DAMPs or modify host targets that are guarded by R proteins (the guard model) (143). Nevertheless, broad detection of effectors by NLRs is conceptually similar to MAMP recognition by PRRs.

Guarded Effector Targets Can Represent Conserved *R* Gene–Mediated Immunity

Multiple *P. syringae* effectors modify RIN4, which is detected by R proteins to trigger ETI (6, 79, 91, 92). Two such effectors, AvrB and AvrRpm1, promote phosphorylation of RIN4, which is detected by the R protein RPM1 (92). Interestingly, the ability to detect AvrB and AvrRpm1 is not restricted to *A. thaliana*. In soybean, recognition of both effectors is mediated by the NLRs Resistance to *Pseudomonas glycinea* 1b and 1r (*Rpg1b* and *Rpg1r*), which are nonorthologous to RPM1 (2–4). The recognition of AvrB by Rpg1b is indirect and requires the presence of one of the four soybean RIN4 homologs (75, 131). Detection of AvrRpm1 by Rpg1r also appears to be RIN4 dependent, as expression of AvrRpt2, which can cleave all four soybean RIN4 homologs, mitigates Rpg1r-mediated AvrRpm1 recognition (4, 75). Thus, independent from *Arabidopsis*, soybean evolved a similar mechanism to detect RIN4 perturbation.

Also, various accessions of common bean can detect AvrRpm1. Two resistance loci, Resistant to *P. syringae* effector AvrRpm1 and 2 (*Rpsar*-1 and *Rpsar*-2), were identified, of which *Rpsar*-1 is syntenic to soybean *Rpg1* (23). Interestingly, Rpg1-r and Rpsar-1 independently evolved the ability to recognize AvrRpm1 and AvrRpt2 expression prior to AvrRpm1 expression-mitigated plant necrosis, again suggesting a common mechanism to detect AvrRpm1 via guarding of RIN4 (23). Various *Nicotiana*, pepper, tomato, and lettuce genotypes can also detect AvrB or AvrRpm1 (75, 160), and the modification sites of *Arabidopsis* RIN4 by AvrB and AvrRpm1 are conserved in RIN4 homologs across the plant kingdom (25). Given the evidence for NLR immune receptors guarding RIN4, the conserved ability to detect AvrB and AvrRpm1, and the conservation of key RIN4 modification sites across a wide taxonomic distribution of plants, it appears that guarding RIN4 is a conserved host immune strategy.

The tomato cell surface receptor-like protein (RLP) Cf-2 guards the apoplastic papain-like cysteine protease $Rcr3^{pim}$, which acts in basal immunity (124). Suppression of $Rcr3^{pim}$ by Avr2, an effector of the leaf mold fungus *Cladosporium fulvum* (124), or by Gr-VAP1, an effector of the nematode *Globodera rostochiensis* (89), elicits Cf-2–mediated resistance (89). This illustrates that independently evolved effectors from a fungal and invertebrate pathogen target the same plant protease, which the plant has evolved to detect. Remarkably, EPIC1 and EPIC2B from the oomycete late blight pathogen *Phytophthora infestans* also interact with $Rcr3^{pim}$ but do not activate Cf-2–dependent resistance (133). This further illustrates that interspecies interactions with plants represent a system of continuous coevolution. Although the resistance protein Cf-2 helped define the gene-for-gene hypothesis, it guards a conserved effector target, representing a plant-perceived ligand similar to MAMPs.

CORE PRINCIPLES OF PLANT-MICROBE INTERACTIONS

Given the limitations of the MTI-ETI dichotomy presented here and elsewhere (13, 121, 139), a renewed examination of the general core principles of molecular plant-microbe interactions is warranted. A first core principle is that invaders, whether successfully colonizing the host or not, are detected through MAMPs, DAMPs, and effectors by host cell receptors. A second core principle is that successful symbionts, irrespective of being pathogens or mutualists, evolved to (*a*) avoid detection of ligands by sequence diversification, posttranslational modification, or loss, or (*b*) directly subvert host immunity by deploying biochemically active effectors. A third core principle is that continued coevolution is shaped by both extra- and intracellular receptors that accurately betray potential invaders, and by any microbial action to allow continued symbiosis. A fourth core principle is that multiple receptor-ligand interactions are taking place simultaneously. Most of these principles are covered in the MTI-ETI dichotomy, but with more restricted definitions and assumptions. Mechanistically, host recognition and invader avoidance of recognition are achieved through a variety of routes that vary in detail but evolved to increase the respective organism's fitness. Importantly, this coevolution is occurring simultaneously both extra- and intracellularly, and not in distinct, separate phases or cellular locations. Consequently, diverse plant perception systems, ligands, and effectors to subvert immunity have evolved to shape and define present-day host-microbe interactions.

AN ALTERNATIVE VIEW OF THE PLANT IMMUNE SYSTEM

The fact that MAMPs are defined from the perspective of the host whereas effectors are defined from the perspective of the invader creates a conceptual conflict that needs to be resolved. Plants deploy a number of receptors that serve to detect invasion through ligand perception. It is clear that immunogenic ligands can be either host- or microbially derived, and that the molecules from which ligands originate can have different intrinsic functions, ranging from general physiology to species-specific life history events. The intrinsic function of the molecule influences the presence and variability of the ligand, but the response to the ligand is not always dictated by the function of the molecule. As such, a more widely applicable view of inducible plant immunity should explicitly separate host perception of a ligand from the physiological or biochemical function of the ligand-derived molecule, and be general enough to incorporate diverse interactions. To this end, we propose an Invasion Model in which host receptors, termed invasion pattern receptors (IPRs), detect either an externally encoded or modified-self ligand that indicates invasion, termed invasion pattern(s) [IP(s)] (**Figure 1*b***). We propose that any molecule could serve as an IP and potentially be detected by an IPR, but the probability of developing a given ligand-receptor complex increases with increasing ligand molecular constraint to retain function, conservation across organisms, importance in facilitating symbiosis, and accessibility. These views are based on the originally proposed core principles of MAMP-PRR innate immunity (65, 100). In this way, we define properties that govern immunogenic ligand-host receptor interactions in conceptual and not absolute terms, and can easily incorporate the diversity of ligands that signify invasion and are important for plant immunity, ranging from flagellin-FLS2 to specific effector–R protein interactions. This model furthermore accounts for host-derived ligands such as DAMPs and modified guardees. The Invasion Model abrogates the need to impose generalizations on whole classes of receptors but rather implies that all classes of immune receptors fall into a range with respect to response (weak to strong), phylogenetic conservation (narrow to broad), invader specificity (strain to kingdom), and signaling (specific to common). Ultimately, any immune receptor can be effective as long as it accurately betrays pathogen presence and elicits an appropriate response.

Perhaps most importantly, the Invasion Model allows a separation between IPs and the molecules or processes that produce IPs. This is important to account for the fact that molecules with any function can contain or produce IPs, but the molecules are not defined from a host perception or response viewpoint. That is, although molecules such as flagellin, EF-Tu, and chitin contain host-perceived patterns, their primary function is for the general physiology of their originator. Likewise, the primary function of pectin is to aid in the structure of the plant cell wall, but oligogalacturonide fragments resulting from pectin degradation are IPs (19, 109). Invader-synthesized molecules, including, but not limited to, toxins, proteasome inhibitors, phosphatases, cell wall–degrading enzymes, silencing suppressors, and transcription activator–like (TAL) effectors, serve a primary function to aid in symbiosis, but from a host perception perspective, these molecules may contain or produce IPs. Any of these molecules may have multiple functions and can be represented on a continuum from primary functionality in the originator to primary involvement in symbiosis. As researchers, this allows us to more accurately describe the function of these molecules as being important for originator physiology, host penetration, enzyme detoxification, host defense suppression, host signaling, nutrient acquisition, and dispersal to name a few, instead of categorizing everything as being a MAMP or an effector. Also, we account for the spectrum of responses that are triggered by an IP originating from any molecule.

Another important component of the Invasion Model is that IP-triggered responses (IPTRs) do not result in immunity by default (**Figure 2**). Following perception of one or more IPs, the resulting IPTR(s) will culminate in two outcomes: the end of symbiosis or continued symbiosis. These two outcomes are mediated by three mechanisms defined from the perspective of the invader: (*a*) failure to suppress IPTR, (*b*) suppression of IPTR, or (*c*) utilization of IPTR. Invaders may use effectors to manipulate the triggered response to influence the outcome of the symbiosis.

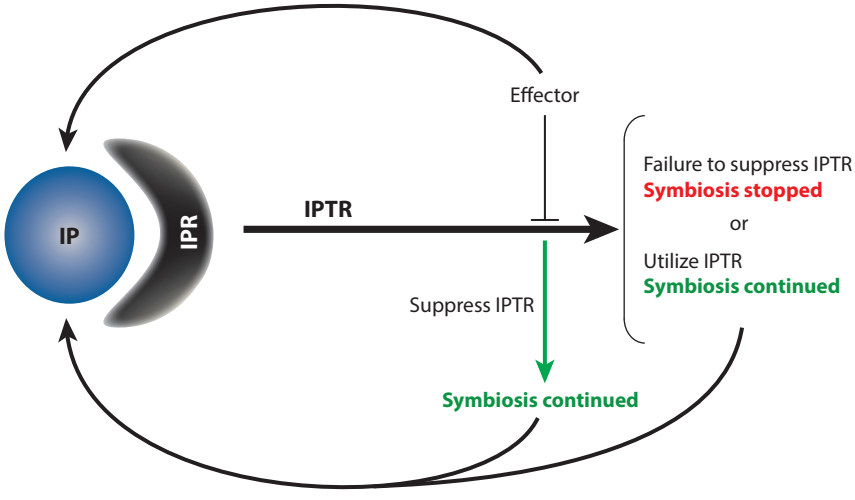

Figure 2

The Invasion Model to describe an attempted plant-invader symbiosis. Upon attempted symbiosis, invasion patterns (IPs) are perceived by plant IP receptors (IPRs), inciting an IP-triggered response (IPTR). Invaders may use effectors to influence the interaction, but if the invader fails to manipulate the IPTR, the symbiosis stops. Potentially, the IPTR may be suppressed (e.g., by biotrophs) or utilized (e.g., by necrotrophs) to continue symbiosis. Continued symbiosis and effector usage may generate host-perceivable IPs, leading to continued IPTR. Collectively, multiple recognition events and invader strategies influence the IPTR and eventually result in termination or continuation of symbiosis.

The use of effectors or the act of continued symbiosis can result in IPs that can also be recognized by IPRs, triggering continued plant responses, which can again result in a continuation or cessation of the interaction. The responses mediated by IPRs are not defined in absolute terms in order to (*a*) accommodate the range of responses that plant immune receptors can trigger, to (*b*) reflect that multiple, synergistic, and/or antagonistic responses can be triggered simultaneously that collectively determine the outcome of the symbiosis, and (*c*) because the way in which plants ultimately stop symbioses is not well understood and not necessarily the same for all types of invaders.

We believe that by separating host perception of IPs from the function of molecules or processes that produce IPs, the Invasion Model is applicable to describe host-invader interactions over a diverse set of systems and to provide a more predictive framework to aid in breeding for durable resistance. In this framework, the search for durable resistance involves focusing on key receptor-ligand interactions that are determined to be critical for invasion.

APPLYING THE INVASION MODEL TO ADDITIONAL INVADERS

A more generalized view of the immune system should integrate the range of interactions that actually represent the plant immune system. Thus, in the following sections, we discuss how the Invasion Model can be applied to diverse systems. This section is not meant to be exhaustive but aims to illustrate this altered perspective of the plant immune system.

Necrotrophs

Like biotrophic pathogens, necrotrophs contain MAMPs that are recognized during host invasion (82). For example, the chitin receptor AtCERK1 mediates immune responses to *Alternaria brassicicola* (102, 154), whereas *B. cinerea* endopolygalacturonases and an unidentified protein from *Sclerotinia sclerotiorum* are recognized as MAMPs by *Arabidopsis* cell surface receptors (161, 162). Necrotrophs also produce DAMPs during host invasion; for example, oligogalacturonides (OGs) are released from plant cell wall pectin by pathogen polygalacturonases that are perceived by the RLK WAK1, which mediates resistance to *B. cinerea* (10, 19). Perception and immunity resulting from MAMPs during necrotrophic colonization are easily explained within the zigzag model, but the importance of DAMPs in the interaction is not reflected by the zigzag model, as DAMPs were omitted.

However, the application of the zigzag model to fully explain necrotrophic interactions is most problematic when considering their "pro-death" invasion strategy (46, 82, 144, 158). This conflict is illustrated by interactions between plant immune receptors and host-specific toxin effectors that many necrotrophs use to hijack the host defense machinery in an inverse gene-for-gene relationship (47, 88). Counter to the gene-for-gene and zigzag models, the interaction between an immune receptor and toxin effector leads to (dominant) susceptibility instead of immunity. One well-described example is provided by *Cochliobolus victoriae*, which produces a cyclic chlorinated pentapeptide, victorin, to cause Victoria blight on oat plants expressing the Vb immune receptor (159). The *Arabidopsis* NLR protein LOV1, which guards the defense-associated thioredoxin TRXh5, mediates *C. victoriae* susceptibility (88). Targeting of TRXh5 by victorin activates LOV1 and incites a cell death response that is exploited by *C. victoriae* (87, 137). Thus, victorin is speculated to have been, or to mimic, a conventional effector of a biotrophic pathogen that was defeated by LOV1 (87). Consistent with this, Victoria blight only affects oat plants carrying the *Pc2* immune receptor that provides resistance against the biotrophic crown rust fungus *Puccinia coronata* (86). Attempts to separate Victoria blight susceptibility from crown rust resistance have been unsuccessful,

suggesting that *Pc2* and *Vb* are the same immune receptor gene (95). Additional examples of necrotrophic effectors used to incite cell death and promote disease have been reported (39, 78).

The molecular components and pathways determining plant-necrotroph or plant-biotroph interactions are generally the same, but how the responses affect the outcomes of the interactions is in stark contrast. The exploitation of immune receptors to generate susceptibility highlights the fact that the plant immune system does not evolve in a vacuum, and immunity to one invader may be detrimental to immunity for another. Plant-necrotroph interactions or other virulence molecules that hijack the plant immune response can be integrated into the Invasion Model as effectors that utilize the IPTR to facilitate a continued symbiosis.

Additional Invaders: Viruses, Nematodes, and Insects

Viruses are one of the most ubiquitous and economically important pathogens of plants. Despite this fact, viral plant immunity is often omitted from the contemporary zigzag model of plant immunity, but attempts have been made to integrate it (106). It is clear, however, that plants have an effective antiviral immune system. Viral dsRNA can be bound and degraded by plant Dicer-like proteins (DCLs), solely through their structure, which activates RNA interference (RNAi) and can result in immunity (12). Viral dsRNA perfectly fits the description of a MAMP (65, 100), but this requires plant DCLs be categorized as PRRs and RNAi as MTI, which is clearly outside of general MTI-ETI usage. To counter RNAi, viruses evolved silencing suppressors to allow for continued disease (71, 72, 151), but plants can detect silencing suppressor activity, which can trigger plant immunity (37, 129). As such, plant immunity to viruses appears to largely correspond with that of other invaders, but the zigzag model's strict definitions are barriers to its inclusion. In the Invasion Model, dsRNA, viral silencing suppressors, and other recognized viral molecules are viewed as IPs. Our description of an IPR is with RLKs, RLPs, and NLRs in mind, but the example of DCLs recognizing dsRNA and activating RNAi fits the concepts of the Invasion Model and warrants inclusion.

In addition to viruses, the zigzag model does not accommodate other nonmicrobial invaders, including nematodes and insects. Yet, it is clear that they both have the capacity to activate and suppress plant immune responses (55, 66). Nematodes secrete effectors to suppress immune responses and increase virulence, and likely produce DAMPs. The same is true for insects that produce herbivore-derived physical and chemical cues that induce defense (34, 62) and utilize effectors to manipulate their hosts (61, 157, 165). For these reasons, we believe the more inclusive Invasion Model is more suitable to describe the plant immune system and more accommodating to future discovery within these systems.

Endophytes and Mutualists

Pathogenic symbioses are typically the only interactions addressed by the zigzag model, but endophytes and mutualists also establish important interactions with plants. The establishment of a mutualistic interaction is complex, but a key step is the signaling and activation of a symbiotic response in plants (113). Interestingly, derivatives of the fungal MAMP chitin are exploited as such a signaling molecule (128). These comprise lipochitooligosaccharide (LCO) nodulation (Nod) factors produced by nitrogen-fixing *Rhizobacteria* that are recognized by leguminous host plants, as well as sulfated and nonsulfated LCO Myc factors and other short nonimmunogenic chitin oligomers produced by arbuscular mychorriza (33, 93, 153). Chitin, Nod, and Myc factors are perceived by cell-surface receptors with extracellular LysM domains (85, 128). LCO perception in symbiosis intertwines with innate immune signaling as rice OsCERK1 was recently shown to

be essential not only for chitin-triggered immunity but also for arbuscular mycorrhizal symbiosis (103). The capacity of host plants to discriminate chitin derivatives from mutualists and pathogens is likely governed by differences in LysM ectodomains of receptors (17, 93, 155). Intriguingly, however, several studies suggest that LCO signaling alone is insufficient to account for a successful mutualistic interaction (85).

Conceivably, hosts perceive MAMPs during the initiation of interactions with endophytes and mutualists (57) that are, consequently, recipients of immune responses (64). Thus, endophytes and mutualists also employ effectors to suppress host immunity (127). The endophytic fungus *Piriformospora indica*, as well as the arbuscular mycorrhiza *Rhizophagus irregularis*, expresses many effector-like small secreted proteins upon interaction with host plants (141, 169). Furthermore, functional analyses show that such effectors play important roles in mutualistic interactions. For example, *R. irregularis* secretes the SP7 effector to attenuate ethylene-mediated immune responses (80), and the ectomycorrhizal fungus *Laccaria bicolor* secretes the MiSSP7 effector in planta to perturb jasmonic acid–mediated immune signaling (119). Such findings argue that successful mutualistic symbioses need to not only stimulate symbiotic signaling pathways in their host plants but also effectively subvert immunity with an adapted effector complement. As mutualists trigger host immune responses and employ effectors to subvert these, their inclusion in a more general model of plant immunity is warranted. The strategies and molecules that are involved in the establishment of mutualistic interactions comply with the Invasion Model, highlighting that it can encompass diverse interactions.

FROM THEORY TO PRACTICE

Irrespective of the model used to describe host-microbe interactions, a key goal is to apply our knowledge to help meet growing agricultural food demand. One application of the Invasion Model in this respect is to aid disease resistance breeding. Conventional breeding for disease resistance often incorporates host immune receptors (RLKs, RLPs, NLRs) (101, 118), but the relative inability to predict a priori whether an immune receptor will confer broad-spectrum durable resistance is a major limitation. If our knowledge of molecular plant-microbe interactions can aid in the identification or engineering of durable disease resistance, plant breeding will be facilitated. Understanding IPs and the biology of a pathogen can identify less variable IPs that, when detected by an IPR, may result in more durable immunity. We believe these principles can provide a rational framework to aid current efforts to utilize our knowledge of the plant immune system (30, 101). Importantly, along with asking how we are going to use the immune system, we need to be thinking about what we are going to detect with it. For this, we need to understand properties that influence IP variability, approaches to identify new IPs, and how IPs can be used to identify new receptors.

As argued throughout, there is no strict distinction between MTI and ETI. Whereas it is generally stated that MTI is more durable and ETI is ephemeral, clear exceptions in agricultural settings have been noted (15, 68, 99) and the idea that PRRs will generically result in durable resistance can be questioned (26, 148). This, coupled with the omission of DAMPs, results in the limited predictive framework of the zigzag model to address durable disease resistance. Additionally, nonhost resistance, originally defined as resistance of a complete plant species to all variants of a particular pathogen species (59), has been proposed as a valuable source for durable resistance (54, 108). There is, however, no single mechanism that underlies nonhost resistance in general because it comprises a multitude of phenomena, including general incompatibility of pathogen and host, lack of particular susceptibility factors, and recognition-based responses that similarly act in MTI and ETI responses (38, 84, 130, 132). Therefore, nonhost resistance should

not be regarded as a general mechanism to be employed or engineered (38) but rather represents a sweeping term comprising many, genetically distinct mechanisms.

It has been argued that the ecology and population dynamics of a pathogen influence resistance durability to a greater extent than the nature of the resistance genes (98). Additionally, a number of researchers from across disciplines have proposed that targeting pathogen virulence genes that contribute to pathogen fitness will increase the resulting durability of resistance (27, 74, 83, 146). As such, we view resistance durability as related to detection of critical IPs. We predict that durable resistance mediated by any type of receptor is related to the combined degree of (*a*) the molecular constraint of the IP and (*b*) the importance of the molecule or process that results in the IP. In this view, developing durable resistance involves identifying important molecularly constrained IPs and then using them to identify or design immune receptors (IPRs). This approach builds on current approaches but would expand the number and types of ligands and receptors currently being pursued.

To address these points, knowledge of how the IP originates and how it is detected by a corresponding IPR is needed. Specifically, does the invader encode the IP or does it originate from the process of invasion? Invader-encoded IPs may require fewer molecular alterations to avoid recognition, making them potentially more variable and immunity resulting from their perception less durable. However, if the invader-encoded IP overlaps with a functional domain of the molecule from which it originates, the IP will be more constrained and IPR-mediated immunity more durable. For example, many directly bound effectors have evolved to avoid detection by mutating key amino acids. The immunogenic epitopes, flg22 and flgII-28 of flagellin, however, are both located on separate loop regions between alpha helices, which may impact the structure and flexibility of flagella, explaining the relative conservation of these epitopes (26). Additionally, an IP that overlaps with an enzymatic domain necessary for the molecule's function will be under purifying selection to maintain enzymatic function and may result in a less variable IP. However, IPs that are molecularly constrained may still be variable if the function of the deriving enzyme is only marginally important for symbiosis. In this example, IP-mediated selection pressure from the host may result in the invader losing the enzyme. Thus, the balance between the molecular constraint of an IP and the importance of the deriving molecule for establishing symbiosis will govern IP variability. Another consideration is for IPs that are not encoded by the invader, but originate from the process of invasion, such as DAMPs or altered guarded targets, which may be evolutionarily more difficult to avoid. These IPs are inherent to the infection process itself and thus evolutionarily less likely to be altered or discarded. For example, any invader that requires an intracellular interaction for successful symbiosis will produce cellular damage (i.e., an IP) as part of its process of invasion. An IPR or an array of IPRs to detect the patterns resulting from this cellular damage could be both broad spectrum and, conceivably, durable. In summary, this basic framework describes how the Invasion Model could be applied to explain the variability and importance of different IPs that are generated during attempted symbiosis.

The life style and biology of a pathogen additionally influence the pathogen's evolutionary potential and thus the variability of an IP (98). That is, the higher the evolutionary potential of an invader, the more probable that an IP-IPR interaction will be overcome through diversification or loss of the IP, or through development of an effector to manipulate the host response to facilitate continued symbiosis. The variability of IPs resulting from invader-expressed molecules is also influenced by their genomic context. IPs that result from molecules in highly variable genomic regions (29, 32, 104, 122, 126) or those that reside on transferable genetic material (48, 90, 112) may result in more variable IPs. This must be balanced, however, by the observation that molecules in these regions typically contribute to invader virulence. For example, it appears that core effectors of *Verticillium dahliae* show limited contribution to virulence, whereas lineage-specific (LS) effectors

show more significant contributions to disease (32). In this instance, the potential durability of resistance mediated by an IPR detecting a *V. dahliae* LS effector-produced IP is mediated by the opposing variability of the region and the importance of the molecule as a virulence factor. These examples argue that one must understand the pathogen being targeted for durable disease resistance.

The number and diversity of IPs generated and perceived during any given invasion are relatively unknown. A number of microbe-produced structural immunogenic epitopes were identified from culture-grown microbial fractionations (7, 31, 41, 42, 51, 67). This process has been key to identifying many immunogenic molecules, but it requires significant investment and potentially results in immunogenic epitopes from a single organism. Additional approaches to more quickly identify robust IPs are needed, such as in silico approaches to identify immunogenic epitopes from bacterial plant pathogens (96). Additional approaches to identify IPs resulting from the process of invasion are needed. The identification of commonly targeted effector hubs (105, 156) could be particularly promising. As such, additional studies are needed to identify how the effector-targeted hub proteins are modified in order to identify the molecular nature of potential IPs. The use of susceptibility factors to facilitate disease (145) may also produce IPs to appropriately signify invasion that could, in turn, be monitored. Additional biochemical approaches could be used to build a catalog of potential IPs resulting from the process of invasion. Taken together, these potential IPs represent an unexplored source of immunogenic ligands.

The IPs that show molecular constraint and originate from important molecules or processes of invasion can be used to identify or engineer an appropriate IPR. Effector-guided breeding (8, 150) can be used to screen plant germplasm against an IP to identify an IPR mediating a desired response. Another option could be to engineer IPRs to detect specific IPs. This could be pursued through a variety of techniques including in vitro evolution of current IPRs for new specificities (40, 58), or orthogonal design (36) of current receptors for related IPs. In this way, IPR-mediated immunity targeting the least variable, most important IPs is likely to result in durable disease resistance.

It is obvious that no single approach will result in durable disease resistance and a number of agronomic practices must be employed (97, 120, 166). Likewise, no single receptor will indefinitely provide durable resistance as innate immune receptors recognize ligands (IPs) for which they activate responses to remove (100). Numerous researchers have suggested that stacking multiple immune receptors will result in more durable immunity, as it is evolutionarily more difficult to overcome multiple recognition events (77, 116). Receptor-mediated resistance can also be combined in a genetic background with other types of quantitative resistance (i.e., 28), which can limit the emergence of receptor-breaking strains (18). This approach also has limitations, however, as combinations of some plant immune receptors are lethal (1, 21) or cause dominant negative suppression of resistance (134).

There are a number of approaches for developing plant receptor-mediated disease resistance. By switching our focus to the type and variability of the ligands that plants perceive to signify invasion, we may expand our approaches to disease control. Using the relationship between the molecular constraint of an IP and the importance of the molecule or process that produces the IP, we can approach durable disease resistance with a focus on what to detect.

SUMMARY POINTS

1. All models represent a snapshot of current ideas based on the available data and require flexibility to be updated and refined.

2. The commonly used MTI-ETI dichotomy to describe the plant immune system is based on observations from a limited number of model plant-microbe interactions but too narrowly defines the plant immune system and the variety of organisms that plants interact with.
3. Plants detect invasion patterns (IPs), which are immunogenic ligands that signify invasion and are produced by the invader or through the process of invasion.
4. The Invasion Model provides a general framework to discuss diverse plant-invader interactions and covers the range of interactions that involve the plant immune system.
5. The relationship between an IP and the molecule or process that produces the IP can be used to predict its variability and decide which IPs to target for durable disease resistance.

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