

CURRENT REVIEW

Emerging Concepts in Effector Biology of Plant-Associated Organisms

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Plant-associated organisms secrete proteins and other molecules to modulate plant defense circuitry and enable colonization of plant tissue. Understanding the molecular function of these secreted molecules, collectively known as effectors, became widely accepted as essential for a mechanistic understanding of the processes underlying plant colonization. This review summarizes recent findings in the field of effector biology and highlights the common concepts that have emerged from the study of cellular plant pathogen effectors.

A diversity of plant pathogens, including bacteria, fungi, oomycetes, and nematodes, secrete proteins and other molecules to different cellular compartments of their hosts to modulate plant defense circuitry and enable parasitic colonization (Abramovitch et al. 2006; Birch et al. 2006; Block et al. 2008; Chisholm et al. 2006; Davis et al. 2008; Kamoun 2006, 2007; Misas-Villamil and van der Hoorn 2008). Understanding the molecular function of these secreted molecules, collectively known as effectors, is widely accepted as critical for a mechanistic understanding of the processes underlying host colonization and pathogenicity.

Major progress in our understanding of effectors has occurred recently. First, the precise biochemical activities of a number of bacterial effectors have been unraveled. Second, the concept of effectors has extended beyond bacterial plant pathogens with the discovery of effectors in fungi, oomycetes, and nematodes. Finally, robust computational methods applied to genome sequence data of plant pathogenic microbes has resulted in genome-wide catalogs of putative effector genes. All these activities significantly increased our knowledge of effectors from a diversity of plant pathogens, their host targets, and how and where these molecules interact and affect the outcome of the plant-pathogen interaction. Remarkably, many commonalities can be noted among the different pathosystems under study. The objective of this review is to summarize and discuss the common threads that have emerged from the study of cellular plant pathogen effectors.

Effectors: Usage and definition.

The usage of the term “effector” became popular in the field of plant-microbe interactions with the discovery that plant

pathogenic gram-negative bacteria utilize a specialized machinery, the type III secretion system (T3SS), to deliver proteins inside host cells (Abramovitch et al. 2006; Block et al. 2008; McCann and Guttman 2008; Zhou and Chai 2008). These proteins, first discovered because of their ability to trigger the hypersensitive response in resistant plants (“avirulence” activity), were later found to contribute to virulence in susceptible plants (typically host plants that lack effective resistance [*R*] genes). Hence, the term avirulence became conceptually restrictive, since the same protein with an avirulence activity in incompatible interactions may display a positive virulence activity in compatible interactions. The term effector addresses this conceptual limitation of the term avirulence. The increase in the use of effector relative to avirulence in the journal *Molecular Plant-Microbe Interactions* is striking and reflects a major paradigm shift in the field (Fig. 1).

More recently, a broader range of plant microbiologists have adopted the term effector and its associated concepts. Indeed, this term is now also routinely used in the fungal and oomycete literature and is becoming increasingly popular in nematology to describe secreted proteins that exert some effect on plant cells. However, the various scientific communities define effectors differently. We favor a broader inclusive definition of the term effector. We define effectors as all pathogen proteins and small molecules that alter host-cell structure and function. These alterations either facilitate infection (virulence factors and toxins) or trigger defense responses (avirulence factors and elicitors) or both (Huitema et al. 2004; Kamoun 2006, 2007). The concept of “extended phenotype” (i.e., “genes whose effects reach beyond the cells in which they reside”) put forward by Richard Dawkins in a classic book (Dawkins 1999) sums up perfectly this view of effectors. Effectors can be viewed as “parasite genes having phenotypic expression in host bodies and behavior” (Dawkins 1999). Indeed, effectors are the products of genes that reside in pathogen genomes but that actually function at the interface with the host plant or even inside plant cells, providing a vivid example of Dawkins’ extended phenotype (Kamoun 2006, 2007).

This broader definition of effectors includes many molecules, such as pathogen-associated molecular patterns (PAMPs), toxins, and degradative enzymes. In the absence of more information, it would be suitable to call these molecules effectors until the exact activities of a pathogen molecule are revealed, after which they may be renamed to reflect their specific activities. For lists of specific definitions, we invite readers to consult earlier publications (Kamoun 2006; van der Hoorn and Kamoun 2008).

Emerging concepts in effector biology.

Many effectors are delivered into host cells. Plant pathogenic bacteria, fungi, oomycetes, and nematodes have evolved the capacity to deliver effector proteins inside host cells through a diversity of mechanisms. Gram-negative bacteria use specialized secretion systems, such as T3SS, to deliver proteins inside host cells (Abramovitch et al. 2006; Block et al. 2008; Galan and Wolf-Watz 2006; McCann and Guttman 2008; Zhou and Chai 2008). Biotrophic fungi and oomycetes have evolved haustoria for this purpose. Haustoria are specialized structures that form within plant cells but remain encased in a modified plant cell membrane, known as the extrahaustorial membrane (Hahn and Mendgen 2001; Panstruga 2003). Haustoria were initially thought to primarily function in nutrient uptake, but more recently, evidence emerged that haustoria take part in the secretion of particular classes of host-translocated fungal and oomycete effectors (Catanzariti et al. 2006; Dodds et al. 2004; Kemen et al. 2005; Whisson et al. 2007). Some fungal proteins, notably the *Pyrenophora tritici-repentis* host-selective toxin ToxA, do not require the pathogen for translocating inside plant cells (Manning and Ciuffetti 2005; Sarma et al. 2005). ToxA travels inside host cells presumably by coopting a plant surface receptor that binds to an Arg-Gly-Asp (RGD) motif (Manning et al. 2008). Plant parasitic nematodes utilize a specialized feeding organ known as the stylet, to inject their effector proteins inside a parasitized plant vascular cell (Davis et al. 2008).

Other effectors act in the apoplast. Some effectors act in the extracellular space at the plant-microbe interface, where they interfere with apoplastic plant defenses (Kamoun 2006; Misas-Villamil and van der Hoorn 2008). Examples include the secreted protein effectors of the tomato fungal pathogen *Cladosporium fulvum*. This fungus is an extracellular parasite of tomato that grows exclusively in the apoplast and does not form haustoria or haustoria-like structures (Rivas and Thomas 2005; Thomma et al. 2005). All known *C. fulvum* effectors, such as Avr2, Avr9, Avr4, and ECP2, are small cysteine-rich proteins that are thought to function exclusively in the apoplast (Thomma et al. 2005). Oomycetes, such as *Phytophthora infestans*, are also known to secrete apoplastic effectors in addition to host translocated (cytoplasmic) effectors (Birch et al. 2006; Damasceno et al. 2008; Kamoun 2006; Rose et al. 2002; Tian et al. 2004, 2005, 2007).

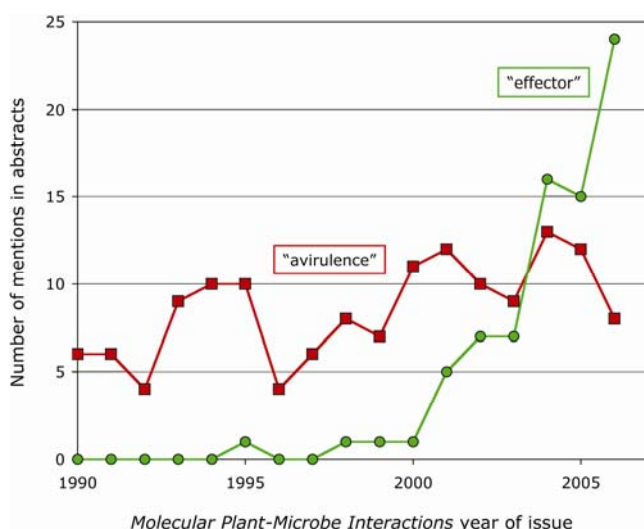


Fig. 1. Effectors: The rise of a concept. The graph illustrates the decline in the use of the term avirulence compared with the term effector in the journal *Molecular Plant-Microbe Interactions*. The numbers were obtained by keyword searches in the journal website for articles published from 1990 to 2006.

One common activity ascribed to many apoplastic effectors of *C. fulvum* and other fungal and oomycete pathogens is their ability to inhibit and protect against plant hydrolytic enzymes, such as proteases, glucanases, and chitinases (reviewed by (Misas-Villamil and van der Hoorn 2008). *C. fulvum* Avr2 is a cysteine protease inhibitor targeting the apoplastic cysteine proteases Rcr3 and PIP1 of tomato (Rooney et al. 2005; Shabab et al. 2008; van Esse et al. 2008). *P. infestans* also secretes cysteine protease inhibitors, such as EPIC2B, which inhibits PIP1 as well as other apoplastic cysteine proteases of tomato (Tian et al. 2007), and EPI1 and EPI10, which are multidomain-secreted serine protease inhibitors of the Kazal family that bind and inhibit the pathogenesis-related (PR) protein P69B, a subtilisin-like serine protease of tomato that is thought to function in defense (Tian et al. 2004, 2005). *Phytophthora* spp. are also known to secrete glucanase inhibitors that inhibit the host apoplastic enzyme endo- β -1,3 glucanase (Damasceno et al. 2008; Rose et al. 2002). It seems likely that many other apoplastic effectors act as host enzyme inhibitors. For example, the secreted AvrP123 from the flax rust fungus *Melampsora lini* shows sequence similarity to Kazal serine protease inhibitors (Catanzariti et al. 2006).

One effector—many host targets. Plant pathogen effectors frequently have more than one host target (Fig. 2). *Pseudomonas syringae* AvrRpt2 is a T3SS effector with proteolytic activ-

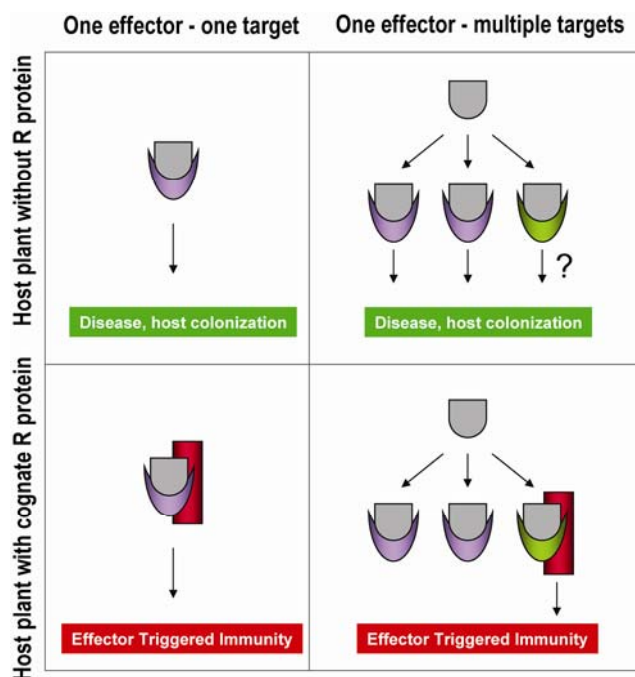


Fig. 2. One effector-many effector targets. The cartoons compare the traditional one pathogen effector-one host effector target model (left panels) to the emerging view that effectors frequently have more than one host target (right panels). These effector targets can be components of the plant defense response that are being inactivated by pathogen effectors, and in such cases have been termed operative effector targets (OT) by Van der Hoorn and Kamoun (2008). In susceptible plants, the interaction between effectors and effector targets results in molecular events that facilitate colonization, such as suppression of defense responses, enhanced disease susceptibility, and elicitation of disease symptoms. In resistant plants, plant resistance (R) proteins recognize the effector-virulence target complex, resulting in the activation of the hypersensitive response. Recognition of effectors by R proteins is often indirect, via perception of a manipulated effector target. These recognized effector targets may contribute to host defense or susceptibility (guarded effector targets) or may not function in defense or susceptibility, thus acting as decoys that trap the effector (Van der Hoorn and Kamoun 2008). Effectors are depicted by gray half circles, OT by purple crescents, guarded effector targets or decoys by green crescents, and R proteins by red squares.

ity against at least five *Arabidopsis* proteins, including the negative defense regulator RIN4 (Chisholm et al. 2005; Takemoto and Jones 2005). AvrPto, another *Pseudomonas syringae* T3SS effector, is a kinase inhibitor that binds and inhibits the tomato kinase Pto (Xing et al. 2007). In addition, AvrPto inhibits the kinase domains of FLS2 and EFR, which are two pathogen recognition receptors, as well as the kinase domain of their signaling partner BAK1 (Shan et al. 2008; Xiang et al. 2008). These transmembrane receptor-like kinase proteins participate in the recognition of conserved pathogen molecules, and their inhibition by AvrPto presumably acts to suppress the innate immune response mediated by these receptors. Other examples of multiple targets include the protease inhibitors Avr2 and EPIC2B, which, as discussed above, inhibit several tomato apoplastic proteases (Shabab et al. 2008; Tian et al. 2007; van Esse et al. 2008).

Each interaction of an effector and a host protein can be either beneficial for the pathogen, have negative consequences, or have neutral effects on the interaction between the pathogen and plant. In light of these ideas, Van der Hoorn and Kamoun (2008) defined operative targets as those host targets that, when manipulated by effectors, result in an altered state of defense or susceptibility. It therefore becomes important to distinguish operative targets from other types of host targets. These thoughts led to the concept that some host targets are decoys, proteins that are not operative targets but that, when perturbed by effectors, trigger host recognition by cognate R proteins (van der Hoorn and Kamoun 2008).

Many effectors suppress plant immunity. Suppression of plant innate immunity has emerged as the primary function of effectors, particularly of T3SS effectors of plant pathogenic bacteria (Abramovitch et al. 2006; Block et al. 2008; Chisholm et al. 2006; Jones and Dangl 2006; Zhou and Chai 2008). Several T3SS effectors contribute to virulence by suppressing basal defenses induced by conserved pathogen epitopes named PAMPs (Hauck et al. 2003; M. G. Kim et al. 2005). Other T3SS effectors suppress hypersensitive cell death elicited by various Avr proteins, explaining, in some cases, earlier observations of epistatic interactions among Avr genes (Abramovitch et al. 2003; Jamir et al. 2004; H. S. Kim et al. 2005; Tsiamis et al. 2000). T3SS effectors probably interfere with host immunity via a diversity of mechanisms, but the effectors studied so far are known to target three plant processes that are key to innate immunity, namely protein turnover, RNA homeostasis, and phosphorylation pathways (Block et al. 2008).

The occurrence of effectors that suppress host cell death has been long hypothesized for biotrophic fungal and oomycete pathogens (Panstruga 2003), based on cytological observations of susceptible interactions and the prevalence of cell death suppressors among bacterial T3SS effectors (Jamir et al. 2004; Janjusevic et al. 2006). Emerging findings indicate that several oomycete RXLR effectors suppress host immunity. *P. infestans* Avr3a suppresses the hypersensitive cell death induced by another *P. infestans* protein, INF1 elicitor, pointing to a possible virulence function (Bos et al. 2006). Another RXLR effector, *P. sojae* Avr1b, also suppresses programmed cell death induced by the mouse protein BAX in yeast and plants (Dou et al. 2008). Sohn and associates (2007) showed that delivery of *Hyaloperonospora parasitica* ATR1 and ATR13 enhances *Pseudomonas syringae* virulence. ATR13 also suppresses callose deposition triggered by *Pseudomonas syringae*, suggesting that it targets basic basal defenses against pathogens (Sohn et al. 2007). These findings indicate that, similar to bacterial T3SS effectors, oomycete RXLR effectors often function in suppression of plant immunity. However, the mechanisms through which RXLR effectors interfere with plant immunity remain to be elucidated.

A recent study illustrates the concept that plant pathogenic fungi can evade host immunity by evolving effectors that suppress R gene-mediated resistance. Houterman and associates (2008) showed that the effector Avr1 of *Fusarium oxysporum* f. sp. *lycopersici* suppresses the resistance response conferred by the R genes *I-2* and *I-3*. No apparent virulence function has been detected for Avr1 on plants that do not carry these *I* genes, suggesting that this effector may solely

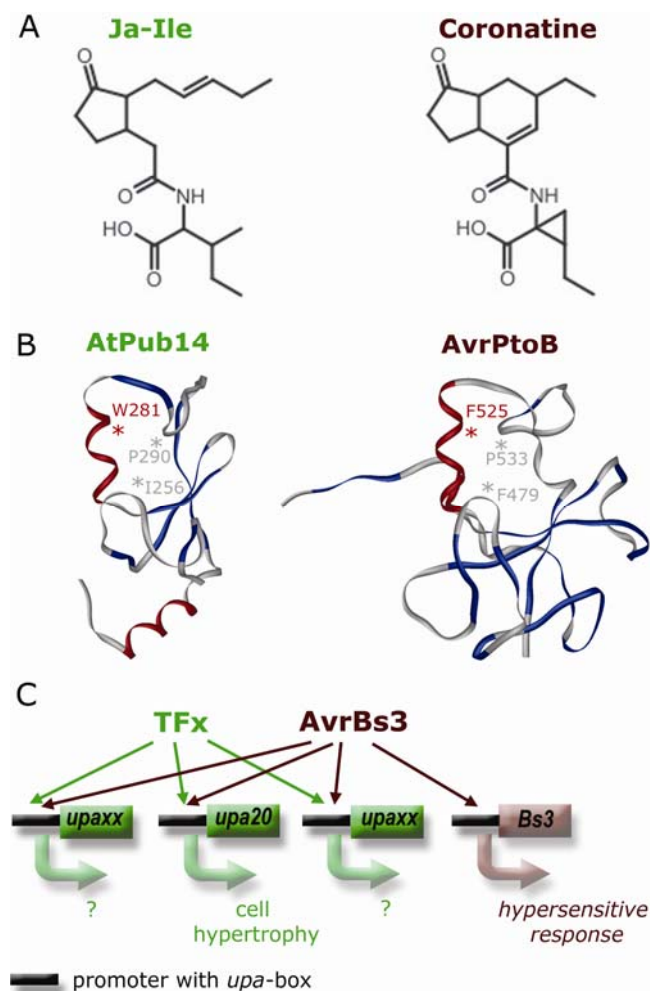


Fig. 3. Effectors mimic plant molecules. In each panel, plant molecules are indicated in green at left and the corresponding mimicking plant pathogen effectors in red at right. **A**, The *Pseudomonas syringae* phytotoxin coronatine mimics jasmonoyl-isoleucine (JA-Ile), which is a crucial plant signaling molecule for regulating plant defense responses (Weiler et al. 1994; Bender et al. 1999). **B**, The *P. syringae* AvrPtoB effector has anti-programmed cell death activity and mimics E3 ubiquitin ligases (Janjusevic et al. 2006), such as *Arabidopsis thaliana* Pub14 (AtPub14), that regulate protein degradation in plants (Andersen et al. 2004). Structures were derived from Protein Data Bank identities 1T1H (AtPub14) and 2FD4 (AvrPtoB) and were visualized in iMol v. 0.4. The three residues shown by asterisks bind the E2 ubiquitin-conjugating enzyme and locate in the conserved α -helix (red ribbon) and two-loop structures (gray ribbon) that form the E2-binding groove (Janjusevic et al. 2006). The locations of the β -sheets (blue ribbon) flanking the lower part of the groove are also conserved. **C**, The *Xanthomonas campestris* pv. *vesicatoria* effector AvrBs3 binds a conserved element (*upa*-box) of promoter regions. In compatible interactions, AvrBs3 induces hypertrophy through induction of the expression of *upa20* and other *upa* genes (*upaxx*) with unknown functions (Kay et al. 2007). In incompatible interactions, AvrBs3 also binds the promoter of the resistance gene *Bs3*, resulting in a hypersensitive response (Romer et al. 2007). AvrBs3 is thought to mimic an unknown plant transcription factor (TFx) that also presumably binds the *upa*-box, and induce *Bs3* transcription only in specific plant developmental stages when specific localized cell death is required.

function in interfering with perception of the pathogen by these R proteins.

Some effectors alter plant behavior and development. As the previous section illustrates, it is now well established that many effectors interfere with host innate immunity. Nonethe-

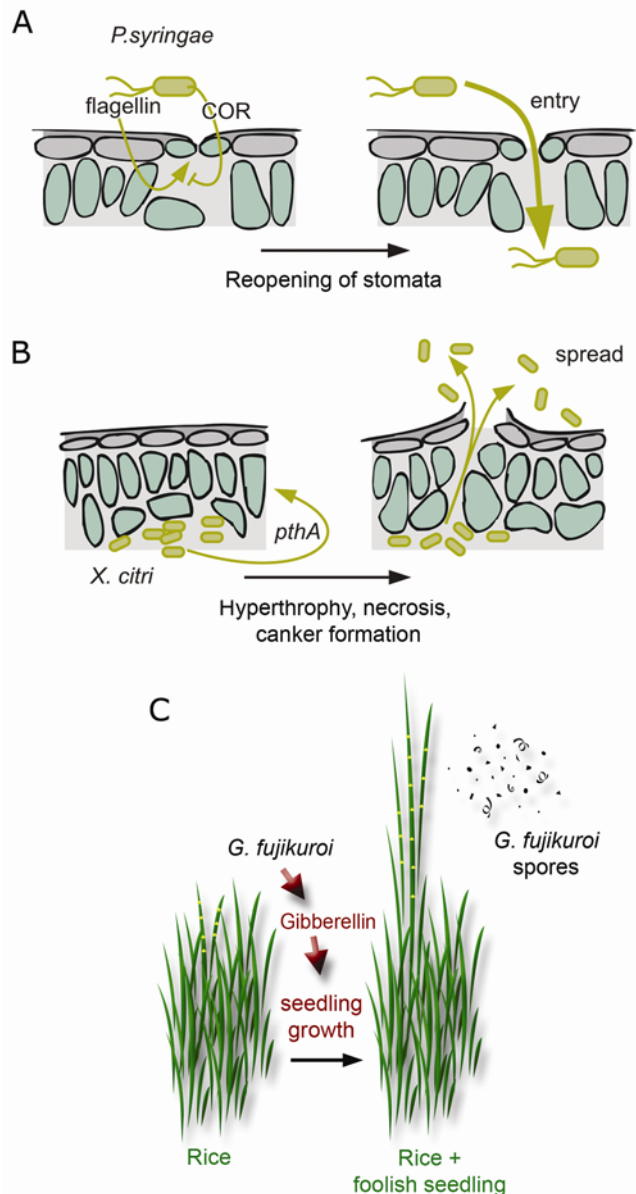


Fig. 4. Effectors can alter plant behavior and development. Each panel illustrates an example of an effector function with the unaffected plant on the left and the outcome of the effector activity on the right. **A**, Plant stomata close upon detection of pathogen-associated molecular patterns from the bacterium *Pseudomonas syringae* (left panel) (Melotto et al. 2006). However, the phytotoxin coronatine (COR) inhibits stomatal closure, resulting in bacterial entry into plant leaves through the open stomata (right panel) (Melotto et al. 2006). **B**, During plant infection, *Xanthomonas citri* grows in the intracellular spaces of the leaf spongy mesophyll (left). The effector PthA induces hyperthrophy, hyperplasia, and necrosis, which result in the formation of cankers on the leaf surface (right) (Duan et al. 1999). *Xanthomonas citri* bacteria ooze from the canker-ruptured epidermis and then spread to other plants by rain splash (Duan et al. 1999). **C**, The fungus *Gibberella fujikuroi* (also known as *Fusarium moniliforme*) (yellow spots) infects a single rice seedling (left). The fungus produces the growth hormone gibberellin, which induces plant elongation, resulting in an elongated (foolish) seedling several inches taller than noninfected seedlings (right). The height of the plant facilitates the spread of airborne fungus spores by the wind.

less, there are instances of effectors that have activities other than suppression of innate immunity. Some effectors alter host plant behavior and morphology. One elegant example is coronatine, which was shown by Melotto and coauthors (2006) to trigger stomatal reopening in *Arabidopsis* and thereby facilitate bacterial entry inside the plant apoplast. *Xanthomonas* effectors of the AvrBs3 family of transcriptional activators are known to induce cellular division and enlargement in susceptible host plants (Duan et al. 1999; Kay et al. 2007) (Fig. 3C). Expression of *Xanthomonas citri* *pthA* in citrus cells is sufficient to cause macroscopic hyperplastic lesions analogous to the canker symptoms caused by the pathogen (Duan et al. 1999) (Fig. 3B). These canker lesions are thought to facilitate bacterial release from infected tissue and to enhance bacterial dissemination. *X. vesicatoria* AvrBs3 is also known to cause cell hypertrophy, although the impact of such a symptom on bacterial fitness is less clear (Kay et al. 2007).

Many other plant-associated organisms are known to alter the morphology of their host plant, resulting in malformations that either create a protective niche or enhance dispersal. Classic examples include rhizobial nodules (Oldroyd and Downie 2008), galls induced by *Agrobacterium* spp. and other bacteria (Chalupowicz et al. 2006), and Witches' broom and other developmental alterations caused by several pathogens such as phytoplasmas (Hogenhout et al. 2008).

In summary, some phytopathogen effectors appear to have activities other than suppression of immunity. It is reasonable to expect that natural selection would favor effectors with any type of phenotypic expression that improves pathogen fitness, and researchers in the field should keep an open mind to effector activities that do not involve the host immune response.

Molecular mimicry by effectors. Although effectors are encoded by pathogen genes, they function in a plant cellular environment and, therefore, could have been selected to mimic plant molecules. Strikingly, many effectors produce analogs and mimics of plant hormones. One example is coronatine, a toxin secreted by several pathovars of *Pseudomonas syringae* that is a structural and functional mimic of the plant hormone jasmonoyl-isoleucine (Fig. 4A) (Bender et al. 1999; Weiler et al. 1994). Coronatine has many effects that enhance bacterial colonization of plants. These include impacting phytohormone pathways, such as jamming the induction of the salicylic acid-mediated resistance response and increasing the opening of plant stomates (Fig. 3A). Other classic examples of phytohormone mimicry in plant pathogens include auxins and cytokinins produced by various bacteria, including *agrobacterium* (Costacurta and Vanderleyden 1995), modified cytokinins produced by the *fas* operons of *Rhodococcus fascians* and *Streptomyces turgidiscabies* (Hogenhout and Loria 2008), and gibberellins produced by several fungi (Kawaide 2006) such as *Gibberella fujikuroi*, which causes the foolish seedling disease of rice (Tudzynski 1999) (Fig. 3C).

Besides hormone mimicry, protein effectors represent several additional striking examples of molecular mimicry as well. The C-terminal region of the *Pseudomonas syringae* type-III effector AvrPtoB, for example, was found to be a structural and functional mimic of eukaryotic E3 ubiquitin ligases (Fig. 4B) (Janjusevic et al. 2006). AvrPtoB-mediated degradation of the target host kinase Fen is dependent on the E3 ubiquitin ligase activity of AvrPto (Rosebrock et al. 2007). Another example of molecular mimicry is the *Xanthomonas vesicatoria* type-III effector AvrBs3, which travels to the host nucleus, where it acts as a transcriptional activator by binding to a conserved promoter sequence called the *upa* box (Kay et al. 2007; Romer et al. 2007) (Fig. 4C). Because the *upa* box is conserved in several pepper genes, AvrBs3 is thought to mimic a yet-to-

be-discovered host transcription factor that also targets the *upa* box. Emerging work by several groups revealed that plant parasitic nematodes secrete a battery of proteins that mimic plant molecules (Davis et al. 2008). Fascinating examples of plant mimics include secreted nematode proteins with similarity to expansins, components of the plant proteasome, and CLAVATA3 signaling peptides. Remarkably, the CLAVATA3-like 4G12 gene of the soybean cyst nematode *Heterodera glycines* complements the *Arabidopsis clv3-1* mutant and, similarly to CLAVATA3, negatively regulates the expression of the *Arabidopsis WUSCHEL* gene (Wang et al. 2005). How these CLAVATA3-mimicking peptides contribute to parasitism is unknown but could involve interfering with plant-cell growth and development (Mitchum et al. 2008).

Effector genes evolve at highly accelerated rates relative to the core genome. Genes that encode effector proteins are expected to be direct targets of the evolutionary forces that drive coevolution between host and pathogen (Ma and Guttman 2008; McCann and Guttman 2008). Effector alleles that increase the reproductive success of the pathogen will be immediately favored by natural selection and positively selected. Indeed, many effector genes have evolved at accelerated rates compared with the pathogen core genome and often display extreme levels of positive selection with significantly higher rates of nonsynonymous to synonymous nucleotide substitutions (K_a/K_s or d_n/d_s ratios greater than 1) (Allen et al. 2004; Dodds et al. 2006; Liu et al. 2005; Ma et al. 2006; Win et al. 2007). In modular effector proteins, such as bacterial T3SS effectors and oomycete RXLR effectors, the different domains are under different selective pressures, depending on whether they function in secretion or carry the effector activity per se. Thus, N-terminal domains, such as the signal peptide, RXLR domain, and T3SS targeting sequence, typically exhibit reduced levels of polymorphisms compared with the C-terminal effector region (Stavrinides et al. 2006; Ma and Guttman 2008; Win et al. 2007).

Besides acting on nucleotide polymorphisms, natural selection is known to act on copy number polymorphisms of effector genes (presence or absence polymorphisms and variation in gene copy number). Effector genes of filamentous pathogens often localize in loci with high genome plasticity including transposon-rich and telomeric regions (Gout et al. 2006; Orbach et al. 2000). K. Yoshida and R. Terauchi (*unpublished data*) recently showed that two effector loci of *Magnaporthe oryzae* display low nucleotide diversity but a high degree of presence or absence polymorphisms. The *P. infestans Avr3b-Avr10-Avr11* locus exhibits remarkable copy number variation resulting in amplification of up to 25 truncated copies of the candidate *Avr* gene *pi3.4* (Jiang et al. 2006). The association of effector genes with plastic genomic loci could confer a mechanism of adaptation to host resistance, perhaps by increasing genetic and epigenetic variation and enabling accelerated evolution.

Some effector targets evolved to evade manipulation by effectors. Since it is becoming evident that effectors enhance disease susceptibility, it can be expected that host target alleles would evolve to elude those effectors. The recessive rice mutations in *xa13* render the promoter of this gene insensitive to transcription-activating effectors of *Xanthomonas oryzae* pv. *oryzae*, thus resulting in resistance to bacterial blight disease (Iyer-Pascuzzi and McCouch 2007; Sugio et al. 2007; Yang et al. 2006) (Fig. 5B). Another recessive rice blast resistance gene, *xa5*, is caused by mutations in transcription factor IIA, which presumably prevents actions by the cognate effector (Iyer-Pascuzzi and McCouch 2007). Furthermore, mutations in elongation factor eIF4E are known to evade interactions with potyvirus effector VPg (Charron et al. 2008). More recently, an

allele of the tomato cysteine protease Rcr3 was identified to carry a mutation that renders the protein insensitive to inhibition by *C. fulvum* Avr2 (Shabab et al. 2008) (Fig. 5A). We expect many additional examples to emerge in the future as researchers exploit next-generation sequencing technologies to systematically probe variation in effector target sequences for evidence of selection. One fascinating question is to fully understand how the three-party interplay between effectors, effector targets, and R proteins evolve, given the conflicting selective forces that are likely to occur in natural populations of plants and pathogens (van der Hoorn and Kamoun 2008).

Identification of effector target alleles that are insensitive to effector manipulation but yet retain their intrinsic function provides an alternative strategy to the usage of classic *R* genes for engineering disease-resistant plants. Mechanistic understanding of the mode of action of effectors is powerful information that can guide the release and deployment of disease resistance in agriculture and is an improvement compared with the hit or miss approach that has been characteristic of plant-resistance breeding so far. One impressive example is the effective management of bacterial blight of rice through the release of resistant cultivars that combine complementary types of resistance, i.e., loss of susceptibility and classic resistance genes (Leung 2008). Resistance encoded by these cultivars proved to be par-

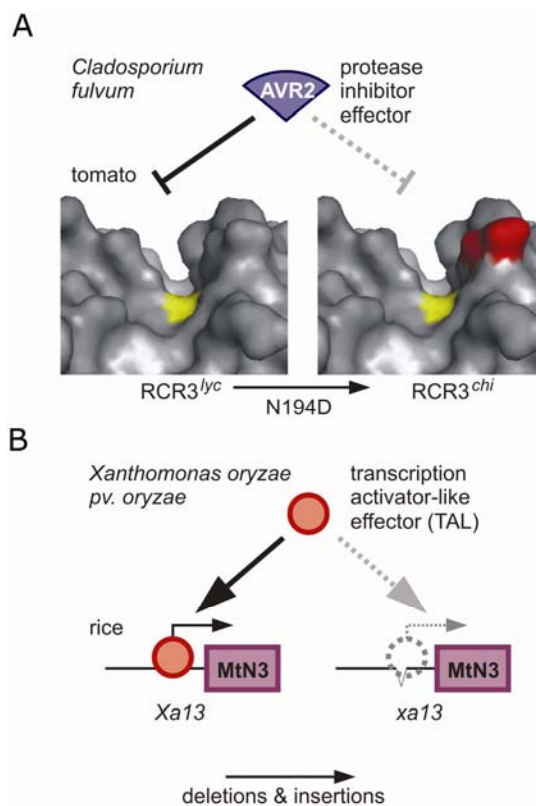


Fig. 5. Effector targets can evolve to evade manipulation by effectors. **A,** The N194D mutation in tomato cysteine protease RCR3 prevents inhibition by the AVR2 effector. In the model of RCR3, the substrate-binding groove with the catalytic cysteine residue (yellow) is flanked by Asn194 in RCR3 of *Solanum lycopersicum* (*lyc*) but is replaced by Asp in RCR3 of *Solanum chilense* (*chi*). This variance reduces the interaction with protease inhibitor AVR2 from the tomato pathogen *Cladosporium fulvum* (Shabab et al. 2008). **B,** Mutations in the promoter of the *Xa13* gene prevents induction by a *Xanthomonas* transcription activator-like (TAL) effector. *Xa13* is a pollen-expressed gene that is induced in leaves during infection by various *Xanthomonas oryzae* pv. *oryzae* strains, presumably mediated by a type III-secreted TAL effector similar to AvrBs3. Mutations in the promoter of *Xa13* prevent induction during infection and cause resistance that is inherited as a recessive trait (Chu et al. 2006).

ticularly durable, even in regions with severe bacterial blight epidemics, and fully justified the investments in effector and resistance research of the prior decade (Leung 2008).

Future issues to be investigated.

In addition to the topics described above, we list some additional questions that we predict will drive research on phytopathogenic effectors in the coming years.

What is the temporal and spatial dimension of effector activity? Are there waves of effector secretion? Are effectors secreted at particular sites at the interface between microbe and plant? Do effectors have distinct functions depending on the stage of the infection process?

Do effectors cooperate? Are there effectors that cannot act in the absence of other effectors? Are there effector protein complexes inside host cells?

Are effectors capable of intercellular trafficking following host delivery? Can host-translocated effectors act beyond the cells in which they are delivered?

How often do distinct pathogens act on common effector targets? Which host proteins are targeted by effectors produced by phylogenetically unrelated pathogens?

Conclusions.

The study of plant pathogen effectors has moved to center stage in the field of plant-microbe interactions. As illustrated in this review, work on effectors has already altered our view of pathogenicity and resulted in the emergence of several new concepts that cut across a range of pathosystems. Undoubtedly, these and other guiding principles will continue to emerge, drive the field, and unite researchers studying unrelated plant pathogens.

The impact of genomics on effector research cannot be underestimated. A recent study illustrates how effector genes mined from the genome sequence of *P. infestans* can be employed in high-throughput screens to discover effectors with avirulence activities and accelerate the cloning of cognate *R* genes (Vleeshouwers et al. 2008). Also, genomics will continue to drive the field by enabling significant discoveries in pathosystems that are traditionally difficult to study and narrowing the gap between traditional model species and other organisms. With the emergence of novel and cheaper DNA sequencing technologies (so called next generation sequencing), the flow of cDNA and genome sequences has reached unprecedented levels. Genome sequences are becoming available for plant-associated microbes and animals that represent an even wider range of lifestyles and phylogenetic groupings. These data are reinforcing the importance of secreted proteins in the associations between microbes and their host plants. For instance, the genome sequence of the mycorrhizal fungus *Laccaria bicolor* revealed an unexpectedly diverse and complex secretome that may significantly alter plant physiology during symbiosis (Martin et al. 2008). Other remarkable examples involve work emerging on phloem-feeding insects such as aphids. Will and associates (2007) recently demonstrated that aphid saliva prevents phloem sieve tube plugging to enable access to phloem sap, probably through the action of saliva proteins. Furthermore, the C002 protein produced in the salivary glands of the pea aphid *Acyrtosiphon pisum* is crucial for successful feeding of this aphid on host plants (Mutti et al. 2008). Considering that the genome of *A. pisum* is being sequenced, it is likely that the identity of other saliva effectors will be unraveled in the near future. The extent to which secreted proteins of mycorrhizal fungi, aphids and a diverse range of other plant associated organisms function as effectors that impact host plants is, therefore, poised to continue to be an exciting topic of research.

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