group II introns. The involvement of Brt in phage tropism switching strongly suggests that an RNA molecule is an intermediate during information transfer. It is possible that substitutions originate from template-dependent misincorporation during Brt-mediated copying of the TR transcript (*4, 5*). Alternatively, a more specific mechanism may be involved, such as modification of the adenine residues in the RNA template (*6*). It is also not clear how the information is transferred from the cDNA copy of the TR to the *mtd* gene, or why the TR itself is not also a target of this pathway. A homing mechanism analogous to that used by group II introns, in which an activity of the reverse transcriptase protein is required for endonucleolytic cleavage of the target DNA, could play this role (*7*).

Not all of the details of this diversity-generating system in BPP-1 have been elucidated, but there is compelling evidence to support the overall model. For example, substitution of the reverse transcriptase gene with a nonfunctional variant or precise removal of TR completely eliminates the ability of the phage to switch states. The importance of the TR is further supported by the observation that engineering a base substitution into a nonvariant position in the TR induces a change in the *mtd* gene in most trophic variants.

In contrast to the binary switch for the tail fiber protein variants of phage Mu (*8*), the BPP-1 phage has the potential to generate more than 9×10^{12} variants of the Mtd protein! Although we do not know the precise subset of these variants that have the substitutions necessary for infection of Bvg^- or Bvg^+ strains of *Bordetella*, the potential to generate a large population of variants suggests that these phages may infect a broad range of bacterial hosts. Moreover, the variance-generating components are located within a rather well-defined cassette, and thus it would not be too surprising to find related cassettes in other biological contexts. This diversity-generating system may prove useful as a general system for targeted in vivo mutagenesis, particularly when this technique is coupled to powerful genetic screens and selection.

The delicate balance in the battle between viruses and their hosts may frequently involve variance-generating systems such as that described by Liu and colleagues. It seems probable that there are many other systems for inducing variation in viruses that have yet to be discovered. Bacterial hosts may seek refuge by altering the expression of phage receptors, but phages can respond by changing their host-recognition apparatus. You can run but you can't hide.

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PERSPECTIVES: PLANT BIOLOGY

Resisting Attack

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Plants must withstand attack by a huge assortment of pathogens (viruses, bacteria, fungi, nematode worms, parasitic plants) as well as predation by herbivores such as insects. To resist assault, plants have a group of resistance (*R*) genes that act in response to perception of complementary avirulence (*avr*) genes expressed by pathogens. Early genetic studies on the interaction of plants with pathogens suggested that the *R* genes encode highly selective receptors that detect the presence of pathogens. Activation of these receptors switches on signaling pathways that set in motion a variety of host defenses, including the hypersensitive necrosis response. The cloning and characterization of the first plant *R* genes and pathogen *avr* genes largely confirmed this model and represented a historic advance in the field of plant pathology. However, there is still much to learn about the intervening signaling pathways that connect initial perception of the pathogen to the plant's ability to resist attack. A big step forward is presented by Azevedo *et al.* (*1*) and Austin *et al.* (*2*) on pages 2073 and 2077 of this issue, with their reports that protein degradation may be a key regulatory event in the *R* gene–triggered signaling pathways of plant defense responses.

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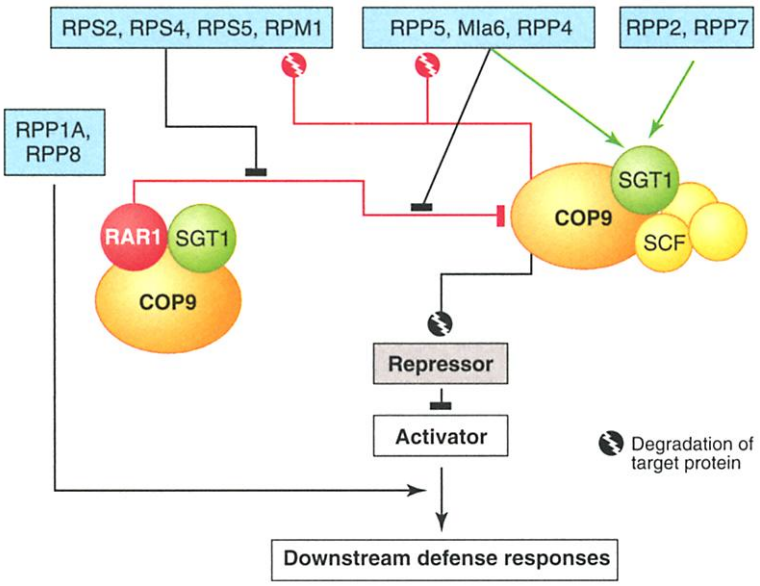
In their quest to elucidate how plants resist disease, investigators have been searching for gene mutations that suppress disease resistance in a bid to discover the downstream components of *R* gene–triggered signaling. This approach has yielded a variety of mutations, some of which are highly specific and suppress only the original *R* gene—for example, mutations in the *pbs1* gene only suppress the activity of *RPS5* (*3*). In contrast, other mutations are less selective and suppress resistance conditioned by a variety of *R* genes (*4*)—for example, mutations in the *EDS1* gene (encoding a lipase-like protein) and in *NDR1* (encoding a putative glycosylphosphatidylinositol-anchored protein) suppress different sets of *R* genes. Mutations in *RAR1*, which encodes a protein of unknown function that is widely distributed in multicellular organisms, also suppress *R* gene–triggered resistance for some *R* genes; in addition, some of these *R* genes are suppressed by mutations in *NDR1* or *EDS1*. Mutant *RAR1* suppresses several disease resistance pathways: it suppresses the activity of an *R* gene called *Mla12*, which mediates resistance to the powdery mildew pathogen in barley (*5*); it suppresses *RPM1* and *RPS5*, which confer resistance against bacterial speck disease in *Arabidopsis* (*6*); and it suppresses *RPP5*, which mediates resistance to downy mildew in *Arabidopsis* (*7*). Although mutant proteins that suppress disease resistance are important in their wild-type forms for plant defense, it has been difficult to elucidate where they fit in R signaling without knowing their biochemical activity or their interacting partners.

In the new work, Azevedo *et al.* (*1*), Austin *et al.* (*2*), and Tor and colleagues (*8*) implicate SGT1, which is known to play a role in protein degradation, in the regulation of R signaling during the plant defense response. Azevedo *et al.* (*1*) found that two forms of SGT1, SGT1a and SGT1b, interact with RAR1 in a two-hybrid screen. Meanwhile, Austin *et al.* (*2*) and Tor *et al.* (*8*) recovered *sgt1b* mutants in genetic screens for suppressors of RPP5-mediated and RPP7-mediated downy mildew resistance in *Arabidopsis*, respectively. Whereas barley appears to have one *SGT1* gene, *Arabidopsis* has two *SGT1* genes, but only one of these (*SGT1b*) is important in transducing defense signals (*1, 2, 8*). In yeast, SGT1 interacts with SKP1, a component of both an SCF ubiquitin ligase and the centromere binding factor 3 complex (*9*). The yeast SCF ubiquitin ligase adds ubiquitin molecules (ubiquitination) to cell cycle

proteins (cyclin-dependent kinase inhibitors and G_1 cyclins), targeting them for degradation by a large protein complex called the proteasome; *sgt1* yeast mutants are unable to degrade cell cycle proteins (*9*). The *SGT1a* and *SGT1b* genes of *Arabidopsis* can rescue yeast *sgt1* mutants, suggesting some conservation of function between SGT1 proteins in plants and yeast (*1*). In addition, SGT1b coimmunoprecipitates with components of SCF complexes in plants, and with components of the COP9 signalosome, a large multiprotein complex first identified as a repressor of plant photomorphogenesis. The COP9 signalosome superficially resembles the lid complex of the 19*S* regulatory subunit of the 26*S* proteosome and interacts with the SCF^{TIR1} complex, modulating degradation of negative regulators of gene expression induced by auxin, a plant growth hormone (*10*). Unlike the situation in yeast, however, there is no evidence for mitotic irregularities in *Arabidopsis sgt1b* mutants, and *sgt1b* null mutants are viable, possibly because SGT1a is able to compensate for SGT1b. These results suggest that SGT1b is important in plant defense signaling mediated by *R* genes and that regulated turnover of an intermediate protein is an important event in at least some *R* gene–triggered signaling cascades.



Plant defense signaling. In one possible model of plant defense signaling, R protein receptors (blue boxes), once activated, stimulate the association of a negative regulator (gray box) with the SGT1-SCF-COP9 complex and/or the RAR1-SGT1-COP9 complex. Association with the SGT1-SCF-COP9 complex may lead to ubiquitination and degradation (). Association with the RAR1-SGT1-COP9 complex may lead to degradation or to inactivation via protein modification. No direct interaction between R proteins and SGT1 or RAR1 has been detected and the signals immediately upstream of SGT1 and RAR1 are unknown. Some R proteins may bypass the negative regulators and stimulate the signal transduction pathways directly. The proteins targeted for turnover are unknown but could include LSD1, 3, or 5, CPR1 or 5, or EDR1. Alternatively, RAR1 or SGT1 may directly activate a positive effector. The *rar1* mutants do not accumulate RPM1 protein (*6*), suggesting that RAR1 acts to stabilize RPM1. This observation implies that, in parallel with the degradation of a negative regulator, RPM1 is degraded () following *R* gene–triggered signaling in a negative feedback loop to limit defense response activation. It is unknown whether other R proteins are similarly degraded following *R* gene–triggered signaling.

The results of the Azevedo *et al.* (*1*), Austin *et al.* (*2*), and Tor *et al.* (*8*) groups raise several intriguing questions, including the identity of the proteins that are targeted for destruction. Azevedo *et al.* (*1*) suggest that a negative regulator of the plant defense response may be targeted for degradation after activation of *R* genes (see the figure). Derepression of a signaling pathway via ubiquitin-targeted protein degradation of a negative regulator has been demonstrated for auxin signaling, providing a strong precedent for this model (*11*). Proteins encoded by genes that enhance (*edr1*) or promote constitutive disease resistance (*cpr*) when mutated could potentially be targets for this sort of derepression (*12–14*). Genes carrying mutations of the *lsd* (lesions stimulating disease) class—which induce lesions reminiscent of the hypersensitive necrosis response—are also candidates for derepression during the plant defense response (*15, 16*). However, so far there is no direct evidence that any of these proteins are targeted for destruction by *R* gene–triggered signaling. The only defense-related protein known to undergo degradation after defense signaling is the R protein RPM1. RPM1 is rapidly degraded following RPM1-triggered signaling at the same time as a hypersensitive necrosis response is initiated (*17*). Unexpectedly, RPM1 is degraded to undetectable levels in *rar1* mutants, suggesting that RAR1 stabilizes RPM1 in some manner (*6*). This observation suggests that one facet of *R* gene–triggered signaling is the degradation of the R protein in a negative feedback loop to limit the activation of downstream defense responses after the initial activation (see the figure). Although this model of regulated protein turnover is attractive, there is no direct evidence for SGT1-dependent protein turnover as yet. Thus, it is also possible that after initiation of an *R* gene–triggered signaling cascade, a protein is modified by RAR1, SGT1, or the complexes that contain these proteins, leading to activation of the plant defense response in the case of a positive effector or inactivation in the case of a negative effector.

The nature of the interactions between the RAR1-SGT1-COP9 and SGT1-SCF-COP9 complexes is unclear, as is the relationship between these complexes and the disease resistance phenotypes of *rar1* and *sgt1* mutants. Some *R* genes are dependent on RAR1, some on SGT1, some on both, and some on neither. Each *R* gene activates a similar spectrum of defense responses, including enhanced accumulation of transcripts for pathogenesis-related proteins and the hypersensitive necrosis response. Although the outcome is similar, these differential requirements for RAR1 and SGT1 indicate that upstream signaling pathways are different. These and related questions will no doubt lead plant pathologists in new directions as they seek to understand the signaling pathways that instigate the plant defense response.

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