propriate host-recipient HLA mismatches. An important issue is to understand why the NK cells mediate GvL rather than GvH. Is this a reflection of their primary engagement with bone marrow–derived cells, or simply with any blood-borne cells? Are other malignant cells (such as blood-borne metastatic tumor cells) also targeted by NK cells, as evidence from numerous studies in mice would suggest, and if so, which molecules are involved? How can the receptor repertoire of NK cells eventually be adapted to the HLA phenotype of the host? A possible answer to the last question is provided by Wang *et al.*'s work (*9*), also reported in this issue on page 2094. These authors have investigated the signaling pathway associated with mouse Ly49 inhibitory receptors that is known to involve the Src homology 2–containing inositol phosphatase SHIP. They show that this phosphatase is important for shaping the NK cell receptor repertoire during development, possibly by controlling the survival of different NK cell subsets.

We look forward to seeing how these new findings translate to the clinical setting, where hopefully NK cells will improve the outcome of hematopoietic cell transplants for patients with leukemia and other malignant diseases.

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PERSPECTIVES: MICROBIOLOGY

A Tail of Two Specifi-cities

Graham F. Hatfull

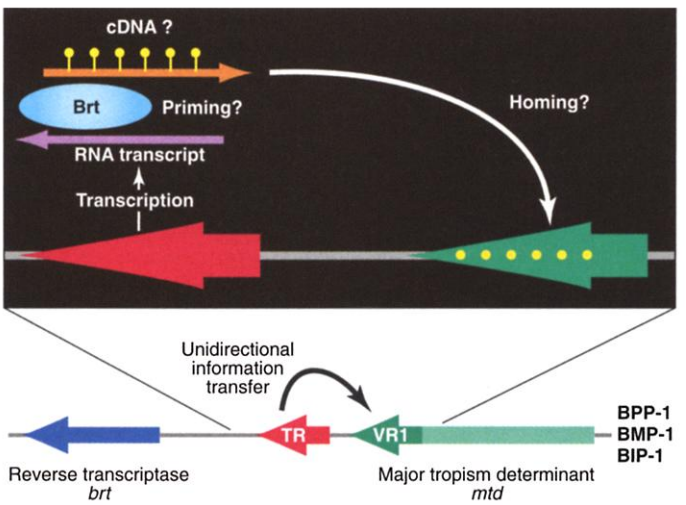
In the world of microbial biowarfare, standing still in the face of a ferocious viral attack is a recipe for disaster. Various subspecies of *Bordetella* bacteria, which cause respiratory illness in mammals including whooping cough in humans, must withstand attack by bacteriophage viruses such as BPP-1. They accomplish this by switching between two distinct phases: One (Bvg^+) expresses virulence genes and colonizes the respiratory tract of hosts, and the other (Bvg^-) is better adapted for growth outside of a host (*1*). Among the genes whose expression is altered on switching between these two phases is *prn*. This gene encodes an adhesion protein, pertactin, which is the receptor for the bacteriophage BPP-1. Thus, BPP-1 infects only the Bvg^+ strain of *Bordetella* that expresses pertactin and not the Bvg^- strain.

But not so fast. On page 2091 of this issue, Liu *et al.* (*2*) show that BPP-1 is not so easily fooled. Remarkably, when faced with this switch in bacterial phenotype, one in a million phage will change tropism to be able to infect the Bvg^- strain. If the bacterium should change back to the Bvg^+ state, then the phage can revert to its original tropism. Because the range of bacterial hosts that a phage infects is typically determined by the nature of its tail fibers, it is not uncommon to find marked variation among phage tail fiber proteins. Some phages use dedicated site-specific recombination systems to switch between alternative tail fiber proteins (*3*). The tropism change in BPP-1 involves a putative tail fiber protein (Mtd), but this change is not dependent on a simple binary switch, as Liu *et al.* show (see the figure) .

Phage BPP-1 normally infects the Bvg^+ but not the Bvg^- strain of *Bordetella*. However, it can assume two additional trophic states: BMP, which infects Bvg^- but not Bvg^+, and BIP, which infects both bacterial strains. The three trophic states of the phage are interconvertible, and switching from one state to another is accompanied by base substitutions in a 134–base pair (bp) segment of the phage genome. This segment, called the variable region (VR1), encodes the carboxyl-terminal 44 amino acids of the *mtd* gene product.

Base substitutions in VR1 are not random but occur predominantly at 22 positions. Most of the base substitutions are in either the first or second positions of codons, and so lead to changes in the amino acid sequence of the Mtd protein. The phage has devised a way to restrict mutations to the 134-bp region, thus avoiding changes that would be deleterious. Just downstream of the *mtd* gene is a nearly identical copy of the 134-bp region, the template repeat (TR), which provides sequence information that is incorporated into the *mtd* gene. Interestingly, all of the 22 highly variable positions in *mtd* have an adenine in the corresponding position in the TR, and there is only one additional adenine in the 134-bp repeat.

How is the sequence information copied from the TR to the *mtd* gene, and why is this a low-fidelity mechanism? Not all parts of the process are yet known, but it is clear that a phage-encoded reverse transcriptase (Brt) is required (see the figure). This enzyme is similar in sequence to the reverse transcriptases of retroviruses and to those encoded by



Tropism changes in bacteriophage. Phages BPP-1, BMP-1, and BIP-1 are closely related trophic variants that differ in their ability to infect Bvg^- and Bvg^+ strains of *Bordetella* bacteria. The end of the *mtd* gene—highly variable among BPP, BMP, and BIP phages—contains a variable region (VR-1) that is about 90% identical to the 134-bp template repeat (TR) located just downstream. Information from the TR is transferred unidirectionally to the VR1 region of *mtd* in a low-fidelity event that is dependent on the phage-encoded reverse transcriptase Brt. The detailed mechanism of information transfer is not known but may involve sequence-dependent misincorporation during Brt-mediated copying of a TR transcript followed by introduction of the new information into VR1. Priming of synthesis of the TR cDNA could be mediated either by an endogenous primer or directly by VR1 after endonucleolytic cleavage.

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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

Marc Nishimura and Shauna Somerville

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