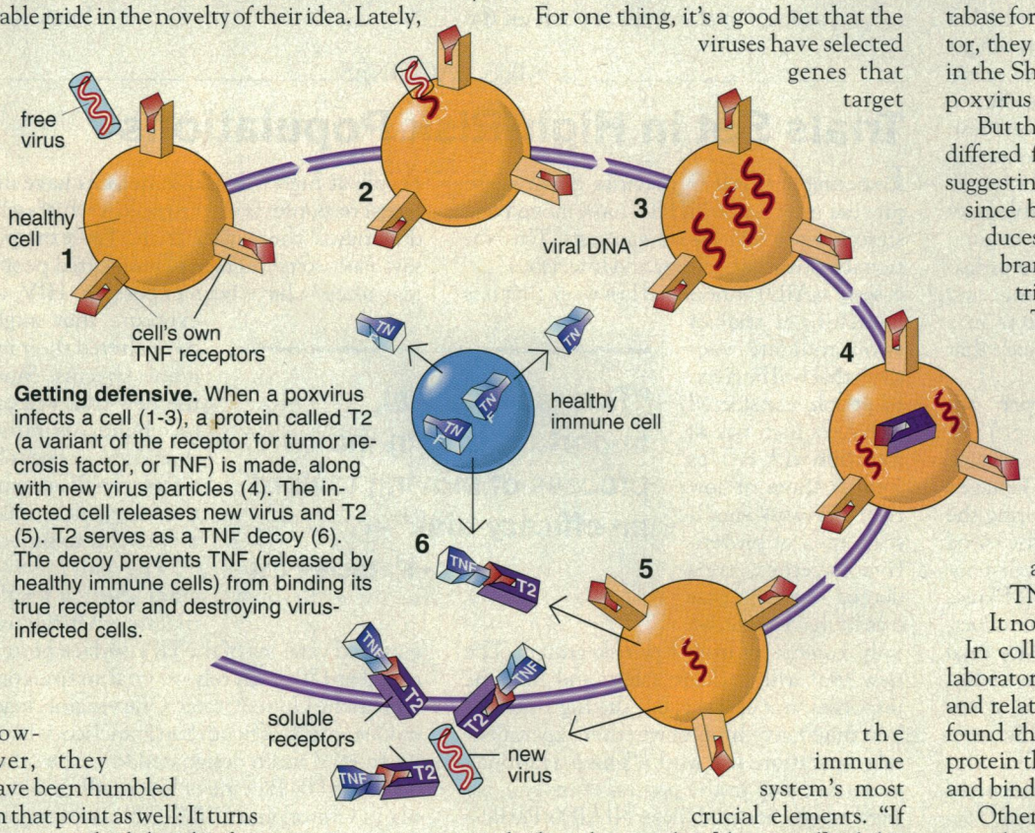
Viruses Launch Their Own 'Star Wars'

By stealing genes and turning key immune-system proteins against the host, viral invaders have learned to elude the body's attacks

One of the most intriguing strategies researchers have been trying out as a means of combating the AIDS virus is to make a soluble form of the receptor—called CD4—that enables the virus to bind to white blood cells, put large quantities of that molecule into the bloodstream, and hope it will mop up free virus. As a result of technical problems, that strategy hasn't yet lived up to the high hopes researchers have for it. Until recently, however, those researchers had retained considerable pride in the novelty of their idea. Lately, however, they have been humbled on that point as well: It turns out viruses had the idea first.



Getting defensive. When a poxvirus infects a cell (1-3), a protein called T2 (a variant of the receptor for tumor necrosis factor, or TNF) is made, along with new virus particles (4). The infected cell releases new virus and T2 (5). T2 serves as a TNF decoy (6). The decoy prevents TNF (released by healthy immune cells) from binding its true receptor and destroying virus-infected cells.

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It has long been apparent that viruses can "steal" genes from their hosts and use them for their own purposes. A growing body of work now shows that among the genes that viruses seem to have pilfered are those for key cell-surface receptors that help the immune system recognize and fight invaders—including viruses. By inducing the host's cells to make soluble versions of these receptors in large quantities, viruses disrupt and decoy the immune system, overloading it with targets much like an aircraft confuses radar-guided missiles with a shower of high-tech tinfoil. And that's only one of many uses of host genes by viruses that have been uncovered in a rush of recent work in many different labs. "It's intellectually very satisfying when you realize" what these viruses are doing, says immunologist Tim Mosmann of the University of Alberta, Edmonton. "The immediate question is, Why didn't we think of this sooner? It's an obvious strategy once you've seen it."

The payoff in this burgeoning area is likely to be more than intellectual satisfaction. For one thing, it's a good bet that the viruses have selected genes that target the immune system's most crucial elements. "If you look at the way that [these viral] inhibitors work, it will point a finger at many—if not all—of the critical regulators of the immune system that are important for that virus," says University of Alberta virologist Grant McFadden. Indeed, says McFadden, this kind of work could provide "a Rosetta stone for the immune system." Beyond that, it could lead to new anti-inflammatory or antiviral drugs. "I've begun to think of these viruses as Brazilian rain forests," says Richard Moyer, a virologist at the University of Florida, Gainesville. "Many of these genes... are eventually going to be therapeutically very useful."

One of the remarkable things about the story is how quickly it has unfolded. The first discovery of viral use of soluble receptors was made only 3 years ago by molecular immunologist Craig Smith and his colleagues at the Seattle-based biotech company Immunex. They had cloned the receptor for tumor necrosis factor (TNF), a potent signaling molecule used by the immune system to turn up the attack on tumors or on virus-infected cells. When the researchers searched the DNA database for sequences related to the TNF receptor, they were startled to find a similar gene in the Shope fibroma virus, a member of the poxvirus family that infects rabbits.

But the Shope virus gene—known as T2—differed from the true TNF receptor gene, suggesting it has evolved a different function since being usurped. The true gene produces a protein anchored in the membranes of many different cell types that triggers a response inside the cell when TNF binds and activates it. The T2 gene, however, seemed to code for a protein that had retained the TNF-binding site but lost the membrane anchor, suggesting it is secreted into the fluid surrounding the virus-infected cells. Smith and his colleagues suggested the free-floating protein might act as a decoy, binding and inactivating TNF before it can reach its target cells.

It now looks as if that guess was inspired: In collaboration with McFadden, whose laboratory focuses on Shope fibroma virus and related poxviruses, the Immunex group found that the T2 gene indeed produces a protein that is secreted by virus-infected cells and binds to TNF.

Other examples weren't long in coming—and one of them showed just how potent such decoys can be. McFadden's group found another T2 gene in a poxvirus called myxoma. Myxoma produces a disease in rabbits that is ordinarily quick and deadly. But when the group infected rabbits with a mutant form of myxoma lacking T2, the rabbits fought off the infection, suggesting T2 decoys are essential for the virus's usual virulence. "I describe [the decoy strategy] as 'virus Star Wars,'" says McFadden, "because the virus is putting out these little shields for itself."

Those early examples set McFadden to wondering whether viruses may have adopted other such Star Wars approaches during

their long co-evolution with their hosts. So his group went searching for other soluble decoys—and didn't have to look far. "We went to myxoma-infected cells, took the most abundantly secreted protein, and sequenced it," says McFadden. "It turned out to be the homolog of the gamma-interferon receptor." Gamma-interferon is another immune-system signal that turns up antiviral defenses. Three weeks ago, McFadden and colleagues Chris Upton and Karen Mossman reported in *Science* that the protein from myxoma binds gamma-interferon and inhibits its activity. "The virus uses the same strategy against gamma-interferon that it uses against TNF," says McFadden. "And we suspect the story is just beginning."

It is already becoming a richly nuanced tale, however. For example, the gene for a third soluble receptor—one that binds the signaling molecule interleukin-1 (IL-1)—has been found in both vaccinia and cowpox virus by two research groups: Geoffrey Smith and Antonio Alcami of Oxford, and a group consisting of Dennis Hruby of Oregon State University, Melanie Spriggs of Immunex, and their co-workers.

And all that is just part of the story, because receptors aren't the only immune-system components that viruses are using illicitly. Indeed, poxviruses apparently find IL-1—a multifunctional immune system regulator—to be an opponent formidable enough to warrant a second strategy to supplement the soluble receptor. Duke University virologist David Pickup and his co-workers found that cowpox virus seems to have acquired a gene for a protease inhibitor that thwarts IL-1 action by blocking the enzyme that converts IL-1 from its inactive to its active form.

Complementary strategies

Like the receptor strategy, the enzyme inhibiting scheme has popped up in multiple examples. Also on the poxviruses' list of apparently pilfered genes is one for a "complement control" protein, so called because it impedes the action of one of a group of enzymes collectively dubbed "complement" that trigger antiviral and antibacterial defenses. The control protein normally keeps complement at bay when it is not needed, but Bernard Moss and his colleagues at the National Institutes of Health (NIH) found that vaccinia virus carries a version of the protein, which it apparently produces during viral infection to help ward off the complement defense.

As if the feat of picking up a helpful host gene with one function were not enough, at least one virus has managed to capture a gene that seems to serve it in two ways: by turning down the immune response to the virus and at the same time turning up production of the very cells the virus infects, thereby giving the virus more juicy targets. This remarkable double play was revealed 3 years ago by Kevin Moore of DNAX Research Institute in Palo Alto, and Tim Mosmann, then also at DNAX. They had discovered and cloned an immune system regulator called interleukin-10 (IL-10), and then found that Epstein-Barr virus (or EBV, a herpes virus that causes mononucleosis) has a similar gene. In the normal immune system, IL-10 seems to turn down the antiviral T cell response when it is not needed and turn up the production of antibody-producing B cells instead. But EBV apparently subverts that function for its own ends by producing IL-10 to turn down the T cell response directed against itself. And the extra bonus for the virus is that IL-10 stimulates production of the B cells EBV infects. "It's the ideal thing for this virus to have captured," says Moore.

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–Richard Moyers

Most of the viral defenses discovered so far have been found by homology to known elements of the immune system. And so far there have been no big shocks for immunologists in the targets that viruses have chosen. "It's not a surprise that a virus would want to interfere with TNF or gamma interferon synthesis or action, but it is a very valuable confirmation," says Mosmann. "The viruses are confirming the models we had in mind." Now researchers, alerted to the general strategy, can go looking for less obvious genes—which could well hold some surprises. "The most interesting gene will be the one for which there is not yet homology," adds NIH's Moss, "because that may be a new [immune-system] factor."

One source of these mystery genes is adenovirus, which causes respiratory infections in humans. Adenovirus has a number of anti-immune genes that don't have obvious counterparts in their hosts. The first was discovered in the 1970s by immunologist Per Peterson and his co-workers at the Scripps Research Institute in San Diego. Peterson studies the class I protein of the major histocompatibility complex, which places pieces of viral proteins called peptides on the surface of an infected cell as a way of marking it for T cell destruction. His group was looking for viral proteins that bound the class I protein, and they found an adenovirus protein that did.

In subsequent studies they discovered that the viral protein keeps the class I molecule in the cell, preventing it from displaying peptides on the surface and thus preventing infected cells from being killed by the immune system. Peterson believes the protein may have derived from an important—and as yet unknown—regulator of the normal process in which the class I protein is loaded with peptides. "My speculation is that we're going to uncover new proteins by studying this one," he says.

Viruses to the rescue

Whether a virus makes use of a well-known immune protein or a dark horse, identifying that protein and the corresponding viral strategy should aid in development of new drugs. "These viruses are clever," says Peterson. "They should give us leads to be able to design drugs that will intervene more specifically." Especially desirable, researchers say, are anti-inflammatory drugs to combat the sometimes destructive effects of an overreactive immune system in conditions such as sepsis or autoimmune disease. Smith says Immunex already has begun clinical trials of a soluble TNF receptor derived from the human protein, as a possible treatment for sepsis.

Another way physicians may someday exploit this knowledge is in the form of new drugs designed to thwart viral defenses. Such drugs would be a boon, since so few therapeutic approaches have been developed for viral diseases. The viruses in which the genes have been found so far aren't themselves substantial threats (smallpox has been eliminated; Epstein Barr virus causes mononucleosis; adenovirus nothing worse than a cold). But weapons against these diseases could lead to treatments that would be useful against more deadly viruses. "I wouldn't go as far as to say that if we understand a given problem from the poxvirus, we'll be able to treat the AIDS virus, for instance," says Peterson, "but the overall gain in knowledge is obviously going to be helpful in devising strategies for other viruses as well." And that's just one of the potential benefits that could come from reading the viral Rosetta stone.

–Marcia Barinaga

Additional Reading

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