lished work, Baker says he has been able to use them to make dendrimer-DNA complexes that have now successfully transferred genes to more than 30 different types of cells with an efficiency up to 1000 times higher than that found by Szoka.

Those results have aroused some interest from gene therapy researchers. "I believe dendrimers have a serious future as vectors for gene therapy," says Claude Nicolau, a professor of medicine at Harvard Medical School, who has spent years working on liposome vectors. Thus far, however, dendrimers have not made the jump from success in the petri dish to success in live animals, he adds. Indeed, it's far from certain that dendrimers will ever make that jump, says James Wilson, director of the Institute for Human Gene Therapy at the University of Pennsylvania in Philadelphia. Polylysines, another DNA-binding synthetic vector, also looked good at transfecting cells in culture, he notes, but they failed miserably when it came to tests in live animals.

Researchers may be more successful in attempts to use dendrimers to move electrons around rather than genes. Larry Miller and his colleagues at the University of Minnesota, for example, have added electronically active groups called imides to the outer branches of PAMAM dendrimers in hopes of engineering a new class of 3D conducting polymers that may have unique electrical properties. The conducting polymers that are currently available, such as polyacetylene, are linear molecules. But in recent years researchers have found that 3D conducting molecules have unique properties not found in their linear counterparts. The soccerball-shaped carbon molecules known as fullerenes, for example, superconduct (conduct electricity without resistance) at a temperature higher than that of any other molecular conductor.

To make dendrimers with the right properties for this job, Miller's group starts with spherical PAMAM dendrimers that have 192 branches to which they attach pancake-shaped imide groups. Miller suspects this will allow electrons to jump from imide to imide around the surface of the sphere (although to demonstrate this he must first fashion the dendrimers into a larger material).

Others think the work holds promise. Formulating the spheres "sounds like a significant advance in terms of controlling the surface chemistry" of dendrimers, according to Martin Bryce, professor of chemistry at the University of Durham in England, who is working toward the same goal but using different conductive molecules as dendrimer add-ons. However, "you shouldn't get too excited about applications yet," he cautions. But a little excitement, the dendrimer-makers feel, is finally warranted.

–Robert F. Service

IMMUNOLOGY

The T Cell Receptor Begins To Reveal Its Many Facets

It's not hard to understand why the T cell receptor is an object of intense interest among immunologists. By recognizing and binding foreign antigens, the receptor (actually a collection of several proteins located in the outer membrane of the T cells of the immune system) helps trigger many of the immune responses that the body needs to fight off viruses and other pathogens. Just as important, it plays a key role in normal T cell development. As researchers delve deeper into how the T cell receptor operates, however, they are finding that its biochemical behavior is not at all what they expected.

Immunologists long assumed that the receptor was a simple on-off switch for the T cell: Bind enough of an appropriate antigen (protein fragment), and the receptor would activate the cell's full range of responses; otherwise nothing would happen. But recent work from several research teams, one of which reports its current results on page 515, shows that it doesn't work that way. Depending on the exact chemical nature of the antigen, the receptor can produce a spectrum of cellular responses, ranging from complete activation to inhibition. "People thought of the receptor as relatively simple and dumb," says Alessandro Sette of the Cytel Corporation in La Jolla, whose group is one of those doing the research. But he adds, it "may be a lot smarter than you think."

"People thought of the receptor as relatively simple and dumb, [but it] may be a lot smarter than you think."

—Alessandro Sette

The "intelligence" of the T cell receptor may underlie such fundamental processes as immunologic memory and "thymic education," in which the thymus gland selects out T cells that recognize and respond to foreign antigens while eliminating those likely to attack the body's own tissues. What's more, it may have implications for preventing rejection of organ transplants and treating autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, which apparently occur because immune cells forget their thymic lessons and mistakenly damage normal tissue.

The current findings are an outgrowth of the growing understanding of immune cell activation that has occurred in the 12 years since the T cell receptor was discovered. Work from many labs has shown that T cells don't recognize antigens by themselves. Instead, they need help from a collaborator, the antigen-presenting cell (APC), which breaks protein antigens into short fragments or peptides. Individual peptides, usually consisting of eight to 14 amino acids, are displayed on the surface of the APC in association with one of the proteins encoded by the genes of the major histocompatibility complex (MHC). What the T cell receptor recognizes and binds to—its "ligand" in the jargon usually used—is a peptide bound to the MHC protein.

Early evidence that the T cell receptor behaves much more subtly than a simple light switch in responding to its ligands came about 4 years ago from Brian Evavold and Paul Allen of Washington University School of Medicine in St. Louis (*Science*, 31 May 1991, p. 1308). They were investigating how changes in the composition of an antigenic peptide affect T cell activation. When they replaced one glutamic acid residue with an aspartic acid residue, they found that the resulting peptide caused the target T cells to display only part of the activation response: The cells released a substance called interleukin-4, which is an immune-system modulator, but they did not undergo the rapid cell division that normally accompanies activation. "In immunology that was a surprising result," says immunologist Ronald Germain of the National Institute of Allergy and Infectious Diseases (NIAID). "The key thing was that it showed that the response could be qualitatively, not just quantitatively, different, depending on the peptide."

Since then, Allen's team has provided additional examples of altered peptides that elicit partial T cell responses, such as stimulating cell-killing activities without causing the release of modulators like interleukin-4 or cell proliferation. These peptides also induce anergy in the T cells, making them unresponsive to stimulation by the unaltered parent peptides. This finding suggests that the T cell receptor's many functions include sending signals that shut the T cell off.

Indeed, this work has been complemented by studies in which researchers, including Sette and Germain, have made altered T cell ligands that block T cell responses to normal peptides without eliciting

partial responses. An altered T cell ligand can "be an agonist [that fully stimulates the T cell receptor] or an antagonist, or fall in between," Germain says.

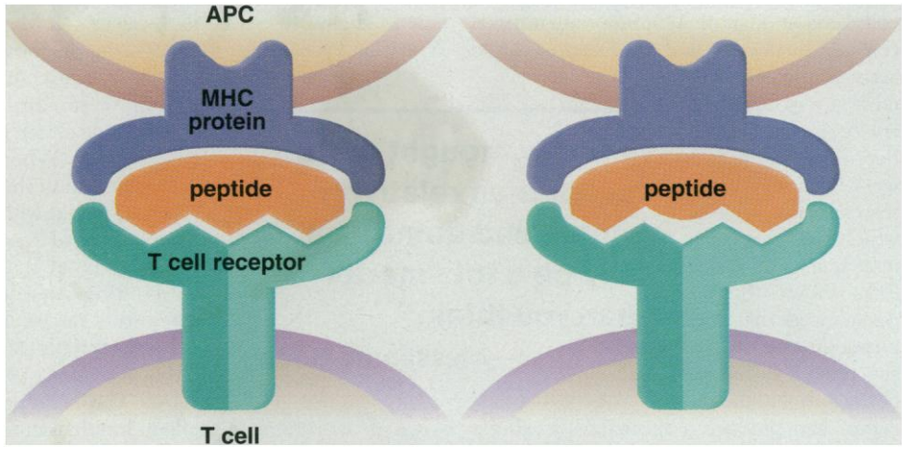
How the T cell receptor can produce such a diverse range of responses remains unclear, but clues are accumulating. For one thing, immunologists know the receptor has a complex structure, including several proteins in addition to the two that interact with the peptide-MHC complex on the APC. This suggests that the modulation of the receptor's signal could depend on what happens to one or more of these proteins as the receptor interacts with its target. As Allen team member Joanne Sloan-Lancaster asks, "Why have such a complicated receptor if it's just an on-off switch?"

And that's where the current *Science* paper, which describes recent work by the Germain group, comes in, as well as a closely related one from the Allen team that appeared in the 2 December issue of *Cell*. To try to get a clearer view of how altered ligands are affecting T cell receptor signaling, these researchers looked at an early event in the signaling pathway that is stimulated by ligand-binding to the T cell receptor: the addition of phosphate groups to certain of the receptor proteins. These phosphorylations, carried out by enzymes called protein tyrosine kinases, are critical for further transmission of signals to the T cell interior.

Both the Allen and Germain teams examined the phosphorylation of one receptor protein, the so-called ζ chain, and obtained similar results. They found that altered ligands stimulate ζ chain phosphorylation, but that the pattern of resulting phosphorylated products differs from that produced by normal antigenic peptides. As an apparent consequence, the next step in the signaling pathway to the cell interior, the activation within the cell of a protein tyrosine kinase called ZAP-70, fails to occur. "We believe that there are various signaling pathways downstream of the [T cell] receptor, and that they can be turned on selectively depending on the phosphorylation of these [associated chains]," says Sloan-Lancaster. "ZAP-70 is not activated. That supports our hypothesis."

In addition, Germain and his NIAID colleague Joaquín Madrenas, who worked in collaboration with Larry Samelson's group at the National Institute of Child Health and Human Development, found that ZAP-70 wasn't itself phosphorylated as it normally should be. That may explain why it didn't get activated.

Although it now seems clear that T cell receptors can produce a varied range of responses, a great many questions remain to be answered about how they do this. Among other things, researchers want to know how binding an altered ligand might lead to changes in such signaling pathway steps as ζ chain phosphorylation and ZAP-70 activation. The current thinking is that the tightness of ligand-binding is likely to be important.



Misfit. For a T cell to be activated, its receptor must first recognize an antigenic peptide combined with an MHC protein on the surface of an antigen-presenting cell (APC). But if the fit isn't exact *(right)*, a T cell might be only partially activated, or its activation might be blocked.

ILLUSTRATION: C. FABER SMITH

Immunologists have found that T cell receptors cluster together in the membrane as a result of ligand-binding, and this clustering is thought to be necessary to produce a response. But changing the amino acids in a peptide is likely to produce a product that fits the T cell receptor less well than the original. "Nine times out of 10 these [altered peptides] are going to have lower affinity for the receptor," says immunologist Michael Bevan of the Howard Hughes Medical Institute at the University of Washington, Seattle. As a result, the altered ligands will bind for shorter lengths of time, and the clusters will have less time to form or will fall apart more rapidly. And that may lead to no response at all, as in the case of the antagonists, or to partial responses.

Despite the many remaining unknowns, immunologists are intrigued by both the biological and therapeutic implications of the work. On the biological side, the ability of different peptides to produce varied T cell responses could be "pretty important in T cell development," says Bevan. He and other immunologists have found that the ability of T cells to survive their passage through the thymus gland, where they learn their lessons, depends on their reactions with self peptide-MHC complexes on thymic cells. To survive, they must be stimulated by this self-MHC interaction, but if they interact too strongly, they die. This helps eliminate dangerous cells that might initiate an autoimmune attack. But those that interact weakly continue to develop. Recent work from Bevan's lab shows that for some T cells this process of positive selection is extremely sensitive to the nature of the peptide in the MHC complex. In particular, those that act as antagonists for mature cells work best at positive selection. Although no one knows what the actual selecting peptides are in the thymus, this result suggests they are of the type that can engage the T cell receptor without producing a strong activation signal. There are, however, other views of how peptides might influence positive selection.

On the therapeutic side, there are indications that this work could help immunologists understand how viruses sometimes successfully withstand immune defenses. Last year, Paul Klenerman and Andrew McMichael of the University of Oxford in the United Kingdom and their colleagues found that naturally occurring variants of peptides from the AIDS virus antagonize the cell-killing activities of T cells from the patients from whom the viruses were isolated. A second team, led by Carlo Ferrari of the University of Parma, Italy, obtained similar results with isolates of hepatitis B virus. (Both teams reported their findings in the 2 June 1994 issue of *Nature*.)

In these cases, of course, the antagonism might be deleterious to patients, but there is also preliminary evidence that antagonist peptides might help patients with autoimmune disease. A condition similar to human multiple sclerosis can be induced in mice by injecting a protein called proteolipid protein (PLP) into their brains. A team led by Vijay Kuchroo of Harvard University, in collaboration with Sette's group at Cytel, has synthesized an altered form of one PLP peptide and shown that it protects mice against PLP's effects if it is injected into the animals before the PLP. "If you preimmunize with the altered peptide, the animals don't get sick," Kuchroo says. A similar strategy might also be used to design better ways of warding off rejection of transplanted organs.

But while these early results are promising, a clinical payoff remains far in the future—if indeed it ever comes. Meanwhile, immunologists have plenty of work to keep them busy while they explore the mysteries of the ever-fascinating T cell receptor.

–Jean Marx