T Cell Shift: Key to AIDS Therapy?

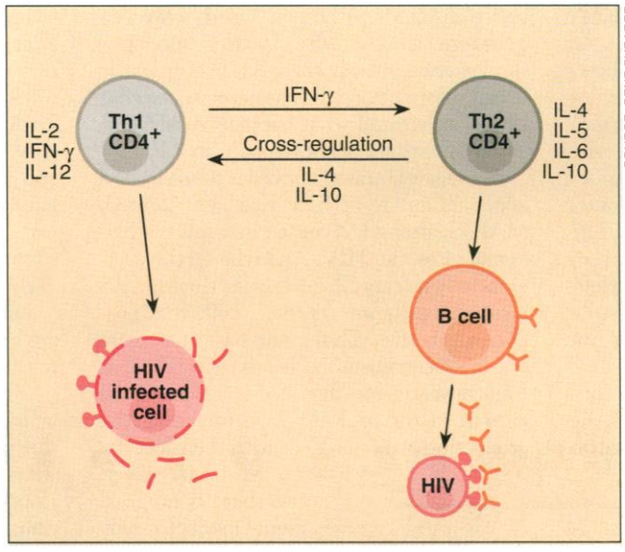
Immunologists are debating whether a shift in immune cell populations causes AIDS patients to decline. The outcome of this debate could guide therapy and vaccine efforts

One of the paradoxes of science is that researchers are simultaneously attracted and repelled by simple theories. They are attracted because nature often follows simple principles—and repelled because an explanation that's too simple often will prove to be wrong. Now AIDS researchers find themselves confronting just such a conundrum. During the past year, a very simple theory that seeks to explain what causes the relentless and ultimately fatal decline of AIDS patients has been gaining great momentum—and thus ever hotter criticism.

The theory holds that a patient's fate is determined by which of two types of immune cell, designated Th1 and Th2, has the upper hand in controlling his or her immune responses. In this view, the Th1 cells are the good guys, helping to stave off the ravages of the disease, while the Th2 cells are the bad guys, contributing to the patient's decline. If correct, the theory would have major implications for efforts to develop AIDS vaccines and therapies. The idea would be to use drugs or vaccines that bolster Th1 responses, while reducing Th2 responses. New results from Osami Kanagawa and colleagues at Washington University School of Medicine suggest that this strategy might work. On page 240 they report the results of experiments in which they showed that mice lacking a Th2 response resist the development of a murine form of AIDS.

But the Kanagawa results certainly won't satisfy everyone, since there is wide disagreement about whether the Th1/Th2 theory can be applied to HIV infection. Ironically, a chief skeptic is none other than Sergio Romagnani, an immunologist at the University of Florence who first showed in 1991 that humans have distinct Th1 and Th2 populations. "This Th1/Th2 story has been considered by a lot of people in too much of a simple way," says Romagnani. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID), heartily agrees. Th1/Th2, says Fauci, "is really being oversimplified with regard to HIV disease and there are a lot of things you have to be careful about."

Immunologist Gene Shearer of the National Cancer Institute (NCI), who first argued for a Th1/Th2 connection to AIDS with NCI co-worker Mario Clerici, is taking the criticism in stride. "Lots of professional immunologists say this is oversimplified," he says. But, Shearer maintains, the data, including those in the Kanagawa paper, are making the theory more and more compelling. "The question becomes how much right are we and how much wrong. We all have to wait and see if it's been oversold."



SOURCE: GENE SHEARER

Shifty business. Does tipping the scale away from a Th1-type immune response and toward Th2 explain the progression of AIDS?

From mice to men

The Th1/Th2 theory stems from work first done in the mid-1980s by Tim Mosmann and Robert Coffman, who at the time both worked for DNAX Research Institute in Palo Alto. Mosmann, Coffman, and their coworkers were studying a category of mouse immune cell known as the T helper (or CD4+) cell, which is the principal cell type destroyed in human AIDS. The DNAX group found they could clone two distinct subtypes of T helpers that were identifiable because each pumped out a different set of cytokines. These are the chemical messengers that activate immune responses and also regulate the interactions between different types of immune cells. One subtype of T helper cell identified by Mosmann and Coffman primarily secreted the cytokines interleukin-2 (IL-2) and gamma interferon. They called these the Th1 cells. A Th2 subset secreted IL-4 and IL-5.

Immunologists were excited about the discovery because it helped them understand the interactions between the two major arms of the immune system. While the divisions are not hard and fast, the cytokines secreted by Th1 cells trigger one arm, the cell-mediated responses that clear the body of infected cells. The Th2 cytokines activate the other arm, leading to the production of antibodies that can prevent cells from becoming infected in the first place. And what turned immunologists' heads was the discovery that a strong Th1 response inhibits a strong Th2 response and vice versa.

But for 5 years, it looked as if such a cross-regulatory system might not be working in humans. Despite intense searching, several labs had failed to find distinct Th1 and Th2 subpopulations in healthy humans. Then Romagnani's lab looked in patients who had various diseases and succeeded. That touched off a vigorous effort to see how the activities of Th1 and Th2 cells might influence the course of human diseases as disparate as leishmaniasis, tuberculosis, syphilis, leprosy—and AIDS.

NCI's Shearer and Clerici began exploring the role of T cell subgroups in AIDS from several angles. One of their most intriguing findings to date is the discovery that HIV-infected people switch from a Th1 to a Th2 state as the disease progresses. In a study published in the March issue of the *Journal of Clinical Investigation*, the NCI researchers reported that when they measured cytokine production by blood cells from 45 HIV-infected, but healthy, people over a period of 15 months, they found that IL-4 production increased while IL-2 production decreased. The researchers suggested that possibly, IL-10, a Th2 cytokine that down-regulates Th1 responses, was responsible for this shift. What is more, says Shearer, only 8% of infected people who had strong IL-2 responses went on to develop AIDS over a 3-year period. In comparison, nearly half the people with weak IL-2 responses went on to develop AIDS. "Whatever the mechanism, our test is predicative of who would develop AIDS," says Shearer.

But because T cells aren't the only immune cells that produce cytokines, the NCI

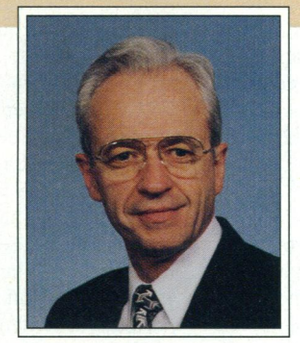
workers couldn't know for sure that the changing cytokine profiles they saw were caused by shifts in the Th1 and Th2 populations themselves. To make that type of assessment, the University of Amsterdam's Frank Miedema and colleagues looked for distinct Th1/Th2 clones in HIV-infected people to see whether their numbers changed as AIDS progresses. They did. "By the first set of clones we saw the [Th1 to Th2] shift and I was really amazed," says Miedema. "I didn't expect such a clearcut shift."

The human studies didn't reveal, however, whether the shift in T cell populations directly contributed to the patients' worsening conditions. And that's where the work of Kanagawa and his colleagues Barbara Vaupel and Shinyo Gayama comes in. It shows that a switch from Th1 to Th2 responses may well account for disease progression in murine acquired immunodeficiency syndrome (MAIDS), a mouse disease that causes symptoms similar to those of human AIDS.

The Kanagawa group reached this conclusion by comparing the effects of the MAIDS virus on normal control mice and on mice that had had their IL-4 producing gene, and thus presumably their Th2 response, "knocked out" by Georges Koehler and Manfred Kopf of the Max Plank Institute for Immunobiology in Freiburg, Germany. The result: Twenty weeks after infecting the IL-4 knockouts with the MAIDS virus, only three of the 28 animals developed swollen lymph nodes, or lymphadenopathy, a symptom of both MAIDS and AIDS. In contrast, 19 of the controls developed lymphadenopathy during that time and the other nine died. Indeed, after 25 weeks, all of the IL-4 knockout mice were alive while all of the controls were dead. Somehow, the lack of IL-4 had made the mice resistant to disease.

"We all have to wait and see if [Th1/Th2 theory] has been oversold."

–Gene Shearer



NIAID's Herbert Morse, a strong proponent of the MAIDS model, calls the Kanagawa group's work "a very striking observation" and says it fits nicely with as yet unpublished work from his group that supports a Th1-predominant cytokine profile being protective in MAIDS. And Phillip Scott of the University of Pennsylvania, who studies leishmaniasis in mice, is similarly impressed. "I think it's an amazing paper," says Scott. "It's one of the first things that really links the MAIDS story to Th2 cells being responsible for the pathology."

Others are more circumspect. "The conclusion that IL-4 or Th2 is required for MAIDS is rather soft," says Donald Mosiers, an AIDS researcher at the Scripps Research Institute who has worked extensively with MAIDS. "An IL-4 knockout affects all the Th2 responses and alters some of the Th1 responses," he says. Mosiers, who moved on from MAIDS to study HIV in mice that have had transplants of human blood cells, also questions whether the MAIDS model is similar enough to human AIDS to provide useful information. "I'm not convinced that if you understand what happens in MAIDS you'll understand what happens in AIDS."

Kanagawa himself concedes that MAIDS applicability to AIDS may be limited. MAIDS, after all, is caused by a murine leukemia virus, not HIV. And where HIV preferentially infects CD4+ T cells, the MAIDS virus primarily infects the B cells that produce antibodies. Though he has yet to tease out the mechanism that leads to the disease, Kanagawa suspects that IL-4 serves as a B cell growth factor in MAIDS, stimulating the production of more virus, which then does the damage. Yet, given that there is no good animal model to study HIV disease, he maintains that MAIDS may well offer important insights about the role of cytokines in the development of AIDS.

As compelling as the Th1/Th2 story is to many AIDS researchers, some, like NIAID's Fauci, have found disturbing inconsistencies. Fauci and co-worker Cecilia Graziosi also looked for a Th1 to Th2 switch in HIV-infected people—and didn't find one. In their experiment, they measured cytokine levels in the lymph nodes of HIV-infected people who ranged from having relatively normal immune systems to severely damaged ones. "Is there a gradual decrease of interferon gamma and IL-2 and an emergence of IL-4 and then IL-10, as the Shearer/Clerici paper suggests?" asks Fauci. "There's nothing like that." What they found is that little IL-4 was made at all stages of AIDS and most IL-10 was made not by T cells but by another kind of immune cell, the macrophage. "Much of the findings with HIV disease can be explained by a dropping out or anergy of CD4 cells which gives the impression of a switch from Th1 to Th2," asserts Fauci.

Romagnani did a similar experiment with peripheral blood cells from about 50 HIV-infected people whose symptoms ranged from mild to severe. "We did not confirm increasing IL-4 or some sort of Th2 switch," he says. Romagnani also looked at more than 100 clones of T helper cells from infected people to see if there was a shift toward Th2 cells as disease progressed. Again, he came up empty handed.

Since these data are preliminary, it's difficult to sort out why these different groups would have such disparate findings. But even if the Th1/Th2 proponents prove their case that a cytokine shift occurs, Romagnani and Fauci don't want the AIDS research community to conclude automatically that the result means that antibodies are bad and cell-mediated immunity is good. For one thing, they point out, the divisions between Th1 and Th2 are not absolute: Th1 cells, for example, do trigger production of antibodies, just not as effectively as Th2 cells. Romagnani and Fauci also contend that the Th1/Th2 nomenclature is being used too loosely: the cytokines Shearer and Clerici are measuring, as with the IL-10, may well not be the products of T helper cells.

Shearer concedes that he doesn't know which cells are responsible for the cytokine shifts, but he argues that the point is that the shifts occur. To reduce confusion, he has stopped referring to Th1 and Th2 cells and simply to Type 1 and Type 2 responses.

AIDS vaccine researchers backing the Th1/Th2 theory, like Jonas Salk of polio vaccine fame, believe it may hold the key to success if a vaccine can "lock" an uninfected person into a Th1-like state (*Science*, 28 May, p. 1270). Monkey experiments are now underway to test this hypothesis.

For therapy, researchers are becoming increasingly interested in treating HIV-infected people with Th1 cytokines. But Barry Bloom, a Howard Hughes Medical Institute Researcher at the Albert Einstein College of Medicine who has long been studying the effects of cytokines on leprosy, cautions that cytokines can be very toxic. He suggests a better strategy would be to give antibodies to the unwanted cytokines. "It's much easier to knock one out," Bloom says.

Nevertheless, Fauci's group currently is testing IL-2 and has had dramatic success (*Science*, 18 June, p. 1712) in some patients. Because he hasn't found Th2 responses in others, however, he believes that IL-2 success has more to do with restoration of cell-mediated immunity than a shutdown of Th2 cells. Genetics Institute in Massachusetts also hopes to begin tests soon of IL-12, a recently discovered Th1 cytokine.

Clerici is confident that a Th1/Th2-type theory—regardless of the nomenclature—will soon win over many critics as more animal and human data now in the pipeline are published. And while he acknowledges that the theory is very simple, he asks, "Who says things have to be difficult to be true?"

–Jon Cohen