



Primi. "It was the kind of thing you do where if it comes out with something, fine; if not, who cares."

To find the virus, Primi and his coworkers used random stretches of DNA called primers to fish DNA out of the blood samples of both the injecting drug users with AIDS and healthy controls. From a patient with the initials SEN, they found a large amount of an unknown virus, which they called SEN-V. Preliminary tests for the same agent in blood samples from patients with non–A-E hepatitis, provided by Mario Rizzetto of the University of Torino in Italy, suggested that they might have isolated the elusive hepatitis virus. Alter then sent Primi coded blood samples from both healthy people and those with non–A-E hepatitis. Primi found the virus in 10 of 12 people with transfusion-associated non–A-E hepatitis, four of 50 transfused people who did not develop disease, and one of 49 people who were not transfused. DiaSorin says the researchers have now analyzed nearly 600 blood samples, finding additional evidence for the virus in 13 of 19 people with unexplained chronic hepatitis.

If Primi and his colleagues have identified the non–A-E hepatitis virus, "it could potentially explain a lot of hepatitis," says Alter. But "the clinical relevance will be whether this virus can be shown to cause chronic liver disease," he points out. "Scientifically, I think it's sound. But it still can fall through. It was not a wise scientific decision to publicize this. It was an economic decision. I would have wanted a lot more data."

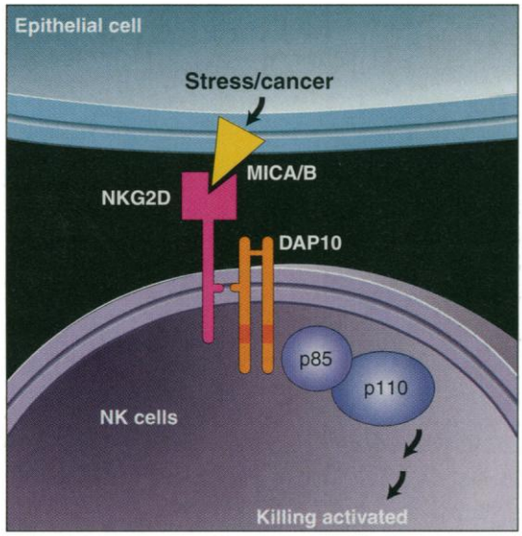
–JON COHEN

IMMUNOLOGY

## A Trigger of Natural (and Other) Killers

When the immune system goes to war against invading pathogens or the insidious internal attack of cancer cells, it can deploy an arsenal of weapons. Some, like the antibody-producing B cells or the T type of killer cells, only attack when set off by a specific antigen. But others, such as the so-called natural killer (NK) cells, are far less picky; they eliminate a variety of infected or cancerous cells. How NK cells are triggered to mount such sweeping attacks, while remaining able to tell friend from foe, has long puzzled immunologists. Now, parts of that mystery appear to be solved.

On page 727, a team led by Thomas Spies at the Fred Hutchinson Cancer Research Center in Seattle reports that it has identified the molecular trigger that may help some NK cells pick their victims, as well as the receptor that recognizes that molecule, a protein called MICA. Other receptors appear to be involved in NK activation, but their molecular triggers are largely unknown. The identification of MICA as the activator of the new receptor is particularly interesting because it suggests that the receptor is key to NK cells' specificity. MICA appears to be switched on in cancer cells or in cells under stress, as may happen when they are infected by a virus. And in a second report, on page 730, a team headed by Joseph Phillips and Lewis Lanier of the DNAX Research Institute in Palo Alto, California, identifies the internal signaling pathway through which the MICA receptor tells NK cells to activate their killing machinery.




**Making contact.** The MICA/B proteins on infected or cancerous cells serve as destruction tags that can be recognized by NK cells. The DAP10 adapter protein then passes the killing signal to other proteins (p85 and p110) in a signaling pathway not used by other NK receptors.

To cellular immunologist Lorenzo Moretta of the University of Genova in Italy, it "makes perfect sense" that MICA is a trigger for NK cells. "In normal cells MICA is not expressed; it's only turned on when something goes wrong," he says. Together, the findings may someday help researchers design drugs that beef up NK responses to cancer or infections.

The road that led to the current discoveries actually began with another cell type—the oddball γδ T cells, which constitute less than 10% of all T cells. The antigen-binding receptors (TCRs) of the much more common αβ T cells operate on a dual-recognition system; they are triggered by antigens displayed on the surface of antigen-presenting cells in conjunction with major histocompatibility complex (MHC) proteins. The γδ TCRs don't require MHC proteins for their activation, however.

Indeed, researchers weren't sure what activates some γδ T cells, but about a year ago, Spies's team found that a population of γδ cells that live in the intestinal lining are triggered when their TCRs contact either of two MHC-related proteins with hitherto unknown functions: MICA and its close relative, MICB. These proteins, the Spies team showed later, seem to be switched on in many tumors of the lung, breast, and other organs—implying that some of the cell-killing γδ T cells act as tumor watchdogs by spotting MICA/B-bearing cancer cells through their antigen receptors.

Because NK cells are themselves well known as tumor-cell killers, Spies and his colleagues, Stefan Bauer and Veronika Groh, wondered whether these or other immune cells would also be capable of recognizing MICA. To their surprise, the researchers found that MICA binds to almost all NK cells. Evidence that MICA marks the cells that display it for killing came when the researchers engineered cells that normally resist killing by NK cells—and that don't make MICA—to display the protein on their surface. NK cells, they found, made short work of these newfound targets.

Bauer also bagged the gene for the MICA receptor, by "subtracting" the active genes in cells that didn't bind MICA from the active genes in cells that do. Out of five candidates, "only one made sense," says Spies. This was the gene encoding a known NK cell protein called NKG2D, whose structure indicated that it is a surface receptor. Further work confirmed that NKG2D is indeed the MICA receptor. For example, Groh found that MICA-positive cancer cells could be protected from NK cells by antibodies against either NKG2D

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or MICA/B.

Meanwhile, Phillips and Lanier were also looking for NK cell receptors, but they were taking a different tack. They were searching through DNA databases for proteins that could transmit NK-activation signals the next step of the way—from the cell surface receptor into the cell. Such a molecule would presumably bind to the active receptor and could thus serve as bait to trap it. Lanier had a clue about the kind of protein to look for, because last year, his team had cloned the gene encoding a protein called DAP12 that performs the same job for another receptor that activates NK cells, and Lanier suspected that a related protein might perform the function for other receptors. Feeding the search algorithms with a *DAP12* sequence, Phillips and his colleagues came up with a new gene, *DAP10*, which resides right next to *DAP12* on human chromosome 19. "So we thought this is worth looking at," recalls Lanier.

The researchers then generated antibodies against DAP10, with which they hoped to pull out any putative NK cell receptor associating with DAP10. They fished out a single protein, which turned out to be NKG2D, the same receptor Spies's group had found. Says Lanier: "They had a ligand, and we had an adapter. We met in the middle at the NKG2D receptor."

By identifying DAP10 as a part of the machinery that relays the MICA signal into the cell, Lanier and Phillips's work may also help explain an unusual feature of the NKG2D receptor. Other immunologists have found that NK cells are endowed with receptors that turn down their killer activity when they contact the body's own MHC molecules. This keeps them from attacking normal cells. But MICA binding to NKG2D can override this inhibition. It may be able to do this, Lanier says, because NKG2D's partner, DAP10, feeds into a different intracellular signaling pathway than the inhibitory signals.

A good many questions still remain about NKG2D's functions, however. Because γδ T cells contain both it and a TCR, and both receptors seem to bind MICA, researchers wonder which of the two receptors is more important in activating these killer cells. Then again, says Spies, the answer may be simple. You may "need both receptors to elicit a strong response" in γδ T cells.

Also unclear is how important the MICA system is for controlling tumors. As immunologist Adrian Hayday of the University of London points out, "a lot of NK cells will kill tumor cells in a culture dish, but they won't do a good job in [the body], because tumor cells seem to have a superb capacity to turn off immune cells." He speculates that MICA recognition may serve mainly to ratchet up responses to pathogen-infected cells.

Whatever the physiological role of the MICA/NKG2D/DAP10 complex eventually turns out to be, however, these molecules are clearly not the whole story of NK cell activation. Indeed, researchers expect more NK cell receptors to emerge from test tubes and gene databases. "There's more to come in NK cell activation," predicts Eric Long of the National Institute of Allergy and Infectious Diseases. "This is a young field, and it's moving fast." –MICHAEL HAGMANN

FRENCH RESEARCH

## Support Builds for Allègre's Reforms

**PARIS**—After more than 3 months of hearings, debates, lab visits, and electronic forums, two parliamentary deputies have delivered their diagnosis of France's ailing research effort and a lengthy prescription for reviving it. Their 140-page report, presented personally to French Prime Minister Lionel Jospin on 22 July, broadly echoes controversial reforms previously suggested by France's research minister, Claude Allègre. Like Allègre, deputies Pierre Cohen and Jean-Yves Le Déaut—both of whom are also active researchers—urge that France break down the barriers between universities and public research organizations, as well as boost both the number of young scientists and their research opportunities.

Although many French scientists had resisted what they saw as Allègre's heavy-handed approach to reforming French research (*Science*, 18 December 1998, p. 2162), the initial response to the deputies' report—which contains 60 proposals urging change through mostly voluntary incentives—has been much more positive. Henri-Edouard Audier, a chemist at the Ecole Polytechnique near Paris who had often chided Allègre for trying to ramrod French science reforms, told *Science* that the proposals were "balanced, realistic, and effective." If they are put in place, Audier says, "it will make a profound change in French research." Harry Bernas, a physicist at the Orsay campus of the University of Paris, says that "Cohen and Le Déaut really listened" to the scientific community. Jospin's staff is now reviewing the recommendations, before the prime minister decides whether to put them in place. (Allègre himself is studying the report and has no comment on it yet, according to his spokesperson.)

Even if the reforms do go forward, however, not everyone thinks they go far enough. Among those disappointed is Pierre Chambon, director of the Institute of Genetics and Molecular and Cellular Biology near Strasbourg, who had argued for

## ScienceScope

**Waiting and Worrying** Preliminary signs are that biomedical research again will be the big winner in the 2000 budget, while other disciplines fight to keep from losing ground.

Last week, the House appropriations subcommittee for Labor, Health and Human Services, and Education scheduled a vote on a bill to raise the budget of the National Institutes of Health by 8.6% in 2000, to $16.95 billion, according to congressional aides. But the meeting was canceled after battles over tax cuts and domestic programs made it impossible to reach agreement. So Representative John Porter (R–IL), the subcommittee chair, put the plan on indefinite hold. The counterpart subcommittee in the Senate, chaired by Arlen Specter (R–PA), hasn't even set a date for a vote.

On Monday the House did take its first step toward funding the National Science Foundation (NSF). But the news wasn't good: The Housing and Urban Development–Veterans Affairs spending panel recommended a 1.5% cut in NSF's current $3.74 billion budget, which the Administration had wanted to raise by 5.8%. The panel deferred all but $35 million of a $146 million information technology initiative, including $35 million for a teraflops computer. However, it did approve $35 million of a proposed $50 million biocomplexity effort.

NSF director Rita Colwell didn't try to mask her disappointment. "We're able and ready to do 21st century science and engineering—but we can't do it on a 20th century budget," she said in a prepared statement. At the same time, NSF official Joel Widder says it could have been "a lot worse" had the committee not used an accounting gimmick: Appropriators declared $5.4 billion for veterans' health care and disaster relief "emergency" funding, so that it wouldn't count against the amount the panel can spend.

NASA received even worse news from the same panel, which cut $1.325 billion from its $13.67 billion budget. "These cuts would gut space exploration," says NASA Administrator Dan Goldin. "NASA has always stepped up to budgetary challenges, but this time [we] plan to fight." The full House was kinder to defense-related research, voting a 5.9% boost, to $8.25 billion, in the science and technology portion of the defense budget. That reverses the Administration's proposed cuts and tops the modest 1.1% increase in the Senate.