Immune Mystery Revealed: How MHC Meets Antigen

Four papers report discovery of a protein that may explain a critical step in cell-mediated immunity

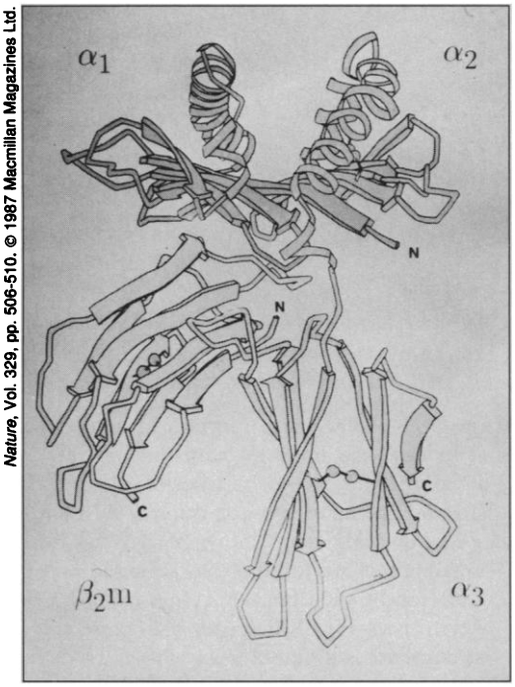
HOW DOES A VIRUS-INFECTED CELL TRIGGER an attack on itself by killer T cells of the immune system? The short answer is that the T cells recognize viral protein fragments displayed on the infected cell's surface by a class I major histocompatibility complex (MHC) protein, a phenomenon known as "antigen presentation." But buried in that answer is a puzzle that has haunted immunologists for years. The protein fragments, or peptides, must make their way across various membranes in the cell to meet the MHC protein and be transported to the cell surface. Yet the peptides lack a key molecular signal that ordinarily enables proteins to cross membranes. So how do they do it?

With the publication of four simultaneous reports in this week's issues of *Nature* and *Science*, the answer may be in. The four papers document the discovery of genes that apparently encode transporter proteins—in mice, rats, and humans—that could help shuttle peptides across intracellular membranes. "I think it's fantastic," says cellular immunologist Frances Brodsky, of the University of California, San Francisco. "It looks like it's going to clear up one of the major mysteries in class I antigen presentation." And beyond solving a basic mystery of cell biology, some immunologists speculate that the transporters may be partly responsible for variations in antigen presentation—as a result of which they might influence an individual's susceptibility to disease, including autoimmune disease.

Every nucleated cell is programmed to decorate its surface with bits of all the proteins it is making, regardless of whether those proteins are normally made by the cell or are produced by viral intruders. For presentation, each peptide is cradled snugly in a special groove in the class I MHC protein. Killer T cells act as inspectors, checking the presented peptides for foreign specimens and killing the cells that display them.

But in order to get to the surface, proteins or peptides must enter the membrane-bound endoplasmic reticulum, which serves as a way station for processing and packaging. Like other cell-surface proteins, the MHC molecules have a special signal sequence that gains them entry to the endoplasmic reticulum, are in fact efficiently presented—in bits and pieces—on the cell surface by the MHC. Townsend concluded that there must be a special transport protein that serves as a pump to move the proteins, or peptides derived from them, across the membranes.

Several years ago, Alain Townsend of John Radcliffe Hospital in Oxford observed that cytoplasmic proteins, which in their intact form lack the signal sequence and hence would never cross into the endoplasmic



Feeling groovy. *Viral antigens are nestled in a groove in the surface of the MHC type I protein, which appears at the top of this model of that protein.*

Last year, in an article in the *Annual Review of Immunology*, Townsend predicted that the pump required by his model might be related to oligopeptide permease, a protein that ferries small peptides into the bacterium *Salmonella*, and therefore may be a member of the ABC (for ATP-binding cassette) family of proteins, which includes, besides the permease, a variety of ATP-powered trans-membrane pumps, such as the multidrug resistance protein that expels chemotherapeutic drugs from some cancer cells. "There is only one known transport system that would fit the bill," Townsend recalls thinking. "That is the ABC transporter."

The findings published this week suggest he may be right. Each of the four groups found genes coding for proteins that appear to be members of the ABC transporter family, and all the genes are located in the chromosomal region where histocompatibility-related genes are clustered.

John Monaco and his co-workers at Virginia Commonwealth University in Richmond, Virginia, whose report appears on page 1723 of this issue of *Science*, happened on two transporter genes in the mouse MHC region, recognized that they may code for the peptide pump Townsend had predicted, and named them HAM-1 and HAM-2, for histocompatibity antigen modifier. John Trowsdale of the Imperial Cancer Research Fund in London and his colleagues (including Townsend) report in *Nature* that they found the human HAM equivalent in a similar search of the human MHC region. Jonathan Howard, of Cambridge University, found the rat HAM equivalent during a search for a gene he calls the class I modifier, whose variability seems to cause rats to reject tissue grafts from otherwise compatible donors; that paper is also in *Nature*.

The fourth team—headed by Thomas Spies of the Dana Farber Cancer Institute in Boston—was the only one that found a transporter gene while actually searching for the cause of a defect in antigen presentation. Spies and his colleagues Robert DeMars of the University of Wisconsin and Elizabeth Mellins and Donald Pious of the University of Washington used human cell lines that have deletions in the MHC region and fail to present antigen even though they make MHC protein. The Spies group found three genes that were deleted in all of the mutants with the defect. An additional defective cell line had all three genes—but failed to express one. The sequence of that gene suggests it is the human counterpart of HAM-1, and its location in the MHC suggests that it's the same one found by Trowsdale's group.

Although Spies' genetic evidence linking the transporter to the presentation defect is strong, confirmation of the transporter's role awaits experiments in which addition of a functional transporter gene restores antigen presentation to a defective cell line. To date, attempts by several labs haven't worked—possibly because deletions in the mutant cell lines have removed more than one essential gene, so that adding back the

transporter gene is not enough to restore function. But Spies has high hopes for restoration experiments that he and DeMars are conducting on the cell line in which the defect seems limited to the transporter gene.

Townsend wants to see a successful restoration experiment before he will declare his prediction fulfilled. "I'm very excited about the possibility that this gene is the transporter," he says, "but . . . the critical experiment hasn't been done yet. Once the genes are added back to restore the phenotype, then nobody will have any doubt."

If that happens, the results may have some significant implications in addition to solving the immediate puzzle. The transporter gene may play a role in selecting which peptides are displayed on the cell surface. Although cells display peptides from virtually all of the proteins they make, genetic variations between individuals do cause their cells to vary in the particular protein fragments they display. Since some peptides are better than others at stimulating the immune system, this can influence the strength of an individual's immune response. Variability in the transporter could be responsible for peptide choice.

"There probably are several steps in the process of antigen presentation where there will be variability between individuals," says Stanford immunologist Hugh McDevitt. "I could imagine two different forms of a pump, which would selectively transport some peptides better than others. But that's just pure speculation at this point."

And if there is variability in the transporter, says McDevitt, it might participate in autoimmune diseases, in which the immune system goes astray and attacks the body's own tissues. The region of DNA where the transporter gene sits seems to be associated with some autoimmune diseases, such as rheumatoid arthritis and diabetes, and researchers are on the lookout for genes in that area whose variability could explain the predisposition. Monaco suggests a scenario in which selective presentation of peptides may allow the immune system to attack healthy tissues; McDevitt plans to study the human transporter genes for such variabilities.

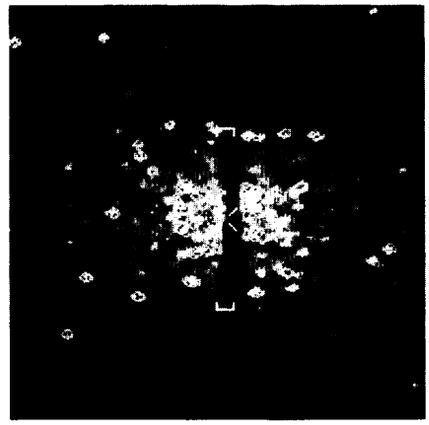
But whether or not the transporter unlocks mysteries such as autoimmunity, immunologists are delighted that it may explain the riddle of peptide transport within the cell. UCSF's Brodsky remembers telling some cell biologists about class I antigen presentation. "They threw up their hands and said it's impossible [for peptides to get from the cytoplasm into the ER]. Now this shows that it's not impossible, that there is a possible explanation."

■ MARCIA BARINAGA

Astro-1: From the Jaws of Defeat

Halfway through the trouble-plagued Astro-1 mission aboard the space shuttle earlier this month, a NASA official asked mission scientist Theodore Gull a crucial question: "Can you pull this thing out of the bucket?" Gull's response was tentative: "I think so but I don't know if there's enough time." But now that the 9-day mission is over, Gull, an astrophysicist at NASA's Goddard Space Flight Center, is downright jubilant. Against all odds, the Astro-1 team repelled an onslaught of technical problems and collected data so good that Gull says, "I'm still floating 4 feet off the floor." "We pulled this mission out of a real jam," he boasts.

The "real jam" was caused by two broken computers, an errant telescope pointing system, and lint-clogged air ducts—which together threatened to turn the $150-million Astro-1 into yet another NASA failure. But in the end, the scientists and engineers running the mission managed to resuscitate remotely three ultraviolet telescopes and one x-ray telescope in the shuttle's 60-foot cargo bay in time to capture data of 135 objects. While the astronomers admit they fell short of their goal of observing 200 targets, what they did get should keep them busy.



Ultraviolet target. *M92, a globular star cluster, was among Astro-1's successes.*

The Astro-1 scientists are particularly fired up by preliminary data from three instruments (they had yet to develop the ultraviolet film from a fourth). A quick look at the data already has revealed some surprises about the ultraviolet sky. This indicates that scientists don't fully understand the violent processes that emit light in the ultraviolet, such as the perturbation of hot gases and intense magnetic fields that surround such energetic objects as active galaxies, quasars, black holes, and rapidly spinning stars. "We're going to rewrite the textbooks," promises Gull. "There's nothing like a lot of solid data to knock down a few theories."

In fact, the findings from one instrument—the Wisconsin Ultraviolet Photo-Polarimeter Experiment (nicknamed WUPPE)—are so strange they already are shaking up theories about the way dust and other material is spewed from rapidly spinning dying stars, known as Be stars, before forming a disk around them. The astronomers are finding that something is preventing polarized light from being scattered by the dust as much as expected. And a look at a well-known old star—Betelgeuse—also is perplexing, because the way polarized light travels through its atmosphere is different from what is predicted by theory.

Not all the early data run counter to expectations, of course. One observation may provide the strongest evidence so far—perhaps even proof—for a massive black hole at the core of the most brilliant quasar ever observed—3C273, in the outskirts of the Milky Way. The Astro researchers also think they have data that could settle once and for all whether the primordial dust that condensed to make the first stars and galaxies still exists and is detectable. And they have announced preliminary results that provide the strongest evidence to date that interstellar dust is made of graphite, a finding that has implications for theories about the way stars are made from this dust.

Another instrument—called the Ultraviolet Imaging Telescope—has collected images of galaxies and stars that are of such good quality that the scientists predict when the film is developed there will be up to 1000 galaxies in every frame, including many never seen before. "It's going to be a guidemap for future observations, especially with the Hubble Space Telescope and if Astro flies again," enthuses Gull.

Yet therein lies the rub: There is virtually no hope that Astro will fly again—even though the array of instruments originally was scheduled to fly at least eight times on the shuttle. NASA assistant associate administrator Joseph K. Alexander confirmed last week that there was no money in the administration's draft 1992 budget for Astro-2. "With regret, we're essentially forced to have to put Astro-2 off the list." It's a bittersweet ending to a tough mission.

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