Immune Molecule's 3-D Structure Revealed

With a thrill akin to that accompanying the first live pictures from the moon, scientists are gazing upon the first three-dimensional pictures of a human leukocyte antigen, or HLA – the mysterious molecular complex that is essential to the body's killer-cell immune response. The pictures, laboriously derived by means of X-ray crystallography, are the work of researchers at Harvard and Stanford universities and appear in the Oct. 8 NATURE. The molecule's newly revealed structure brings a decade of immunology research into perspective, and opens new possibilities for manipulating the immune system to fight a broad spectrum of diseases and immune abnormalities.

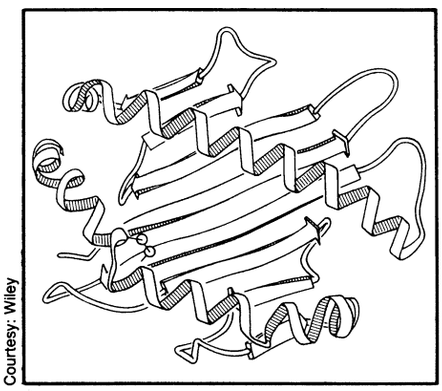
With few exceptions, existing immune-boosting and immune-suppressing drugs are designed to affect antibody-mediated rather than HLA-mediated immunity, in which killer T-lymphocytes attack foreign invaders. Scientists have recognized the existence of HLA since 1974, and for years have gathered bits of information about this all-important ingredient of cellular immunity.

But an understanding of the molecule's function – and how to manipulate it – has always been limited by the lack of knowledge about its structure. How is it, scientists wanted to know, that HLA binds to disease-causing antigens and then presents these antigens to killer T-cells, thus initiating their aggressive immune response?

To discern the molecule's three-dimensional shape, Donald C. Wiley, Mark A. Saper and their colleagues at Harvard, and Pamela J. Bjorkman at Stanford, managed to culture human cells containing an especially pure form of one particular variant of HLA. They then crystallized the purified HLA in two different ways, and subjected the tiny crystals to intense bursts of X-rays. By comparing the resulting patterns of scattered X-rays for the two crystal variants, the researchers were able to "back-calculate" an electron density map that effectively shows the atomic structure of the molecule with a resolution of 3.5 angstroms or ten-billionths of a meter.

"At the chemical level it should now be possible to figure out how foreign antigens are recognized by T-cells," Wiley told SCIENCE NEWS. "It's one of those things where immediately upon looking at the structure a lot of things start to make sense."

One thing that made immediate sense was the way in which HLA binds key pieces of invading foreign antigens, or peptides. The researchers found that the string of amino acids that makes up the HLA molecule is uniquely folded upon itself into a mass that is shaped like a flat-bottomed ravine. Each wall of the ravine is made of an amino acid coil, or helix, and the ravine is just big enough to accommodate a piece of foreign peptide.



Courtesy: Wiley

Schematic drawing of HLA. Foreign peptide would nestle in the "ravine" between the two helices.

By sketching HLA's already-known amino acid sequence onto its newly discovered three-dimensional structure, the researchers found that nearly all of the amino acids that previously had been identified as being involved in the binding of foreign peptides end up inside the HLA ravine. Other evidence virtually confirms that this ravine is indeed HLA's peptide-binding site. It's thought that killer T-cells can straddle the two ravine walls and "read" the amino acid code of the captured foreign peptide, and that the T-cells are thus "programmed" to seek out and attack other identical proteins.

With a better understanding of this programming process, the researchers foresee being able to manipulate the immune system with custom-made synthetic peptides. Indeed, they say, rationally designed peptides could in theory either act as vaccines or, in the case of immune-suppressing peptides, be useful as therapies for autoimmune diseases or to suppress graft rejection.

"Fifteen years ago this wouldn't have been so great, because it was so hard to synthesize peptides," Wiley says. "But now we can synthesize peptides like crazy. Everybody can make them, and in great quantities. Now it's a whole new ball game."

– R. Weiss

Jarring notice of California quake dangers

The magnitude 6.1 earthquake that rattled Los Angeles on Oct. 1 was a jolting reminder of the hazards of living in earthquake country. Along with its aftershocks, the quake was responsible for at least six deaths and more than $100 million in damage, giving Angelinos a tiny taste of a much larger quake expected to hit the San Andreas fault in the next several decades.

But even though the Oct. 1 quake sprang from the same forces straining the San Andreas, seismologists say it was too far from the San Andreas to release that fault's strain or alter the likelihood of the predicted great quake. The recent shaker was centered in Rosemead, 55 kilometers west of the San Andreas.

California earthquakes result from the Pacific plate's northwest drive past the North American plate at a rate of 5.6 centimeters a year. Near Rosemead, the San Andreas slides only 2.5 cm/yr, leaving the rest of the motion for nearby faults.

The recent earthquake, however, was only "a little detail" of this larger motion, says seismologist Lucille Jones at the U.S. Geological Survey in Pasadena, Calif. The quake's main scientific significance, she says, is that it may help researchers understand the processes by which faults end at sedimentary basins. It broke at the tip of the northwest-trending Whittier fault, which, like most California faults, is mostly strike-slip, with the blocks sliding past one another horizontally. This earthquake, however, was a thrust quake, with one block being pushed up over the other at the end of the Whittier fault.

It was the region's strongest quake in 16 years. Essentially, says Jones, it was not predicted. However, she adds, the day before the quake she had noticed that 11 months had passed since there had been an earthquake of magnitude 4 or greater. This was the longest such "quiescence" period for the area in 55 years of record keeping. The previous quiescence period had lasted nine months and ended untheatrically with a magnitude 4 quake.

The interesting thing about the more recent quiescent period, says Jones, is that southern California was quiet except that Los Angeles was rocked by more magnitude 3 quakes than usual. The problem now, she says, "is that we don't have any idea of how often something like that is followed by a major event. But maybe in the next years, this will seem significant and we might be able to use it to predict future earthquakes."

In the meantime, residents will have to prepare for the inevitable. Magnitude 6 quakes occur in southern California every four or five years, and the San Andreas's "big one" still lies in wait.

– S. Weisburd