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## Structural Biology Reveals How T Cells Recognize Transplanted Tissue

Before T cells are sent into battle, these sentinels of the immune system must complete a rigorous educational process. There are basically two things a T cell must demonstrate before it makes the grade. It must recognize specific molecules on the surface of foreign cells. And it must refrain from attacking the body's own healthy cells.

But researchers who spy on T cells for a living know that there are also gray areas where T cells can cause trouble. One such example is transplanting healthy foreign tissue, such as a heart or kidney. Researchers have long puzzled over how T cells can recognize both self and foreign cells. This flexibility, they say, may improve the immune system's chances of catching and destroying a broad range of pathogens. But it also presents a major clinical obstacle, leading to rejection of genetically mismatched organ transplants.

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Now, researchers led by Howard Hughes Medical Institute investigator K. Christopher Garcia have established how the structure of receptors on the surface of T cells enables this dual recognition, a phenomenon known as alloreactivity.

Garcia and his colleagues found that T-cell receptors that adeptly recognize foreign or self antigen-displaying molecules can do so using highly divergent structural solutions. Garcia and his colleagues at the Stanford University School of Medicine collaborated with researchers led by co-author David Kranz of the University of Illinois at Urbana-Champaign. The researchers published their findings in the April 6, 2007, issue of the journal *Cell*.

The immune system's rejection of transplanted organs has been difficult to explain from an evolutionary perspective, according to Garcia. Transplantation from person to person is not something that human biology could have ever anticipated, he said. We evolved immunity against pathogens, but why would we evolve immunity against each other? We are not pathogens for each other, so why when you get a liver transplant from a genetically mismatched person do you reject that liver? I think these findings about the basis of alloreactivity expand our understanding of this process. Better understanding of the fundamental underpinnings of the immune system could help in developing new ways to prevent transplant rejection by damping alloreactivity, he said.

In humans and most other vertebrates, molecules known as major histocompatibility (MHC) proteins are nestled into the outer membranes of all cells. Short protein fragments fit into the MHC proteins, where they are seen and recognized by T cells. In most cases, the T cells ignore MHC molecules that display fragments of protein from the body's own cells. But when they detect an MHC molecule carrying a protein fragment from a bacterium, virus, or other invader, the T cells launch an attack.

Structural biologists have captured detailed images of various T cell receptors clasping onto MHC molecules and their cargo, but these pictures have left them puzzled as to how a single T cell receptor can recognize structurally distinct MHCs. Many scientists suspected that although the shape of MHC molecules varies between individuals, they might share some similarity that T cells receptors could recognize.

Using x-ray crystallography, Garcia and his colleagues set out to analyze how the structure of a specific type of T-cell receptor changed depending on whether it was grabbing onto a self or foreign MHC molecule. In x-ray crystallography, crystals of protein are bombarded with intense x-ray beams. As the x-rays pass through and bounce off of atoms in the crystal, they leave a diffraction pattern, which can then be analyzed to determine the three-dimensional shape of the protein.

Naturally occurring T-cell receptor and protein-MHC complexes have proven difficult to crystallize, so Kranz and his colleagues used novel protein engineering techniques to create smaller, stable versions.

These structures, as well as other experiments we did, showed that the T-cell receptor uses a completely different recognition mechanism for the foreign and self MHC-protein complex, said Garcia. Instead of recognizing the similarities, it actually recognizes the differences between them. This was a huge surprise, and it has significant implications for understanding the co-evolution of genes for T-cell receptors and for MHC proteins, he said.

There is likely some kind of recognition code between T-cell receptors and MHC molecules, because they have co-evolved. And the fact that the T cell recognizes the foreign MHC in an alternative way from how it recognizes the self MHC means that the T-cell receptor has not only co-evolved with self MHC genes; it has also co-evolved with foreign MHC genes as well. Thus,

said Garcia, the body's vast repertoire of T cell receptors has evolved a memory of the MHC molecules that recognize foreign as well as self proteins.

Garcia said understanding how a T-cell receptor employs different binding strategies could help biologists understand how other proteins can bind to very different molecules. There are a lot of cases of one protein binding many different proteins, and the general explanation has traditionally been molecular mimicry—that these cross-reactive molecules somehow mimic one another structurally, he said. But in this study we found that it was possible to have robust binding solutions for very structurally divergent molecules in the absence of any mimicry. So, one need not invoke molecular mimicry, or any structural similarities, in cases where one protein reacts with many proteins, he said.