How T Cells Recognize Potentially Harmful Invaders

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DENVER — Researchers at National Jewish Health have answered a long-standing question about how the immune system selects T cells that recognize and attack potentially harmful invaders, while leaving alone a body's own tissues. More specifically, the research team led by Professor of Immunology Philippa Marrack, PhD, and graduate student James P. Scott-Browne, showed that T cells have evolved a genetic predisposition to bind with MHC molecules, which present pieces of possible invaders to T cells for inspection. Their findings are being published in the April 23, 2009, issue of the journal *Nature.*

"This tells us that the recognition of antigen by T cells is so important that evolution will select for any characteristic that helps T cells better recognize invaders," said Dr. Marrack.

T cells act as both sentinels and destroyers. Hundreds of billions of T cells roam the human body searching for anything that doesn't belong and may be harmful. Once a potential invader is detected, some T cells directly attack infected cells, while others call in additional defensive resources.

The T cell's main sensory organ is its aß T-cell receptor, a protein that sits on its surface. As a T cell circulates through the body, it encounters other cells. Some of these cells display pieces of foreign molecules, known as antigens, on their surface. They are either infected cells signaling their infection or scavenger cells that have gobbled up invaders or pieces of them. These cells hold the antigen in a molecule known as the major histocompatibility complex, or MHC. The MHC-antigen complex has been likened to a hotdog (antigen) held in a bun (MHC). If a T cell's receptor is the right shape it can bind to the MHC-antigen complex, thus recognizing the presence of a foreign invader.

The immune system pumps out billions of T cells, each carrying a slightly different T-cell receptor capable of binding to and recognizing a different MHC-antigen complex. In this manner, T cells form a defensive army capable or recognizing just about any potential enemy.

How does it produce such a formidable defense, one that attacks only foreigners but not the body it is protecting? It all happens in the thymus, a little organ just under the breastbone. There, immature T cells are selected to live or die, based on the binding properties of their receptors. Each immature T cell constructs its own unique receptor from a variety of genetically determined units, known as V, D, and J segments, plus a smattering of random amino acids that connect these segments. There are more than a trillion different possible combinations.

Many of those combination make excellent sentinel/warriors for the immune system. But many of these random combination would sense and attack molecules that are part of the body's own tissue, which is what happens in autoimmune diseases such as diabetes, lupus or rheumatoid arthritis. Others recognize nothing and offer no benefit.

So, a two-step process has evolved to weed out the bad or useless and release the good. The first step positively selects for T cells capable of recognizing MHC, the molecule that holds and presents antigens. If an immature T-cell receptor can bind to an MHC molecule holding a self-antigen, it triggers a signal that saves the T cell from suicide. The second step, negative selection, eliminates T cells with receptors that bind too strongly to the MHC-self-antigen complex. (This concept was initially demonstrated National Jewish Health by Dr. Marrack and Dr. John Kappler in 1987.) Thus the thymus acts something like Goldilocks, selecting for survival just the right T cell whose receptor binds strongly enough, but not too strongly to the MHC-antigen complex. Less than one percent of the immature T cells survive this selection process; the vast majority are eliminated before they can leave the thymus.

For several decades immunologists have wondered about this original population of immature T cells. Are they just a completely random set of T cell receptors out of which a relatively tiny population of MHC-recognizing T cells emerge? Or do all the immature T cells begin life with a built-in, genetically programmed affinity for the MHC molecule? Dr. Marrack and Mr. Scott-Browne sought to answer this question.

Recent evidence had suggested that almost all T cells bind the MHC-antigen complex in a similar, diagonal manner, and that three amino acids, found in a specific location on many T-cell receptors, were especially important for this binding. So, the researchers created mutant T cells that had different amino acids at those suspected binding sites. They found that the mutant T-cell receptors bound MHC-antigens less strongly.

Next, they transferred these mutant T cells into mice to see what effect they might have on the immune system. In mice whose T-cell receptors lacked these crucial amino acids, fewer T cells survived the selection process and were released into the body. Also, T cells that did survive had a less diverse population of receptors.

Thus, the researchers concluded, the relatively constant, genetically determined sections of the T-cell receptors contain specific sections that predispose them to recognize and bind the MHC molecule. The more diverse parts of the T-cell receptor help determine how the receptors recognize specific antigens.

‘I believe we provide a clear answer to a question that has puzzled immunologists for more than 40 years," said Mr. Scott-Browne. "Selective pressure has shaped T-cell receptor genes so that they are genetically programmed to recognized the MHC molecule that presents antigens. This is such an critical function within the immune system that it may be better to genetically encode it, rather than leave it simply to chance."

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