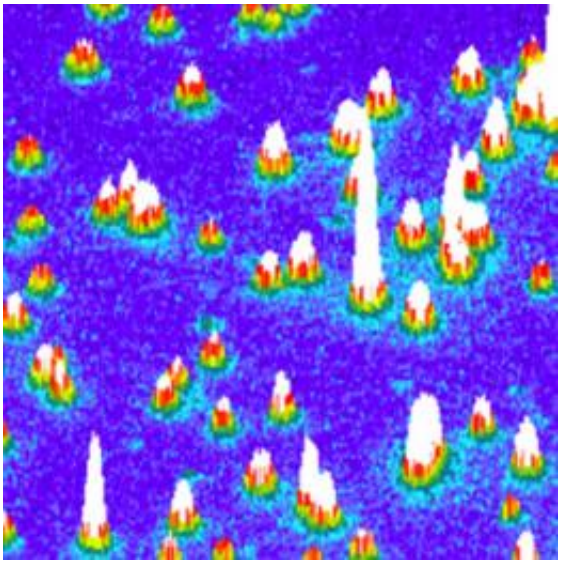
Immune system uses heart channel to select powerful defenders

August 16 2012, By Michael C. Purdy



Immune T cells take in calcium as part of a screening process in the thymus. The testing ensures that the T cells react neither too strongly nor too weakly. Each "island" in this image is an individual T cell; the height of the island indicates the amount of calcium they have taken in.

(Medical Xpress) -- When the body makes immune T cells, it relies on a molecular channel more commonly seen in nerves and heart muscles to ensure that the powerful T cells have the right mixture of aggressiveness and restraint, researchers at Washington University School of Medicine in St. Louis have discovered.

Scientists report online in Nature Immunology that fledgling T cells

temporarily make a protein that creates an opening in their surfaces known as a voltage-gated sodium channel. The cells only make the protein at key points in a testing process that occurs in the thymus, an immune organ located near the heart. The channel allows the cells to "hear" the results of testing, which eliminates an estimated 95 percent of potential T cells.

"The thymus applies a kind of Goldilocks principle, seeking the cells that are just right, rather than those that are too hot or too cold," says senior author Paul Allen, PhD, the Robert L. Kroc Professor of Pathology and Immunology. "The goal is not only to screen out the T cells that won't react to invaders, but also to eliminate over-reactive T cells that could attack the body and cause autoimmune diseases. The voltage-gated sodium channel is the opening through which the T cell learns its fate."

According to Allen, the finding is an important step forward in understanding how the immune system builds a repertoire of tens of millions of T cells, each primed to fight individual bacterial and viral invaders. Understanding this process will help scientists find better ways to control and enhance the immune system's ability to fight diseases and cancer.

T cells develop in the thymus from a bone-marrow derived precursor. Each cell has a different receptor on its surface that is produced by scrambling the body's own genetic material. The vast majority of these cells will never be activated, but some will match proteins found in infectious agents and help the body recognize and kill those agents.

After they are created, the cells are tested in the thymus. This includes tests of their ability to recognize a special molecule found on the surface of most cells. The molecule holds pieces of proteins made inside the cell in a fashion similar to a bun holding a hot dog. This display helps the T

cells recognize infected cells by revealing pieces of proteins made by the infectious agent. When they encounter proteins made by bacterial or viral invaders, the T cells attack the infected cells.

“During the thymus testing process, though, the hot dogs are pieces of the body’s own proteins,” Allen explains. “The test is repeated multiple times with samples of many different proteins. Ideally, the T cell will recognize these assemblies but will not attack them because they are proteins made by the self.”

If the T cell doesn’t recognize the hot dog in a bun at all, it soon dies from lack of interaction with other cells. If it attacks too strongly, the T cell needs to be killed.

“What has puzzled immunologists for some time is how the results of this testing are conveyed to the T cell,” Allen says. “The positive selection or ‘you passed the test’ signal comes from a weak interaction between the T cell and the hot dog. Weak interactions are normally associated with weak signals, and in this case the signal is a sustained flow of calcium ions into the T cell.”

The voltage-gated sodium channel empowers the T cell to transform this trickle of calcium into a strong signal.

In earlier research, Allen identified a protein that helps a specific T cell pass the thymus tests. For the new study, Wan-Lin Lo, a graduate student, used a gene chip to monitor the proteins made by that cell as it passed through the thymus’ tests.

“We learned the cells were making these voltage-gated sodium channels at exactly the right times when they needed to be more sensitive to signals from the thymus,” Allen says. “These channels and their ability to amplify and sustain signals are well-known from their extensive use in

nerve cells and muscles including the heart."

Allen plans additional research with Washington University colleagues who work more regularly with the voltage-gated sodium channel and other similar channels to learn more about the channel's functions in this unusual context.

More information: Lo W-L, Donermeyer DL, Allen PM. A voltage-gated sodium channel is essential for the positive selection of CD4+ T cells. *Nature Immunology*, doi:10.1038/ni.2379

Provided by Washington University School of Medicine in St. Louis

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