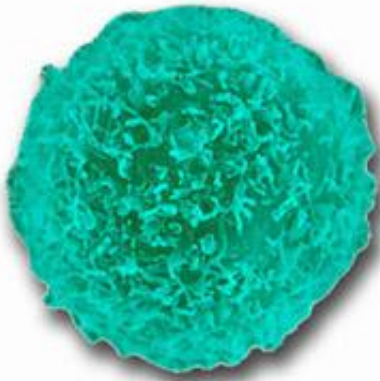


Researchers zero in on a way to switch off T-cells that cause leukemia

March 5 2010, By Melissa Beattie-Moss



A human T-cell. Image: AJ Cann

(PhysOrg.com) -- Thanks to research that combines molecular biology with computer modeling, we may be several steps closer to winning the battle against a rare form of blood cancer known as large granular lymphocyte leukemia.

Thomas Loughran, director of Penn State Hershey Cancer Institute, and Réka Albert, professor of physics and biology at the University Park campus, worked together to better understand the molecular pathways and hundreds of genes and proteins inside a cell that determine its life cycle.

Their study, published in October 2008 in the *Proceedings of the National Academy of Sciences (PNAS)*, suggests that there are two key proteins controlling "the on/off switch" in the malfunctioning killer-T cells that cause this type of leukemia. Says Albert, "Our model suggests that if we keep a specific signaling protein called NF κ B in the 'off' state, we can reverse the disease."

The study, funded by the National Institutes of Health and the National Science Foundation, first took shape because Loughran and his colleagues at the Cancer Institute wanted to investigate why, in rare cases, the body's normal immune response to fighting infection goes awry and causes disease.

In a normal immune system, explains Loughran, the body produces large numbers of a type of white blood cell called cytotoxic T-cells or killer T-cells. These cells are "programmed" by the body for a very narrow and specific mission: to kill infected cells and then die themselves.

Loughran said that occasionally, these killer cells fail to follow their scripted lifecycle.

"When these cells don't die as expected, they expand gradually over time and start attacking the body itself," he said. "They can attack the joints to cause autoimmune diseases such as rheumatoid arthritis, and attack the bone marrow to cause leukemia."

Loughran knew that, to find answers, he'd need to zero in on the exact location of the malfunctioning signaling system. This system is the way cells send and receive instructions -- and a broken system might explain why some T-cells never receive the crucial "self-destruct" message. To unravel the mystery of these rogue killer-T cells, Loughran called on Albert to construct an intricate computer model of the signaling network involved in both the activation of the T-cells, as well as their

programmed death.

Albert brought impressive knowledge to bear on the problem. A disciple of acclaimed network researcher Albert-Laszlo Barabasi and co-author with him of the concept now known as the Barabasi-Albert model -- she explains her work as an attempt "to find the mathematical model that will most accurately describe how a system changes over time."

When researchers are investigating a complex problem in a biological system, such as drought stress in plants or diseases in animals or people, a computational representation can help them predict likely outcomes, Albert said. In this case, "the biggest challenge for constructing the computational model was to think about the disease as a state that includes the deregulation of the signaling network that guides activation-induced cell death in T cells," she said.

It took several years of effort by a very talented graduate student, Ranran Zhang (the first author of the *PNAS* paper), guided by two mentors, to make this crucial step, said Albert.

"Afterward we were able to use methodology that my group has developed and used successfully in the context of other biological regulatory networks. Nevertheless, this is the most complex dynamic model we have constructed so far."

Among the billions of possibilities projected by the model, the researchers determined that two proteins -- IL-15 and PDGF -- appear to be crucial in keeping the T-cells alive and growing.

"You need the presence of both these proteins, as well as the signaling protein NF κ B, to create conditions in which the cytotoxic T-cells can proliferate," said Loughran.

Essentially, Loughran said, "We are looking for the master control switches that keep these cells alive. When we used drugs to block NF κ B in cells from leukemia patients, we found a significant increase in mortality among the abnormal T-cells."

Someday Loughran hopes our control of these "master switches" may allow us to turn off the long-lived killer T-cells that cause [leukemia](#), as well as harness their errant behavior to combat other deadly infectious diseases.

Provided by Pennsylvania State University

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