MedicalXpress

Silencing a protein could kill T-Cells, reverse leukemia

October 22 2008

Blocking the signals from a protein that activates cells in the immune system could help kill cells that cause a rare form of blood cancer, according to physicists and oncologists who combined computer modeling and molecular biology in their discovery.

Researchers say the breakthrough could provide more efficient ways of targeting diseases such as leukemia, and help in the potential development of vaccines for viruses that cause AIDS.

The human immune system has a two-part strategy when dealing with infections. It generates antibodies that bind with bacteria and viruses to neutralize them. For a short time, the immune system also produces large numbers of a type of white blood cell, cytotoxic T-cell that kills other infected cells.

Once the pathogens are eliminated, these killer T-cells quickly die on their own, save for a few that remain in case the same infection returns. But in rare cases, these cells fail to follow their scripted lifecycle.

"When these cells don't normally die, they expand gradually over time and start attacking the body itself," said Thomas Loughran, M.D., lead author and director of Penn State Hershey Cancer Institute. "They can attack the joints to cause autoimmune diseases such as rheumatoid arthritis, and attack the bone marrow to cause leukemia."

Loughran, professor of medicine, and his Penn State colleagues are

trying to tease out the conditions that cause the abnormal expansion of T-cells and trigger a disease known as large granular lymphocyte leukemia. So they constructed an intricate computer model illustrating the signaling network involved in the activation of the T-cells, as well as their programmed death.

The network model strings together complex data of molecular pathways inside a cell involving hundreds of genes and proteins and tries to predict an outcome based on how the genes and proteins interact.

"The interactions among proteins make them turn ON or OFF or intermittently ON or OFF to get billions of possibilities with hundreds of proteins," said Reka Albert, co-author and Penn State associate professor of physics and biology. "By simulating the protein interactions and tracing the ON/OFF states of all those proteins at the same time, we can see whether the cells live or die."

Albert explains that the model could help researchers zero in on the exact location of the signaling abnormalities that are keeping T-cells from dying. Once that is known, specific genes or proteins could be targeted with drugs to get rid of the abnormality.

Sifting through the billions of possibilities projected by the model, the researchers have found two proteins – IL-15 and PDGF – that appear to be crucial in keeping the T-cells alive. While IL-15 is key to the survival and activation of T-cells, PDGF stimulates the growth of those cells.

"You need the presence of both these proteins to create conditions in which the cytotoxic T-cells can proliferate," said Loughran, whose team's findings were recently published this week in the *Proceedings of the National Academy of Sciences*. "That is a major point of the discovery."

The researchers have also discovered another signaling protein -- NFêB -- controlled by the two proteins, which protects cancer cells from dying if it is over expressed.

"NFêB controls a host of other proteins related to inflammation in the body and our model suggests that if we keep it in the OFF state, it is able to induce cell death in the T-cells," explained Albert, who, together with graduate student Ranran Zhang, created the model. "In other words, we can reverse the disease by setting this molecule OFF."

When researchers blocked NFêB with drugs in cells from leukemia patients, they found a significant increase in mortality among the abnormal T-cells, suggesting that NFêB helps in the survival of leukemia cells.

"Basically when this protein is inhibited and not expressed anymore, the cells die," said Loughran. "It validates our model."

It is still unclear as to what prevents the T-cells from dying off, though researchers suspect that a chronic virus might be continually activating the cells. However, there is no clear evidence for the theory, but network modeling may be a start.

According to Albert, such models could save time and money in pointing out promising candidates – genes and proteins – for drug delivery. "Our model provides a shortlist of therapeutic targets that can be manipulated with drugs to kill off leukemia cells," she added.

The Penn State researchers are also looking to harness errant behavior of the T-cells in combating other deadly diseases.

"In complicated infections like HIV, and in diseases such as cancer, you need to have an immune response that comprises both antibodies and

cytotoxic T-cells," explained Loughran. "The problem is nobody has been able to generate a long-lived cytotoxic T-cell response in normal people."

Since T-cells in people suffering from large granular lymphocyte leukemia are active, long-lived, and function like killer T-cells, Loughran believes that if his team can unlock the secret behind these cells' longevity, then T-cells in normal healthy people could be equipped with the same ability to fend off other deadly infections.

"The key is to find the master control switches that keep these cells alive," said Loughran, whose work is funded by the National Institutes of Health and the National Science Foundation. "And maybe those could be blocked directly."

Source: Penn State