Team identifies molecular switch enabling immune cells to better fight disease

January 20 2013

A research team led by the La Jolla Institute for Allergy & Immunology has discovered the mechanism that enables CD4 helper T cells to assume the more aggressive role of killer T cells in mounting an immune attack against viruses, cancerous tumors and other damaged or infected cells. The finding, made in collaboration with researchers from the RIKEN Institute in Japan, could enable the development of more potent drugs for AIDS, cancer and many other diseases based on using this mechanism to trigger larger armies of killer T cells against infected or damaged cells.

CD4 helper T cells, which normally assist other cells of the immune system during an infection, and CD8 killer T cells, which directly attack and eliminate infected cells, are two of the body's most important immune cells for defending against diseases. Earlier research studies have shown that helper T cells can become killer cells in some instances. However, the specific mechanism of action that allowed this to occur was not known until now.

"We have identified the molecular switch that enables CD4 T cells to override their programming as helper cells and transform into cytolytic (killer) cells," said La Jolla Institute scientist and study co-leader Hilde Cheroutre, Ph.D. "Our team also showed that these transformed helper T cells represent a separate and distinct population of cells. They are not a subset of TH-1 helper cells as previously thought."

Jay A. Berzofsky, M.D., Ph.D., chief of the Vaccine Branch at the

National Cancer Institute's Center for Cancer Research, called the finding "a major advance" that provides new understanding about the cell's lineage and basic mechanisms. Dr. Berzofsky was among the researchers whose work in the 1980s first demonstrated that helper cells could convert to killer cells. "Understanding how these cells derive and what causes them to switch from helper T cells to cytolytic T cells is an important step to learning how to manipulate them in disease," he said, noting it could lead to novel approaches "either to turn these cells off in autoimmune disease or turn them on in infectious diseases."

He added that the finding could also have important implications in cancer. "We need all of the cytolytic machinery that we can get to try to destroy cancers," he said. "If we can learn to turn them on, I think it's reasonable to believe that these cytolytic T cells can play an important role in controlling cancer."

The findings were published today in *Nature Immunology* in a paper entitled "Transcriptional reprogramming of mature CD4 helper T cells generates distinct MHC class II-restricted cytotoxic T lymphocytes." Dr. Cheroutre is co-senior author on the study together with Dr. Ichiro Taniuchi of the RIKEN Research Center for Allergy and Immunology in Yokohama, Kanagawa, Japan. First authors on the paper are: Mohammad Mushtaq Husain, Ph.D., of the La Jolla Institute; Daniel Mucida, Ph.D., formerly of the La Jolla Institute, now at Rockefeller University; Femke van Wijk, Ph.D., formerly of the La Jolla Institute, now at the University Medical Center Utrecht, The Netherlands, and Sawako Muroi, of the RIKEN Institute.

Mitchell Kronenberg, Ph.D., La Jolla Institute president & chief scientific officer, said the study reflects the very successful collaboration between the La Jolla Institute and RIKEN in Japan, which have joined efforts on a number of projects over the years.

In the study, the researchers found that a certain transcription factor, which are molecules in the cell nucleus that control the activity of cells, continually suppresses the killer T cell lineage in helper T cells. Using mice, the team showed that turning off this transcription factor (ThPOK) enabled the helper cells in the body's peripheral areas, like the blood, spleen and the intestine, to override their original programming and to become killer T cells. "While our work focused on the intestines, we found that helper T cells in all tissues of the body have the potential to become killer cells in response to recognition of viral, tumor or other antigens in the context of cytokines such as IL-15," said Dr. Cheroutre.

Jonathan Braun, M.D., chair of the Department of Pathology and Laboratory Medicine at UCLA's David Geffen School of Medicine, praised the study as laying the groundwork for using T helper cells in a much more aggressive manner. "Helper T cells are mainly understood for their role in regulating other immune cells," he said. "This work reveals how they themselves can be triggered to become the action cells in the immune response. This opens new possibilities for how to manipulate them therapeutically in disease."

Dr. Cheroutre said the transformation of CD 4 helper T cells into killer cells already occurs in the body naturally. "Our finding could help to explain a number of occurrences that we haven't really understood up to this point, such as why some people can be chronically infected with HIV without developing AIDS." In these instances, Dr. Cheroutre is convinced that CD4 helper T cells must be taking over the role of killer cells after the CD8 T cells become exhausted. "It's like the helper cells can come in as reinforcements to keep the virus under control. If we can develop ways to artificially trigger that process, we may be able to significantly help people with HIV and other chronic infections."

While scientists would want to trigger a larger army of virus-specific killer cells in the case of infections, the opposite would be true in

inflammation-fueled autoimmune diseases, like rheumatoid arthritis or multiple sclerosis, said Dr. Cheroutre. "The CD4 T cells are the bad wolves in inflammatory diseases because they often trigger more pro-inflammatory cells which worsen these conditions," she said. "With this knowledge, we may be able to prevent that by coaxing the CD4 killer cells to become regulatory cells instead, which is another one of their potential functions. In regulatory mode, the CD4 T cells suppress the immune system. This suppression reduces inflammatory cells, which is what we want to do in autoimmune diseases."

However in cancer, the CD4 T cell's regulatory function becomes problematic because they inhibit the killer T cells from destroying cancerous cells. This is because of their built-in mechanism to keep T cells from attacking the body's own cells, said Dr. Cheroutre. "Cancer cells develop from our own cells and only look a little different from healthy cells," she explained. "The killer T cells can sense that they are different and decide to eliminate them. However, the CD4 regulatory T cells frequently suppress the killer T cells and prevent them from destroying the cancerous cells. This is often how cancer cells can escape the immune system's normal action of stamping out bad cells."

Dr. Cheroutre said she believes it may be possible, using the newly discovered mechanism, to turn the CD4 regulatory T cells into killer cells that would aid, rather than block, the immune system's attack on cancerous cells.

More information: Taniuchi, I. Cheroutre, H. et al. "Transcriptional reprogramming of mature CD4+ helper T cells generates distinct MHC class II–restricted cytotoxic T lymphocytes." *Nature Immunology*, 2013, DOI: 10.1038/ni.2523

Provided by La Jolla Institute for Allergy and Immunology