Researchers identify cell group key to Lyme disease arthritis

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A research team led by the La Jolla Institute for Allergy & Immunology and Albany Medical College has illuminated the important role of natural killer (NK) T cells in Lyme disease, demonstrating that the once little understood white blood cells are central to clearing the bacterial infection and reducing the intensity and duration of arthritis associated with Lyme disease.

"Our findings are that the NK T cells are critical to preventing the chronic inflammatory infection that causes Lyme arthritis and they participate in clearing the bacteria which cause it," said Mitchell Kronenberg, Ph.D., the La Jolla Institute's president & scientific director and co-senior author on the study, which used a mouse model of Lyme disease. Lyme disease is caused by Borrelia burgdorferi, a bacterium transmitted to humans by the bite of infected deer ticks. Typical symptoms include fever, headache, fatigue, and sometimes skin rashes. If left untreated, it can spread to the joints, the heart and the nervous system, and it can lead to serious health problems. Lyme disease currently is the most common vector (insect)-borne disease in the United States.

"What this study demonstrates is that NK T cells are an important part of our defense against Lyme disease," said Timothy J. Sellati, Ph.D., an associate professor at Albany Medical College and co-senior author on the study. "This offers the possibility that we can exploit that knowledge therapeutically and potentially develop immunological agents that can trigger more NK T cells to aide in fighting this disease." Sellati added

that "NK T cells alone cannot clear Lyme disease, but are a key part of a collective immune defense."

The study's findings are outlined in a paper, "NKT cells prevent chronic joint inflammation after infection with Borrelia burgdorferi," published this week in the online version of the journal *Proceedings of the National Academy of Sciences*.

In an earlier study published in *Nature Immunology*, Kronenberg, Sellati and co-workers had shown that a glycolipid, a type of fat, found in the membrane of Borrelia burgdorferi triggered an immune response from the NK T cells. "We had found that if you gave that lipid to mice or humans, it would activate NK T cells," Kronenberg said. While this suggested the cells might play a significant role in Lyme disease, "we were missing in vivo (in the body) evidence showing that the NK T cells were activated following infection and were important for killing and clearing the Lyme disease bacteria," he said, noting that the latest study demonstrates this in an animal model.

Sellati said the finding is particularly important because it opens new lines of investigation as to the causes of chronic Lyme disease. "That's what's so exciting when you identify a new cell type as playing a central role in preventing the disease process," he said. "So in those individuals who have a more severe form of the disease, you can study their NK T cells and see if there's some deficiency that prevents those NK T cells from killing and clearing the bacteria."

In their studies, the researchers worked to model the natural route of Lyme disease infection as closely as possible. "The way people typically get Lyme disease is that they're out hiking and they get bitten by a deer tick," said Kronenberg. "So what we did in the lab was to get ticks infected with Borrelia burgdorferi from collaborators at the University of Connecticut Health Science Center and then used those ticks to infect

mice in a confined and controlled environment."

The researchers used one group of mice genetically engineered not to have NK T cells, while the control group had the cells. "The mice that didn't have NK T cells were not as capable of clearing the (Lyme disease) bacteria," Kronenberg said. "And they developed a chronic arthritis, while the control mice did not." He said the results were quite marked. "You could see under the microscope more numerous inflammatory cells in the joints of the mice that lacked the NK T cells weeks after infection."

Discovered in the 1990s, NK T cells are disease-fighting white blood cells of the immune system whose inner workings are still being defined. While most T cells respond to foreign proteins to protect the body, NK T cells are unique in that they respond to glycolipids, which are natural biochemicals made of linked fat and sugar. Prized for initiating a fast and vigorous immune response, NK T cells are emerging as a subject of significant scientific interest because of their potential for fighting bacterial infections and cancer. Kronenberg and Sellati have been among the nation's leaders in studying these cells.

Kronenberg's laboratory was among the first to identify bacteria which naturally induce an immune response from the NK T cells. Thus far, he has identified two such bacteria— Borrelia burgdorferi and Sphingomonas species, a fairly benign bacteria found throughout the environment. However, he believes many other types of bacteria may also trigger the NK T cells. "This is an exciting possibility that needs to be further explored as it could lead to the development of treatments for many bacterial diseases."

Source: La Jolla Institute for Allergy and Immunology