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People with Job's syndrome lack specific immune cells

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Scientists have made another major breakthrough--the second in the past year--in understanding a rare immune disorder called Job's syndrome. Job's syndrome is characterized by recurrent and often severe bacterial and fungal infections leading to outbreaks of abscesses and boils. Other symptoms of the disease include lung infections, problems in facial and dental development, curved spine and high risk of bone fractures. While individuals with Job's syndrome often have normal life spans with intensive medical supervision, life-threatening complications from infections are a constant concern.

Now, scientists at the National Institutes of Health (NIH) have shown that Job's sufferers lack a specific type of infection-fighting white blood cell called Th17 cell, making them vulnerable to attacks by bacteria and fungi. The study was a collaborative effort of investigators from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), both components of NIH.

Th17 cells produce a protein called interleukin-17 (IL-17) and are known to play a major role in protection against invading pathogens. They are critical for recruiting other microbe-fighting immune cells called neutrophils to the site of infection. The study, which included 13 patients diagnosed with Job's syndrome, revealed that Th17 cells were lacking in these patients. This is also the first demonstration of a human genetic disease where researchers have not been able to generate Th17 cells in laboratory experiments using blood samples from patients with

Job's syndrome.

The new findings strongly suggests that Th17 cells are important in the control of Staphylococcus bacteria and certain fungal infections and the research has the potential to uncover why certain people who do not have Job's syndrome are prone to Staphylococcus and other fungal infections.

Although only 250 cases of Job's syndrome have been reported since the disease was first described in 1966, NIH scientists have been studying the disease for 30 years. In September 2007, NIAID issued a press release about the first major breakthrough. NIAID scientists and their colleagues had discovered a mutation in the gene that makes a specific protein known to help alert and direct immune system responses to stop invading pathogens. The proteins coded by this gene are called signal transducer and activator of transcription 3 (STAT3).

With the current study, a team led by Daniel Douek, M.D., Ph.D., chief of the Human Immunology Section of the NIAID Vaccine Research Center, the research was carried a step further based on the knowledge that the gene that makes STAT3 is involved in the differentiation of Th17 cells. The researchers hypothesized that Job's patients may be lacking Th17 cells and that the absence of these cells may contribute to the immune deficiency that results in recurrence of particular types of infections characteristic to Job's syndrome. The research study, which included 13 patients diagnosed with Job's syndrome, revealed that Th17 cells were lacking in these patients, while 10 healthy controls and also seven patients who had some Job's-like symptoms, but no mutation in STAT3, had the Th17 cells.

It is known that patients with Job's syndrome (technically known as hyperimmunoglobulin E syndrome, or HIES) have an elevated level of immunoglobulin E (IgE) antibodies and it is not clear to researchers why these people have high levels of IgE. Researchers say a future research

study will likely explore the relationship between Th17 cells and the level of IgE antibodies and find out if the absence of Th17 cells in Job's patients disrupts the immune system in a way that raises the level of these antibodies.

In conclusion, the investigators note that their research provides useful insights into why Job's syndrome patients are so susceptible to repeated infections with fungus and Staphylococcus bacteria and documents the roles of STAT3 and IL-17 in humans.

Source: National Institute of Allergy and Infectious Diseases