Scientists find a novel mechanism that controls the development of autoimmunity

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Scientists at the National Institutes of Health have found a mechanism in the immune systems of mice that can lead to the development of autoimmune disease when turned off. The findings shed light on the processes that lead to the development of autoimmunity and could also have implications for the development of drugs to increase the immune response in diseases such as cancer and HIV. The study paper appears online today in the journal *Nature*.

The scientists from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Allergy and Infectious Diseases (NIAID), both part of the NIH, studied immune system T cells – specifically the helper T cell, an immune system component that helps other cells fight infection. They focused on the protein furin, an enzyme that plays an important role in the functioning of T cells.

Scientists have been limited in their ability to study the protein furin, because other enzymes can perform some of the same functions. Also, furin is essential to life, so scientists have been unable to create a mouse without furin that lives past the embryo stage of development. Since the NIH scientists were unable to see what a mouse without furin would look like, they collaborated with Belgium scientists to create a mouse without furin only in T cells. What they discovered was that mice without furin in these cells developed systemic autoimmune disease. This means that the immune systems of the mice attacked their own cells and tissues throughout their bodies.

"We already know that furin seems to have roles in a variety of human diseases, such as cancer, cystic fibrosis and infectious diseases," says lead author Marko Pesu, Ph.D., in the NIAMS' Molecular Immunology and Inflammation Branch. "These findings show that having no furin in certain immune system cells can increase the immune response and lead to autoimmune disease in mice."

The researchers found that deleting furin in helper T cells affected the functioning of two types of T cells, regulatory and effector T cells. The former cells, also called Tregs, promote immune tolerance to the body's own cells and tissues. Upon further examination, the researchers found that mice lacking furin in Tregs had lower levels of a specific protein, TGF-ß1, which is produced by these cells and is important for their ability to preserve immune tolerance. However, the researchers noted that effector T cells also produce TGF-ß1. They found that furin is also needed for TGF-ß1 production by effector T cells and that the absence of furin in effectors makes these cells more aggressive in causing autoimmune disease and tissue damage.

"Inhibiting furin has been thought to reduce growth of malignant cells or to block infections by preventing essential activation of a pathogen," says study author and NIAMS' Scientific Director John J. O'Shea, M.D., chief of the NIAMS' Molecular Immunology and Inflammation Branch. "However, these results suggest that the development of drug interventions could have an unexpected side effect of increasing the risk of developing autoimmune disease."

Source: NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases

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