Scientists find link between allergic and autoimmune diseases in mouse study

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(Medical Xpress)—Scientists at the National Institutes of Health, and their colleagues, have discovered that a gene called BACH2 may play a central role in the development of diverse allergic and autoimmune diseases, such as multiple sclerosis, asthma, Crohn's disease, celiac disease, and type-1 diabetes. In autoimmune diseases, the immune system attacks normal cells and tissues in the body that are generally recognized as "self" and do not normally trigger immune responses. Autoimmunity can occur in infectious diseases and cancer.

The results of previous research had shown that people with minor variations in the BACH2 gene often develop allergic or autoimmune diseases, and that a common factor in these diseases is a compromised immune system. In this study in mice, the Bach2 gene was found to be a critical regulator of the immune system's reactivity. The study, headed by researchers at the National Cancer Institute (NCI) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), both part of NIH, and their colleagues appeared online in *Nature*, June 2, 2013.

The finding that a single component of the immune system plays such a broad role in regulating immune function may explain why people with allergic and autoimmune diseases commonly have alterations in the BACH2 gene, said NCI researcher Rahul Roychoudhuri, M.D. "This may be the first step in developing novel therapies for these disorders."

Studies known as genome-wide association studies, which analyze genetic variants among people to determine whether specific variants are associated with particular traits, were critical to the discovery. These studies showed that DNA from patients with diverse autoimmune disorders often had minor alterations in the BACH2 gene, which laid the foundation for this research.

"What was exciting was the opportunity to apply cutting-edge technology permitted by the completion of the Human Genome Project," said NIAMS scientific director John O'Shea, M.D. "Using genome-wide approaches we were able to map the action of Bach2 across all genes. This enabled us to gain a clearer understanding of Bach2's key role in the immune system."

The immune system is comprised of a variety of cell types that must act in unison to maintain a healthy balance. White blood cells called CD4+T cells play a dual role within the immune system. Some CD4+T cells activate immune responses, whereas others, called regulatory T cells, function in the opposite direction by constraining immune responses. This duality is important because uncontrolled immune responses may result in immune system attacks against the body's own cells and tissues, which occurs in allergic and autoimmune diseases. One of the hallmarks of uncontrolled immune responses is excessive tissue inflammation. Although tissue inflammation is a normal part of immune responses, excessive inflammation can lead to tissue and organ damage and may be potentially lethal. How CD4+T cells become either activating/inflammatory or regulatory is not well understood, according to the researchers.

"We found that the Bach2 gene played a key role in regulating the switch between inflammatory and regulatory cells in mice," said NIAMS researcher Kiyoshi Hirahara, M.D. "The loss of the Bach2 gene in CD4+ T cells caused them to become inflammatory, even in situations that would normally result in the formation of protective regulatory cells."

The team found that if mice lacked the Bach2 gene their cells became inflammatory and the mice died of autoimmune diseases within the first few months of life. When they re-inserted Bach2 (using gene therapy) into Bach2-deficient cells, their ability to

produce regulatory cells was restored.

"Although genes have been found that play specific roles in either inflammatory cells or regulatory cells, Bach2 regulates the choice between the two cell types, resulting in its critical role in maintaining the immune system's healthy balance," said NCI principal investigator, Nicholas P. Restifo, M.D., "It's apt that the gene shares its name with the famous composer Bach, since it orchestrates many components of the immune response, which, like the diverse instruments of an orchestra, must act in unison to achieve symphonic harmony."

Restifo suggests that these findings have implications for cancer as well, since cancers co-opt regulatory T cells to prevent their own destruction by antitumor immune responses. He and his colleagues are now working toward manipulating the activity of the Bach2 gene, with the goal of developing a new cancer immunotherapy. Also, as this study was in mice, it must be replicated in humans before its findings can be applied in a clinical setting.

More information: O'Shea, J. et al. Bach2 represses effector programmes to stabilize Treg-mediated immune homeostasis, *Nature*, online June 2, 2013. DOI: 10.1038/nature12199.

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