Gene regulates immune cells' ability to harm the body

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A recently identified gene allows immune cells to start the self-destructive processes thought to underlie autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis, researchers at Washington University School of Medicine in St. Louis have found.

Researchers showed that mice without the Batf gene lacked a type of inflammatory immune cell and were resistant to a procedure that normally induces an autoimmune condition similar to human MS. They plan to look for other genes and proteins influenced by Batf that could be targets for new treatments for autoimmune diseases.

"Batf allows immune cells to head down a pathway that's been a very hot topic in immunology because of its potential links to autoimmune disease," says senior author Kenneth Murphy, M.D., Ph.D., professor of pathology and immunology and a Howard Hughes Medical Institute investigator. "We showed that Batf regulates the only other gene previously revealed to control this pathway, so Batf may have quite a bit to teach us about autoimmunity."

The findings appear in *Nature* on July 16.

Lead author Barbara Schraml, Ph.D., found that the loss of Batf affected immune cells known as T cells. Normally T cells take on specialized roles, becoming cells that promote various defensive responses or that recruit inflammatory cells to sites of infection. In mice without Batf, though, one of those roles was blocked: the mice had no inflammatory

Th17 cells.

Researchers including Murphy first identified the Th17 pathway four years ago. While such cells help defend the body from bacterial infections, scientists have found that IL17, an inflammatory compound made by Th17 cells, is frequently present at sites of active autoimmune disease.

"Th17 cells draw in other immune cells to the site," Murphy says. "It makes the Th17 cell a bit like the instigator of an autoimmune riot—lots of cells rush in, and harmful things can start to happen."

Batf is a transcription factor, which means that the protein made from the gene acts to turn the production of proteins from other genes on and off. Its only previously identified role was as a partner with another common transcription factor.

Schraml showed that Batf had to be present for Th17 cells to make ROR-gamma-T, the only other gene known to force T cells to become Th17 cells. She also found that the presence of Batf made it possible for T cells to make more IL17.

"Normally transcription factors do not make ideal drug targets, but our Batf-knockout mice provide a unique tool to find the other proteins that are important in the development of Th17 cells," says Murphy. "Those proteins could be good targets for treatments for autoimmune diseases."

More information: Schraml BU, Hildner K, Ise W, Lee W-L, Smith WA-E, Solomon B, Sahota G, Sim J, Mukasa R, Cemerski S, Hatton RD, Stormo GD, Weaver CT, Russell JH, Murphy TL, Murphy KM. The AP-1 transcription factor Batf controls TH17 differentiation. *Nature*, July 16, 2009.

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