Inflammation 'on switch' also serves as 'off switch'

January 21 2010

In a surprising finding, researchers at North Carolina State University have discovered the critical importance of a protein previously believed to be a redundant "on switch" for certain immune-system responses.

Scientists previously understood that the protein called TAB2 activates inflammation, an important biological process that stimulates wound-healing and prevents invasion of harmful organisms. But scientists considered TAB2 nonessential to the process due to the redundant function of a cousin protein, called TAB3, which has no trouble serving as an "on switch" to activate the inflammation process in TAB2's absence.

In a study published in the Jan. 22 edition of the Journal of Biological Chemistry, the NC State researchers show that underestimating TAB2 can be dangerous. Rather than merely serving as an "on switch," TAB2 also serves as an "off switch" that turns off the inflammation process. When TAB2 is absent or knocked out in cell cultures, the inflammation process continues unabated.

Too much inflammation can be a really bad thing. It is associated with human diseases including certain cancers, inflammatory bowel syndrome and psoriasis.

Knowing more about the regulatory mechanisms in cells may one day lead to drugs that can target excessive inflammation, say NC State's Dr. Jun Ninomiya-Tsuji, associate professor of environmental and molecular

toxicology, and her graduate student, Peter Broglie, the lead authors of the paper describing the study.

In the study, Ninomiya-Tsuji and Broglie show that cells lacking TAB2 had a prolonged inflammation response. Normally, TAB2 can be counted on to bring a protein called TAK1 close to tumor necrosis factor , or TNF, a circulating molecule that is a normal component of the

immune system. Bringing TAK1 close to TNF activates TAK1, thereby starting the inflammatory response.

In normal systems, this inflammatory response would be quickly regulated to prevent too much inflammation. This is done by a regulating molecule called PP6, which deactivates TAK1, and, therefore, the inflammation process. When TAB2 was absent or knocked out, however, PP6 did not shut down TAK1. The NC State scientists infer, then, that TAB2 has a heretofore unknown function - it brings TAK1 close enough to PP6 to halt the inflammation process.

The NC State scientists were so surprised by the finding that, Broglie says, "Dr. Ninomiya-Tsuji made me replicate the study three times."

The study was funded by a grant to Ninomiya-Tsuji from the National Institutes of Health. Co-authors of the paper included scientists from the University of Virginia and two Japanese universities - Nagoya University and Osaka University.

More information: "A TAK1 kinase adaptor, TAB2, plays dual roles in TAK1 signaling by recruiting both an activator and an inhibitor of TAK1 kinase in TNF signaling pathway". Authors: Peter Broglie and Jun Ninomiya-Tsuji, North Carolina State University; Kunihiro Matsumoto, Nagoya University; Shizuo Akira, Osaka University; David L. Brautigan, University of Virginia, Published: Jan. 22, 2010, in *Journal of Biological*

Chemistry

Provided by North Carolina State University