SOUTHWESTERN NEWS

Contact: Susan A. Steeves
(214) 648-3404
or E-mail: ssteev@mednet.swmed.edu

DISCOVERY SUGGESTS NEW METHOD TO HALT INFLAMMATORY AND AUTOIMMUNE DISEASES

DALLAS – October 22, 1997 – A steroid produced in the adrenal glands can halt production of a molecule integral to inflammatory and autoimmune afflictions such as rheumatoid arthritis and lupus, reported researchers at UT Southwestern Medical Center at Dallas.

The scientists described their finding that the hormone glucocorticoid can inhibit expression of the tumor necrosis factor alpha (TNF-alpha) gene in the November issue of the journal *Molecular and Cellular Biology.* Glucocorticoid blocks an enzyme -- Jun n-terminal kinase (JNK)/stress-activated protein kinases (SAPK) -- that is part of the signaling pathway controlling cell behavior.

"TNF has become a very interesting molecule because it plays such a central role in a variety of diseases, so anything affecting TNF production might potentially be a drug," said Dr. Thomas Geppert, UT Southwestern associate professor of internal medicine. "Current approaches to block TNF production are expensive and require repeated injections, but if we could come up with a pill that blocks TNF production it would be a real breakthrough."

Previous research showed that glucocorticoids are among the most potent and clinically important immunosuppressant drugs, but it was not known how they inhibit inflammation. This research suggests a mechanism for this effect.

"Glucocorticoids inhibit lipopolysaccharide (LPS)-induced TNF production," Geppert said. "It looks like steroids bar TNF production by blocking JNK activation. That is interesting because steroids play such an important role in the therapy of

(MORE)

inflammatory disorders. Although steroids are frequently effective, they have significant toxicity. It is hoped a lot of that immunosuppressant effect of steroids might be through their effects on TNF and much of its toxicity might be mediated through other pathways."

For example, although the glucocorticoids may decrease arthritis symptoms, they frequently cause osteoporosis, weight gain, cataracts, heart disease or diabetes because they regulate carbohydrate and protein metabolism, stimulate glucose production and elevate blood pressure.

"Understanding how glucocorticoids work biochemically will lead to better drugs that don't have these side effects," Geppert said.

Geppert's research team will next attempt to understand the mechanism by which steroids affect JNK activation.

"We need to understand the whole signaling pathway in order to identify events that are unique to TNF production. If these events are specific to TNF production, drugs that inhibit them will be less likely to affect other signaling pathways leading to side effects. The development of drugs with the ability to block inflammation as well as steroids do but without the side effects is the dream of most physicians who deal with inflammatory disorders like arthritis, asthma or colitis."

Other researchers who participated in the study were Dr. Melanie Cobb, professor of pharmacology and holder of the Jane and Bill Browning Jr. Chair in Medical Science, and Jennifer Swantek, research fellow in internal medicine.

This study was funded in part by the American Heart Association.

###