New pathway involved in rheumatoid arthritis identified

April 13 2010

Investigators from Hospital for Special Surgery have identified a pathway involved in turning off inflammation that does not work properly in people with inflammatory arthritis. The finding, reported in the April 23 issue of the journal *Immunity*, could lead to the development of new therapeutic approaches to treating arthritis in the future.

"This is the first study to link this pathway to rheumatoid arthritis. In the twenty years or so that I have been studying regulation of inflammation, this seems to be the most potent inhibitory mechanism that we have seen," said Lionel Ivashkiv, M.D., associate chief scientific officer at Hospital for Special Surgery in New York City and lead author of the study that has appeared online ahead of print.

For several years, Dr. Ivashkiv's lab has been studying what regulates the production of cytokines in inflammatory diseases. Cytokines are small proteins that regulate inflammation; some cytokines spark inflammation and some cytokines are anti-inflammatory. By identifying pathways involved in cytokine production, the researchers hope to open up new therapeutic avenues for diseases such as arthritis in which cytokine production does not work properly.

Prior to this study, researchers knew that so-called immunoreceptor tyrosine-based activation motif (ITAM)-coupled receptors were involved in regulating inflammation, but they did not know how the ITAM pathways actually turned off inflammatory signaling. Previous

studies had shown that the ITAM pathway signaling components directly suppressed so-called Toll-like receptor signaling molecules involved in inflammation, but there was a hint that an alternative pathway may also be involved. The researchers thought that maybe the ITAM pathway might be involved in triggering another pathway that then inhibits inflammation.

In studies using white blood cells similar to those that cause disease, the researchers set out to investigate what signaling pathways might be induced by the activation of ITAM-associated receptors. They used fibrin(ogen) and immune complexes, proteins that are highly expressed at inflammatory sites, to activate the ITAM-associated receptors and then watched what happened. The researchers found that activation of the ITAM receptor set off a pathway known as DAP12-Syk-Pyk2-p38-MSK that was dependent on calcium signaling and discouraged pro-inflammatory cytokine production.

They also found that ITAM receptors induce IL-10, an anti-inflammatory cytokine, and proteins SOCS3, ABIN-3, A20, and Hes1 that have been implicated in the suppression of cytokines.
In other studies, they showed that this ITAM inhibitory pathway does not work properly in people with inflammatory arthritis.

"When we looked at macrophages from patients with arthritis, we found that the whole inhibitory pathway would not work," Dr. Ivashkiv said. "What this study suggests is that one of the things that contributes to inflammation in arthritis is crippling of beneficial pathways that usually serve to turn inflammation off." He said clinicians in the future may be able to focus on therapies that will augment or reinstitute these beneficial or homeostatic pathways as a way of turning off inflammation in chronic arthritis.

"Before this study we knew that ITAM-coupled receptors had the

potential to inhibit inflammatory cytokine production, but there was very limited knowledge about how that worked," Dr. Ivashkiv said. "What we accomplished with the study is that we have increased our understanding of an indirect inhibitory mechanism that we think can serve as the basis for designing new approaches to therapy. This work implicates for the first time a negative role for calcium signaling downstream of these ITAM-coupled receptors and explains how that works,"

He added that investigators believe that there is extensive crosstalk among the various pathways and they think that the ITAM receptors play a very important role in deciding how all the signaling gets integrated. "In terms of the homeostatic pathways that control inflammation, we think that this pathway that we have described is one of the strongest ones. It completely turns things off," Dr. Ivashkiv said. "What you usually see are these partial inhibitions or attenuations in terms of inflammatory cytokine production. What we saw was a complete inhibition of the response."

Dr. Ivashkiv said future work would focus on further elucidating molecular details of the pathway and further testing of its importance in arthritis and animal models of disease.

Provided by Hospital for Special Surgery