

New therapeutic target identified for rheumatoid arthritis

November 5 2008

Researchers at Hospital for Special Surgery have identified a potential new therapeutic target that could be used to treat inflammatory disorders, such as rheumatoid arthritis.

The study, published online ahead of print, will appear Nov. 15 in the journal *Immunity*. Specifically, the study reveals that two molecular pathways, the Notch and Toll-like receptor pathways, are linked and that manipulating a protein called RBP-J involved in both pathways, could serve as a treatment for rheumatoid arthritis.

"This is a basic science papers with translational and clinical implications, as it identifies a potential new therapeutic target in the treatment of inflammatory disorders," said Lionel Ivashkiv, M.D., director of Basic Research at Hospital for Special Surgery in New York City. He said that drugs, so-called gamma secretase inhibitors that hit this new target, are actually in trials for the treatment of another disease, leukemia.

Previous research has shown that activation of certain cell surface receptors called Toll-like receptors leads to the production of inflammatory proteins or cytokines. Researchers have also known that a protein called interferon gamma can increase inflammatory response, but they didn't know the exact mechanism.

To find out, they turned to microarray analysis, a method of surveying an entire genome to determine which genes are being expressed or which

are responsible for a certain condition. Using this technology with human macrophages, white blood cells that are vital to the development of inflammatory response, they identified a subset of genes that were turned on by the activation of Toll-like receptors and inhibited by interferon gamma. This subset of genes included genes that are involved in the Notch signaling pathway. For some time, scientists have known that the Notch signaling pathway regulates cell differentiation, proliferation, survival and development.

"Before this study, we knew that the Notch pathway was important in development and that the Toll-like receptor pathways were important in acute inflammation, and now we know that those two things are linked in acute inflammation and cytokine production," said Dr. Ivashkiv.

When molecules dock on the Toll-like receptors of macrophages, proteins including interleukin-6, which has been implicated in rheumatoid arthritis, are produced. In another experiment, investigators showed that the production of interleukin-6 was decreased if a protein called RBP-J was not present. Investigators also found that interfering with the production of RBP-J decreased the activation of certain Notch target genes.

"The Toll-like receptors regulate the Notch pathway, but the Notch pathways also regulates the Toll-like receptors, and it all seems to be through this RBP-J protein," said Dr. Ivashkiv. He says that other studies have shown that drugs called gamma secretase inhibitors have been shown to interfere with the Notch pathway and thus could be used to treat rheumatoid arthritis by decreasing the amount of interleukin-6.

Source: Hospital for Special Surgery

Citation: New therapeutic target identified for rheumatoid arthritis (2008, November 5) retrieved 23 April 2024 from

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