# Scientists find new mechanism by which cell signaling pathway contributes to rheumatoid arthritis development

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A new study led by researchers at Hospital for Special Surgery identifies the mechanism by which a cell signaling pathway contributes to the development of rheumatoid arthritis (RA). In addition, the study provides evidence that drugs under development for diseases such as cancer could potentially be used to treat RA. Rheumatoid arthritis, a systemic inflammatory autoimmune disease that can be crippling, impacts over a million adults in the United States.

"We uncovered a novel mechanism by which the Notch pathway could contribute to RA, said Xiaoyu Hu, M.D., Ph.D., a research scientist at Hospital for Special Surgery in New York City and principal investigator of the study. The study appears online in advance of print in *Nature Immunology*.

Prior to this study, researchers knew that an intracellular molecular pathway called Notch is involved in diseases such as cancer. In the last year, other scientists conducted a genome wide association study to identify genes that were linked to the development of rheumatoid arthritis. They discovered that a certain mutation in a gene involved in the Notch pathway puts patients at risk for RA, but nobody knew just how it was involved.

"We were intrigued. Nothing has been known about how the Notch pathway is important to RA," said Dr. Hu. Working with researchers at

other institutions in the United States and abroad, HSS investigators started putting two and two together and noted that Notch might be involved in a misfiring of the immune system that is commonly seen in RA.

The researchers designed experiments to test whether the Notch pathway had an influence on macrophages, a type of white blood cell that is most commonly known for gobbling up pathogens but which can also cause inflammation. Macrophages that have gone awry possess widespread pro-inflammatory and destructive capabilities that can critically contribute to acute and chronic rheumatoid arthritis. "In the case of RA, inflammatory macrophages attack joints and they produce inflammatory mediators that basically sustain inflammation in joints," said Dr. Hu.

In experiments, researchers found that knockout mice that lack the Notch pathway in macrophages were unable to produce certain type of macrophages and exhibited a lesser inflammatory phenotype.

"Notch is essential for the development and function of a cell type called the inflammatory macrophages and if this pathway is missing in mice, then you don't get good differentiation of the inflammatory macrophages," said Dr. Hu. In a nutshell, the Notch pathway is essential for the differentiation and function of inflammatory macrophages, and these macrophages are critical for human RA pathogenesis.

In a series of test tube studies, the researchers flushed out the specifics of how Notch influences the molecular cascade that leads to generation of inflammatory macrophage. In another experiment, the investigators used an inhibitor of the Notch pathway called GSI-34 that is under development and showed that this drug could inhibit the function of macrophages.

The researchers say the study provides the first explanation of how

Notch contributes to rheumatoid arthritis pathogenesis. It also shows, for the first time, that investigational Notch inhibitors under development for cancer and Alzheimer's could potentially be used to treat RA. Several Notch inhibitors are under development by various companies and a few are currently in Phase III trials.

"Before this study, the Notch pathway has been implicated mainly in cancer, but in this study we define how it is connected to RA," said Dr. Hu.

Provided by Hospital for Special Surgery