Scientists identify molecular gatekeeper of arthritis

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Elimination of a molecular gatekeeper leads to the development of arthritis in mice, scientists report in a study published in the *Journal of Experimental Medicine*. The newly discovered gatekeeper is a protein that determines the fate - survival or death - of damaging cells that mistakenly attack the body's own tissues and lead to autoimmune disorders such as arthritis.

Better understanding how arthritis develops will offer scientists an opportunity to explore new types of treatments for patients whose arthritis has not been effectively treated with current therapies.

"This finding is an encouraging step forward for researchers, clinicians and arthritis sufferers, many of whom fail available therapies," said lead researcher Frances Lund, Ph.D., professor of Medicine in the Division of Allergy/Immunology and Rheumatology at the University of Rochester Medical Center. "An added bonus is that this finding may help in the search for new treatments for other autoimmune disorders, such as lupus."

The protein at the center of the new finding, known as Gαq (G alpha q), is part of a larger signaling pathway that Lund and collaborators from across the United States and China investigated in mice. Gαq regulates B cells, one type of immune cell that the body maintains to fight off invaders like bacteria, viruses and parasites. While most B cells help defend the body, some B cells are autoreactive - they turn against the body's own tissues.

In mice, Gαq normally stops autoreactive B cells from building up in tissues by suppressing the pro-survival signaling pathway uncovered by Lund's team. When Gαq is eliminated, autoreactive B cells are able to pass through internal 'checkpoints' that typically get rid of these harmful cells, creating a buildup of the cells that contributes to the development of autoimmune disease.

Several new studies expanding on the current finding are in the works, including testing whether drug compounds that alter the expression or activity of Gαq in mice can slow the development of autoimmunity. Beyond preclinical testing in mice, researchers also hope to start screening Gαq levels in patients to learn more about how the protein works in humans.

According to Lund, "There is a subset of cardiac patients who, due to an inherited genetic mutation, have increased levels of Gαq. We are now looking to see if some arthritis patients have mutations that favor decreased levels of Gαq. If we find these patients, someday we may be able to design targeted, personalized therapy for this subpopulation of arthritis sufferers."

"In the past few decades, nearly all of the really important advances in rheumatology have started with basic studies like this one" said Richard John Looney, M.D., a rheumatologist and professor of Medicine at the University of Rochester Medical Center. "I will be particularly interested in the translational studies that will be starting soon, as they may result in new applications such as assessing the risk someone may develop lupus or other autoimmune diseases."

Lund's research also led to the creation of a new mouse model of arthritis. By eliminating Gαq, the disease just happens in mice, as opposed to previous mouse models which require injecting an antigen or foreign body, such as collagen, into mice to trigger an immune response.

The new model more closely mirrors how autoimmunity starts and progresses in humans, and may be used in the future to test new drugs in development.

"Our goal is to move the knowledge we've gained from basic research to meaningful results that will ultimately help patients, and our main finding coupled with the creation of an improved mouse model puts us in a very strong position to do that," said Lund.

As with many discoveries, the new finding came about unexpectedly. Scientists in Lund's lab were looking at cell migration to try to identify the molecular signals that cause inflammation in tissues in Gαq knockout mice. They noticed that as they grew older, the mice's joints swelled and it appeared as though they were getting arthritis. Lund's team pursued the lead, which led to the discovery of the protein's role in the development of the disease and the creation of the new mouse model.

Provided by University of Rochester Medical Center