Researchers identify new arthritis severity gene

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A new gene associated with disease severity in models of rheumatoid arthritis has been identified by researchers at the Icahn School of Medicine at Mount Sinai. The discovery could provide a new pathway for treatment and a way to measure the prognosis of patients diagnosed with the autoimmune condition.

Through a series of experiments—on synovial cells from the inner lining

of joints in humans and animals, and in animal models of arthritis —Percio S. Gulko, MD, Chief of the Division of Rheumatology, Lillian and Henry M. Stratton Professor of Medicine (Rheumatology), and senior author on the paper, and his colleagues were able to show that the gene HIP1 is a driver in inflammatory arthritis severity. This is the first time that HIP1 has been implicated in arthritis severity and in cell invasiveness. The findings will be published online in *Annals of the Rheumatic Diseases* on Thursday, July 26.

Rheumatoid arthritis is a chronic disease affecting more than 1.3 million Americans. The disease can cause disability and deformation of joints and affects roughly 1 percent of the world's population. Drugs currently available to treat rheumatoid arthritis target the body's immune response but raise the risk of immunosuppression and susceptibility to infections such as herpes zoster and pneumonia.

"There have been major advances in the treatment of rheumatoid arthritis in the past 20 years, but disease remission still remains uncommon. Most drugs today target inflammation but often that is not enough to control disease," says Dr. Gulko. "At my laboratory, we have been looking for alternative strategies. In this research, we have focused on understanding the regulation of disease severity and joint damage. Our discovery led us to the synovial fibroblasts, cells inside the joint."

Through genetic strategies including linkage mapping and congenic breeding, in which specific chromosome fragments in arthritis-susceptible rodent strains are replaced with chromosome fragments from arthritis-resistant strains, Dr. Gulko and his co-researchers identified a chromosomal region that controls arthritis severity and joint damage.

This region contained 41 genes. They sequenced those genes and discovered a mutation in HIP1, a gene previously unrelated to arthritis or inflammation. The lab was then able to show that the different forms

(alleles) of HIP1 affected the behavior of the synovial fibroblast, the cells that line the tissue in the inner surface of joints, by reducing or augmenting invasiveness of the cells. Synovial fibroblast enables local repair and production of the fluid that lubricates joints and nourishes the joint cartilage. In people with rheumatoid arthritis, the synovial fibroblasts increase in numbers (hyperplasia) and become invasive, and the synovial tissue becomes infiltrated with immune cells, causing joint swelling and pain. This invasive behavior is known to correlate with joint damage in patients with rheumatoid arthritis.

With this crucial information, the researchers moved on to the next experiment in synovial fibroblasts derived from patients with rheumatoid arthritis. The researchers knocked down (removed) the HIP1 gene in these synovial fibroblasts. Removing HIP1 significantly reduced the ability of the rheumatoid arthritis synovial fibroblasts to respond to PDGF (platelet-derived growth factor), a potent inducer of synovial fibroblast invasiveness expressed in increased levels in the joints of patients with rheumatoid arthritis. Knockdown of HIP1 prevented the activation of the signaling molecule Rac1, which is key for synovial fibroblast invasiveness. Dr. Gulko and his colleagues also studied HIP1-deficient mice. These mice were protected, and developed a milder form of the arthritis.

Previous research had found that increased HIP1 expression in certain cancers and correlated with worse prognosis in prostate cancer patients. Therefore, Dr. Gulko's findings also have potential relevance for cancer biology and the understanding of cancer cell invasion and metastasis.

"These new discoveries raise the future possibility of targeting HIP1 to treat rheumatoid arthritis, and also of quantifying HIP1 levels in the blood or synovial fluid cells to predict disease outcome," said Dr. Gulko.

Dr. Gulko's research provides a framework for a potential new target for

therapy and, perhaps, a new predictor of a patient's prognosis. He and his colleagues plan in the future to investigate the feasibility of a drug that would target the HIP1 gene. "We are aiming for a novel way of treating the disease. One that targets the synovial fibroblast, while sparing the immune system outside the joint," he says.

Provided by The Mount Sinai Hospital

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