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Pore formation in cell membranes linked to triggers of rheumatoid arthritis

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Experiments by scientists at Johns Hopkins and in Boston have unraveled two biological mechanisms as the major cause of protein citrullination in rheumatoid arthritis. Protein citrullination is suspected of sparking the immune system and driving the cascade of events leading to the disease.

In a report to be published online in the journal *Science Translational Medicine* on Oct. 30, the research team describes how it found pore-forming pathways in cell membranes that are associated with the abnormal citrullination occurring in rheumatoid joints. The pathways, called perforin and complement (also known as membrane attack complex, or MAC), are normally used by the immune system to fight pathogens.

Researchers say such disruptions in cell membrane integrity produce enzyme-activating imbalances of calcium ions. The activated enzymes, called PADs, are known to citrullinate specific, protein-forming amino acids in hand, knee, foot, and elbow joints, setting off the inflammatory immune response that is rheumatoid arthritis' hallmark.

According to researchers, the latest study findings open up a whole new field of study into rheumatoid arthritis' origin and into the mechanisms that might start the disease process.

"For a long time, it has been suspected that immune pathways activated in response to pathogens play a role in initiating immune responses in

rheumatoid arthritis," says senior study investigator and rheumatologist Felipe Andrade, M.D., Ph.D.

"This study offers a renewed framework to support and to study this hypothesis, and provides novel targets that may be amenable for monitoring and treatment," says Andrade, an assistant professor at the Johns Hopkins University School of Medicine.

In the study, researchers initially identified that cells obtained from the joints of patients with rheumatoid arthritis contain a unique pattern of citrullination, which they termed cellular hypercitrullination. Lab experiments showed that this pattern was not reproduced by cell death and cell activating pathways previously thought to be responsible for the process. Some stimuli induced citrullination, but none induced the hypercitrullination seen in the disease.

"This was a surprising finding and suggests that the pathological citrullination occurring in the rheumatoid joint differs qualitatively and quantitatively from the citrullination occurring under physiological conditions," says Andrade.

Of 20 stimuli studied, all known to promote inflammatory pathways active in the rheumatoid joint, only two, perforin and MAC, reproduced the hypercitrullination detected in rheumatoid arthritis patients.

Andrade says the series of experiments, which took three years to complete, represents the first evidence that perforin and MAC are active contributors in generating the targets to the immune response, or auto-antigens, thought to initiate and maintain inflammation in rheumatoid arthritis. Perforin and MAC were previously believed to play secondary roles in rheumatoid joint destruction.

"Our results suggest that inhibiting these pathways may have real benefit

in patients and represent an important field of study for investigating new and alternative treatments," says Andrade.

Andrade and his team next plan to determine the mechanisms responsible for abnormal activation of the perforin and MAC pathways in rheumatoid joints. He says this may lead to the identification of the earliest components that initiate the disease process.

The team also plans to define novel biomarkers to monitor the citrullination activity induced by these pathways in people with rheumatoid arthritis, with the goal of matching levels to disease progression and response to treatment.

More information: "Immune-Mediated Pore-Forming Pathways Induce Cellular Hypercitrullination and Generate Citrullinated Autoantigens in Rheumatoid Arthritis," by V. Romero et al. *Science Translational Medicine*, 2013.

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