

Inflammation In Rheumatoid Arthritis

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Unexpected Discovery Made By Scientists Exploring Inflammation In Rheumatoid Arthritis

Arthritis News

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BOSTON — What makes joints in people with rheumatoid arthritis, and related conditions like Lyme disease or lupus, so susceptible to attack by the body's immune system, leading to painful flare-ups and deterioration? The answer may surprise you.

The answer did surprise investigators at Joslin Diabetes Center and Massachusetts General Hospital (MGH) in Boston, who gained a novel insight into this question in a recent collaborative study. Their report appeared in the January 29 online issue of Nature Immunology, and is scheduled to appear in the February print edition.

Working with an animal model of rheumatoid arthritis, the researchers discovered that histamine, a small molecule usually associated with asthma and allergy, is produced as part of the inflammatory process during the development of arthritis. Histamine made the blood vessels surrounding the joints especially vulnerable to leakage, and thereby rendered the joints more susceptible to inflammatory attack. The researchers believe that this is true not only in rheumatoid arthritis, but perhaps also in other autoimmune conditions with which arthritis is associated, such as lupus, and in some infectious diseases, like Lyme disease.

"For patients with rheumatoid arthritis, these new findings raise the possibility that medications designed to prevent the blood vessels from becoming leaky might one day be used to delay the onset of arthritis or to prevent flare-ups of disease," said Christophe Benoist, M.D., Ph.D., who led the study together with Diane Mathis, Ph.D., and Ralph Weissleder, M.D., Ph.D. Drs. Mathis and Benoist head Joslin's Section on Immunology and Immunogenetics, hold the William T. Young Chair in Diabetes Research at Joslin, and are Professors of Medicine at Harvard Medical School. Dr. Weissleder heads the Center for Molecular Imaging Research at MGH and is a Professor of Radiology at Harvard Medical

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School.

While the Joslin lab focuses its work on type 1 diabetes, arthritis has several related mechanisms. Like type 1 diabetes, rheumatoid arthritis is an autoimmune disease, in which the body's immune system attacks itself as though fighting off an enemy invader.

The Arthritis Foundation reports the number of Americans with arthritis or chronic joint symptoms has risen from 35 million to 66 million (nearly 1 in 3 adults) in 2005. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the lining, or synovium, of the joints. It is one of the most severe forms of arthritis and can lead to long-term joint damage, resulting in chronic pain, loss of function and disability. RA affects 1 percent of the U.S. population or 2.1 million Americans, mostly women.

In their study, the researchers developed a new microscopic imaging method to visualize changes in blood vessel permeability in anesthetized mice. Within minutes following the delivery of arthritis-causing antibodies to the mice, the blood vessels around the joints became temporarily leaky, making it easier for the antibodies to enter the joint spaces. There, the antibodies set off a cascade of inflammatory cells and molecules, eventually resulting in arthritis.

"The big surprise was that the other blood vessels throughout the body did not become leaky, suggesting that there is something special about the vessels in the joints," says Bryce Binstadt, M.D., Ph.D., of Joslin and Children's Hospital Boston, lead author on the study.

In trying to identify the special feature, the investigators made the even more unexpected discovery that histamine was responsible for the joint blood vessel leakiness — in fact, the researchers could mimic the effect of the antibodies on blood vessel leakiness by just injecting histamine.

Other researchers participating in the study included Pratik R. Patel, Herlen Alencar, M.D., and Umar Mahmood, M.D., Ph.D., of the Center for Molecular Imaging Research, Massachusetts General Hospital; Peter A. Nigrovic, M.D., of Children's Hospital and Brigham and Women's Hospital, Boston; and David M. Lee, M.D., Ph.D., of Brigham and Women's Hospital.