Research Update
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# The Role of Leukotriene B4 in Inflammatory Arthritis

A hallmark of rheumatoid arthritis is inflammation of synovial tissue, which forms the joint lining and produces lubricating and cushioning synovial fluid. To create new therapies to battle this inflammation, scientists must understand the mechanisms by which inflammation occurs. Inflammation is a complex reaction, the many details of which are only beginning to be elucidated. Understanding the interactions of the different chemicals that work within and between cells will ultimately allow scientists to piece together the enormous puzzle of inflammation, autoimmunity, and disease progression.

**What problem was studied?**
An important step in synovial inflammation is the recruitment of leukocytes (white blood cells) into the joint synovial fluid and tissue. A number of growth factors, called chemokines or inflammatory mediators, are involved in recruiting leukocytes to the synovium. Leukotrienes are among the inflammatory mediators found in an inflamed joint.

A team of researchers from Brigham and Women's Hospital, Harvard Medical School, in Boston and Merck Frosst Centre for Therapeutic Research in Quebec sought to determine the role of leukotriene B4 (LTB4) in leukocyte recruitment and inflammation. This team of scientists included Arthritis Foundation-funded researchers Mei Chen, MD, PhD, and David M. Lee, MD, PhD. The information gathered from this study will help scientists understand how inflammation happens, and could eventually lead to new therapeutic agents that can help slow or stop the inflammatory process and joint damage.

**What was done in the study and what were the results?**
Different strains of mice that have been bred to lack specific genetic characteristics were used in a series of experiments. Some of these mice developed inflammatory arthritis and some did not; some of the mice produced leukotrienes and some were genetically unable to produce leukotrienes.

The concentrations of LTB4 in joint tissue of arthritic mice and nonarthritic control mice were determined. Levels of LTB4 were significantly elevated in the joint tissues of mice with chronic arthritis. No leukotrienes were detected in the joint tissues of mice without arthritis.

To show that a temporal relationship exists between the generation of leukotrienes and the development of clinical arthritis, a time analysis was performed that assessed levels of LTB4 in the joint after the arthritis-inducing chemical was given to the susceptible mice. Increasing concentrations of LTB4 correlated strongly with increasing arthritis severity while the disease was becoming established.

For leukotrienes to be synthesized in the body, an enzyme called 5-lipoxygenase (5-LO) must be present. It was found that a strain of mice deficient in 5-LO were resistant to the development of arthritis after being administered an arthritis-inciting chemical. This provided additional proof that leukotrienes hold an important role in inflammatory arthritis.

To confirm the critical role of leukotrienes in arthritis induction in susceptible mice, researchers used a pharmacologic inhibitor of 5-LO. Mice were given either the inhibitor or a control two days before the mice were injected with the arthritis-provoking chemical. The mice receiving the 5-LO inhibitor did not develop arthritis.

To help determine the role of leukotrienes in the perpetuation of inflammatory arthritis rather than in the induction of arthritis, another experiment was performed. Susceptible mice were injected with the inciting chemical and were allowed to develop arthritis. Some of these arthritic mice were then given the 5-LO inhibitor, thereby stopping their bodies from synthesizing leukotrienes, and some were given a control substance. Results revealed that the 5-LO inhibitor decreased clinical arthritis to approximately 20 percent of that evident in the control mice.

The investigators then queried which white blood cells produce leukotrienes in the inflamed joint. By specifically transferring neutrophils, they were able to show that neutrophils provide a significant amount of leukotrienes to help drive the arthritic inflammation.

**What's the relevance to people with inflammatory arthritis?**
The findings of these researchers confirm previous observations regarding the role of leukotrienes in animal models of arthritis. Additional studies by this same team focused on how leukotrienes recruit leukocytes to the synovium. All of their important findings increase our knowledge of the inflammatory process, which will lead to new therapies for arthritis.

**Chen M, Lam BK, Kanaoka Y, et al. Neutrophil-derived leukotriene B4 is required for inflammatory arthritis. J Exp Med 2006;203:837–42. PMID: 16567388**

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