An Autoimmune Trigger for Arthritis

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RESEARCH

Gut Bacterium Sparks Disease

A single species of bacterium that lives in the gut can trigger a cascade of immune responses that ultimately result in arthritis, researchers report.

The lab of HMS professors of pathology Christophe Benoist and Diane Mathis collaborated with a New York University lab led by Dan Littman to investigate the connection between arthritis and the body's destructive autoimmune response, an attack against the self.

Using a mouse model, the team demonstrated a link between the disease, a normally occurring species of gut bacteria and the development of specific immune cells and circulating antibodies. When transgenic mice designed to serve as a model for inflammatory arthritis were raised in a germ-free environment, the onset and the severity of their arthritis symptoms were eased, the researchers found. Arthritis was rapidly induced, however, following the introduction of a single bacterial species.

These findings suggest that in the advance of arthritis, the interaction between genetic susceptibility and environmental factors is at play.

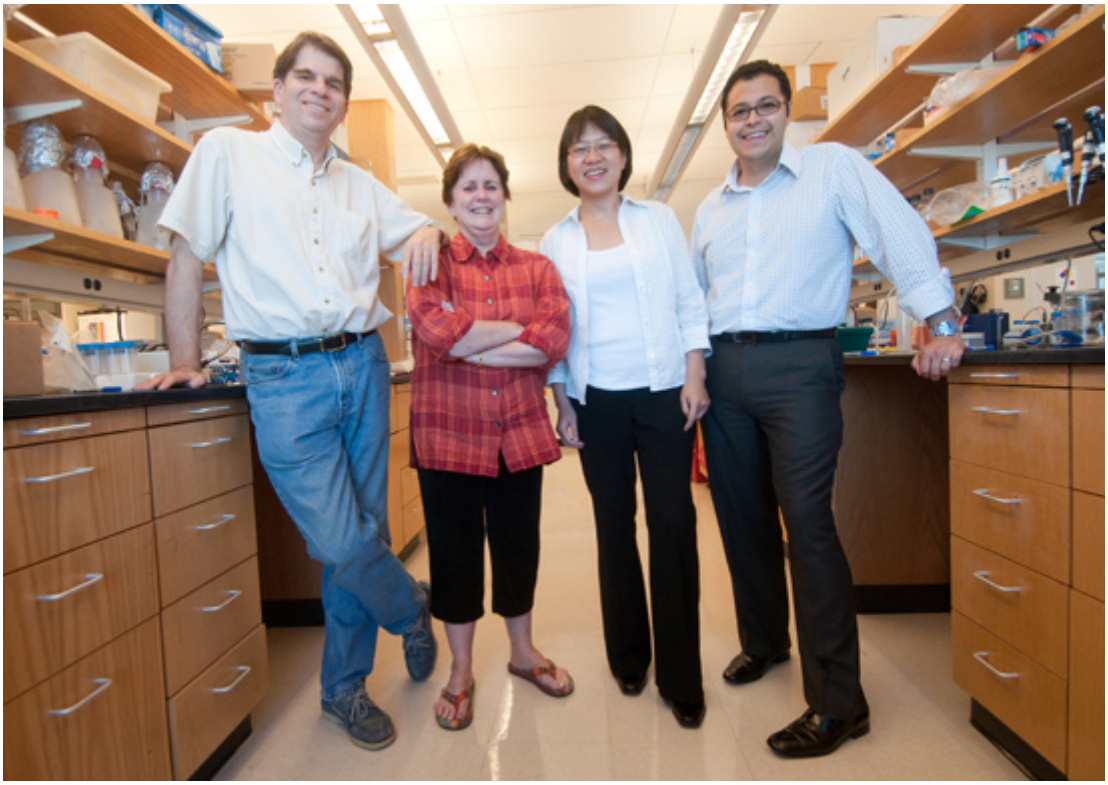

Photo by Joshua Touster

From left, Christophe Benoit, Diane Mathis, Hsin-Jung Wu and pathology fellow Jaime Darce used a single species of bacteria to induce an autoimmune flurry that in a mouse model resulted in arthritis.

Immunity Gone Awry

The human gut, like that of most mammals, is filled with thousands of species of bacteria, many of which aid in the development of a normal, healthy immune system. Helpful gut-residing bacteria may also play a role in immune system disorders, especially autoimmune diseases. One such disorder is rheumatoid arthritis, a chronic and progressive condition that causes inflammation of the joints.

Mice used in the study, published in the June 25 edition of the journal *Immunity*, "share immunological abnormalities," as well as many clinical and anatomical features, that have been recognized in human rheumatoid arthritis, said Hsin-Jung Wu, lead author and a postdoctoral research associate in pathology at HMS. In this transgenic mouse strain, certain immune system T cells initiate arthritis by helping another set of immune cells to produce self-directed antibodies, which cause the disease.

The researchers found that mice raised in a germ-free environment had lower levels of arthritis-causing autoantibodies than mice nurtured in a non–germ-free facility. The germ-free mice also showed an earlier onset and increased severity of the disease. This

demonstrated that development of their arthritis was dependent upon normally occurring microbes, Mathis said.

At three weeks of age, the mice were transferred to a non–germ-free facility, where researchers introduced a single bacterial species into their systems: segmented filamentous bacteria. The mice rapidly began producing more autoantibodies and developed arthritis within just four days.

“In the absence of all bacteria, these mice didn’t develop arthritis,” said Mathis. “But the introduction of a single bacterium was enough to jump-start the immune process that leads to development of the disease.”

By using microarray analysis to examine the expression of thousands of genes at once, the researchers were able to determine why the mice weren’t getting sick in the germ-free environment. Focusing on the spleen, the home of most cells that secrete arthritis-causing autoantibodies, the researchers found that the germ-free mice had deficiencies in a T cell subset called T helper 17 cells. T helper 17 cells appear to be absolutely required for arthritis, Mathis said; such cells do not arise in a germ-free environment.

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—Diane Mathis

Genes and Environment

The bacteria do not cause one to “catch” arthritis, Mathis emphasizes. “It’s more that you have the genetic susceptibility, and this bacterium creates an environment that allows this genetic susceptibility to play out,” she said. “It’s an interaction between genetics and the environment.”

The chain of events is complex. Germ-free conditions result in a lack of normally occurring bacteria, which results in fewer T helper 17 cells, leading to low levels of circulating antibodies. The final result is the attenuation of arthritis in a strain of mouse that is highly likely to develop the disease.

One surprising finding, Mathis noted, is that bacteria in the gut are able to influence the development of an autoimmune disease that affects other organs and tissues. Diseases such as irritable bowel syndrome have been linked to gut-residing bacteria, but this study is unique in revealing a mechanism by which a gut bacterium influences an autoimmune response ending in joint pain and inflammation.

Mathis and her colleagues will use this mouse model of arthritis to answer questions about the link between the disease and autoimmunity. They plan to explore how these bacteria promote the development of T helper 17 cells and to explore connections between this mechanism and other autoimmune diseases, particularly type 1 diabetes.

—Mary Bates

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