

Spleen May Be Target of Successful Therapy for Lupus

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Researchers at the University of California, San Diego (UCSD) School of Medicine have found clues that might lead to better treatment of lupus, showing that the spleen is the likely source of cells that are the origin of the disease. Michael Karin, Ph.D., professor of pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, led the study to be published on line September 14 in advance of publication in the September issue of the journal *Immunity*.

The researchers worked with transgenic mouse models that were engineered to overproduce a special cytokine – a hormone which regulates immunity – called BAFF, a B-cell activating factor that is elevated in patients with lupus and other autoimmune diseases. The B cells are responsible for the production of antibodies in the body. Mice overproducing BAFF develop systemic lupus erythematosus (SLE)-like disease, very similar to human lupus, which is estimated to affect one in a thousand Americans, 90 percent of them women.

The research study showed that that a compartment of the spleen called the marginal zone is where the majority of autoreactive B cells are found. The scientists transplanted immune cells from the spleen's marginal zone in the mice with lupus into mice without their own B cells, and found that they immediately gave rise to pathogenic antibodies.

When the enlarged marginal zone cell pool in the mouse model was removed or reduced, the disease was prevented or strongly diminished.

“The study proved without a doubt that the transplanted B cells were the source of lupus auto-antibodies,” said Gregg Silverman, M.D. professor of medicine in UCSD's Translational Oncology Program and contributor to the paper. “Identifying the spleen's marginal zone as the likely source of these tissue-damaging antibodies gives us important insights into the cause of lupus as well as a target for new therapies.”

The researchers also studied B-cell activation in two signalling pathways, called the classical and alternative NF-kB pathways, that contribute to the development of lupus. The scientists discovered that while each pathway is required for the pathogenesis of antibodies that cause the autoimmune disease, neither works alone.

“Either pathway would be a suitable target for therapy,” said Karin, whose lab first identified the two NF- κ B pathways several years ago. “Both are critical to production of pathogenic B cells that destroy the body’s own cells in lupus.” However, he added that targeting one of the NF- κ B pathways called the classical pathway would eliminate B cells throughout the entire body. This is the drawback of other therapies currently recommended for lupus patients, as they destroy the body’s immune cells which are needed to fight off other infection.

Karin added that genetic manipulation of the animals, or the timing of the splenectomy in the cycle of the lupus-like disease might have contributed to the outcome. Therefore more research is needed to draw a definite conclusion, though their studies ruled out the lymph nodes or the bone marrow – where B cells are born – as contributors to the effect.

“The study tells us important things about the pathogenesis of disease in a mouse model that is very close to human lupus,” Karin said. In mice, as in humans, the disease leads to overproduction of anti-DNA antibodies and immune deposits in the kidneys, which can result in fatal kidney damage.

Lupus is a chronic autoimmune disease that, for unknown reasons, causes the immune system to attack the body's own tissue and organs, including the joints, kidneys, heart, lungs, brain, blood, or skin. Difficult to diagnose and treat, patients may see several physicians before learning they have lupus. The disease is much more common in women than men, usually is first diagnosed between the ages of 15 and 44 years, and is two to three times more common in persons of color. Patients often take many different medications to control lupus, which has symptoms ranging from mild to life-threatening, including aching or swollen joints, skin rashes, kidney damage, anemia and hair loss.

Additional contributors to the study include leader author Thomas Enzler and Giuseppina Bonizzi, UCSD Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology; Gregg J. Silverman, UCSD Rheumatic Disease Core Center; Dennis C. Otero, UCSD Division of Biological Sciences; George F. Widhopf, UCSD Division of Hematology/Oncology; and Amy Anzelon-Mills and Robert C. Rickert, Burnham Institute for Medical Research, La Jolla, CA.

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