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B-cell discovery suggests why women suffer more autoimmune disease

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Researchers at National Jewish Health have discovered a type of cell that may contribute to autoimmune disease and suggests why diseases such as lupus, multiple sclerosis and rheumatoid arthritis strike women more frequently than men. The cells, a subset of immune-system B cells, make autoantibodies, which bind to and attack the body's own tissue. The researchers reported in the August 4, 2011, issue of the journal *Blood*, that they found higher levels of these cells in elderly female mice, young and old mice prone to autoimmune disease, and humans with autoimmune diseases. National Jewish Health has applied for a patent for a method to treat autoimmune disease by depleting these cells.

"We believe these cells could be useful in the diagnosis and treatment of autoimmune diseases, and may help us understand general mechanisms underlying autoimmunity," said senior author Philippa Marrack, PhD, Professor of Immunology at National Jewish Health.

Autoimmune diseases occur when the immune system begins attacking its own tissues rather than external pathogens. Several autoimmune diseases, including lupus, rheumatoid arthritis and multiple sclerosis, afflict women anywhere from two to 10 times as often as they do males. Although sex hormones are known to play a role in autoimmune disease, other factors are involved in these gender differences.

The research team came across the new cells when they were examining differential expression of X-chromosome genes in healthy male and female mice. They discovered a previously undescribed type of B cell,

which expressed the cell-surface protein CD11c. The protein is an integrin, which helps cells attach to other cells or to an extracellular matrix. The researchers are not certain what role integrin might play in autoimmunity or if it is merely a marker for another mediator of autoimmunity.

These cells increase as healthy female mice age, but remain at constant low levels in healthy male mice. As a result, the researchers named the cells Age-associated B Cells or ABCs. The researchers also found higher levels of ABCs in young and old mice that are prone to autoimmune disease. They could detect the elevated ABC levels before any disease developed and even before autoantibodies appeared, suggesting a role for these cells in early detection of disease.

The researchers also found an almost identical type of cell in the blood many human autoimmune patients. In women with rheumatoid arthritis the presence of these cells increased with age.

ABCs in mice produce antibodies against chromatin, the combination of proteins and DNA that make up chromosomes in the cell nucleus. When they depleted the ABCs in mice, autoantibody levels fell, suggesting a potential treatment for autoimmune diseases. National Jewish Health has applied for a patent on the method of depleting the cells to treat autoimmune disease.

The researchers also found that activation of these cells requires stimulation of TLR7, a cell-surface receptor involved in innate immune responses. The gene for TLR7 is located on the X chromosome. Women have two X chromosomes, men an X and a Y chromosome. Normally one copy of the X chromosome in women is silenced so that it does not produce excess protein. But the silencing is not always complete, and women commonly express elevated levels of some X-chromosome genes.

"Not only do these cells appear more frequently in females, their activation depends on a gene of which women have two copies and men only one," said Anatoly V. Rubtsov, PhD, first author and postdoctoral fellow at National Jewish Health. "This could help us understand why women suffer many autoimmune diseases more often than men."

Provided by National Jewish Health