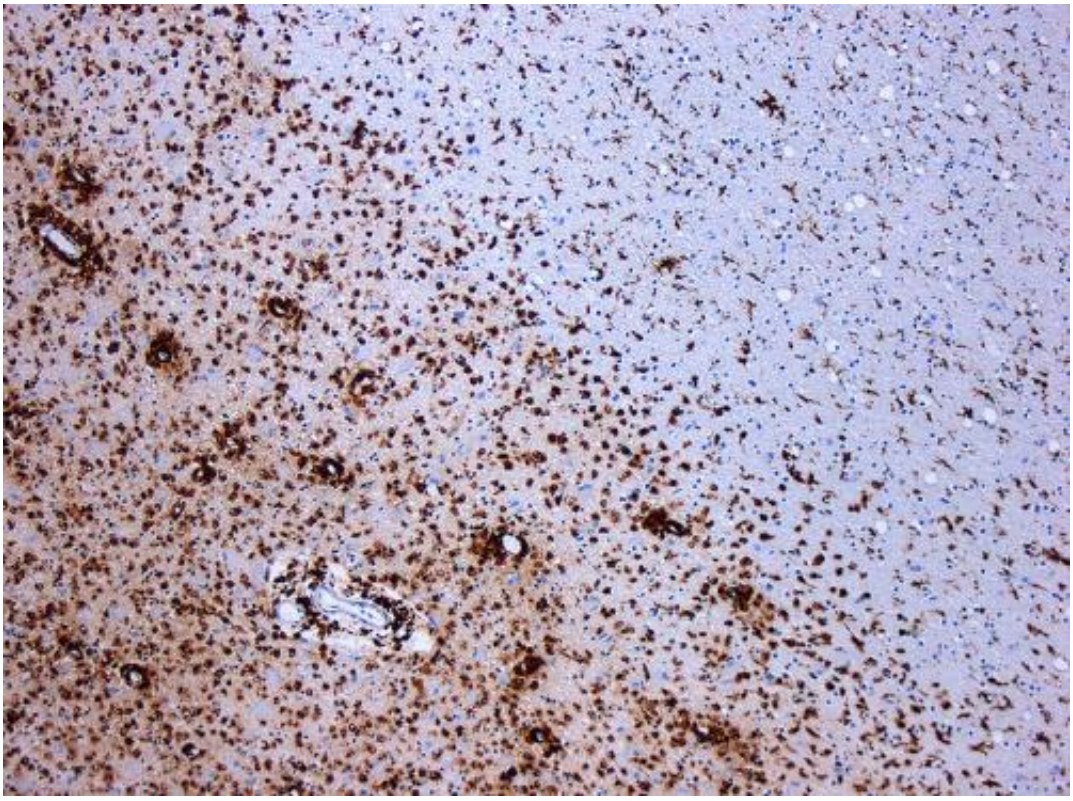
Protecting women from multiple sclerosis

May 28 2015



Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion. Original scale 1:100. Credit: CC BY-SA 3.0 Marvin 101/Wikipedia

An innocent mistake made by a graduate student in a Northwestern Medicine lab (she accidentally used male mice instead of female mice during an experiment) has led scientists to a novel discovery that offers new insight into why women are more likely than men to develop

autoimmune diseases such as multiple sclerosis (MS).

The finding, detailed in a paper published in *The Journal of Immunology*, focuses on a type of white blood cell, the innate lymphoid cell, that exhibits different immune activities in males versus females.

MS is a disease that affects the brain and spinal cord and is the result of a dysregulated immune response. Using a mouse model of MS in which only females get disease, this study showed that innate lymphoid cells are activated and protect male mice from the disease. Although female mice have these same cells, they remain inactive and do not protect them.

The research opens up new avenues for investigation into sex-determined disease susceptibility and could one day lead to better therapies for both men and women with MS and other autoimmune diseases.

"Women are three to four times more likely than men to develop MS, and much of the current research focuses on the question, 'Why do females get worse disease?'" said Melissa Brown, lead author of the study and professor of microbiology-immunology at Northwestern University Feinberg School of Medicine.

"Now, thanks to a serendipitous moment in the laboratory, we are approaching this research from the opposite way, asking, 'Why are males protected from disease?'" Brown said. "Understanding the mechanisms that limit disease in men can provide information that could be used in future therapy to block disease progression in women."

Like most laboratories that study the mouse model of MS, female mice were used in almost all of Brown's experiments.

"When we induce the disease in this strain of female mice, virtually 100 percent of them get very sick," Brown said. "Male mice either get no disease or very little, so MS researchers typically use females in their studies."

A few years ago, a new graduate student in Brown's laboratory was asked to run an experiment using two groups of female mice. One group was normal; the other had a genetic mutation in a growth factor receptor (c-kit) that prevented the development of a subset of immune cells.

Previous experiments in Brown's lab showed that female mice with the mutation didn't get as sick as normal mice, and Brown was looking into reasons why. However, instead of using females, the graduate student chose male littermates from each group.

"It was an honest mistake, but the results were striking; the male mice with the mutation got very, very sick," Brown said. "Because this strain of male mice never get very sick, I thought there was some sort of mistake, so I asked the student to repeat the experiment."

The results were the same. Brown and colleagues realized that the mutation was behaving differently in males and females. Brown asked Abigail Russi, a Feinberg MD/PhD student working in her lab, to investigate further.

Russi found that mice with the c-kit mutation lacked type 2 innate lymphoid cells. These cells are normally present in bone marrow, lymph nodes and the thymus of both males and females. The researchers think that in males these cells produce a protein that may help to protect from the disease by interfering with the damaging immune response.

"In the paper we show that when these cells are missing in the males with the mutation, that changes the whole immune response of the male

animals and causes this lack of protection," Russi said. "We are now looking at what activates these cells preferentially in males and not in females. The next question is can we activate the innate lymphoid cells in females to decrease disease susceptibility?"

This isn't the first sex difference study in the field of MS research. In the 1990s, scientists found that testosterone was a protective hormone for women with MS, but long-term treatment of women with MS with testosterone is not a viable option because of undesirable side effects.

Type 2 innate lymphoid cells have been well studied in allergy, where they are thought to promote allergic inflammation. But this is the first study to show these cells exhibit sex differences in their activity and actually can protect in autoimmune disease. Early trials are underway, and the scientists are hoping they will find clues to explain potential activators of these cells and whether those activators can be used in therapy.

The findings could lead to a new approach to designing drug therapy that modulates instead of completely suppresses the immune system of MS patients, shifting the response to one that is not so damaging.

"The hope is to target these cells in a sex-specific way and provide a therapy with fewer side effects," Brown said. "This early research may have implications for understanding other diseases such as lupus and rheumatoid arthritis, which also show a female bias."

Provided by Northwestern University

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