

Understanding Sex Differences in Autoimmune Disease

Additional understanding of Xist and its associated proteins may point researchers towards better testing and treatments.

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In autoimmune diseases, the immune system mistakenly identifies some of the body's own cells as a threat and attacks them. Up to 50 million people in the U.S. live with an autoimmune disease, such as lupus, multiple sclerosis, rheumatoid arthritis, or other, rarer disorders. Most cases of autoimmune disease are thought to arise from a combination of genetic risk factors and exposures to one or more stressors on the body.

Four of every five people diagnosed with an autoimmune disease are female. Researchers have been looking for differences in genes and hormones that may explain this sex difference in incidence, but many pieces of the puzzle remain missing.

Females have two X chromosomes, while males have only one, along with a smaller Y chromosome. To prevent a double dose of all the genes on the X chromosome, one of the X chromosomes in every cell of the female body is randomly inactivated by a long piece of functional RNA called Xist and the more than 80 proteins that associate with it—together called the Xist RNP complex.

A research team led by Dr. Howard Chang from Stanford University noted that some proteins associated with this complex were recognized by autoantibodies—the immune system proteins that attack normal cells in autoimmune diseases. In a new study, funded in part by NIH, they further examined the relationship between the Xist RNP complex and autoimmunity. Their results were [published on February 1, 2024, in Cell](#).

The researchers used two strains of mice. One was resistant to developing autoimmune diseases, while autoimmunity could be easily triggered in the other. They engineered male mice in both strains to produce a form of Xist that wouldn't shut down their X chromosomes.

In the resistant strain, male mice that produced Xist didn't develop autoimmunity after exposure to an environmental trigger. But in the vulnerable strain, more than 60% of the males that produced Xist developed severe autoimmune disease after they were given a trigger. In comparison, male mice of this strain that didn't make Xist did not develop autoimmunity in

response to the trigger.

The researchers next looked at autoantibodies to XIST—the human version of Xist—and related proteins in the blood of people. Autoantibodies to dozens of proteins associated with the XIST RNP were found in people with autoimmune diseases but not in those without an autoimmune condition. Many of these same autoantibodies were found in the mice that developed autoimmune disease. Some had previously been associated with autoimmune disease, but others were novel.

“Every cell in a woman’s body produces XIST,” Chang notes, but for several decades, researchers relied on male animals and cell lines for their studies. That made it less likely these anti-XIST-complex antibodies would be seen.

While the XIST RNP complex alone does not cause an autoimmune response, these findings suggest that it may help trigger it in people who are vulnerable. More work is needed to understand exactly which proteins in the complex may be responsible. Such research may lead to more sensitive testing that can catch autoimmune diseases earlier. It could also lead to the development of new approaches to prevent autoimmune diseases.

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