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Democracy Dies in Darkness

Scientists found a major clue why 4 of 5 autoimmune patients are women

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An international team led by scientists at Stanford University has discovered a probable explanation for a decades-old biological mystery: why vastly more women than men suffer from autoimmune diseases such as lupus and rheumatoid arthritis.

Women account for about 80 percent of the people afflicted with autoimmune diseases, a collection of more than 100 ailments that burden a combined 50 million Americans, according to the nonprofit Autoimmune Association. In simple terms, these illnesses manipulate the body's immune system to attack healthy tissue.

In a paper published Thursday in the journal Cell, researchers present new evidence that a molecule called Xist — pronounced like the word "exist" and found only in women — is a major culprit in these diseases.

Better understanding of this molecule could lead to new tests that catch autoimmune diseases sooner and, in the longer term, to new and more effective treatments, researchers said.

Women typically have two X chromosomes, while men usually have an X and a Y. Chromosomes are tight bundles of genetic material that carry instructions for making proteins. Xist plays a crucial role by inactivating one of the X chromosomes in women, averting what would otherwise be a disastrous overproduction of proteins.

However, the research team found that, in the process, Xist also generates strange molecular complexes linked to many autoimmune diseases.

Although scientists conducted much of their work in mice, they made an intriguing discovery involving human patients: The Xist complexes — long strands of RNA entangled with DNA and proteins — trigger a chemical response in people that is a hallmark of autoimmune diseases.

Discovery of the role played by the Xist molecule does not explain how men get these diseases, or why a few autoimmune diseases, such as Type 1 diabetes, have a higher incidence among men.

“Clearly there’s got to be more, because one-tenth of lupus patients are men,” said David Karp, chief of the division of rheumatic diseases at the UT Southwestern Medical Center in Dallas. “So it’s not the only answer, but it’s a very interesting piece of the puzzle.”

A tale of two X’s

Autoimmune diseases have long proved difficult to address. Treatments are limited, and many of the diseases are chronic, requiring lifelong management. Most have no cure, leaving millions of Americans hoping that science will eventually offer better explanations for these ailments.

Stephanie Buxhoeveden was 25 when she began experiencing vision problems in her left eye and found herself unable to hold a syringe in her left hand — a critical tool for her nursing job. The reason: multiple sclerosis, an autoimmune condition in which the immune system attacks the protective covering of the brain, spinal cord and optic nerves.

“I was overwhelmed and scared because I knew there was no cure,” the Virginia resident said. “All of these things that I had laid out, planned and worked really hard for all of a sudden were completely up in the air and no longer guaranteed.”

Previous theories had suggested that the gender imbalance in these diseases might be caused by the main female hormones, estrogen and progesterone, or by the mere presence of a second X chromosome.

A tantalizing clue stemmed from men who have two X chromosomes and one Y chromosome, a rare condition called Klinefelter syndrome. These men run a much higher risk of suffering from autoimmune diseases, suggesting that the number of X chromosomes plays an important role.

Howard Y. Chang, senior author on the Cell paper and professor of dermatology and genetics at Stanford, said he began thinking about the ideas that led to the new discovery when he identified more than 100 proteins that either bind directly to Xist or to other proteins that bind to Xist. Looking at those collaborator proteins, he noticed that many had been linked to autoimmune diseases.

Chang and his team engineered male mice that produced Xist to test whether males that made the molecule would also have higher rates of autoimmune diseases.

Since Xist by itself is not sufficient to cause an autoimmune disease, the scientists used an environmental trigger to induce a lupus-like disease in these mice. They observed that male mice then produced Xist at levels close to those of regular female mice, and well above those of regular male mice.

In humans, genetics and environmental factors, such as a viral or bacterial infection, can also help trigger autoimmune diseases.

The scientists obtained serums from human patients with dermatomyositis, a rare autoimmune disease that causes muscle weakness and skin rash. Serum is the part of the blood that contains antibodies that fight disease. They found that in these patients, Xist complexes produce what are called autoantibodies. Instead of defending the body from invaders, as an antibody would, the autoantibody targets features of the body.

Inactivation of the second X chromosome remains an important process "that you don't necessarily want to get rid of or tinker with too much," said Karp of UT Southwestern.

"But this work takes it in a totally different direction, and says that the mechanism that is needed to turn off the second X chromosome, that mechanism in itself might be responsible for generating autoimmunity," Karp said.

A better understanding of the mechanisms in these diseases would be significant if researchers can use it to develop new diagnostic tools, he added: "We are still using laboratory tests that were developed in the 1940s and '50s and '60s because they were easy to do, and they detected the most robust autoimmune responses."

A long road to new treatments

Jeffrey A. Sparks, an associate physician and director of immuno-oncology and autoimmunity at Brigham and Women's Hospital, said that it will be interesting to see how the treatment options available now might fit into this newfound mechanism.

"The sky's the limit here," said Sparks, who was not involved in the study, adding, "I think once you understand the fundamental mechanisms, you could think about developing therapies, early detection and preventions."

Major advances in treatment, though, may be years away, according to Keith B. Elkon, an adjunct professor of immunology and associate director at the Center for Innate Immunity and Immune Disease at the University of Washington.

Still, he said, scientific breakthroughs in the past 20 years have prolonged the lives of many people with autoimmune conditions.

"In 1950, if you've got a diagnosis of lupus, it would have been as bad as getting a diagnosis of cancer," Elkon said. "But over the last 15, 20 years there've been really striking breakthroughs in understanding disease. It's at the cusp of now being manageable."

Buxhoeveden, who is now 36 and a PhD candidate in nursing, is using immunosuppressants to manage her MS. She said she was encouraged by the fact that "we've made progress like this study to better understand what it is that triggers it."