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For Immediate Release

LJI scientists explore the importance of sex-based differences in the immune system

Sex chromosomes make a big difference for disease risk—but hormones and environmental cues play their parts

LA JOLLA, CA—Many diseases affect men and women differently. Asthma tends to strike men earlier in life, yet more women develop asthma as they get older. Parkinson's is more common in men, but Alzheimer's is more common in women.

The differences are even more stark when it comes to autoimmune disease. Women are around two and a half times more likely than men to develop multiple sclerosis and nine times more likely to develop lupus.

Why would some diseases strike one sex more than another? And why do some tissues, such as the lungs and brain, seem especially vulnerable to these sex-based differences?

To answer these questions, scientists at La Jolla Institute for Immunology (LJI) are leading new research into how our immune cells defend specific parts of the body.

In a new [Science review](#), LJI Professor, President & CEO [Erica Ollmann Saphire, Ph.D., MBA](#), and LJI Associate Professor [Sonia Sharma, Ph.D.](#), examine how genetics, sex hormones, and environmental factors come together to shape the immune system.

"In just the last two years, LJI scientists have uncovered a whole new body of information about how the immune systems of men and women are very different," says Saphire. "We're looking at what is genetically encoded in our XX or XY chromosomes, and how hormones like estrogen and testosterone affect what is genetically programmed into our immune cells."

In the paper, the researchers define biological sex (in an immunology context) as the presence of XX chromosomes in females and XY chromosomes in males. "Every cell in your body is either XX or XY," says Saphire. "That X chromosome has many, many immune-related genes. Women have two copies of each. That gives them, in a sense, twice the palette of colors to paint from in formulating an immune response. It can also give them a stronger immune response for those genes that are doubly active - active in both copies simultaneously."

Sex hormones are important for much more than reproductive function. Immune cells can also sense hormones such as estrogen and testosterone and use them to determine which genes to turn on or off and which ones to turn on more brightly or dim. This means similar immune cells can do different things, depending on whether that cell is from a male or a female.

Further, female cells vary in which of their two copies of X is "turned on." As a result, women have organs with a collage, or mosaic, of immune cells that work differently in different tissues. This innate "variety" of immune cells appears to be an effective way to ward off infectious disease (women are better than men at fighting off pathogens such as SARS-CoV-2).

But scientists have also found that having more genes from X chromosomes may predispose women to autoimmune disease. This increased X chromosome "dosage" is closely linked to a higher risk for autoimmune diseases such as Sjögren's syndrome and scleroderma.

New research into sex-based immune system differences is also critical for developing new cancer immunotherapies, Sharma explains.

"We're increasingly understanding how sex-based differences affect disease outcomes. When it comes to medicine, one size doesn't fit everybody," says Sharma, who directs LJI's [Center for Sex-Based Differences in the Immune System](#). "This is leading to new research, particularly in the cancer field, toward precision medicine. We're asking how a person's individual immune system is contributing to controlling that cancer through immunotherapy."

Saphire and Sharma also highlight environmental factors, such as nutrition and chemical exposures, that may add to the complex interplay of chromosomes and sex hormones. Men and women also appear to have some signature differences in their skin and gut microbiomes.

The researchers hope these foundational discoveries can lead to medical advances for all, and they're working with collaborators across the country to move this research forward. "It takes a team to translate these findings," says Sharma.

The new review, titled "[Sex differences in tissue-specific immunity and immunology](#)," includes co-author Alicia Gibbons of LJI and UC San Diego.

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About La Jolla Institute

La Jolla Institute for Immunology is dedicated to understanding the intricacies and power of the immune system so that we may apply that knowledge to promote human health and prevent a wide range of diseases. Since its founding in 1988 as an independent, nonprofit research organization,

the Institute has made numerous advances leading toward its goal: life without disease. Visit lji.org for more information.

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