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'Master regulator' in genes may make women more susceptible to autoimmune diseases

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Women represent nearly 8 out of every 10 people with autoimmune diseases. Although the hugely disproportionate statistics are well known, the scientific community is still trying to figure out why women's immune systems are more likely to become overactive and attack their own healthy cells.

Researchers at the University of Michigan recently released a study in *Nature Immunology* that explores why women are more often afflicted with autoimmune diseases. The paper propels their research, and eventual goal of finding successful treatment, in a different direction from existing work on sex hormones.

"We found a completely new angle," says senior author Johann Gudjonsson, M.D., Ph.D., U-M assistant professor of dermatology. "Our team identified a gene expression difference between the sexes that is associated with susceptibility to autoimmune disease."

Autoimmune diseases take many forms across the body, from psoriasis patches on the skin to lupus throughout the body to rheumatoid arthritis in the joints, yet all conditions affect women at a higher rate. It often takes years to get a correct diagnosis for these chronic diseases. There are no cures for the estimated 7.5 percent of people in the U.S. dealing with them, and current treatments come with devastating side effects.

Expanding psoriasis work

"It's important to examine changes to the skin in diagnosis and treatment of autoimmune disease," Gudjonsson says. For example, four of 11 criteria for a lupus diagnosis relate to the skin, with features like rashes.

His lab has focused on autoimmune diseases of the skin. The researchers decided to take a broader approach with this study, investigating gene expression in the skin of healthy subjects, including skin biopsy samples from 31 females and 51 males.

"We found some striking differences in gene expression between the women and men," says first author Yun Liang, Ph.D., a U-M dermatology research investigator. In total, 661 genes were expressed differently between the sexes.

"Many of those genes had immune function, and overlapped with genetic pathways and risk genes that related to autoimmune diseases," Liang says.

Following that finding, the team was able to identify what they are calling VGLL3, a master regulator of the female-biased immune network.

"This previously unknown inflammatory pathway promotes autoimmunity in women," says Gudjonsson, also the Frances and Kenneth Eisenberg Emerging Scholar in the Taubman Emerging Scholars Program. VGLL3 was also active in men with autoimmune diseases.

The role of sex hormones

Much of the existing work on gender differences in autoimmune diseases focuses on sex hormones, investigating the effects of hormones on women's immune systems to explain the disparity.

However, the novel inflammatory pathway U-M researchers identified as VGLL3 is not hormonally regulated.

"We found no evidence of involvement of estrogen or testosterone in the immune differences we observed between women and men," Gudjonsson says. "Identifying a separate regulatory mechanism could be a huge advance in gender-focused autoimmune research."

Next steps

This study, according to Gudjonsson, provides direction for future investigation into the identified pathway and how it is regulated.

"Learning more about these disease processes in each gender will provide opportunities for therapeutic interventions we did not imagine before, including both prevention and treatment," Gudjonsson says.According to the researchers, this is one of the first studies to conclusively demonstrate that it is critical for immunological research to study and analyze female and male samples differently.

More information: A gene network regulated by the transcription factor VGLL3 as a promoter of sex-biased autoimmune diseases, *Nature Immunology*, nature.com/articles/doi:10.1038/ni.3643

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