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Landmark Publication in *Cell* Sheds New Light on Why Immune Responses of Women and Men Differ

Publication Points to Long Noncoding RNA, XIST, as Playing a Role in Female-biased Immunity

Research Funded in part by the Scleroderma Research Foundation

SAN FRANCISCO, Calif., April 2, 2021 -- The Scleroderma Research Foundation, the nation's largest nonprofit funder of scleroderma research, announced today the publication of a paper in the leading journal *Cell* titled, "B cell-specific XIST complex enforces X-inactivation and restricts atypical B cells". The paper identifies several novel functions of XIST, the long noncoding RNA (lncRNA) that silences the genes of the second X chromosome in females. Dr. Howard Y. Chang and his group at Stanford University, including first author Dr. Bingfei Yu, believe their findings shed light on why female immune responses can differ from those of males: XIST is continuously required to silence certain X-linked genes in adult female B cells, and failure of this process results in the production of atypical B cells.

According to Dr. Chang, "Atypical B cells are specialized B cells that help activate our body's responses to infection, but they can also respond to self-antigens. Higher numbers of atypical B cells are also associated with female-biased autoimmune disease and aging. In this paper, we show for the first time that XIST is continuously required in human adult female B cells to silence a subset of X-linked immune genes such as TLR7. We also show that dysregulation of XIST results in two events: enhanced transcription of TLR7 and the development of atypical B cells, which may play an important role in some forms of autoimmunity."

Many autoimmune diseases, such as lupus and scleroderma, affect more females than males: nine of ten lupus patients are female, and four of every five scleroderma patients are female. Additionally, biological males who have an extra X chromosome (Klinefelter syndrome, XXY) also have an increased susceptibility to some female-biased autoimmune diseases. This has led researchers such as Drs. Chang and Yu to investigate the role of the extra X chromosome in autoimmunity.

The lncRNA XIST is required for X inactivation, which silences the genes on the additional X chromosome in females. Until recently it was thought that once silenced, X inactivation was stably maintained throughout life through DNA methylation and that XIST activity was no longer required. However, recent studies have revealed that X inactivation is not stable in female naïve B and T cells and that certain genes found on the X chromosome, like TLR7, can escape X inactivation in B cells, giving female B cells twice the amount of these immune signaling proteins.

Dr. Chang and his group discovered how XIST continually shuts down gene expression on the second X chromosome in female B cells. They found that XIST finds new protein partners in B cells, and together they slow down the enzyme that turns information from DNA to RNA.

Dr. Chang noted, "Like stop signs on a highway, XIST slows down the traffic on the B cell inactive X chromosome to prevent immune genes, like TLR7, from going into overdrive."

B cells make antibodies that fight infections. However, antibodies can also target self-proteins, a defining characteristic of autoimmune diseases. Autoantibodies are diagnostic for many autoimmune diseases, including scleroderma. B cells go through step-wise stages of development, from naïve B cells to expanded memory cells that can make many more copies of themselves and secrete more potent antibodies. Dr. Chang's group found that loss of XIST activity helps naïve B cells become atypical memory cells, completing the journey to a long-term source of potent autoantibodies.

Dr. Chang and his group were also able to see the effect of loss of XIST activity in cells from patients. When they looked at single-cell transcription data from patients with female-biased autoimmunity (lupus) or COVID-19 infection, they found altered activity of XIST coupled with increased transcription of TLR7 in atypical memory B cells.

This work revealed a way to track individual B cells that have escaped from XIST in patients with autoimmune diseases, and it identified TLR7 and several immune signaling proteins as potential targets to address female-biased immunity.

According to Scleroderma Research Foundation Chairman Luke Evnin, Ph.D., "The research done by Dr. Chang and his team sheds new light on immunity and autoimmunity in females. The paradigm for expanded functions of XIST presented in this paper may well turn out to be relevant to how the functioning of other immune cells may differ in females as well. These differences may be a double-edged sword: potentially helpful in the case of infection, but also having the potential to promote autoimmunity. At the Scleroderma Research Foundation, it is our hope that Dr. Chang's continuing research effort will lead to therapeutic interventions for patients with autoimmune diseases, including scleroderma."

Dr. Chang's group is currently looking for atypical B cells in scleroderma-associated pulmonary arterial hypertension, where clonally expanded B cells have been identified.

The project was funded in part by the Scleroderma Research Foundation.

About the Scleroderma Research Foundation

The Scleroderma Research Foundation is the nation's largest non-profit funder of scleroderma research. The mission of the Scleroderma Research Foundation is to fund and facilitate the most promising, highest quality research aimed at new treatments and, ultimately, a cure for scleroderma.

For more information, call (800) 441-CURE (2873) or visit www.SRFcure.org.

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