Autoimmunity

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New insights into female sex-biased autoimmunity

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Autoimmune diseases occur when an exaggerated or misdirected immune response damages healthy tissues or organs. Many autoimmune diseases predominantly affect women, but the biological mechanisms underlying this sex bias are incompletely understood. A new study in *Cell* used mouse models to show that the Xist RNA protein complex, present only in females, may underlie female-biased autoimmunity.

Although numerous studies have focused on the influence of sex hormones on sex-biased autoimmune diseases, increasing evidence suggests that genetic mechanisms linked to sex chromosomes contribute to sex bias in immune responses. In female mammals, which have two X chromosomes, X-chromosome inactivation ensures that X-chromosomal genes are not expressed twice. This critical epigenetic process is orchestrated by the long non-coding RNA (lncRNA) Xist and its associated ribonucleoprotein (RNP) complex. Many Xist partner proteins have been associated with autoimmune disorders, prompting Dou and colleagues to investigate the impact of the XIST RNP in autoimmune predilection.

For their study, the investigators developed a new transgenic mouse model that enables inducible expression of Xist (tgXist). They introduced a truncated version of Xist (non-silencing allele) under the control of a tetracycline-inducible system into an autosome in the autoimmune-prone SJL/J strain background. With this model, the researchers were able to induce Xist RNP formation in male animals, which have only one X chromosome and one Y chromosome, and study the effects of this female-specific lncRNA in a male background. The researchers combined their approach with the use of a chemically induced systemic lupus erythematosus (SLE) mouse model, which mimics human SLE, including autoantibody development, and demonstrates a strong female bias.

The findings show that male SJL/J mice expressing transgenic Xist developed more severe multi-organ pathology in the pristane-induced SLE model than wild-type males, with the majority of tgXist male mice experiencing female-level severe pathology. Pristane-treated males expressing Xist also showed increased atypical B cell activity and decreased immune modulatory programs in B and T cells compared with pristane-treated wild-type males.

Altogether, these results support a role for Xist RNPs in the development of severe autoimmunity, which may drive the sex-biased female preponderance for developing autoimmune diseases.

Alexandra Le Bras

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