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AUTOIMMUNITY

TLR7 evades silencing in human immune cells

> These findings suggest that a higher *TLR7* dosage arising from XCI escape connects the presence of two X chromosomes with an increased risk of developing SLE

The incidence of systemic lupus erythematosus (SLE) is markedly increased in women and in men with Klinefelter syndrome who have an XXY karyotype. Initial work in mice led to the hypothesis that increased dosage of *TLR7* — which encodes the intracellular nucleic acid sensor Toll-like receptor 7 — due to escape of X chromosome inactivation (XCI) could contribute to sex bias in SLE. However, such escape had never been demonstrated in primary human cells.

Now, using single-cell reverse transcription PCR (RT-PCR) and RNA-fluorescence in situ hybridization (RNA-FISH), Jean-Charles Guéry and colleagues show that *TLR7* escapes XCI in substantial fractions of distinct B cell, monocyte and plasmacytoid dendritic cell populations from healthy women and from men with Klinefelter syndrome. They also report that, when using TLR7-specific ligands in proliferation and differentiation assays, B cells with biallelic expression of TLR7 are preferentially enriched within plasma cell lines and are more likely to undergo IgG class switch than monoallelic cells."These findings suggest that a higher TLR7 dosage arising from XCI escape connects the presence of two X chromosomes with an increased risk of developing SLE," says Guéry.

Next, the researchers want to assess whether the level of *TLR7* biallelism is different between women with SLE and healthy individuals. "The evolution of SLE disease severity and responses to treatment are hard to predict, so patient stratification based on *TLR7* biallelism could be helpful," says Guéry. Moreover, they plan to further investigate how increased TLR7 expression translates to enhanced functional responses at the single-cell level.

"The strategy of assessing biallelic expression that we developed in this study could also be adapted to investigate other important X chromosome-linked immunity-related genes," concludes Guéry.

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