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Understanding Epigenetics of Sex Bias in Immune reactions by X chromosome inactivation

Immune functions have a general sex bias, with women showing stronger immune responses to pathogens and being more susceptible than men to autoimmune diseases. The presence of two X chromosomes has been widely associated with autoimmunity, independently of sex hormones. This might be explained by a failure of the mammalian sex-dosage compensation mechanism by which one of the two female X chromosomes is transcriptionally silenced. X chromosome inactivation (XCI) is controlled by the long non coding RNA XIST, which coats the inactive X chromosome (Xi) and recruits further chromatin repressive complexes. I have previously shown that delocalization of XIST from the underlying Xi chromosome territory is associated with increased gene escape from Xi silencing and/or reactivation1,2. Here, we show that XIST RNA is delocalized in human T lymphocytes and comes back onto the Xi upon activation. Interestingly, XIST re-localization is incomplete and delayed in Multiple Sclerosis (MS) patients, an autoimmune disease that affects women more than men (3:1 ratio). This suggests that lymphocytes might have a more dynamic control of XCI leading to a wider number of genes escaping silencing and further hampered in autoimmune conditions. To test this hypothesis, we performed single-cell RNA sequencing on human T lymphocytes from MS patients and healthy controls and identified sex-differences in cell subtypes and gene expression. Notably, we have validated Xi escape of sex-differentially expressed genes and are currently investigating both the mechanistic role of XIST delocalization and the functional impact of candidate gene overexpression in specific lymphocyte subpopulations. The lastest results will be presented.

References

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