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Researchers explore role of androgens in shaping sex differences

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Sex differences are widespread across human development, physiological processes, and diseases, making it important to characterize the impact of sex differences in these areas. Understanding the regulatory mechanisms associated with these differences, including the role of androgens, is also vital for clinical translation—especially for diseases more prevalent in one sex.

To answer these questions, a team led by Prof. Gao Dong and Prof.

Chen Luonan from the Center for Excellence in Molecular Cell Science, Shanghai Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences, Prof. Bai Fan from Peking University, and Prof. Yu Chen from the Shenzhen Bay Laboratory, deeply explored the role of androgens in shaping sex differences at the molecular and cellular levels. Their study is published in *Nature*.

The researchers developed a detailed single-cell transcriptomic map from 17 different tissues of the mouse (Mus musculus). Using this dataset, they analyzed sex differences in depth and investigated how androgens influence these differences through specific molecular pathways and cell types. They also explored the implications of their findings on sex-biased diseases.

They then pinpointed the genes (i.e., AASB-DEGs) among these various tissues and cell types whose expression is sex-biased and directly influenced by androgens. These genes, including Egfr, Fos, and Il33, were highlighted as potential targets for precision medicine by modulating the androgen pathway.

The researchers also detailed how androgens affect the prevalence of certain cell types across sexes in various tissues, notably within immune cell populations. A key finding was the identification of group 2 innate lymphoid cells (ILC2s), which play a role in inflammation and enhancing PD-1 blockade therapy.

Interestingly, ILC2s exhibited the highest androgen receptor (Ar) expression levels among the major immune cell types. The presence of these cells was notably affected by androgen levels, suggesting a mechanism by which androgens influence immune responses and disease susceptibility.

By integrating their findings with data from the UK Biobank, the

researchers discovered that the most common risk genes for multiple sex-biased diseases were major histocompatibility complex (MHC) genes, some of which showed sex differences or were androgen-responsive. Cross-species analyses based on this atlas also identified associations between cell types and sex-biased diseases.

Overall, this study sheds light on the intricate ways in which androgens contribute to sex differences at the cellular and molecular levels and provides the foundation for developing targeted therapies for sex-biased diseases by modulating the androgen pathway.

More information: Dong Gao, Sex differences orchestrated by androgens at single-cell resolution, *Nature* (2024). DOI: 10.1038/s41586-024-07291-6.
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