ATRX-Mediated Sex Difference in HIV-1 Replication in CD4⁺ T cells

212

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BACKGROUND

- Sex differences in HIV-1 disease manifestations are well described[1].
- Better control of viral replication after HIV-1 infection in women living with HIV-1 (WLWH) is observed with lower viral loads in females early in infection[2].
- Many studies have shown better immune-mediated control of HIV-1 in WLWH attributed to type I IFN response by immune cells[3].
- Less is known about cell-intrinsic control of HIV-1 in CD4 T cells.
- ATRX is known to serve as a restriction factor for DNA viruses[4,5].
- ATRX is encoded by the X chromosome.
- X chromosomal genes can escape from X chromosomal inactivation (XCI) in human cells.

X-Chromosomal ATRX can serve as a host restriction factor in HIV-1 infection. Increased ATRX expression in female CD4⁺ T cells results in lower HIV-1 replication.

HYPOTHESIS

We hypothesize that ATRX is a host cell-intrinsic restriction factor for HIV-1, and that escape from XCI of ATRX results in increased expression of ATRX in female cells allowing for better HIV-1 control.

METHODS

- Quantification of ATRX levels in CD4⁺ T cells by scRNA sequencing and flow cytometry.
- Assessment of escape of ATRX from XCI using RNA Fish on female cells.
- HIV-1 infection of human CD4⁺ T cells from females and males.
- siRNA mediated knockdown of ATRX in CD4⁺ T cells.

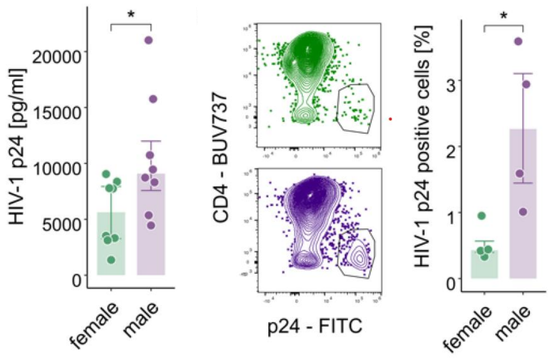
CONCLUSIONS

- Reduced HIV-1 replication in female CD4⁺ T cells.
- ATRX expression is increased in female CD4⁺ T cells.
- ATRX escapes from X chromosomal inactivation.
- HIV-1 infection increases upon ATRX knockdown.

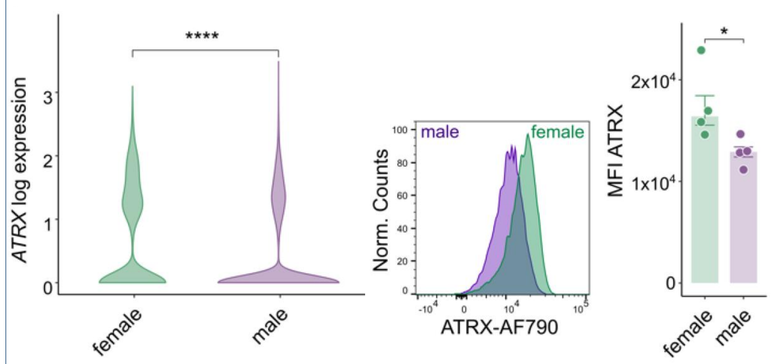
Here, we identify ATRX as a new host restriction factor of HIV-1, and demonstrate superior ATRX-dependent control of HIV-1 replication in female cells.

RESULTS

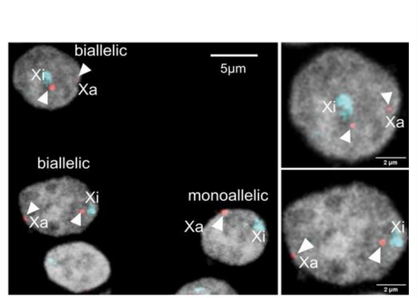
Reduced HIV-1 replication in female CD4+T cells



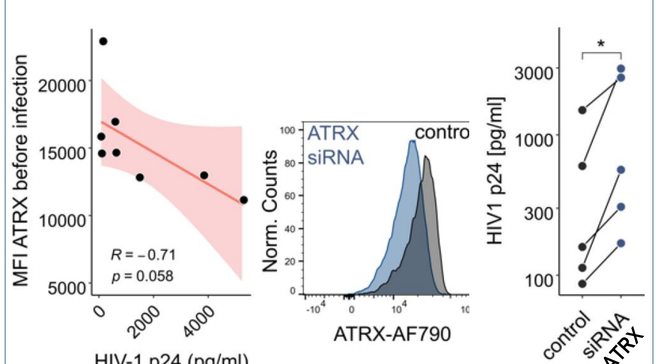
Increased ATRX expression in female CD4+ T cells



Escape of ATRX from XCI



ATRX serves as a host restriction factor of HIV-1



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ADDITIONAL KEY INFORMATION

We would like to clarify that the terms “female” and “male” refer to the attributed biological sex at birth in any of the participants. For this, we used the information reported by the medical staff. We want to acknowledge that this categorization might divert from the gender and/or other criteria regarding the self-identification of any of the participants.

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