Aging promotes reactivation of the Barr body at distal chromosome regions

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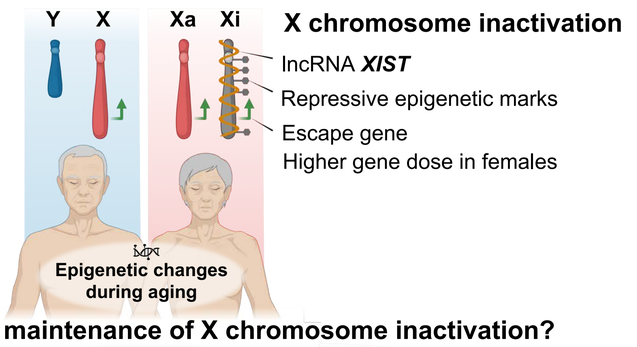
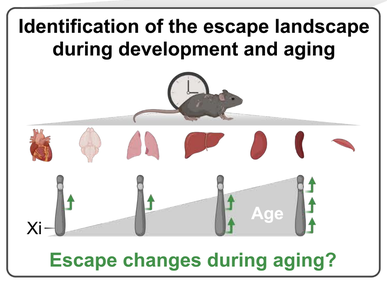
nature aging

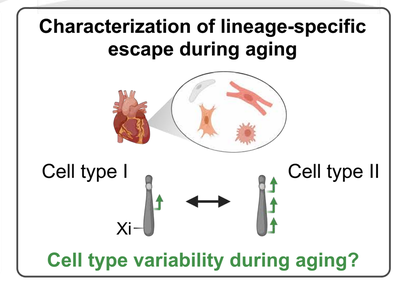
Aim

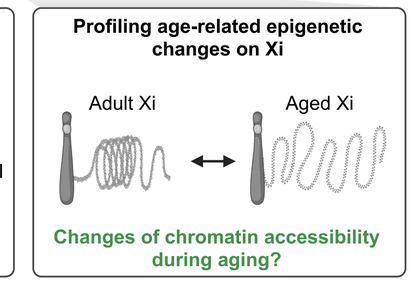
To achieve X-linked gene dosage balance between the sexes, one X chromosome is randomly inactivated in women early in development, forming a compact chromatin structure known as the Barr body. However, some genes evade this inactivation process and are consequently expressed from both X chromosomes. This results in a higher gene dose in women compared to men, which may contribute to sex-specific differences in physiology and disease. While stable silencing of the Barr body is crucial for preserving a gene dosage balance between sexes, it remains unclear whether silencing is maintained during aging. In this study, we used allele-specific multi-omics approaches to examine the dynamics of genes escaping X chromosome inactivation throughout mouse development and aging.



Does aging affect the maintenance of X chromosome inactivation?

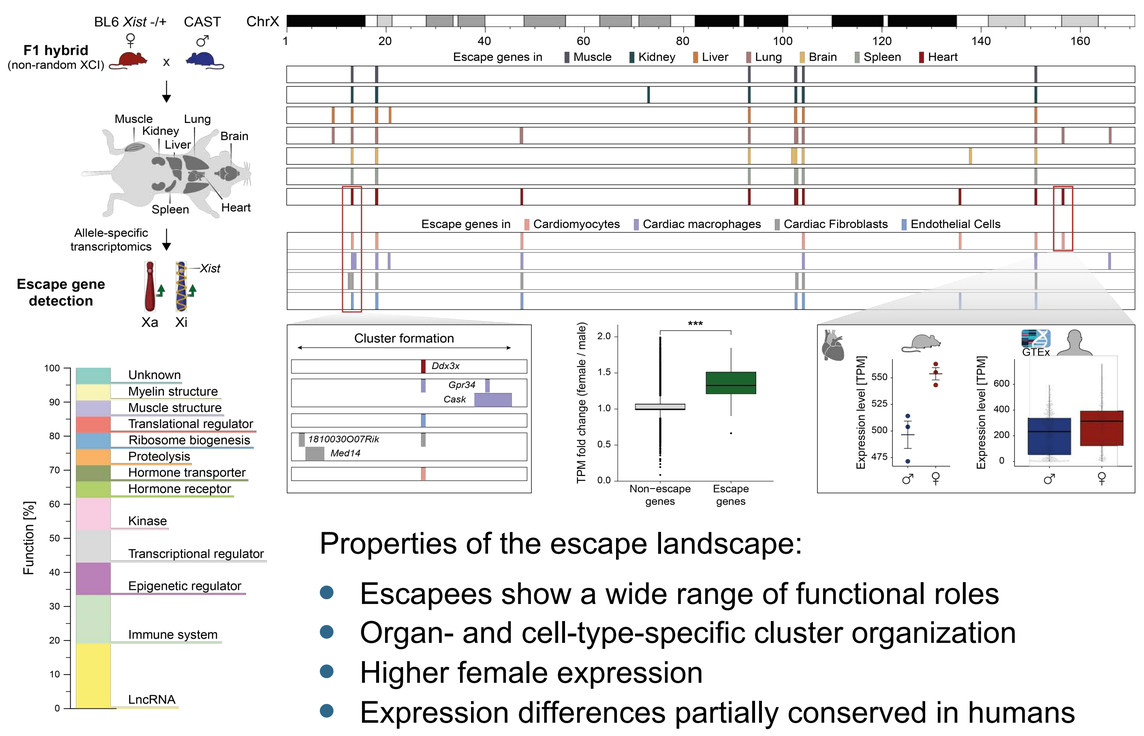






Results

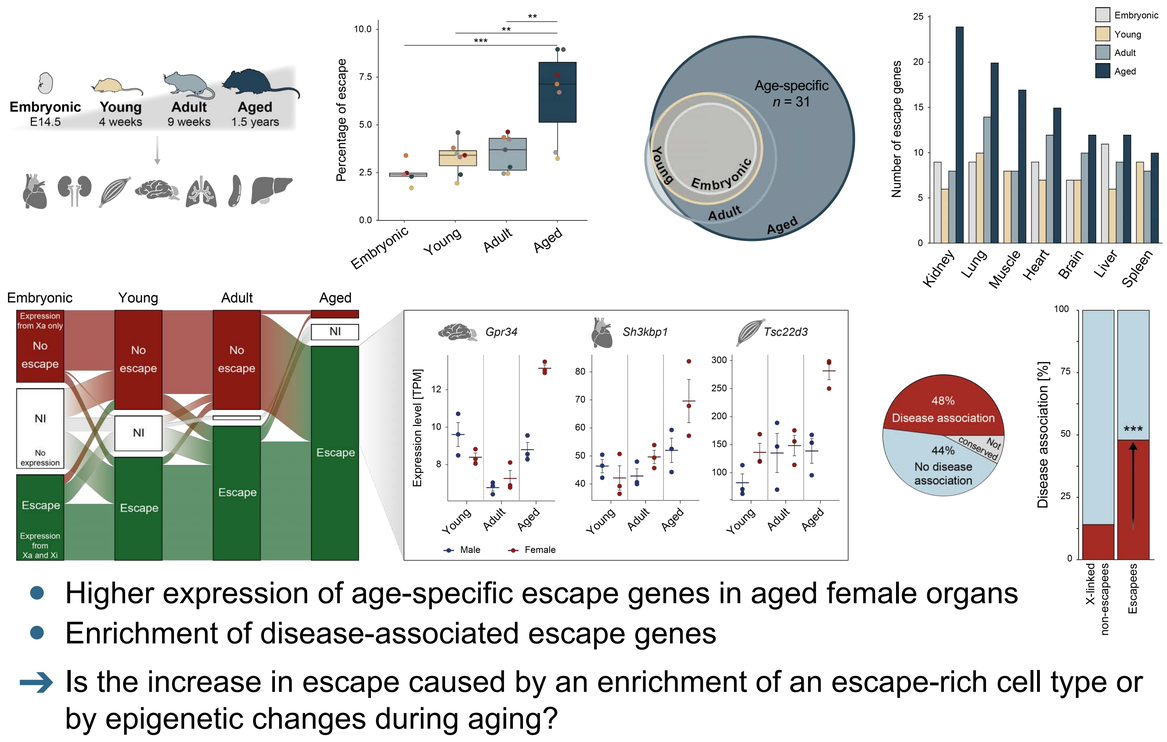
1. The escape landscape shows organ and cell type specificity



Properties of the escape landscape:

- Escapees show a wide range of functional roles
- Organ- and cell-type-specific cluster organization
- Higher female expression
- Expression differences partially conserved in humans

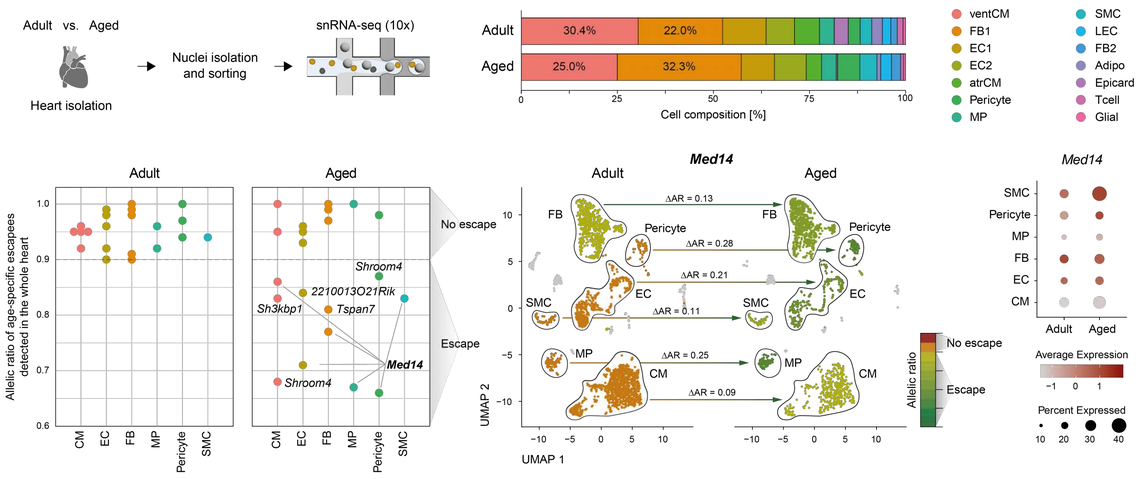
2. Escape increases during aging across organs



- Higher expression of age-specific escape genes in aged female organs
- Enrichment of disease-associated escape genes

➔ Is the increase in escape caused by an enrichment of an escape-rich cell type or by epigenetic changes during aging?

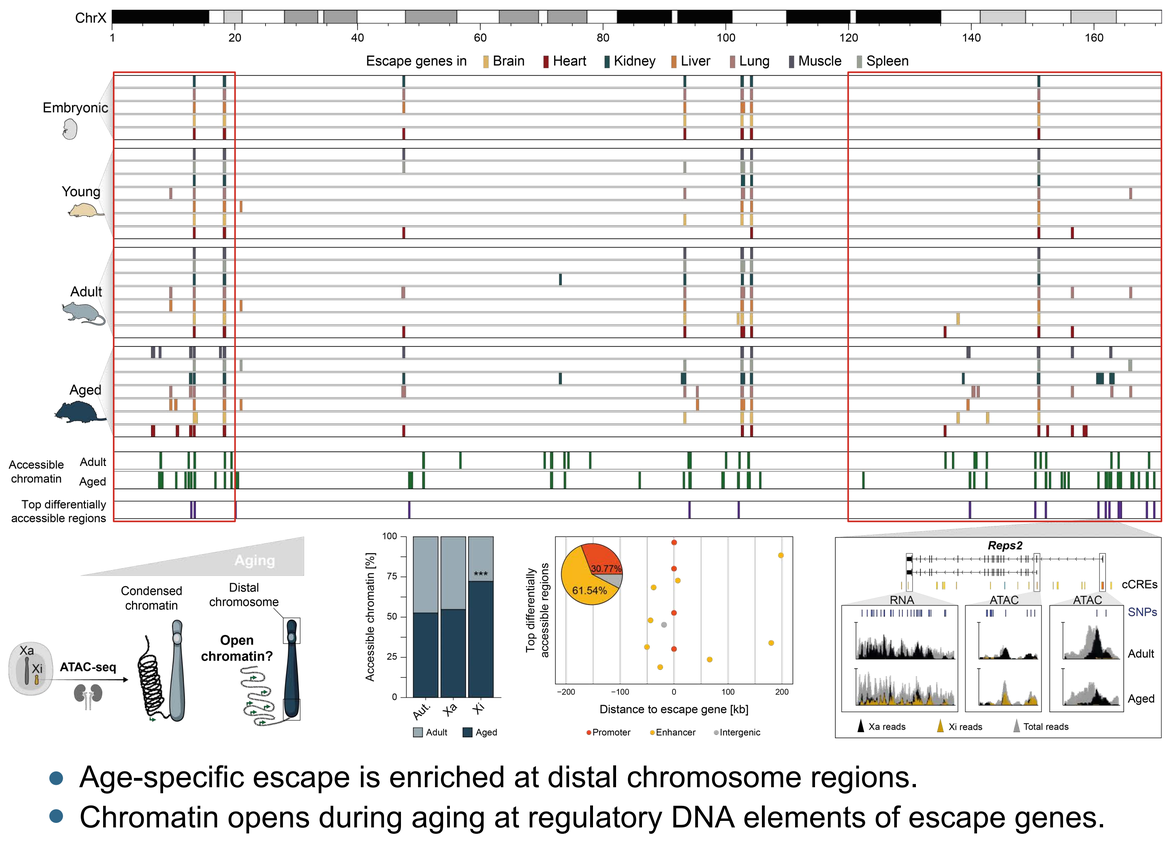
3. Age-specific escape manifests within distinct cell types



- Fibroblasts are enriched in the aged heart.
- Age-specific escape occurs in every examined cell type.

➔ Despite a shift in cell-type populations in the aging heart, age-specific escape manifests within distinct cell types, indicating that age-related epigenetic changes promote gene escape.

4. Aging loosens distal Xi regions at regulators of escapees

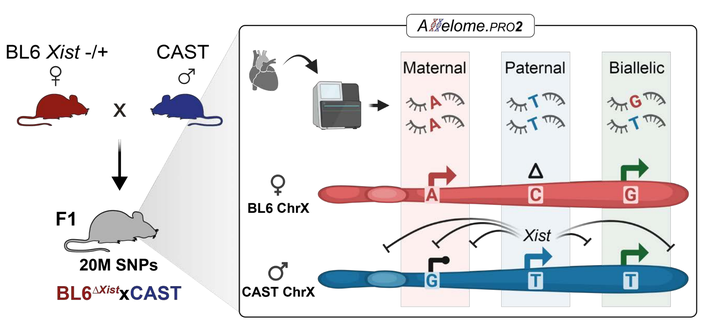


- Age-specific escape is enriched at distal chromosome regions.
- Chromatin opens during aging at regulatory DNA elements of escape genes.

Methods

The combination of the *Xist* mouse model and Allelome.PRO2 enables allele-specific analysis of the X chromosome

- *Allelome.PRO2* assigns sequencing reads to alleles using SNPs from genetically distinct strains.
- A maternal heterozygous *Xist* deletion skews XCI toward the paternal X, enabling escape gene detection.



Summary

In this study, we used allele-specific multi-omics to catalog genes escaping X chromosome inactivation throughout mouse development and aging. We found substantially elevated escape rates during aging across organs, occurring in multiple distinct cell types and concentrated at distal chromosome regions. Consistently, chromatin accessibility increased across multiple megabases at chromosome ends, affecting regulatory DNA elements of escapees. As several age-specific escapees are linked to human diseases, their elevated expression in females might contribute to the sex bias of age-related diseases.

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