AGING AND SEX CHROMOSOMES

Traditionally the differences in sex have been attributed to gonadal hormones. In a major review just published in *Science* Dubal et al. (1) have put together evidence that the sex chromosomes themselves play an independent role, acting at the cell level regardless of gonadal hormones. The authors invite us to look at the X and the Y chromosomes very differently, as active determinants of how we age and which diseases we develop.

X chromosome: about 15 to 30% of genes escape inactivation on the inactive X in humans (X escape); so, females carry a higher dose of some X-linked genes. There may be deviation from the 50:50 ratio of which X remains active, maternal or paternal X (X-skew). Inactivation appears not to be a fixed state as it can partially reverse with age (XCR). One X is lost in cells of women as they age (one X is lost in over 35% of the cells after age 80); this mosaic loss of an X (mLOX) is another factor that adds to variability between individuals.

Y chromosome: mosaic loss of the Y (mLOY) is the most common acquired chromosomal alteration in aging men. It is associated with cancer, cardiac fibrosis, Alzheimer's disease and infections; mouse models suggest it is a cause, not just a marker.

These mechanisms help explain why women live longer, why autoimmune diseases such as lupus and multiple sclerosis are more frequent in females, and why men and women can respond differently to the same cancer therapy.

Further studies should define functions of individual X-and Y-linked genes, X-linked imprinting, X-X and X-Y interactions across tissues, aging, and diseases. Longitudinal studies are needed to define the biological consequences, and clinical relevance of mLOY, mLOX, XCI escape, XCR, X-skew, and other age-and disease-related changes in sex chromosome biology. The authors propose that in the future, sex chromosomes should be incorporated into genome-wide association studies (GWASs) and other genomic analyses.

1. https://www.science.org/doi/10.1126/science.aeh0145