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*Review Article*

# X-Chromosome Inactivation

**Nicklaus Jamie***

Department of Pathology, University of Washington, United States

*Corresponding Author's E-mail: jamienicklaus@rediff.com

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**Abstract**

One of the two X chromosomes in female cells randomly becomes inactive throughout development. When the Xist genes transcribed RNA covers the whole X chromosome on the X chromosome from which it is produced, inactivation takes place. Nesterova and colleagues examine the function of the RNA interference pathway enzyme Dicer in the DNA methylation of the Xist promoter in the inaugural issue of Epigenetics and Chromatin. In order to equalise the dosage of X chromosome gene products between XX females and XY men, one X chromosome must be transcriptionally silenced in female mammalian cells. Early in development, the X chromosome becomes inactive in the embryo (Edem et al., 2012). Equal chances exist for both X chromosomes to be silenced. Once established, silencing is enduring because the identical X chromosome stays inactive in all succeeding cell generations. As a result, each female is made up of a mosaic of cells in which the X gene from either the mother or the father is silenced. In the first issue of Epigenetics and Chromatin, Nesterova and colleagues provide new insight into the regulation of this process. In order to equalise the amounts of X-linked gene expression across the sexes in mammalian female cells, X-chromosome inactivation (XCI) is one type of dosage compensation. Due to inactivation escape and skewing, XCI is linked to a variety of disorders, and the severity of these diseases also heavily depends on the state of XCI. Three categories may be made of them: X-linked disorders, XCI escape-related illnesses, and X-chromosome aneuploidy. Here, we evaluate representative illnesses in terms of their description, signs, and symptoms, as well as XCI's part in their aetiology (Haratym 2002)

## INTRODUCTION

Females' one X chromosomes chromatin structure and content are substantially altered by X inactivation, an intricate multi-layer epigenetic process. The heterochromatic inactive X chromosome assumes a distinctive 3D bipartite shape and resides at the nucleolus or nuclear periphery. The recruitment of proteins that catalyse the chromatin and DNA modifications for silence, the regulation of chromatin condensation, and the position of the inactive X chromosome are all influenced by X-linked lncRNA loci and their transcripts. It is unclear how certain genes maintain their expression while being enmeshed in heterochromatin because a portion of them evade X inactivation. Male and female escape genes express themselves differently, which can result in physiological sex differences (Tela et al., 2016). We discuss recent researches that highlight difficulties in comprehending how lncRNAs regulate the structural characteristics, epigenetic changes, and nuclear placement of the dormant X chromosome. Second, we examine the functions of escape genes in eliciting sex differences in health and disease and highlight recent results concerning the distribution of genes that escape X inactivation based on single cell research (Chaudhry et al., 2014).

The unique heteromorphic chromosomes that control sex differentiation emerged as a result of the evolution of the mammalian sex chromosomes from a pair of autosomes. The X chromosome has numerous genes (900–1500), is present in two copies in females and one copy in men, and has fewer genes (around 70) and is exclusively found in males. This leads to the imbalanced gene dosage between the sexes and between X-linked and autosomal genes. Both X upregulation of expressed genes in men and females, as well as X inactivation or silence of one X chromosome in females emerged as dosage compensation mechanisms to correct these imbalances. Here, we concentrate on X chromosome inactivation (XCI), a process that silences an

arbitrary X chromosome during the early stages of female embryogenesis. XCI is characterised by a series of molecular processes that start soon after embryo implantation and are faithfully maintained in all somatic cells of an individual. This characteristic makes XCI an effective model for studying the structural and epigenetic modifications connected to gene silencing (Yunusa et al., 2018). The long non-coding RNA (lncRNA) Xist coats the future dormant X chromosome (Xi) in cis to begin this intricate process. During the early stages of development, layers of chromatin and DNA modifications are set in place over the course of several days for stable transcriptional silencing of each gene on the Xi by proteins that were first recruited by Xist RNA. These alterations result in significant adjustments to the 3D structure and placement of the Xi, both of which depend on X-linked lncRNA loci. The lncRNA locus Dxz4 serves as a barrier between the two superdomains of chromatin condensation that make up the bipartite shape that the Xi adopts (Mohamed 2017). The Xi also visits the nucleolus, which is made possible by the lncRNA Firre. A subset of developmentally important genes continues to be expressed from the Xi, albeit at a lesser level, in spite of the several levels of gene suppression that serves to stabilise XCI. These escape genes develop structural and chromatin characteristics more typical of areas of active transcription. These genes may express themselves more strongly in females, resulting in sex differences in both normal physiology and illness vulnerability. A variety of harmful phenotypes, including as infertility, intellectual impairment, immunological disorders, and cancer, are influenced by abnormal escape gene dosage (Kingsley et al., 2016).

The X chromosome inactivation (XCI) process, which is developmentally controlled, includes the successive acquisition of silencing markers on the X chromosome. There are two types of XCI patterns: imprinted and random. While the bulk of XCI characteristics are similar between the two patterns, there are minor variations that reflect the kind and degree of inactivation stability. With the mouse model system, the majority of research on XCI in animals has been done. The female mouse zygote possesses both active X chromosomes at the time of fertilisation. During development, the first cleavage results in the first inactivation. Since the inactivation is imprinted, it solely affects the paternal X chromosome. Cells from the inner cell mass (ICM) later activate the inactive X after the blastocyst has developed (Friday et al., 2015). The trophectoderm and the primitive endoderm still contain their imprinted paternal XCI from the initial cleavage, but the ICM cells have both active X chromosomes at this time. The ICM cells will then inactivate one of their X chromosomes once more only after differentiating, although this time stochastically as opposed to the initial cleavage event. The second wave of inactivation will result in a random XCI in each cell since the ICM cells are the source of the embryo proper, and throughout development its progeny will preserve that specific Xi. The primordial germ cells (PGC) are an anomaly in that they reactivate their Xi at a later stage of mouse development (E11.5–E13.5) and that the female germ cells maintain this state (Yusuf et al., 2017).

Monoallelic Xist gene expression starts both random and imprinted XCI. Epigenetic alterations brought on by its expression include the loss of transcription factors, RNA polymerase II, and euchromatic markers. In contrast to random XCI, which maintains stability from the time of establishment through several cell divisions over the course of a complete existence, imprinted XCI is transient. Therefore, the methods for CpG island methylation are used to produce stable random XCI. Compared to histone modifications, which are typical of imprinted XCI and early epigenetic processes of random inactivation, this alteration is thought to be more permanent. Despite the fact that XCI only happens for a brief period of time throughout mouse development, it is hypothesised that the kinetics of gene silencing vary. There is proof that during differentiation, genes close to the X chromosome inactivation centre (XIC) are first silenced (Ozer et al., 2008). The "escape" from inactivation, which occurs in XCI, is another intriguing event. Although the bulk of the genes on the Xi are completely silenced, some are still able to express on both active and inactive X chromosomes. A recent study employing the transgenic technique indicated that while the precise mechanism for genes avoiding XCI is not entirely known, it is likely an inherent characteristic of a particular locus. The endogenous expression pattern could be reproduced by randomly integrating BAC clones harbouring typically silent or escaping gene (Jarid1c) locations into the X chromosome of female ESC lines. The authors came to the conclusion that a locus' susceptibility to XCI can be predicted by its DNA sequence alone. It has been thought that the "inactive" X chromosome (Xi) has minimal effect on the "active" X (Xa) in Trans. We measured the expression of the Xi and Xa genes in people with one Xa and zero to three Xis to verify this. Our linear modelling identified Xi and Xa transcriptomes as modular, and 38% (162/423) of expressed X chromosome genes saw substantial Xi-driven alterations in expression. We discovered that many of these Xi-driven alterations (121 genes) are influenced by the modification of Xa transcript levels by Xi by combining allele-specific analysis. We found 10 X chromosome genes that are most likely to be responsible for sex differences in common diseases and sex chromosome aneuploidy syndromes by combining metrics of evolutionary restriction. We draw the conclusion that the human X chromosomes are controlled in Trans by Xi's regulation of specific Xa genes, as well as in cis by Xi-wide transcriptional attenuation. Each gene has a unique set of these cis and Tran's effects.

# CONCLUSION

Depending on the pattern of X-chromosome inactivation, X-linked illnesses impact female patients differently, resulting in a wide spectrum of phenotypes. The majority

of the researches presented, as can be seen in the review up top, are case studies, and a larger sample size would be helpful in exploring the connection between skewed X inactivation and phenotypic severity. Since the XCI skewing pattern differs between various cell types even in the same individual, it is also crucial to take note of the cell type while doing the analysis. The ideal way to investigate the connection between XCI skewing and the severity of the trait in female heterozygotes would also be to examine samples from the afflicted organs. To facilitate the development of further therapeutic options, targeted reactivation of the normal allele on the Xi gene. While much is known about the numerous lncRNAs and proteins that regulate the structural and epigenetic characteristics of the Xi and its silencing, further research is still needed to determine exactly how these molecules work. It will be very interesting to describe parameters involved in nuclear compartmentalization and phase separation in terms of the 3D structure of the Xi. To connect the Xi's unique 3D structure and nuclear position with its distinctive epigenetic environment, more research is required. Additionally, there is limited information available on the contacts between each X chromosome and the remainder of the genome in female cells and tissues, as well as these contacts with the heterochromatic Y chromosome in male cells and tissues. There is little knowledge of the tissue-specific variations in chromosomal organisation inside the nucleus, and few functional investigations have looked at the effects of changing chromosomal position. Further functional researches on the epigenetic mechanisms governing escape from XCI are also necessary. Because there are so few meaningful polymorphisms in humans, current methods to find escape genes in particular cell types and tissues are unfortunately constrained. To construct maps of gene expression or accessibility in a whole organism, some approaches for single-cell analysis enable investigations in thousands of cells in tissues, as demonstrated, for instance, in a newly published atlas of mouse tissues/cell types. Although there is strong evidence that sex variations in illness susceptibility exist, it will need rigorous dose modification to fully understand the function of each sex-linked gene.

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