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Study identifies mechanism affecting X chromosome that could lead to novel therapies for rare and common diseases

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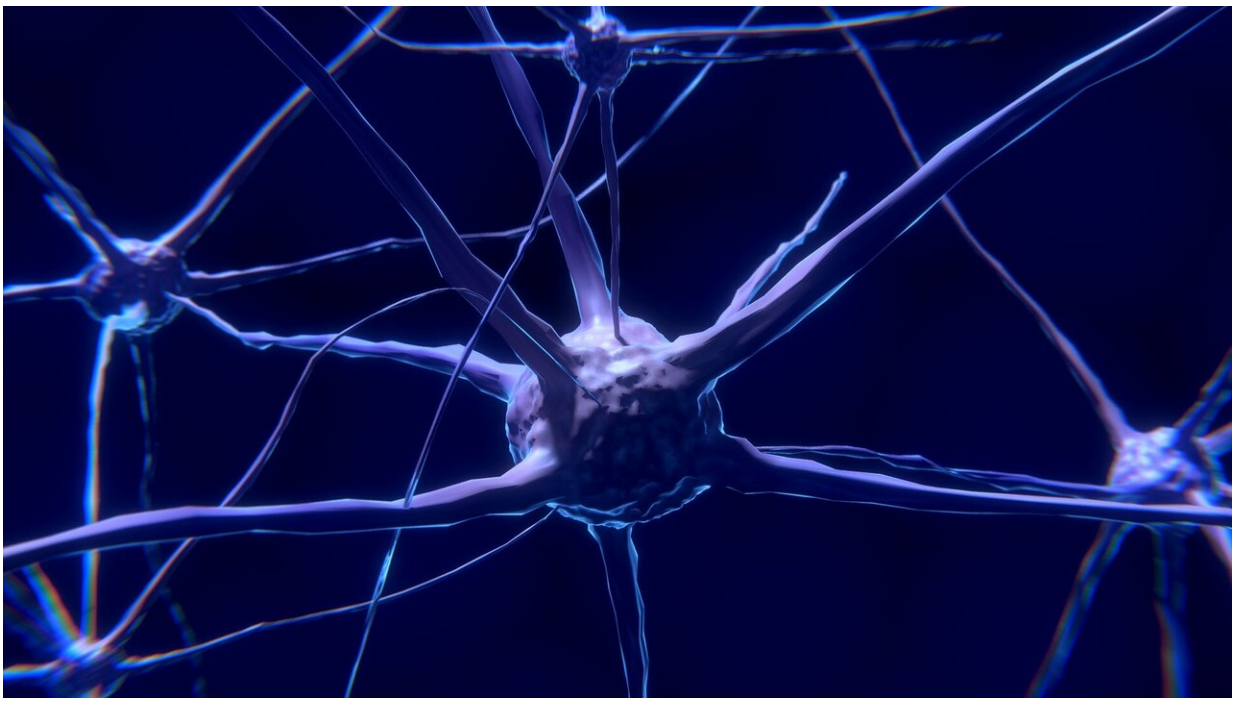

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Researchers at Massachusetts General Hospital have identified a key mechanism in X chromosome inactivation, a phenomenon that may hold clues that lead to treatments for certain rare congenital disorders. Their findings, published in the journal *Developmental Cell* on June 11, 2020,

may also aid in the creation of novel medicines for certain cancers.

Female humans and other mammals have two copies of the X chromosome in each of their cells. Both X chromosomes contain many genes, so only one of the pair can be active; having both X chromosomes expressing genes would be toxic to the cell. For this reason, female mammals developed a mechanism called X chromosome inactivation, which silences one chromosome, explains Jeannie Lee, MD, Ph.D., of the Department of Molecular Biology at Mass General, senior author of the *Developmental Cell* study.

Learning how to inactivate and reactivate an X chromosome would have important implications for medicine. A notable category of beneficiaries could be people with certain congenital diseases known as X-linked disorders, which are caused by mutations in genes on the X chromosome. One example is Rett syndrome, a disorder brought on by a mutation in a gene called MECP2 that almost always occurs in girls and results in profound problems with language, learning, coordination, and other brain functions. In theory, it may be possible to treat a disorder like Rett syndrome by reactivating the X chromosome. "Why don't we put the dormant X chromosome to work and rescue the cells that are lacking a proper copy of MECP2?" asks Lee.

The goal of X chromosome reactivation has led scientists to focus on epigenetic factors, which turn genes "on" or "off" without altering the genetic code. Silencing genes on the X chromosome occurs when a form of noncoding RNA called Xist spreads across the X chromosome, explains Lee. However, Xist doesn't act alone: It must attract proteins called Polycomb repressive complexes (PRC) 1 and 2 to complete inactivation of the X chromosome.

But how Xist pulls in PRC1 and PRC2 had been unclear and the subject of debate. Research indicates that repeating sequences of nucleotides on

Xist called Repeat A and Repeat B appear to act as magnets for these proteins. Yet some recent research suggests that Repeat A plays no role.

Study Details

In the new study, Lee and her colleagues showed that both Repeat A and Repeat B are needed to attract PRC1 and PRC2 and complete X chromosome inactivation. By deleting Repeat A from Xist in mouse embryonic stem cells, they found that X chromosome inactivation is not only thwarted, but one X chromosome is eliminated entirely in order for the cells to survive in culture. In human females, when one X chromosome is missing, the result is Turner syndrome, which affects stature, fertility, and other physical traits.

Understanding how Xist "recruits" PRC1 and PRC2 could have far-reaching implications, especially since the latter plays a key role in maintaining overall cell health. "We think that through interfering with the Xist recruitment of Polycomb and other silencing complexes, we may eventually be able to treat X-linked diseases like Rett syndrome and perhaps even cancer," says Lee.

More information: David Colognori et al. Xist Repeats A and B Account for Two Distinct Phases of X Inactivation Establishment, *Developmental Cell* (2020). DOI: 10.1016/j.devcel.2020.05.021

Provided by Massachusetts General Hospital