Researchers identify key RNA "gatekeeper" in gene expression, pointing to possible new drug targets

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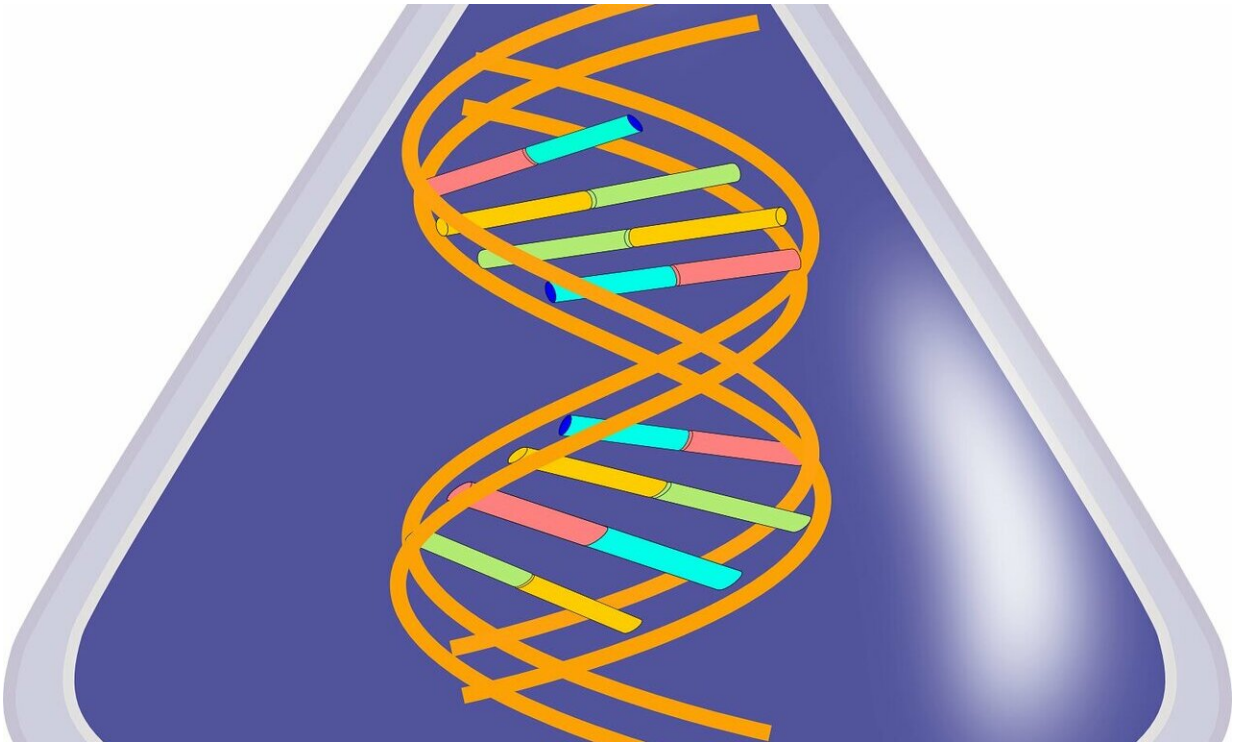

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An important player in the healthy development of female embryos turns out also to play a key role in regulating the behavior of chromosome loops and gene expression in both sexes, according to a new study by

researchers at Massachusetts General Hospital (MGH). These findings, reported in the journal *Cell*, could help create new targets for drug development.

Chromosomes are long, string-like structures made up of DNA, RNA and proteins. A chromosome must fold into a loop in order to fit into the nucleus of a cell. These loops bring together distant genetic material. "Genes and control elements—sequences that regulate genes—have to communicate with one another for the cell to work properly," says the senior author of the paper, Jeannie Lee, MD, Ph.D., of the Department of Molecular Biology at MGH. "Chromosome looping is kind of like bringing people together in a conference room so they can talk to one another."

These interactions within a chromosome loop regulate gene expression, that is, whether a gene is turned "on" and thus producing proteins or turned "off." Chromosome loops are in constant flux, growing and contracting as they change their composition of genes in response to environmental stimuli and the body's developmental needs. Returning to the conference room metaphor, a protein called CTCF acts as a door, explains Lee, and it was already known that a chromosome loop may have multiple sets of double doors—some open, some closed. "But what wasn't known is how these doors open and close," explains Lee. "Who are the gatekeepers?"

The answer proved to be a surprise. Lee and her team discovered that a form of RNA known as Jpx is a gatekeeper that regulates the behavior of CTCF in chromosome looping. Jpx RNA was no stranger to Lee and her fellow investigators. Eight years ago, they showed that this noncoding form of RNA is a key player in the phenomenon known as X chromosome inactivation, which is essential for normal development in all female mammals, including humans. Jpx RNA helps count X chromosomes in female cells very early in development; if two are

detected, one X chromosome is inactivated, or silenced.

However, Lee's group, which included postdoctoral fellow Hyun Jung Oh, Ph.D., first author of the study, found that Jpx RNA also determines what combination of double doors are open at any given time by "evicting" CTCF from the chromatin (a substance within a chromosome). "Jpx regulates whether multiple doors are open or just one, as well as which panels of double doors are open, left or right," says Lee. "By regulating that process, Jpx determines how big the chromatin loop is and, therefore, which genes around the loop are expressed."

Jpx is the first form of RNA to be identified as playing a vital role in regulating the behavior of CTCF, but there will be many others, predicts Lee. That's exciting, she says, because there are probably 10 times more varieties of RNA than there are proteins. While Jpx regulates genes involved in early in the development of an embryo, other RNAs awaiting discovery may regulate the formation of chromosome loops that influence the risk for cancer, autoimmune disorders and other diseases, says Lee. Identifying these RNA could speed the development of effective new medications.

More information: Hyun Jung Oh et al, Jpx RNA regulates CTCF anchor site selection and formation of chromosome loops, *Cell* (2021). DOI: 10.1016/j.cell.2021.11.012

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