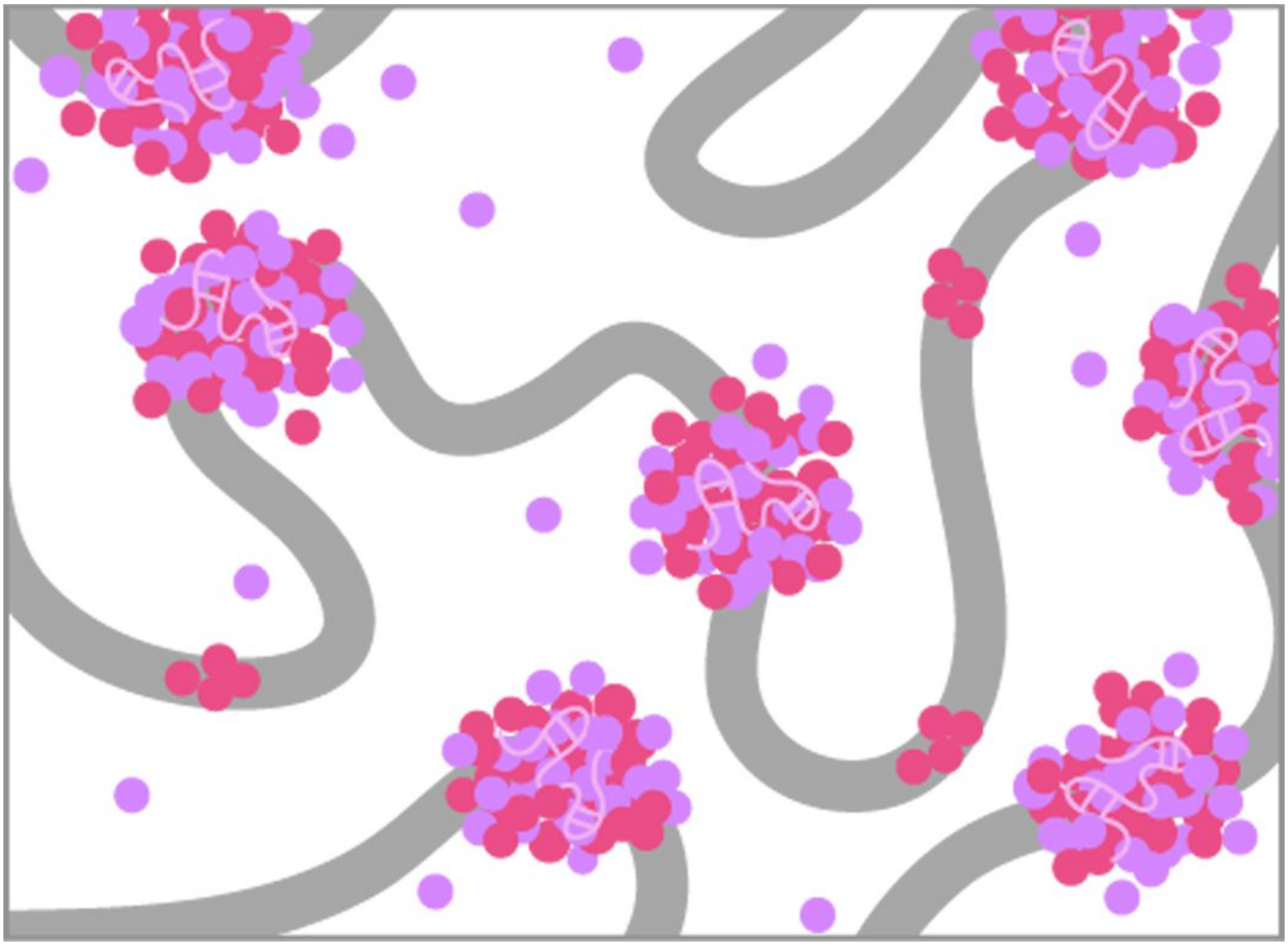
HEALTH + BEHAVIOR

Xist marks the spot: How an RNA molecule silences the X chromosome

UCLA researchers use super-resolution microscopy to reveal surprising new details about X inactivation



Cell

This illustration shows how the RNA molecule Xist (represented by thin, pink wiggly lines) recruits large clusters of additional molecules (lavender and red) to spots along the X chromosome (gray) in order to silence the chromosome's genes.

Sarah C.P. Williams | November 12, 2021

In one of the mysteries of mammalian development, every cell in the early female embryo shuts down one of its two copies of the X chromosome, leaving just one functional. For years, the mechanics behind this X chromosome inactivation have been murky, but scientists from the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA have now taken a major step forward in understanding the process.

Their findings, based on research on mouse stem cells, upend previous assumptions about how X inactivation is initiated in female embryos and could lead to new ways to treat some genetic disorders, as well as a better understanding of how genes on other chromosomes are silenced.

"X inactivation is one of the most fundamentally important processes in development, and I think this study is a slam dunk in finally understanding it," said Kathrin Plath, a professor of biological chemistry and senior author of the paper, published in the journal Cell.

Because female cells have two X chromosomes and male cells have only one X and a Y, the inactivation process prevents females from receiving a double dose of X-related proteins. In some female cells, the X inherited from the mother is silenced, while in others, the X from the father is shut off — in a seemingly random fashion.

Scientists have known for nearly three decades that an RNA molecule known as Xist is required for X chromosome inactivation early in embryonic development. They've also known that hundreds of other proteins interact with Xist. But in the absence of clear evidence, most in the field have assumed, mistakenly, that many copies of Xist coat the targeted X chromosome or constantly move around between locations on the X, interacting directly with each of the more than 1,000 genes on the chromosome to induce their silencing.

In the new study, Plath and her colleagues tagged individual molecules with fluorescence and used super-resolution microscopy to observe their precise locations on the chromosome. The team was then able to watch the movements of Xist and dozens of interacting proteins as X chromosomes were being inactivated in the embryonic stem cells of female mice. They discovered that pairs of Xist were located at just 50 spots along the chromosome, for a total of 100 molecules of Xist.

"It was kind of shocking to us that from just 50 sites, Xist manages to silence a thousand genes," said UCLA associate project scientist Yolanda Markaki, first author of the paper.

Instead of interacting directly with every gene on the chromosome, Markaki and Plath showed, these Xist pairs act as hubs, or protein magnets, recruiting thousands of proteins to their spots on the chromosome. Then, specialized proteins pull the chromosome into a tightly condensed shape so that every section is in the vicinity of one of these 50 large clouds of proteins. From there, gene silencing proteins within these complexes bind to each gene, shutting it off.

"The key insight here is that Xist RNA is not acting directly on the X chromosome but is more of an architectural molecule that sets up proteins to do their job," Plath said.

The team also identified the proteins, called Polycomb group proteins, responsible for twisting the X chromosome into the necessary shape. Without the Polycomb proteins, only those sections of the X chromosome already near one of the 50 Xist sites become inactivated, the researchers found.

The findings could help explain how molecules similar to Xist, called long non-coding RNAs, or lncRNAs, interact with genes other than those on the X chromosome. Many lncRNAs are present in only very low numbers in cells, which has made scientists puzzled about their function.

"Now we know that to silence an entire chromosome, you only need 100 Xist molecules, so it's easy to see how a few molecules are sufficient to set up little compartments of gene regulation," Plath said.

The observations also could point to new ways of treating diseases, she said. For example, the reactivation of the silenced X may serve as a strategy to treat diseases associated with the X chromosome in females, such as Rett syndrome. Understanding how silencing occurs opens the door to understanding how to reverse the process in differentiated cells if needed.

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