Tags on RNA silence X chromosome in females

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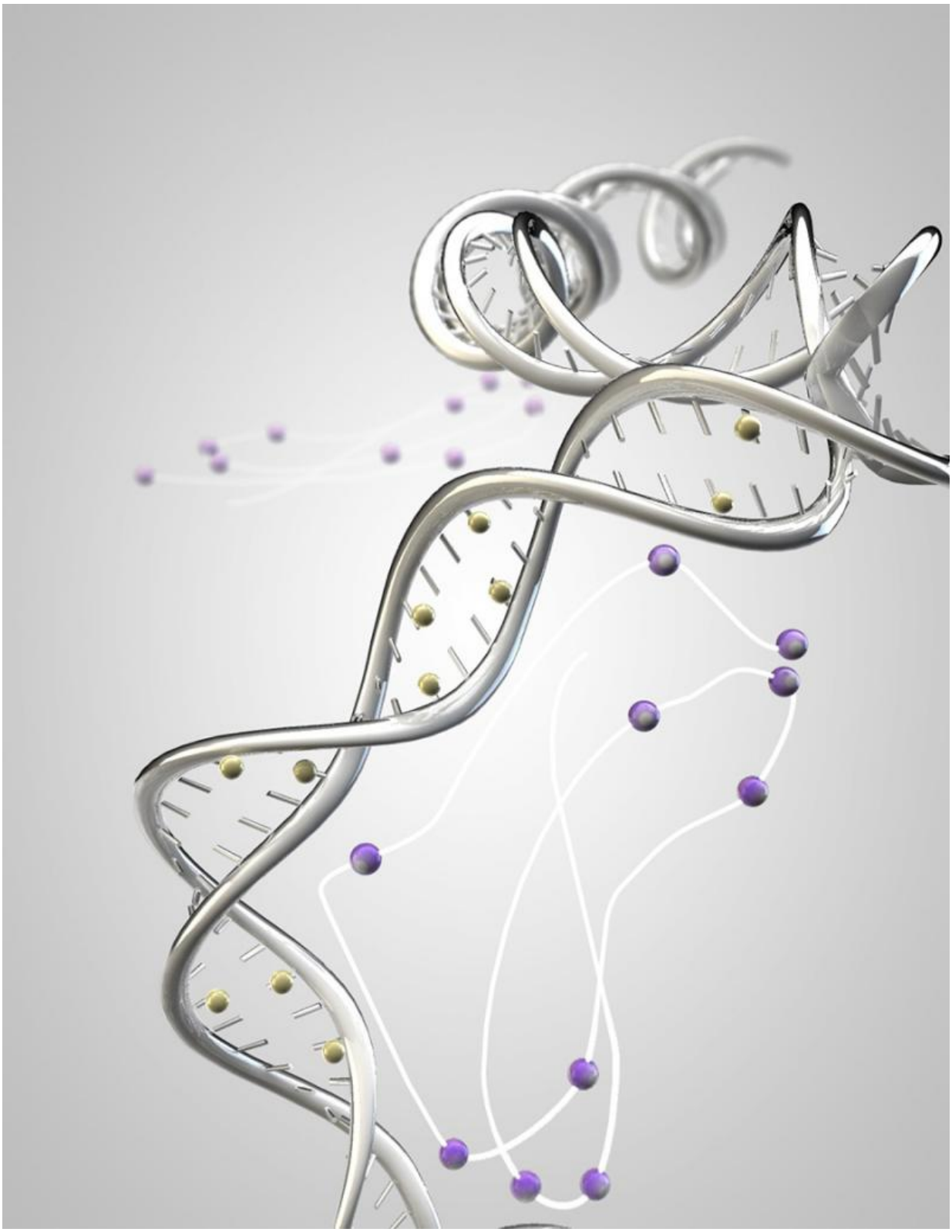

Methyl marks on the RNA XIST enable it to trigger X chromosome inactivation.

Credit: Ella Marushchenko/Provided

The addition of a chemical tag on an RNA molecule is the critical switch that inactivates one X chromosome in every cell, ensuring healthy development in all female mammals, according to new research by Weill Cornell Medicine investigators. The findings, reported Sept. 7 in *Nature*, could offer researchers a new scientific avenue to pursue treatments for X-linked chromosomal diseases in females such as Rett syndrome.

All cells in female mammals contain two X chromosomes, but only one is needed for proper cell function and development. To ensure the proper expression level of genes on the X chromosome, one of the chromosomes is randomly inactivated in every cell in a female mammal. This occurs during embryonic development; once an X chromosome is inactivated, it stays inactive throughout the lifetime of the organism.

The process of X chromosome inactivation is triggered by an RNA called XIST. XIST is a long RNA that attaches to the X chromosome to initiate X inactivation. The Weill Cornell Medicine investigators demonstrated that XIST is not alone empowered to turn off an X chromosome in every cell of a female mammal. Rather, XIST is activated once a chemical tag, called a methyl group, is added all along the length of the RNA. The addition of methyl groups enables XIST to function to inactivate the X chromosome.

"XIST attaches itself at different points all along the X chromosome, silencing the genes that are located on the X chromosome," said senior author Dr. Samie Jaffrey, a professor of pharmacology at Weill Cornell Medicine. "But exactly how the XIST RNA is capable of silencing genes has been a puzzle. Our study found that XIST is not functional until methyl groups are attached. These act as docking sites to recruit proteins

that initiate a cascade of events leading to X chromosome inactivation."

Jaffrey and his colleagues demonstrated in a 2012 study that many RNAs in the cell contain methyl modifications. "We found that methyl modification is a normal feature of most RNAs in the cell," Jaffrey said. "This includes messenger RNAs that encode proteins, as well as noncoding RNAs such as XIST.

"We were particularly surprised by the unusually high number of methyl groups in XIST. That seemed very suspicious," Jaffrey added. "So we wanted to explore what would happen if we took away the ability of the cell to make methyl modifications in XIST."

The researchers used human and mouse cells to study what would happen if they turned off a cell's ability to tag XIST with methyl groups. They found that cells that could not methylate XIST were not able to carry out X chromosome inactivation.

The researchers also found a protein, called DC1, that binds to every methyl group on XIST and enables it suppress the X chromosome. When they removed DC1 from the cells, XIST was unable to turn off the X chromosome.

"Not only does XIST need methylation, but it also needs DC1 to bind to the methyl groups in XIST," said Deepak Patil, a postdoctoral associate in Jaffrey's laboratory and first-author of the study. "The process of X chromosome suppression is a cascade. Methylation of XIST is the switch that starts the process, recruiting DC1, and subsequently the proteins that inactivate the X chromosome."

Understanding how X chromosome inactivation occurs may enable researchers to develop therapies for a variety of diseases caused by mutations of genes on the X chromosome. In many cases, women with

these diseases have one normal and one mutated X chromosome, but it is the normal chromosome that has been suppressed. One example is Rett syndrome, a neurodevelopmental disorder in females in which an X-linked mutation causes neurons to make insufficient amounts of a protein needed for normal neurological development, resulting in a form of autism.

"If we can understand how the normal X chromosome is turned off, we can start to figure out how to turn it back on and get the body to produce those necessary proteins," Jaffrey said. "We hope to block methylation of XIST in order to restore gene expression in Rett syndrome and similar genetic diseases in females carried on the X chromosome."

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