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New study rewrites textbook on key genetic phenomenon

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Because females carry two copies of the X chromosome to males' one X and one Y, they harbor a potentially toxic double dose of the over 1000 genes that reside on the X chromosome.

To compensate for this imbalance, mammals such as mice and humans shut down one entire X-chromosome through a phenomenon known as X-inactivation. For almost two decades, researchers have believed that one particular gene, called Xist, provides the molecular trigger of X-inactivation.

Now, a new UNC study appearing online July 1 in the journal *Nature* disputes the current dogma by showing that this process can occur even in the absence of this gene.

"Our study contradicts what is written in the textbooks," said senior study author Terry Magnuson, Ph.D., Sarah Graham Kenan Professor and chair of genetics, director of the Carolina Center for Genome Sciences and a member of the UNC Lineberger Comprehensive Cancer Center. "Everybody thought that Xist triggers X-inactivation, but now we have to rethink how this important process starts."

Previous studies showed that the Xist gene was active or "turned on" early in the course of X-inactivation and that disruptions in the gene resulted in irregular X-inactivation, eventually leading to the accepted assumption that Xist was the trigger. But it wasn't clear in the literature if this genetic phenomenon would initiate if Xist isn't present, said lead

study author Sundeep Kalantry, Ph.D., postdoctoral fellow in the UNC department of genetics.

Kalantry used three different molecular techniques to look at X-inactivation in the embryos of mice that were genetically engineered to contain a defective Xist gene on their future inactive X-chromosome. He discovered that the genes on this X-chromosome could be silenced regardless of whether they produced Xist. But while Xist was not absolutely required to start X-inactivation, without it genes along the X-chromosome eventually became active again. Thus, Xist appears to stabilize silencing of the X-chromosome over the long term.

Unlike most genes, the Xist gene doesn't code for a protein. Rather, it acts at the level of RNA - a copy of the DNA genetic sequence - which serves to recruit protein complexes through a process known as epigenetics. These proteins then form a molecular scaffold along the inactive-X chromosome that can stably silence the genes contained within it. The UNC researchers are now actively investigating how this chromosomal remodeling begins in the first place.

"If we can figure out the mechanism that triggers X-inactivation, we can potentially apply this knowledge to diseases that have an epigenetic component," Kalantry said. "So it can have implications not only in fundamentally understanding X-inactivation but also to gain insight into the increasing array of illnesses where the epigenetic machinery has gone awry - such as in prostate and breast cancers."

Source: University of North Carolina School of Medicine (news : web)