news briefs

Sonic Hedgehog Pathway Influences Tumor Growth

The rapid proliferation of cells without differentiation, known as oncogensis, is a crucial feature of tumor growth and is thought to be controlled by complex cell signaling pathways. In normal tissue, rapid proliferation is accompanied by immediate, almost simultaneous differentiation. The two processes are regulated by coupled signal cascades in the cell in order to ensure proper tissue growth (1). New research conducted by Harvard scientists at the Dana-Farber Cancer Institute has shown how the breakdown in the coupling of proliferation and differentiation can be observed by mutating the Sonic Hedgehog protein in tissue stem cells (2).

The study used a selectively designed mutagen—an agent for inducing mutations—of Hedgehog to investigate the nature the protein's interactions with proteoglycans, proteins long understood to be involved in the Hedgehog signaling pathway (1). Cell populations with the Hedgehog mutagen were unable to make proteoglycan interactions but were otherwise fully functional. The study found that cells that could not interact with proteoglycans underwent normal differentiation but stagnant growth. Hedgehog-proteoglycan interactions were shown to promote proliferation independent of differentiation. The selective promotion of intracellular pathways that lead to proliferation is a characteristic feature of tumor growth and suggests an important role for Hedgehog signal control in oncogenesis and thereby tumor formation(2).

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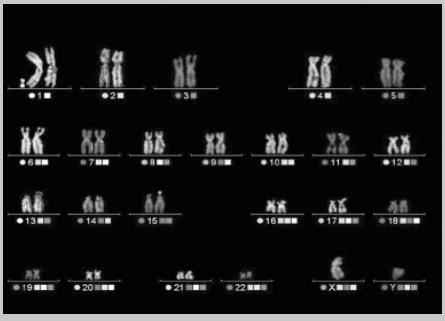
1. S.C. Desborder and Sanson, B. "The Glypican Dally-like is required for Hedgehog signaling in the embryonic epidermis of *Drosophila." Development* 130, 6245-55. (2003).

2. R. Segal and Chan, J. "Proteoglycan interactions with Sonic Hedgehog specify mitogenic responses." *Nature Neuroscience* **12**, 409 - 417 (2009).

X Chromosome Inactivation



credit: http://www.nasa.gov/images/content/173934main_Chromosome4.jpg

Men and women are almost genetically identical: they both have two copies of each chromosome except for the sex chromosomes. The sex chromosomes, X and Y, however trivial they may seem, are the reason for the difference between men and women. Women have two X chromosomes while men have only one. Since women have two X chromosomes, you may expect the effect of the X chromosome to be doubled in women. This, however, is not the case: men and women have been shown to express the same level of X chromosome proteins. And so, one might wonder, how is this possible?

It has been found that one of the female X chromosome is in fact *silenced*, which prevents the chromosome from producing any proteins (1). When one protein is silenced only the other can be active. Accordingly, women function as though they too only have one X chromosome. Xist and Tsix, two fragments of RNA coded for by the X chromosome, have been shown to play a critical role in this silencing. While Xist is identified as the protein responsible for turning off the chromosome, Tsix reduces Xist levels and thus allows the chromosome to remain active. Although RNA is usually translated into protein, Xist and Tsix are not; both exist inside the cell as RNA. The issue that arises concerns how Xist and Tsix function to silence the X chromosome if neither directly encode proteins.

This mystery is currently being investigated by scientists at Harvard Medical School. A team of biologists has found that a small region of Xist, called RepA, is made in excess and actually recruits a cluster of proteins known as a Polycomb complex, PRC2 for short (1). PRC2 then helps in the production of more Xist and, as such, aids in silencing the chromosome. Tsix prevents Xist from binding to PRC2, which causes lower levels of Xist. These scientists have discovered that the Xist RNA molecule recruits the PRC2 protein complex and that this association is necessary for the silencing of the second X chromosome present in women.

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1. J. Zhao et al. "Polycomb Proteins Targeted by a Short Repeat RNA to the Mouse X Chromosome." *Science* 322, 750 (2008).