Medical Xpress

Study of placenta unexpectedly leads to cancer gene

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University of Rochester Medical Center scientists discovered a gene mutation that impairs the placenta and also is influential in cancer development, according to a study published online December 16, 2008, in the journal *PLoS (Public Library of Science) Biology*.

The investigation is the first to link the key placental gene, SENP2, to the well-known p53 protein, which is defective in 50 percent of all cancers.

Until now, the SENP2 gene's role in early embryo development was not known. As a result of making the connection between SENP2 and the potent cancer stimuli, it will be possible to gain more insight into the complex genetic network involved in cancer, and to develop new therapies, said lead author Wei Hsu, Ph.D., associate professor of Biomedical Genetics and Oncology, of the James P. Wilmot Cancer Center.

Hsu and former graduate student Shang-Yi Chiu, currently a postdoctoral fellow at Howard Hughes Medical Institute, Dana-Farber Cancer Institute at Harvard University, have been investigating how cellular signaling triggered by gene mutations affect embryo development in mice. The goal is to better understand the genetic causes and possible treatments for a number of diseases.

"What we discovered was an unexpected interaction between an old player, p53, and a new player, SENP2," said Hsu, who also has an

appointment in the URMC Center for Oral Biology.

SENP2 (SUMO-specific protease 2) is highly expressed in trophoblast cells, which are the stem cells required to form the placenta. The placenta surrounds, protects and nourishes the developing fetus. While investigating disruption of placental formation in a mouse model, Hsu's team observed that embryos lacking SENP2 failed to properly make placental tissue.

The failure occurred, researchers discovered, because the cells that give rise to the placental tissues had undergone cell cycle arrest, and were trapped in a state of suspended growth. Next, researchers set out to find SENP2 target proteins that could be involved in arresting cell growth.

In the journey, they discovered that p53 – or proteins that modify p53 activity – were harmed by the SENP2 deficiency. The consequence was that p53 could no longer perform its vital job as a tumor suppressor. When p53 is functioning normally, it acts as a crucial guardian of the genome, or a checkpoint, by fixing genetic mistakes as they arise.

But when the p53 molecule is aberrantly regulated, either by an outside virus or an inherited genetic abnormality, the risk of cancer is higher because p53 cannot perform its job.

Researchers also found that SENP2 indirectly regulates p53 activity through another protein called Mdm2, which was already known to be involved in some cancers. In cells lacking SENP2, the Mdm2 becomes trapped in the nucleus, and is unable to halt p53, allowing it to accumulate within the cell. This disruption leads to distinct problems in cell cycle progression and normal gene replication.

Source: University of Rochester