Loss of 'guardian angel' gene prompts premature birth

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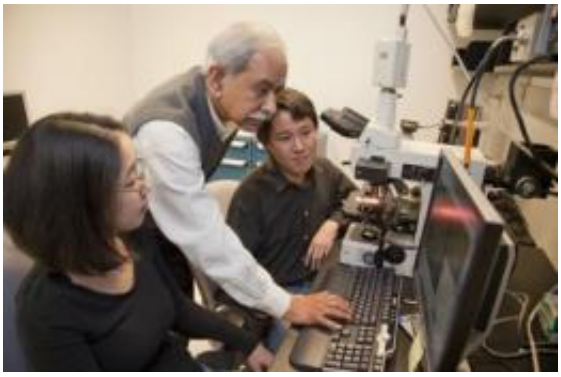

Sudhansu K. Dey, Ph.D., (center), director of Reproductive Sciences at Cincinnati Children's Hospital Medical Center, and study co-authors Takiko Daikoku (left), and Yasushi Hirota, (right), review microscopic images in their laboratory from new research pointing to the p53 gene as critical to healthy pregnancy and birth. The study appears online Feb. 1 in the Journal of Clinical Investigation. Credit: Cincinnati Children's Hospital Medical Center

Mutation of a gene that helps protect the body from genetic instability leads to cellular and molecular changes in the pregnant uterus that trigger premature birth, according to a study appearing online Feb. 1 in the *Journal of Clinical Investigation*.

The research by scientists in the Division of Reproductive Sciences, part of the Perinatal Institute at Cincinnati Children's Hospital Medical Center, sheds new light on the still poorly understood genetic and

physiological reasons for preterm births. The findings could help lead to the development of new strategies for treating and preventing prematurity, according to Sudhansu K. Dey, Ph.D., director of Reproductive Sciences at Cincinnati Children's and the study's senior investigator.

"Preterm birth and prematurity are problems that pose huge long-term social and economic liabilities, and there is an urgent need for research with new approaches to combat this public health concern," Dr. Dey said.

Premature birth is responsible for 30 percent of all neonatal deaths, is a significant cause of long-term disability, and costs $26 billion a year in the United States, according to estimates from the National Academy of Sciences' Institute of Medicine.

In the current study, researchers targeted certain signaling pathways that function both in pregnancy and during the formation of cancerous tumors. Signaling pathways are chains of molecular interactions that promote cellular communication. During pregnancy, the pathways analyzed by the researchers are usually tightly regulated. In tumor development, however, they become dysfunctional.

The scientists started with a pathway linked to the tumor suppressor gene known as transformation-related protein 53 (Trp53), which encodes another protein known as p53. Mutations of Trp53 are found in a variety of cancers, but its function in female reproduction and other normal physiological processes is not well understood. The role of p53, sometimes referred to as "the guardian angel gene," is to help preserve genetic stability and prevent mutation.

The researchers wanted to test the importance of uterine p53 in female reproduction, but the availability of suitable mouse models for clinically

relevant preterm labor studies is limited. This led Dr. Dey and his team to develop a new mouse model. They generated mice that had the Trp53 gene conditionally deleted in the uterus, causing a deficiency of uterine p53 and removing its influence from the pregnancy process.

The team observed that when the mice mated with fertile males they had normal ovulation, fertilization and embryo implantation. Deficiency of p53, however, activated other signaling pathways in the uterus (involving the proteins pAkt and p21) that set the stage for premature birth.

Activation of pAkt and p21 prompted decidual cells - which surround implanting embryos - to mature too quickly to terminal differentiation and senescence, a state where they can no longer divide. Decidual cells are supposed to support the fetus and help form the placenta, but in the p53 deficient uteri they didn't develop properly because of early senescence. This then triggered an enzyme called COX2, which stimulated production of a molecule called PGF2α.

COX2-derived PGF2α has been linked in previous literature to smooth muscle contraction and the onset of labor. In the current study, activation of the pathway prompted ill-timed contraction of smooth muscles in the uterus and caused the mice to give early birth. Among the mice generated by the Cincinnati Children's team, more than 50 percent experienced premature birth and neonatal death of their offspring.

The researchers said their findings are striking because preterm birth can be corrected by oral administration of celecoxib, a drug that inhibits COX2 activity.

Dr. Dey said the study emphasizes the critical role p53 plays in healthy pregnancy and delivery, adding that future prematurity studies should focus more closely on p53 and the reproductive processes it helps control. He also said the mouse model generated by his team will be a

valuable tool for studying the pregnancy process and preterm labor in humans.

Provided by Cincinnati Children's Hospital Medical Center