Researchers find possible therapeutic strategy to combat premature birth

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Scientists who developed a novel mouse model mimicking human preterm labor have described a molecular signaling pathway underlying preterm birth and targeted it to stop the problem.

In a study to be published online the week of Oct. 24 by *PNAS* (Proceedings of the National Academy of Sciences), the researchers report their findings may lead to new strategies for combating this major global health issue in humans. The study was led by scientists in the division of Reproductive Sciences and Perinatal Institute at Cincinnati Children's Hospital Medical Center.

They point to molecular signals from the protein complex mTORC1 (mammalian target of rapamycin complex 1). In laboratory tests, the signals contributed to early aging in uterine cells, preterm labor and stillbirth in the genetically modified mice. When researchers gave the mice a low dose of rapamycin – a known inhibitor of mTORC1 signaling – it stopped the early aging of uterine cells and premature birth.

"Our findings show an unanticipated role for mTORC1 signaling in preterm birth in mice and may help us better understand the mechanism of birth timing in humans," says Sudhansu K. Dey, PhD., who led the study and is director of Reproductive Sciences at Cincinnati Children's. "Whether these findings have direct relevance in human birth requires further investigation, although these data could help us develop new and improved strategies to combat this international health problem."

Among a wide array of adverse effects, premature birth can result in underdeveloped organs and organ systems – especially in the respiratory system. It also creates a greater risk for cerebral palsy, as well as learning and developmental disabilities. Globally there are nearly 13 million premature births and more than 3 million stillbirths annually. Prematurity is also a direct cause of more than one million neonatal deaths each year.

Earlier studies have linked mTOR signaling to aging in cells and structures in organisms, as well as metabolism. Signals from mTOR have also been connected to interactions with different molecular pathways in human tumor growth.

Rapamycin is an immunosuppressant drug widely used to prevent organ rejection in transplant surgery. Previous studies have shown rapamycin can ease respiratory distress caused by enhanced mTORC1 signaling in the premature lungs of preterm mice. The drug also has been tested in humans for treating tumors in the disease tuberous sclerosis and in certain cancers, because of its affinity for blocking mTOR signaling.

Dey and his colleagues decided to test whether mTORC1's known role in premature aging would also influence the biology of uterine cells and preterm birth in mice. The mice were modified so they lacked the protein p53 in their uteri. The p53 protein – sometimes referred to as "guardian of the genome" – acts as master regulator in multicellular organisms by controlling cell cycles and helping prevent tumor growth.

Through a series of complementary experiments, the researchers tested the different molecular interactions and influence of mTORC1 on preterm birth. They identified a novel "signaling axis" critical to birth timing in mice comprised by three proteins: mTOR, p21, and COX2. They also report that inhibiting any of these three proteins prevented premature aging in uterine cells and the preterm births.

The researchers say future studies will probe even deeper into the molecular interactions of mTORC1 in mouse prematurity to see if there may be different molecular targets and opportunities for therapeutic intervention.

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