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Stem cell discovery sheds light on placenta development

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GAINESVILLE, Fla. — Researchers studying embryonic stem cells have explored the first fork in the developmental road, getting a new look at what happens when fertilized eggs differentiate to build either an embryo or a placenta.

By manipulating a specific gene in a mouse blastocyst — the structure that develops from a fertilized egg but is not yet an actual embryo — scientists with the University of Florida's McKnight Brain Institute and the Harvard Stem Cell Institute caused cells destined to build an embryo to instead change direction and build the cell mass that leads to the placenta.

Writing in today's (Monday, June 9) online edition of *Nature Genetics*, the scientists reveal a cellular signaling mechanism in place at the earliest developmental stage.

Understanding the conditions that cause these cells to go off to different fates may have a bearing on health problems such as ectopic pregnancy, which occurs when the embryo develops outside of the womb in about 1 of 60 pregnancies, or molar pregnancy, which is abnormal tissue growth within the uterus that affects about 1 in every 1,000 pregnancies.

"We originally were exploring factors that might cause embryonic stem cells to become malignant — there is a concern that these cells may cause tumors," said Chi-Wei Lu, Ph.D., an associate neuroscientist at the UF College of Medicine and lead author of the study. "Our experiments led us to discover the signal that initiates the process of embryonic tissue differentiation."

By activating a gene called Ras in cells bathed in a very specific culture medium, scientists were able to cause embryonic stem cells — which originate from the inner cell mass of the blastocyst — to become more like the trophoblastic stem cells that give rise to the placenta from the outer portion of the blastocyst.

Researchers marked these newly minted cells, which they called ES-TS cells, and injected them into mouse embryos. Instead of joining the stem cells that build the embryo, ES-TS cells joined the stem cells that build the placenta. Furthermore, when scientists transferred the engineered mouse embryos to foster mothers, the ES-TS cells went to work exclusively laying the foundation for the placenta.

"This paper highlights the value of embryonic stem cells for understanding early development," said senior author George Q. Daley, M.D., Ph.D., an associate professor of biological chemistry and molecular pharmacology at Harvard Medical School and an associate professor of pediatrics at Children's Hospital Boston. "Embryonic stem cells are more plastic than we had thought. By simply activating the Ras gene, we changed the fate of embryonic stem cells to an entirely unexpected tissue — the placenta. This surprising result has given us an unanticipated insight into early embryo development."

The technique of genetically modifying the cells and growing them in a special medium could be valuable for additional research.

"This is exciting because events that only occur in the early stages of embryonic development are very difficult to study," Lu said. "Just a few models exist, and even in mice, only a limited amount of embryos can be harvested. Now we can culture these cells and have unlimited material to study."

Researchers are only beginning to understand the natural chemical environments that allow for production of different tissues.

"What is nice is that what she has observed in cultures appears to be quite similar to what goes on in early development in animals," said R. Michael Roberts, D.Phil., a professor of molecular biology at the C.S. Bond Life Sciences Center at the University of Missouri-Columbia who did not participate in the research. "Normally, mouse embryonic stem cells aren't easily converted along the pathway to form placental cells, while human embryonic stem cells undergo this transition quite easily. This has always been a puzzle. What she has shown is you can make mouse embryonic stem cells convert unidirectionally to trophoblasts by activating a single gene. This is very helpful for understanding how the placenta develops."

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