Genetically distinct cells reveal nature's strategy for avoiding pregnancy complications

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Researchers add a new twist to the more than century old biological principles of Mendelian inheritance - describing a small group of cells in pregnant mothers that promote genetic fitness and multi-generational reproductive health.

Scientists at Cincinnati Children's Hospital Medical Center report their findings online July 23 in *Cell*. The study suggests a scientific basis for developing new therapies to promote reproductive health and prevent pregnancy complications like prematurity and stillbirth, according to Sing Sing Way, MD, PhD, senior author and pediatrician in the Division of Infectious Diseases and the Perinatal Institute at Cincinnati Children's.

Mendelian inheritance dictates that reproductive and genetic health is anchored by two parents each passing along only half of their chromosomes to children. The current study reports this is further enhanced across generations by women retaining genetically distinct cells that they pass along to their daughters, granddaughters and great granddaughters. The cells help avoid pregnancy complications by keeping the immune system from attacking the fetus as an invading pathogen.

What makes these maternal cells unique is they are microchimeric, according to researchers. This means the cells are genetically different

from the mother and her female offspring. The cells prevent the immune system from rejecting the fetus by coaxing regulatory T cells into recognizing and accepting non-inherited maternal antigens. This suppresses the T cells and holds off an immune system attack.

"Our data suggest that Mendelian genetics is enhanced by maternal-to-offspring transmission of these microchimeric cells from one generation to the next," Way said. "Microchimeric maternal cells can be viewed as mother's little genetic helpers, which are shared in offspring to enforce cross-generational reproductive health."

Serious Health Challenge

Complications arise in about one out of eight human pregnancies. Premature birth - which can lead to a lifetime of chronic illness - along with preeclampsia and stillbirth remain serious global health problems, including in the United States.

Way said pregnancy complications usually occur when the mother's immune system mistakenly attacks the developing fetus as an invading pathogen. Working with mouse models, the authors found protection against pregnancy complications is dramatically enhanced in pregnant mothers with regulatory T cells that are specific for and recognize non-inherited maternal antigen (NIMA).

Although the research was in genetically bred mice, Way said the findings should apply widely to human pregnancies and other mammals requiring in utero development. Mice in the study were engineered so researchers could track the microchimeric maternal cells and T cells that recognize NIMA.

The researchers also noted that mouse pregnancies sired by males having NIMA traits overlapping those of his partner - and those of her mother -

were especially resilient against complications.

Nature's Way

Physicians and scientists have known for some time that tolerance to non-inherited maternal antigen exists and can be used to improve outcomes after solid organ or stem cell transplants. Way and his colleagues took into consideration existing research on this phenomenon when designing the current study.

"From a basic biological perspective, mammals did not develop tolerance to non-inherited maternal antigen so that people could have successful transplants, although clearly it is very beneficial in this context," Way said. "There had to be a more fundamental biological reason for it and that is what we discovered in this study."

Researchers are following up the current paper with additional studies into how maternal cells retained in offspring promote immune tolerance. After confirming the molecular details of nature's process for achieving fetal tolerance and resiliency against pregnancy complications, Way said the mechanisms could be mimicked to design new therapies for improving reproductive health and human pregnancy outcomes.

Provided by Cincinnati Children's Hospital Medical Center