Immune cells in the uterus help nourish fetus during early pregnancy

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An artistic representation of how decidual NK cells promote fetal growth during early pregnancy. Credit: Binqing Fu

Natural killer cells are among the most abundant immune cells in the uterus during the first trimester of pregnancy, but their numbers decline substantially after the placenta forms. A study published December 19th in the journal *Immunity* shows that this transient cell population helps to optimize maternal nourishment of the fetus at early stages of development. The researchers identified a specific subset of uterine natural killer cells that secrete growth-promoting factors in humans and mice, and further demonstrated that transfer of these cells can reverse impaired fetal growth in pregnant mice.

"These findings not only reveal new properties of natural killer cells during early pregnancy, but also point to approaches for therapeutic administration of natural killer cells in order to reverse restricted nourishment within the uterine microenvironment," says co-senior study author Haiming Wei of the University of Science and Technology of China. "The study will have major implications for our approach to adoptive cell therapy strategies for the generation of not only natural killer cells against pathogens and tumors, but also natural killer cells supporting body development and tissue engineering."

Acting as our bodies' frontline defense system, natural killer cells guard against tumors and launch attacks against infections. For decades, natural killer cells in the uterus have been studied as an example of specialized immune cells endowed with unique functions that developed during the evolution of mammalian pregnancy. For example, uterine natural killer cells promote immune balance and the growth of blood vessels in the placenta, having a positive impact on birth weight as well as fetal growth. But until now, it was not clear which subset of natural killer cells in the uterus are responsible for promoting fetal growth, or whether these cells help to optimize fetal nourishment at early developmental stages.

In the new study, Wei and co-senior author Zhigang Tian of the University of Science and Technology of China discovered that a specific subset of natural killer cells in the human uterine lining secretes growth-promoting factors called pleiotrophin and osteoglycin, which are involved in wide-ranging developmental processes. This subset of cells made up a smaller proportion of natural killer cells in the uterine lining of patients who experienced recurrent spontaneous abortion (42%) compared to healthy females (81%). These findings suggest that insufficient secretion of growth-promoting factors by a specific subset of natural killer cells may be responsible for restricted fetal development in humans.

Additional studies in mouse models showed that a deficiency in this subset of natural killer cells resulted in severe fetal growth restriction and defective development of the fetal skeletal system. Remarkably, the transfer of uterine-like natural killer cells reversed fetal growth impairments in these mice. But for now, it remains unclear whether the growth-promoting factors affect fetal development directly by crossing the maternal-fetal barrier or indirectly by promoting the formation of the placenta and the growth of blood vessels.

From a clinical perspective, natural killer cell-based immunotherapy has been widely used to treat cancer. For the purpose of promoting fetal growth in humans, it may be possible to transfer natural killer cells via intravenous infusion or the administration of a vaginal suppository to mothers, avoiding the need for invasive procedures. Moreover, uterus-like natural killer cells are a much safer alternative than pluripotent stem cells because they are less likely to induce tumor formation.

"Additional studies are needed to explore the most suitable protocols to induce uterus-like natural killer cells that secrete growth-promoting factors in a human system, and to improve the feasibility of applying these uterus-like natural killer cells to patients," Tian says. "This study

provides an avenue for treating fetal growth restriction, recurrent spontaneous abortion with unknown reasons, and age-related fetal loss by improving the uterus microenvironment."

More information: *Immunity*, Fu, B., Zhou, Y., and Ni, X., et al.: "Natural Killer Cells Promote Fetal Development through the Secretion of Growth-Promoting Factors." www.cell.com/immunity/fulltext … 1074-7613(17)30519-8 , DOI: 10.1016/j.immuni.2017.11.018

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