KUMC researchers shed light on the placenta's key role in fetal development

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By Alissa Poh

M.A. Karim Rumi, PhD; Damayanti Chakraborty; and Michael J. Soares, PhD

A pregnant woman may have many things on her mind during obstetric checkups, but worrying about her placenta is probably not among them.

However, the placenta is more than just the means through which mother and fetus are connected. A properly formed placenta is essential for the fetus to get an accurate sense of its nutritional surroundings. Poor nutrition at this point could signal to the unborn baby that harsh conditions await, resulting in birth characteristics such as small body size and metabolism adapted to cope with a lack of food. Problems could then arise if things change after birth. For example, a wealth of epidemiological and clinical data show that people born small but growing up in affluent environments are more likely to be obese and have a higher risk for coronary heart disease and type 2 diabetes.

Recent research from the University of Kansas Medical Center zeroes in on the intricacies of placenta formation.

"What we've found, broadly speaking, is that the environment within the uterus can reshape the placenta and determine how effective it is," says Damayanti Chakraborty, a predoctoral fellow in KUMC's Department of Pathology and Laboratory Medicine and primary author on the study, published in the September 2011 issue of the *Proceedings of the National Academy of Sciences*.

Once a fertilized egg develops and attaches to the womb, the placenta forms and grows, redirecting nutrients to the developing fetus. The placenta contains stem cells — cells that, over time, develop into distinct "trophoblast" cell populations with highly specialized functions. For example, some cells make hormones that influence the mother's metabolism and stimulate nutrient flow, while others transport those nutrients to the fetus.

Another specialized group of trophoblast cells enters the mother's uterus, wrapping around and reshaping nearby blood vessels called uterine spiral arteries. With this move, the mother's circulation is connected to that of the fetus, and her remodeled blood vessels are opened up for efficient nutrient exchange.

If something interferes with trophoblast cells' ability to enter the uterus and establish new blood connections, it could severely restrict fetal growth. The mother may also experience skyrocketing blood pressure and life-threatening cardiovascular symptoms, a medical condition known as preeclampsia.

"It's important that we understand how stem cells in the placenta differentiate to carry out specific functions," says Michael J. Soares, PhD, the paper's senior author and the director of KUMC's Institute for Reproductive Health and Regenerative Medicine. "These cells basically govern the restructuring of uterine spiral arteries and are key to a successful pregnancy."

By carefully studying these biological events in pregnant rats, Chakraborty and Soares, along with two colleagues, M.A. Karim Rumi, PhD, and Toshihiro Konno, PhD, have found that natural killer (NK) cells help determine when specialized trophoblast cells target blood vessels surrounding the uterus. NK cells, a type of white blood cell, form part of the innate immune system — the body's first line of defense against pathogens.

While their numbers dwindle to barely detectable levels later in gestation, NK cells make up 70 to 80 percent of white blood cells that accumulate within the uterus during the early to middle stages of pregnancy. "We wanted to figure out what they were doing during this particular window of time," Chakraborty says. She began exploring the significance of NK cells by looking at what happened when they were experimentally removed from the picture.

When Chakraborty removed NK cells from pregnant rats, she observed an initial delay in the development of the uterine spiral arteries. Then, massive numbers of trophoblast cells flowed in and reshaped the uterine blood vessels.

She also noted that in the absence of NK cells, oxygen levels in the vicinity of the developing placenta dropped, spurring trophoblast cells to take on different roles and one group to move toward uterine blood vessels.

Trophoblast cell sensitivity to oxygen affects how and when they take on a specific function. Chakraborty reckons that NK cells orchestrate the timing of invasive trophoblast cell activities in readying uterine blood vessels to connect with the fetus.

"Think of the process of establishing blood-vessel connections between the mother and fetus as occurring in two waves," Soares says. "First, NK cells are recruited to the uterus during pregnancy where they promote initial stages of uterine spiral artery development. By ensuring that the developing placenta has sufficient oxygen, NK cells effectively delay the second wave - where trophoblast cells remodel the uterine blood vessels and increase their ability to transport nutrients to the fetus - so it doesn't happen ahead of schedule."

Chakraborty and Soares think that a protein called hypoxia inducible factor (HIF) is a player in the process. Low oxygen triggers a series of cellular activities directed by HIF; Chakraborty has shown that activating HIF increases the trophoblast cells' ability to enter the uterus, but if she eliminates HIF, trophoblast cells that are supposed to move toward the uterus fail to form.

To better understand all these observations, Chakraborty is now studying how HIF acts within the cell and learning more about how HIF communicates with its molecular targets. "There's probably a whole cascade of factors involved," she says.

Her work may eventually help illuminate the complexities of fetal programming — basically, the highly malleable interplay between a developing fetus and its environment.

"We still don't fully understand why and how the environmental cues a fetus receives can lead to adult health problems," Soares says. However, knowing that early life events influence later susceptibility to certain diseases, and that placenta formation is an important early event, he hopes Chakraborty's research will lead toward broader, hopefully even therapeutic, applications.

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