New findings provide insight on long-standing pregnancy mystery

June 7 2012

Researchers at NYU School of Medicine have made an important discovery that partially answers the long-standing question of why a mother's immune system does not reject a developing fetus as foreign tissue.

"Our manuscript addresses a fundamental question in the fields of transplantation immunology and reproductive biology, namely, how do the fetus and placenta, which express antigens that are disparate from the mother, avoid being rejected by the maternal immune system during pregnancy?" explained lead investigator Adrian Erlebacher, MD, PhD, associate professor of pathology and a member of the NYU Cancer Institute at NYU Langone Medical Center. "What we found was completely unexpected at every level."

The researchers discovered that embryo implantation sets off a process that ultimately turns off a key pathway required for the immune system to attack foreign bodies. As a result, immune cells are never recruited to the site of implantation and therefore cannot harm the developing fetus.

The study, funded by grants from the National Institutes of Health and the American Cancer Society, appears in the June 8 issue of *Science*.

A central feature of the body's natural immune defense against transplanted foreign tissues and pathogens is the production of chemokines as a result of the local inflammatory response. The chemokines recruit various kinds of immune cells, including activated T

cells, which accumulate and attack the tissue or pathogen. The chemokine-mediated recruitment of activated T cells to sites of inflammation is an integral part of the immune response.

During pregnancy however, the foreign antigens of the developing fetus and the placenta come into direct contact with cells of the maternal immune system, but fail to evoke the typical tissue rejection response seen with organ transplants.

Several years ago, Erlebacher and his research team found that T cells, poised to attack the fetus as a foreign body, were somehow unable to perform their intended role. The finding prompted the researchers to wonder if perhaps there was some sort of barrier preventing the T cells from reaching the fetus. They turned their attention to studying the properties of the decidua, the specialized structure that encases the fetus and placenta, and there, in a mouse model, they found new answers.

The research team has discovered that the onset of pregnancy causes the genes that are responsible for recruiting immune cells to sites of inflammation to be turned off within the decidua. As a result of these changes, T cells are not able to accumulate inside the decidua and therefore do not attack the fetus and placenta.

Specifically, they revealed that the implantation of an embryo changes the packaging of certain chemokine genes in the nuclei of the developing decidua's stromal cells. The change in the DNA packaging permanently deactivates, or "silences," the chemokine genes. Consequently, the chemokines are not expressed and T cells are not recruited to the site of embryo implantation.

Also of note, the observed change in the DNA packaging was a so-called 'epigenetic' modification, meaning a modification that changes gene expression without the presence of a hereditable gene mutation.

"These findings give insight into mechanisms of fetal-maternal immune tolerance, as well as reveal the epigenetic modification of chemokine genes within tissue stromal cells as a modality for limiting the trafficking of activated T cells," Dr. Erlebacher said. "It turns out that the cells that typically secrete the chemoattractants to bring the T cells to sites of inflammation are inhibited from doing so in the context of the pregnant uterus. The decidua appears instead as a zone of relative immunological inactivity."

Inappropriate regulation of this process, Dr. Erlebacher explained, could cause inflammation and the accumulation of immune cells at the maternal-fetal interface, which could lead to complications of human pregnancy, including preterm labor, spontaneous abortion and preeclampsia.

Erlebacher and his team will next look to see if these epigenetic modifications are also present within the human decidua, and whether the failure to generate them appropriately is associated with complications of human pregnancy. He explained that the study's findings also raise the possibility that the same kind of mechanism could enhance a tumor's ability to survive inside its host. The findings could have implications for autoimmune diseases, organ transplantation and cancer, as well as pregnancy.

"This is a very exciting finding for us because it gives a satisfying explanation for why the fetus isn't rejected during pregnancy, which is a fundamental question for the medical community with clear implications for human pregnancy," Dr. Erlebacher said. "It also reveals a new modality for controlling T cell trafficking in peripheral tissues that could provide insight into a myriad of other conditions and diseases."

More information: "Chemokine Gene Silencing in Decidual Stromal Cells Limits T Cell Access to the Maternal-Fetal Interface," by P. Nancy

et al., *Science*, 2012.