Mother's immune system may block fetal treatments for blood diseases

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Pediatric researchers have resolved an apparent contradiction in the field of prenatal cell transplantation— a medical approach that holds future promise in correcting sickle cell disease and other serious congenital blood disorders. In a new study in animals, the researchers showed that the mother's immune response interferes with the offspring's earlier ability to tolerate transplanted donor cells.

The study team concludes that focusing on transplant techniques that avoid the maternal immune response may allow scientists to take advantage of fetal tolerance to achieve a long-sought goal of treating blood diseases prenatally.

While cautioning that much work must be done to understand how these animal findings apply to humans, the current findings are "surprising but reassuring," said study leader Alan W. Flake, M.D., of the Children's Center for Clinical Research at The Children's Hospital of Philadelphia.

The study appeared online August 3 in the Journal of Clinical Investigation.

For over 50 years, explained Flake, it has been a fundamental precept of immunology that a fetus tolerates foreign antigens in a window-of-opportunity period before its immune system fully develops the capacity to mount an immune response. Scientists assumed that by carefully introducing donor cells and stimulating a fetus to develop tolerance to those cells, one could set the stage for a later organ or cellular transplant

that would not be rejected by a more mature immune system.

As prenatal diagnosis has continued to become available for a greater number of congenital diseases, scientists have considered the possibility of correcting blood disorders such as sickle cell disease or thalassemia. After first transplanting a small number of healthy cells in an early-stage fetus to establish tolerance, a second dose of transplanted cells later in gestation would proliferate, and treat the blood disorder before birth. Researchers use hematopoietic cells—stem cells that that develop into blood cells—in this technique, in utero hematopoietic cell transplantation (IUHCT).

However, over the years, Flake's team and other research groups found that IUHCT studies in animal models yielded inconsistent results, ranging from no tolerance to transplants to full tolerance and every degree of tolerance in between. Contrary to the concept of fetal tolerance, an immune barrier seemed to be acting against transplanted cells.

The current study, done in mice, solves the puzzle of an apparent immune barrier. Newborn mice (pups) that received cell transplants in utero were divided into two groups. Mice nursed by their biological mothers lost the transplanted donor cells, while mice nursed by foster mothers retained those donor cells.

The mothers whose fetuses received the donor cells transplants had developed antibodies against those cells, and subsequently transmitted those antibodies to their pups through breast milk. "Those antibodies in the breast milk triggered rejection of the transplanted blood cells in the pups," said Flake. "But in the absence of a maternal immune response, we confirmed that immune tolerance does occur in the early-gestation fetus 100 percent of the time."

Of course, mouse biology is not the same as human biology, and Flake added, "Mouse time is not the same as human time." Because mice have such a brief gestational period, the mother's immune response didn't develop until after the birth of her pups, and was therefore transferred by breastfeeding. In large animals and humans, said Flake, the more likely route of maternal-to-fetal transmission would be through the placenta late in pregnancy, and not through postnatal breastfeeding.

However, it remains an open question whether the mouse findings are applicable to larger mammals and especially to humans. Flake's study team is continuing their investigations in larger animal models.

Looking forward to techniques to avoid maternal immune reactions to prenatal cell transplants, Flake proposed two possibilities. One would be use the mother as a source of donor cells, which would not stimulate an unwanted immune response. Another strategy could involve inducing the generation of increased numbers of T regulatory cells; those cells normally act to prevent the fetus from inappropriately reacting against maternal cells.

The ultimate goal, said Flake, is to develop IUHCT as a prenatal treatment for any congenital blood disorder that may currently be treated with postnatal bone marrow transplants. That would include sickle cell disease, thalassemia, and some inherited immunodeficiency diseases. Currently such postnatal transplants are risky and relatively rare.

"Our current finding is not a clinical breakthrough," added Flake. "But it does offer new potential to the field of cellular transplantation."

Source: Children's Hospital of Philadelphia (news : web)