”Transfer of Fetal Cells with Multilineage Potential to Maternal Tissue” (2004), by Kiarash Khosrotehrani et al.

In 2004, a team of researchers at Tufts-New England Medical Center in Boston, Massachusetts, investigated the fetal cells that remained in the maternal blood stream after pregnancy. The results were published in ”Transfer of Fetal Cells with Multilineage Potential to Maternal Tissue.” The team working on that research included Kiarash Khosrotehrani, Kirby L. Johnson, Dong Hyun Cha, Robert N. Salomon, and Diana W. Bianchi. The researchers reported that the fetal cells passed to a pregnant woman during pregnancy could develop into multiple cell types in her organs. They studied these differentiated fetal cells in a cohort of women fighting different diseases. The researchers found that the fetal cells in the women differentiated into different cell types under the influence of maternal tissues, and that those differentiated cells concentrated in the tissue surrounding diseased tissues. According to the team, this response could be a therapeutic response to the disease in the once pregnant woman. The research indicated the long lasting effects of pregnancy in a woman's body.

In 1990, Bianchi published ”Isolation of fetal DNA from nucleated erythrocytes in maternal blood,” reporting the detection of intact fetal cells in the blood of women who had been pregnant. Those cells had been passed to the woman during pregnancy, through the placenta. Some considered the discovery an early step toward the development of non-invasive prenatal genetic tests, in which doctors could draw blood from a pregnant woman and isolate the fetal cells within it. Those cells could then be genetically sequenced to determine genetic and chromosomal abnormalities of the fetus, without any intervention on the fetus or the womb. However, the small number of intact fetal cells found within the maternal blood sample limited this technique. Within a single maternal blood sample, doctors could retrieve only 0.1 to 1 ng of intact fetal cells. A nanogram (ng) is one billionth of a gram, and a sample of only 1 ng left researchers little genetic material for analysis. Researchers largely abandoned the use of intact fetal cells as a method of non-invasive prenatal genetic analysis.

Researchers continued to study the fetal cells found within maternal blood for other reasons. In their experiment, Khosrotehrani, Johnson, Cha, Salomon, and Bianchi hypothesized that fetal cells, transferred to maternal blood during pregnancy, could develop into multiple cell types within the woman's body. Due to Bianchi's earlier work in detecting these intact fetal cells in maternal blood, the team knew that a detectable amount of fetal cells were transferred to the pregnant woman during pregnancy. The 2004 experiment was designed to determine what happened to these fetal cells after pregnancy. Khosrotehrani was a postdoctoral student, while Johnson, Cha, Salomon, and Bianchi were researchers or professors at Tufts.

In 2004, Khosrotehrani and his team looked for what they called microchimeric fetal cells in different maternal tissue samples. Chimeras are organisms in which some of the cells have one set of DNA, and others have a different set. Fetal cells are present in the maternal blood stream after any length of gestation, meaning that even if a fetus is aborted, fetal cells will still be in a woman's bloodstream. This experiment referred to those remaining cells as microchimeric fetal cells because the woman contains two different cell lines: that of her own cells, as well as that of the fetal cells. The transferred fetal cells are often specialized fetal progenitor cells. These cells are hematopoietic stem cells, meaning that they are fetal cells that can differentiate to become many different types of blood cells in a fetus. In this study, Khosrotehrani and his team sought to identify fetal cells that had differentiated in the woman's body under the influence of maternal cells.

Khosrotehrani's team analyzed maternal tissue samples from ten women fighting diseases such as cancer and autoimmune diseases. They chose those ten women for two reasons. The first was

that the women had high numbers of fetal cells in their blood stream. Although fetal cells are transferred to women during pregnancy, the number of cells transferred varies. Those women had higher than average levels of fetal cells. The experimenters acknowledged that these numbers biased their results in some way. The second reason those women were selected was because they had all carried male fetuses, and the researchers could more easily detect the fetal cells of males in a female body, as male cells are chromosomally different from the maternal cells. Female fetal cells were harder to detect. As a control, Khosrotehrani's team also examined tissue samples from eleven women with no history of male pregnancy and that were not fighting diseases.

The research team first analyzed the tissues using fluorescence in situ hybridization (FISH), a technique to detect certain strains of DNA. In this case, FISH was used to detect a DNA sequence carried only on the Y chromosome, a strain that would not appear in any maternal cells, as maternal cells do not have a Y chromosome and cannot manifest this DNA sequence. The researchers then used immunolabeling, a technique using antigens and the matching antibodies to detect the presence of specific kinds of cells, to determine the cell type of these fetal cells. They knew that the fetal cells transferred to the woman all started as fetal cells that could differentiate into multiple blood cell types, and they sought to see if these cells had remained undifferentiated or if they had developed into different cell types.

In the ten maternal tissue samples they studied, the researchers found seven hundred and one male fetal cells. These fetal cells showed cell differentiation based on the tissues in which they were found. In the eleven control samples, with no histories of male pregnancy, the team found no male cells. Additionally, all of those cells had differentiated into different blood cell types. However, the cells took on the characteristics of different cells based on the maternal environment. For example, in a woman fighting liver cancer, the fetal cells found near the liver had some characteristics of liver cells. Moreover, differentiated fetal cells concentrated around the sites of maternal disease. In the case of a woman with liver cancer, there were high concentrations of fetal cells in the tissue surrounding the liver, but not in the diseased tissue of the liver itself. The differentiated fetal cells were just on the exterior of the woman's diseased tissue.

Khosrotehrani's team's results confirmed the hypothesis that intact fetal cells acquired during pregnancy can differentiate into multiple cell types in different maternal tissue types. The study called this population of fetal cells as pregnancy-associated progenitor cells. The fetal cells transferred to the maternal blood stream during pregnancy differentiated into different blood cell types, but depending on the cell's environment, they have the characteristics of other cell types. The study also showed that there were high concentrations of these cells in the tissue surrounding maternal disease. The researchers theorized that this concentration may be an immunological or therapeutic response by the fetal cells in response to the maternal disease.

Sources

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