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The Effects of Fetal Microchimerism on Maternal Health

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Abstract

Maternal-fetal cellular trafficking is the bidirectional passage of cells between the fetus and mother during pregnancy. The presence of fetal cells in maternal circulation, brain, and muscles is known as fetal microchimerism. During pregnancy, fetal cells can be obtained from the mother's blood for prenatal diagnosis of the fetus. Furthermore, it has been confirmed that fetal microchimerism persists decades later in women who have been pregnant. Investigation of the long-term consequences of fetal microchimerism is a frontier of active study, with preliminary results pointing to both beneficial and adverse effects. This review will examine the relevant literary information on fetal microchimerism during pregnancy and provide current knowledge regarding the long-term effects of naturally acquired fetal microchimerism.

Introduction

Microchimerism is the presence of two genetically distinct cell populations in the same individual. Foreign cells and DNA are found in an individual's plasma or tissues that originated from a genetically different individual. Naturally acquired microchimerism is commonly observed and results from the maternal-fetal exchange of cells and DNA during pregnancy. (Gammill & Nelson 2010) In pregnancy, there is transplacental two-way trafficking of living fetal cells from the fetus into the maternal circulation, and cells from maternal circulation impart in the fetus. (Naik, Shrivastava, Suryawanshi, & Gupta 2019) This paper provides an overview of the role of fetal cell microchimerism in autoimmune and cancerous diseases. The mechanisms by which fetal microchimerism is believed to modulate the protection against cancer or tumor progression will be discussed, along with future research directions.

Methods

This document was written by researching peer-reviewed scholarly articles and medical journals to assess the newest research and methods in fetal microchimerism. The information and data were gathered from numerous sources, including databases such as Google Scholar, Touro Library, The National Center for Biotechnology Information, and The National Institute of Health. Keyphrases searched included, "fetal microchimerism," "the effects of fetal microchimerism," and "fetal microchimerism in autoimmune disorders." All the content was carefully selected, compared, and analyzed to assure its validity and determine the articles' standpoint.

Fetal Microchimerism

Microchimerism is the fetus's cell legacy after pregnancy. Fetal stem cells can leave the fetus and migrate across the placenta to engraft in the maternal bone marrow and other tissues. The transfer of fetal progenitor stem cells begins four or five weeks after fertilization and continues throughout the pregnancy. This form of microchimerism occurs in both male and female embryos, but the detection of male microchimerism in maternal tissue is easier to detect due to the unique presence of Y-chromosome in the women. (Miech, 2010)

Fetal microchimerism has been reported in the peripheral blood of women in cellular subsets, including lymphoid-lineage and myeloid-lineage cells. An experiment was done to evaluate microchimerism in CD66b sorted granulocytes. Granulocytes were isolated from the peripheral blood of healthy women. CD66b+ cells were then isolated by fluorescence-activated cell sorting, and a panel of polymorphism-specific quantitative assays was employed to investigate the presence of fetal and maternal microchimerism. One-third of the women tested positive for at least one form of microchimerism. 40% had maternal microchimerism compared to 15% who had fetal microchimerism. The maternal and fetal origin CD66b+ cells are strong evidence for an active microchimeric hematopoietic stem and progenitor cell niche. Higher proportions of women might test positive for even larger quantities of microchimerism if more sensitive assays were available. (Sunku, Gadi, Lacoste, Guthrie, & Nelson, 2010)

Fetal DNA in Maternal Plasma During Pregnancy

Another study was undertaken to evaluate fetal DNA in maternal plasma and urine. DNA was isolated from plasma and urine samples of 80 pregnant women, ranging from 7 to 40 weeks of gestation. Their DNA underwent amplification for Y specific chromosome DNA via a nested polymerase chain reaction. The postpartum analysis of fetal gender showed that 25 women carried female fetuses and 55 male fetuses. Among the 55 women bearing male fetuses, Y chromosome-specific signals were detected in 96% of their plasma and 38% of their urine samples. (Al-Yatama et al., 2001) The detection of fetal sex chromosomes with Y-chromosome-PCR has a specificity of 100% and a sensitivity of 96%, which increases along with gestational age. This minor lack of sensitivity explains why Y-chromosome signals were only located in 96% of the plasma of pregnant women. (Rijnders et al.) The analysis of their results with respect to gestational age showed no significant difference in the Y chromosome-specific DNA detection. These results showed that fetus-specific DNA was detected in the maternal plasma by nested PCR. (Al-Yatama et al., 2001)

Fetal DNA is present in low concentration in maternal plasma increasing throughout pregnancy with a 0.1% increase each week from 10 to 20 weeks' gestation, followed

by a 1% increase each week from the 21st week until term. (Taglauer et al.) Clinical tests have tried to capitalize on this DNA to identify the baby's sex, determine whether the child and mother have Rh incompatibility, and identify chromosomal disorders. (LeslieDec, et al. 2017)

Many early investigations of fetomaternal cell trafficking sought to develop methods whereby noninvasive prenatal diagnosis of genetic disorders could be achieved. (Gammill & Nelson 2010) Noninvasive testing would ameliorate the risk of fetal miscarriage associated with current invasive procedures such as amniocentesis. This non-invasive prenatal test is a blood test, and between 25 and 42.5 milliliters are collected. (Bianchi, Williams, Pelletier, Klinger, & Shuber 1996) The main conditions for which prenatal diagnosis is considered are monogenic diseases, when the causation of the disease results from one gene, and therefore, is easier to detect and obtains conclusive results. Fetal DNA circulates in a high background of maternal DNA and is isolated and amplified using polymerase chain reaction technology. However, even after that, maternally inherited fetal alleles are very difficult to identify from maternal plasma, therefore, scientists have focused on the detection of paternally inherited fetal alleles that are not present in the maternal genome. The diagnosis of autosomal dominant diseases transmitted by the father could be made noninvasively. Also, by detecting the paternally inherited fetal alleles, one can exclude the fetal inheritance of autosomal recessive diseases. The discovery of free cellular fetal DNA in maternal plasma has offered new approaches for noninvasive diagnosis, and fetal isolation analysis is now possible. (Lun et al., 2008)

Fetal DNA in Maternal Plasma After Pregnancy

Microchimerism occurs as a result of the fetomaternal transfusion of blood cells across the placenta during pregnancy. After delivery, once the placenta has been expelled, fetal-origin cells should hypothetically depart from the maternal circulation. Nevertheless, studies of women who had given birth to a male child showed a high incidence of male cells in their blood after delivery. Additionally, some women have displayed male cells in their tissues up to 27 years postpartum after having birthed a male child. This event can be interpreted to mean that fetal cells transferred from the fetus to the mother during pregnancy established permanent microchimerism in the maternal body. This permanency was reported in 30–50% of women who gave birth to a male child. (Sato, Fujimori, Sato, & Ohto, 2008)

There is an increased fetal-to-maternal transfer of progenitor cells during an abortion procedure as the placenta is being destroyed. Maximized fetal cell trafficking following a medical abortion was confirmed in an in vivo model. Since the embryonic circulatory system is established in the first trimester of pregnancy, there is a greater chance for the transfer of a larger number of progenitor T cells during the first-trimester termination of pregnancy. Therefore, women who had an elective abortion in their first or second trimester have a greater tendency towards fetal microchimerism. (Miech, 2010)

Male microchimerism in women without sons and the correlation of microchimerism to prior pregnancy history was researched. Y-chromosome-specific quantitative PCR was used to test peripheral blood mononuclear cells of 120 women. Women were categorized into four groups based on their pregnancy histories. Group A was nulligravid and displayed 10% male microchimerism, Group B had induced abortions and displayed 57%, Group C had spontaneous abortions and displayed 22%, and Group D had only daughters and displayed 8%. Male microchimerism prevalence was the greatest by a significant amount in those with induced abortions. Other possible sources of male microchimerism, such as those obtained in Groups A and D, include unrecognized spontaneous abortion or a vanished male twin. (Yan et al., 2005)

Autoimmune Effects on The Mother

It has been theorized that the persistence and abundance of fetal microchimerism are dependent on numerous factors, including the immunogenetic relationships between mother and fetus, and perhaps between and preexisting inhabitants of the maternal system, from her mother or previous children. (Gammill & Nelson 2010)

Fetal microchimerism, a form of trans-placental stem cell transplant, helps to explain the etiology, diversity of tissue pathology, predilection for females, and increase in the annual incidence of autoimmune diseases in women. (Miech, 2010) Fetal stem cells can differentiate into mature and competent cells, such as lymphocytes and monocytes. Fetal cells in maternal circulation or tissues may mediate a graft vs. host disease, which can lead to the development of autoimmune diseases. Women comprise 80% of people with autoimmune diseases. Researchers have begun investigating the association of micro-chimerism with autoimmune diseases that predominately affect women. (Naik, Shrivastava, Suryawanshi, & Gupta 2019)

Fetal microchimeric cells in maternal tissues led to the discovery of a positive correlation between fetal microchimerism and autoimmune diseases in women. Progenitor cells in the fetal immune system, such as T cells, monocytes, macrophages, lymphocytes, and NK cells, are among the many fetal cell types that can be transferred to maternal tissues. In maternal tissues, the fetal microchimeric

progenitor immature T cells are capable of self-renewal, proliferation, and differentiation. Progenitor cell activation can result in the production of autocrine and paracrine inflammatory responses in autoimmune diseases. Triggering agents that activate these fetal microchimeric immune cells to attack the maternal host cells resulting in autoimmune disease have not yet been identified. Suspected triggers include viral or bacterial agents, abnormal localized tissue protein, and drugs. Microchimerism in affected tissues is more likely to be abundant in women with autoimmune diseases than in women with non-autoimmune diseases. (Miech, 2010)

Pregnancy alters symptoms of autoimmune diseases. The maternal immune system develops a tolerance to the fetus, and the suppression of the maternal response is lifted postpartum. Fetal tolerance may explain why some autoimmune disease symptoms decrease during pregnancy in some women. (Boddy, Fortunato, Sayres, & Aktipis, 2015) Autoimmune diseases are often repressed during pregnancy and exasperate postpartum. It was then hypothesized that fetal cells in maternal circulation might be important in influencing autoimmune disease in pregnancy and postpartum. (Ando, Imaizumi, Graves, Unger, & Davies, 2002) Systemic sclerosis provided the first evidence for the involvement of fetal microchimerism with autoimmune diseases. Patients frequently had fetal cells not only in peripheral blood, but also in skin lesions. The hyperthyroidism of Graves' disease frequently abates during pregnancy and exacerbates after childbearing. (Ando, Imaizumi, Graves, Unger, & Davies, 2002) Between 43 and 75% of patients with rheumatoid arthritis exhibit amelioration of some or all their rheumatoid arthritis symptoms during pregnancy. Additionally, in rheumatoid arthritis patients, symptoms tend not only to show improvement during pregnancy, but an exacerbation of symptoms postpartum. Correspondingly, the rate of relapse declines with pregnancy in women diagnosed with multiple sclerosis, with the lowest rate in the third trimester. Relapse rates return to pre-pregnancy levels postpartum. This framework suggests that a contributor to autoimmune disease development may be the maternal immune response to the presence of fetal cells that invade maternal tissues. (Boddy, Fortunato, Sayres, & Aktipis, 2015)

The risk of developing an autoimmune disease in parous women is higher after the first year postpartum. Fetal cells in the thyroid may contribute to thyroid cancer risk or susceptibility to other thyroid diseases. Current research suggests an association with postpartum thyroid tissue and thyroid diseases. Fetal cells are more abundant in the thyroid tissue and blood of women with Graves' disease and Hashimoto's thyroiditis, compared to healthy controls. Also, the risk of autoimmune disease in parous women is significantly higher after the first year postpartum. This knowledge suggests that the presence of fetal cells in the thyroid is associated with a maternal disease rather than health. (Boddy, Fortunato, Sayres, & Aktipis, 2015)

Autoimmune thyroid disease affects reproductive-aged women. It commonly initiates or exacerbates postpartum, and so the involvement of fetal microchimerism was suspected. Autoimmune thyroid disease does have e a profound relationship with pregnancy. Autoimmune thyroid disease involves autoimmune antigens, such as the TSHR, Tg, and TPO. Placental immune suppression during pregnancy lessens the activity of autoimmune thyroid disease, as seen in the remission of Graves' disease. However, exacerbation of preexisting autoimmune thyroid diseases or initiation of autoimmune thyroid disease is also common postpartum. Increased titers of thyroid autoantibodies have been observed in the postpartum. Graves' disease has also been shown to be most markedly suppressed by pregnancy itself, but; however, up to 60% of Graves' disease patients of childbearing age have been reported to develop this disease within one year of delivery. (Ando & Davies, 2003)

Cancerous Effects on the Mother

During pregnancy, fetal cells enter the maternal body, cross the placenta, and are found frequently in the maternal lung. It was generally accepted that the fetal cells in the lung were passing through the mother's pulmonary circulation; however, the presence of fetal cells in the lung shows an association with cancer. A study reported higher levels of male DNA and significantly more fetal cells in the lung and thymus tissue in the diseased lung compared to healthy bone marrow from the same person. (Boddy, Fortunato, Sayres, & Aktipis, 2015) Fetal cells have also been detected as clusters in lung tumors in women decades after pregnancy. Their tumor frequency was higher in lung tumors than in the healthy surrounding lung tissue. The fetal cells may be recruited from the bone marrow to the tumor sites where they assumed their role in immunosurveillance and tissue repair. (Naik, Shrivastava, Suryawanshi, & Gupta 2019)

Fetal cells are frequently found in normal breast tissue postpartum women. The research presents a complicated picture of fetal cell's role in breast cancer. Fetal cells are found less the tissue and blood of women with breast cancer compared to healthy controls. (Boddy, Fortunato, Sayres, & Aktipis, 2015) It was reasoned that naturally acquired allogeneic immune cells in the form of fetal microchimerism might correlate with protection from the development of breast cancer. Fetal microchimerism was found in higher quantities in healthy women compared

to breast cancer patients, 43% to 14%, respectfully. This shows a correlation between the role of fetal allogeneic cells as malignant cell immune surveillance and protection from breast cancer. (Gadi & Nelson, 2007)

Reduced risk of breast cancer is recognized among parous compared to nulliparous women. Eighty-two women were tested for male DNA in peripheral blood, presumed from a prior pregnancy with a male fetus. Forty-seven of the subjects were healthy, and 35 had breast cancer. The levels of male DNA were determined by real-time PCR for a Y chromosome-specific gene in DNA extracted from peripheral blood mononuclear cells. Fetal microchimerism was found in 43% of healthy women and 14% in women with breast cancer. These findings suggest that allogeneic fetal microchimerism may contribute to a reduction in the risk of breast cancer. (Gadi & Nelson, 2007)

Through the evolutionary history of fetal microchimerism in the maternal body, it is possible that it now has a role in normal breast tissue physiology. The maternal mammary gland hosts stem cells that contribute to the development of normal breast tissue and can be transferred to the neonate during lactation. Mouse fibroblast fetal cells have been shown to differentiate into mammary epithelioid cells when exposed to lactation hormones in vitro, and a functional mammary gland has been generated from a single stem cell in a pregnancy mouse model. This suggests that fetal progenitor cells play a role in breast morphology and maternal milk supply. (Boddy, Fortunato, Sayres, & Aktipis, 2015)

Pregnancy at older ages has been linked to risk for ovarian cancer. Given the data that microchimeric cells in parous women decline overtime after pregnancy, and that ovarian cancer develops most commonly in postmenopausal women, fetal microchimerism may play a protective role in ovarian cancer as well. (Naik, Shrivastava, Suryawanshi, & Gupta 2019)

Neurological Effects on the Mother

It was unknown whether fetal cells, which are capable of crossing the placental barrier to enter maternal blood, could also cross the blood-brain barrier and enter the maternal brain. To determine if fetal cells could enter the maternal brain during pregnancy, female wild-type mice were crossed with green mice. Their offspring ubiquitously expressing the enhanced green fluorescent protein. Green mouse fetal cells were found in the maternal brain, and quantitative real-time PCR of genomic DNA for the enhanced green fluorescent protein gene showed that more fetal cells were present in the maternal brain for weeks postpartum than on the day of birth. After an excitotoxic lesion to the brain, more fetal cells were detected in the injured region. For weeks postpartum, enhanced green fluorescent protein-positive green mouse fetal cells in the maternal brain were found to adopt locations, morphologies, and expression of immunohistochemical markers indicative of astrocytes, neurons, oligodendrocyte, and macrophage-like cell types. The expression of morphological and histochemical characteristics of these cells was confirmed on the identification of fetal cells in the maternal brain by Y chromosome fluorescence hybridization. The characterization of these cells that allow them to cross both the placental and blood-brain barriers and to target the injured brain may improve selection procedures for isolation of stem or progenitor cells for brain repair by infusions. (Tan et al., 2005)

Several studies have found male DNA in human and maternal mouse brains, but the function of these cells is not entirely known. One study found that fetal cell DNA in numerous regions of the maternal brain, even decades after the woman had birthed a son, suggesting that fetal microchimerism in the human maternal brain may be long-lasting. (Boddy, Fortunato, Sayres, & Aktipis, 2015) A team led by autoimmunity researcher, J. Lee Nelson sought to discover how leftover fetal cells affect the brain. They took samples from autopsied brains of 59 women. Male DNA evidence was found in the brains of 63% of the participants. The male DNA was scattered across several brain regions. Studies have hypothesized that the risk of Alzheimer's disease increases with an increasing number of pregnancies, so the team also examined the brains for signs of the disease. Of the 59 women, 33 had Alzheimer's disease. Compared to healthy controls, fetal cells were found to be less common in the brains of women who had Alzheimer's disease. That correlation suggests that the presence of fetal cells in the maternal brains helps protect women against Alzheimer's disease. (PhillipsSep, et al. 2017)

Conclusion

The placenta is unique because it allows for intimate contact between maternal and fetal cells at the maternal-fetal interface throughout pregnancy. (Than et al.) During pregnancy, the semi-allogeneic fetus is protected from rejection by the maternal immune system. (Trowsdale and Betz) It was hypothesized that the semi allogeneic fetus could survive due to the regulation of the immunologic interactions between mother and fetus. Such regulation can be caused by functional suppression of the maternal immune response or a lack of fetal antigen expression. (Morelli et al.)

In the human placenta, fetal trophoblast cells do not express MHC HLA-A and B molecules, which are responsible for allograft rejection in humans. (Chen et al.)

Mixed hematopoietic chimerism, the state in which bone marrow hematopoietic stem cells from two genetically different animals coexist, remains the most robust tool for tolerance induction. Unfortunately, bone marrow or hematopoietic stem cell transplantation for patients awaiting solid organ transplantation remains at high-risk, due to the dangers of graft-versus-host disease. (Zavazava) Human embryonic stem cells express low levels of (MHC)-I antigens and lack expression of MHC-II antigens. These stem cells must engraft in the transplant recipient, inducing tolerance to foreign cells, and reducing the immune targeting of the transplant. Upon injection into immunocompetent mice, human embryonic stem cells are unable to produce an immune response. Human embryonic stem cells may provide a potential tool for the induction of immunotolerance. Further studies in human embryonic stem cells immunobiology are warranted and may reveal unique mechanisms that account for the immunological properties of human embryonic stem cells. (Menendez et al.)

Fetal cells and DNA go beyond the womb and into maternal blood and tissues during pregnancy and can last long after birth. In some instances, fetal microchimerism contributes to perturbations in maternal immunity that may contribute to autoimmune diseases. In other cases, these interactions seem to benefit long-term maternal health by allowing fetal microchimerism cells to act as allogeneic surveyors in her system. Fetal microchimerism has potential implications for the understanding of women's health and disease pathology postpartum. The pregnant mother mshould never be viewed as merely an incubator. Rather, microchimerism expands the biological bonds that are established between the pregnant mother and her fetus.

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