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Maternal-fetal cellular trafficking: clinical implications and consequences

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Abstract

Purpose of review—Maternal-fetal cellular trafficking (MFCT) is the bidirectional passage of cells between mother and fetus during pregnancy. This results in the presence of fetal cells in the maternal circulation, known as fetal microchimerism, and maternal cells in the fetal circulation, known as maternal microchimerism. The biologic role of this bidirectional passage of cells during pregnancy is not known, although it has been implicated in development of the fetal immune system, tolerance mechanisms during pregnancy, tissue repair in autoimmune disease and cancer, and immune surveillance.

Recent findings—Clinical utility of MFCT has been identified in prenatal testing for aneuploidies and prediction of pregnancy complications. Additionally, this transplacental passage of cells has been implicated in the delicate balance between immunologic priming and tolerance which can influence the occurrence of autoimmune disease and transplantation outcomes. Ongoing studies are evaluating the utility of microchimerism in predicting the risk of graft rejection in transplantation.

Summary—In this review, we will discuss the clinical implications of MFCT in pregnancy, fetal surgery, autoimmune disease, transplantation, and cancer.

Keywords

maternal-fetal cellular trafficking; maternal microchimerism; fetal microchimerism; fetal surgery

Introduction

Maternal-fetal cellular trafficking (MFCT) is the bidirectional passage of cells between mother and fetus during pregnancy. This results in the presence of fetal cells in the maternal circulation, known as fetal microchimerism, and maternal cells in the fetal circulation, known as maternal microchimerism. Fetal microchimerism was first reported in 1893 by Georg Schmorl who identified placental trophoblast cells in mothers who died of eclampsia [1]. Since that time, there have been reports of fetal cells persisting in the maternal circulation decades after pregnancy [2, 3], as well as in maternal organs such as bone

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marrow [3], kidney, liver, and heart [4]. Maternal microchimerism was first described in 1963 when maternal leukocytes and platelets were identified in cord blood [5]. These maternal cells have been found to circulate in healthy, immunocompetent individuals into adult life [6]. This bidirectional trafficking of cells is a normal phenomenon and begins at 7 weeks, increases steadily throughout gestation, and peaks at parturition [7]. At delivery, fetal microchimerism has been reported in 51%, and maternal microchimerism in 42% of normal pregnancies [8].

Detection of maternal-fetal microchimerism in human blood and tissues uses *in situ* hybridization to identify whole cells [3] and polymerase chain reaction (PCR) to identify DNA that originates from the mother or fetus. Initial studies examined gender mismatches using primers to loci on the Y chromosome [2, 8]. Subsequently, non-shared HLA-DR alleles between mother and fetus, known as informative alleles, have been used to distinguish one set of genetic material from another [6, 9]. In mice, flow cytometry can be used to evaluate the number and types of cells that traffic using antibodies to markers that distinguish maternal and fetal cells [10].

Since microchimerism does not occur in all pregnancies, there are likely fetal, maternal, and/or placental signals that control cellular movement across the placental barrier rather than nonspecific leakiness. The mechanism of trans-placental cell trafficking involves VEGF and integrin-dependent pathways, but the molecular signals that initiate the process are unknown [11]. Altered MFCT has been associated with disruption of the feto-maternal interface in cases of fetal surgery [9], preeclampsia [12], and pregnancy termination [13], suggesting a role for the placenta in regulating cell migration. Additionally, altered levels of microchimerism are associated with differences in histocompatibility, suggesting that an immune response between mother and fetus promotes or hinders either cell trafficking, or the survival of trafficked cells [14, 15].

The biologic role of this bidirectional movement of cells during pregnancy is unclear, although it is implicated in development of the fetal immune system [16], tolerance mechanisms during pregnancy [17], tissue repair in autoimmune disease [18-21] and cancer [22], and immune surveillance [23]. Additionally, it is involved in the delicate balance between immunologic priming [24] and tolerance [25], which can influence transplantation outcomes and the occurrence of autoimmune disease. Clinical utility of MFCT has been identified in prenatal testing for aneuploidies [26] and prediction of pregnancy complications [27, 28]. Ongoing studies are evaluating the use of microchimerism in predicting the risk of graft rejection in transplantation [10, 29]. In this review, we will discuss the clinical implications of MFCT in pregnancy, fetal surgery, autoimmune disease, transplantation, and cancer.

Pregnancy

MFCT has been implicated in the development of the fetal immune system with resultant induction of tolerance during pregnancy [17]. In a normal gestation, mechanisms within the maternal immune system have been identified to accept a semi-allogeneic fetus [30-32], although the fetal immune system may also be involved. Bidirectional cell trafficking across

the placenta can lead to fetal T cell acceptance of maternal antigens by inducing the development of fetal regulatory T cells [17]. Further evidence for this phenomenon is found in studies of rhesus (Rh) antigen. A Rh negative woman carrying a Rh positive fetus is less likely to produce anti-Rh antibodies if their mother was Rh positive [33], suggesting that in utero exposure to maternal antigen results in tolerance induction. This form of “education” of the fetal immune system by circulating maternal cells has been demonstrated in other models. In mouse fetuses, maternal microchimerism increases after in utero stem cell transplantation and can limit engraftment of hematopoietic cells transplanted into the fetus [10]. Interestingly, even after maternal T cells are no longer present in the fetus, there is an ongoing decrease in the recipients’ engraftment levels, which suggests priming of the fetal immune system [10]. Similarly, murine fetuses exposed to microchimeric maternal T cells reactive to pancreatic beta cells demonstrate an increased incidence of auto-immune diabetes. However, the T cells that infiltrate the islet are fetal, not maternal in origin [16]. Thus, microchimeric maternal cells may have both a beneficial and harmful role in fetal immune development.

Alterations in this naturally-occurring phenomenon have been associated with pregnancy complications. Increased number of fetal cells or cell-free DNA has been identified in pregnancies affected with preeclampsia [12], preterm labor [34, 35], and intrauterine growth restriction [36]. In preeclampsia, it has been proposed that failure of trophoblast invasion during the second trimester, with increasing metabolic demands of the fetoplacental unit, leads to hypoxia, release of apoptotic DNA in the intervillous space, and subsequently into the maternal circulation [27]. Second trimester cell-free fetal DNA levels in the maternal circulation have been evaluated as a screening tool in asymptomatic, low risk pregnancies to identify patients that may be at higher risk of developing complications. While some studies have found these levels useful in predicting patients that will develop preterm delivery [28] and preeclampsia [27, 37], others have not [38].

Fetal anomalies such as congenital diaphragmatic hernia (CDH) [39] and aneuploidy [26, 40] have been associated with altered MFCT. We recently reported that fetuses with severe CDH have increased levels of maternal microchimerism, and higher levels of inflammatory mediators in cord blood [39]. Such changes in the levels of microchimerism may result from alterations in the inflammatory milieu leading to increased trafficking in pregnancies carrying anomalous fetuses, or from increased proliferation of trafficked maternal cells in the fetus. Regarding aneuploidy, levels of fetal cell-free DNA in maternal plasma are higher in trisomy 21, and lower with trisomy 18, 13, and monosomy X [26]. The presence of fetal cells or cell-free DNA within maternal circulation is a critical area of research since it may provide a non-invasive mechanism for prenatal diagnosis of certain fetal conditions such as hemoglobinopathies [41] and chromosomal anomalies [26, 40].

Fetal surgery

Fetal surgery results in alterations in MFCT in both humans [9, 42] and mice [10]. In patients undergoing fetal myelomeningocele repair, there are increased numbers of maternal cells within the fetal circulation compared to both healthy pregnancies and patients undergoing routine postnatal repair [9]. These changes in MFCT are not immediate, since

patients undergoing fetal surgery at the time of birth have unchanged levels of maternal microchimerism [9]. In twin-to-twin transfusion syndrome, increased levels of cell free DNA have been found in the maternal circulation after laser coagulation of vascular anastomoses [42], although levels of mRNA are unchanged [43]. High levels of cell-free DNA twenty-four hours after the procedure are associated with a longer procedure time, larger number of vessels ablated, and intrauterine fetal demise of at least one twin, thus may be a marker for placental injury [42].

With improved prenatal diagnosis and advances in fetal surgical procedures, indications for prenatal intervention have broadened [44-46] but these procedures are limited by preterm labor and other pregnancy complications [44, 45]. Alterations in post-surgical levels chimerism may be due to fetal cytokine production leading to changes in trans-placental cellular trafficking, or proliferation of maternal cells already present in the fetal circulation. We have shown that maternal T cells can cause demise of allogeneic fetuses after fetal intervention, suggesting a pathogenic role for such alterations in trafficking in this context [47]. Understanding the effects of fetal intervention on cellular trafficking, and whether these changes are causative in the onset of pregnancy complications may help identify new treatment strategies.

Autoimmune disease

Autoimmune diseases occur more frequently in women after their child-bearing years, which has led to the hypothesis that MFCT during pregnancy may be involved in the pathogenesis of these conditions [48]. Women with systemic sclerosis have increased rates of fetal microchimerism in peripheral blood and in skin lesions [49]. Similarly, fetal cells are more commonly detected in thyroid specimens of women with Hashimoto's thyroiditis [50] and Graves' disease [51], and in the peripheral blood of those with scleroderma [52]. While mechanisms of autoimmunity are not known, it is possible that microchimeric cells could function as effector cells. Male T cell clones obtained from mothers with sons have been found to react against maternal HLA antigens [53]. Since several autoimmune conditions resemble chronic graft versus host disease seen in transplantation, it is believed that fetal cells may contribute to anti-maternal graft versus host reactions.

There is much debate as to whether fetal cells in the maternal tissues contribute to autoimmunity, tissue regeneration, or whether microchimeric fetal cells are identified because of increased proliferation in an inflammatory environment. Fetal cells found in mothers have multi-lineage potential [19] and can differentiate into various cell types in maternal organs including blood [54], skin [55], and central nervous system [56]. Additionally, they have been found to participate in tissue regeneration after injury in the maternal liver [57] and kidney [58], and are not usually detected in other maternal organs in the absence of injury [57, 59]. As a result of these stem cell-like properties, fetal cells in the maternal circulation have been termed pregnancy-associated progenitor cells (PAPC) [60].

With the association of fetal microchimerism in maternal autoimmune disease, studies have explored the role of maternal microchimerism in pediatric autoimmune disease. Maternal cells have been detected with higher frequency in cardiac specimens of patients with

neonatal lupus syndrome [20], in the blood and pancreas of patients with type I diabetes [61], in blood and muscle of patients with juvenile dermatomyositis [62], in the skin of children with pityriasis lichenoides [18], in the liver of children with biliary atresia [63], and in the intestine of patients with Hirschsprung's disease [64]. Similar to fetal microchimerism, it is not known whether maternal microchimerism contributes to autoimmunity or to tissue regeneration. Maternal cells adopt a cardiomyocyte phenotype in neonatal lupus [20], produce insulin in type I diabetes [21], and differentiate into keratinocytes in inflammatory skin diseases [18], supporting the theory that maternal stem cells cross the placental barrier and differentiate to participate in regeneration. Not all studies support this hypothesis. In a mouse model of renal inflammation, maternal microchimerism was not found to differ between acute injury, chronic injury and control animals [65].

Transplantation

The continued presence of maternal cells in offspring and resultant induction of fetal regulatory T cells [17] may have implications in organ transplantation when a child receives a maternal graft. Initial studies in mice found that in utero exposure to antigen results in acceptance of transplanted organs expressing that antigen [66]. Subsequent studies showed that maternal microchimerism is associated with tolerance to noninherited maternal antigens (NIMA), and must be maintained with breastfeeding [25]. The mechanism leading to tolerance may be the partial deletion of B cells with high affinity for NIMA [67] or the induction of NIMA-specific T regulatory cells [68]. This hypothesis was further explored in human studies of mother-to-child transplants. In bone marrow transplantation, improved patient survival was seen in children with acute leukemia receiving maternal stem cell transplantation compared to paternal grafts, although rates of graft versus host disease and rejection were not affected [69]. We evaluated graft survival in pediatric patients with biliary atresia, a condition with high levels of maternal microchimerism, and reported increased survival when the hepatic graft is obtained from the mother compared to the father [70]. There is no advantage to a maternal graft in patients who undergo liver transplantation for conditions other than biliary atresia, suggesting that increased maternal microchimerism may be the underlying etiology for tolerance [70]. In renal transplants, sibling grafts mismatched for NIMA have improved survival compared to those that are mismatched for non-inherited paternal antigens (NIPA) [71, 72], implying that exposure of a child to NIMA during fetal life results in tolerance.

Conversely, maternal microchimerism may result in sensitization with subsequent rejection of the transplanted organ. Studies in mice have demonstrated that neonates develop cytotoxic responses to low doses of NIMA, suggesting that in utero exposure results in priming rather than tolerance [24]. Additionally, murine maternal T cells in the fetus can actively limit engraftment of transplanted cells after in utero hematopoietic transplantation [10]. In human transplantation, several studies have not demonstrated an advantage to maternal renal grafts [73, 74], and have identified higher rates of acute rejection in renal [71] and stem cell [75] grafts mismatched for NIMA. In severe combined immunodeficiency (SCID), graft versus host disease has been associated with circulating maternal T cells, which may have a proliferative advantage in these patients [76].

Since microchimerism may lead to either host tolerance or sensitization, and therefore acceptance or rejection of organ grafts, predicting this response would have clinical significance in transplantation. To predict the risk of graft versus host disease, Hirayama et al. devised an assay that combines the results of mixed lymphocyte reaction (MLR), which classifies patients into high and low responders based on NIMA exposure, and enzyme-linked immunospot (ELISPOT), which is used to identify IFN γ -producing alloreactive cells [77]. In the mouse model, the group with a low response to NIMA was found to have high levels of maternal microchimerism, and lower results for the ELISPOT assay [77]. Preliminary results in humans shows that it may predict development of graft versus host disease prior to transplantation [29].

Maternal cancer

Fetal microchimerism has been identified in maternal cancer. Women with breast cancer have increased rates of fetal microchimerism in blood [23] and breast tissue [78] compared to healthy women. Patients with papillary thyroid cancer have low circulating levels of fetal microchimerism and high numbers of fetal cells in tumor tissue [22]. In the lung, fetal cells cluster at sites of tumor rather than in surrounding healthy tissue [79].

The role of fetal cells in maternal tissues is not clear, although several proposals include promotion of tumorigenesis, protection by immune surveillance, and participation in tissue repair, which may be dictated by the phenotype adopted by these cells. Fetal cells express mesenchymal markers in breast cancer specimens [80], epithelial and hematologic phenotypes in cervical cancer [81], and endothelial characteristics in melanoma [82]. Those with hematologic differentiation are thought to participate in tumor destruction, whereas fetal cells with mesenchymal or epithelial phenotype could participate in repair processes. Cells with endothelial characteristics, on the other hand, are thought to play a role in angiogenesis and tumor progression.

Conclusions

Maternal and fetal microchimerism have long-term implications in health and disease. Both tolerogenic and immunogenic forms of microchimerism have been identified and have consequences in pregnancy, autoimmune disease, and transplantation. Furthermore, the bidirectional exchange of cells between mother and fetus allows for the acquisition of stem cell populations with a variety of phenotypes that can participate in tissue repair in autoimmune conditions and maternal cancer. The utility of this biologic phenomenon is being explored in clinical practice for the prenatal diagnosis of aneuploidy, the prediction of pregnancy complications, and the identification of patients at risk of organ rejection in transplantation.

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Bullet Points

- Maternal-fetal cellular trafficking (MFCT) is the bidirectional passage of cells between mother and fetus during pregnancy which results in the presence of fetal cells in the maternal circulation, known as fetal microchimerism, and maternal cells in the fetal circulation, or maternal microchimerism.
- The biologic role of this bidirectional passage of cells during pregnancy is not known, although it is implicated in development of the fetal immune system, tolerance mechanisms during pregnancy, tissue repair in autoimmune disease and cancer, and immune surveillance.
- This transplacental passage of cells is also involved in the delicate balance between immunologic priming and tolerance which can influence the health of the pregnancy, as well as transplantation outcomes and the occurrence of autoimmune disease.
- Clinical utility of MFCT has been identified in prenatal testing for aneuploidies, prediction of pregnancy complications, and ongoing studies are evaluating the use of microchimerism in predicting the risk of graft rejection in transplantation.