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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 IFNγ-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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References

1. Lapaire O, Holzgreve W, Oosterwijk JC, Brinkhaus R, Bianchi DW. Georg Schmorl on trophoblasts in the maternal circulation. Placenta. 2007; 28:1–5. [PubMed: 16620961]
2. Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc Natl Acad Sci U S A. 1996; 93:705–8. [PubMed: 8570620]
3. O'Donoghue K, Chan J, de la Fuente J, Kennea N, Sandison A, Anderson JR, Roberts IA, Fisk NM. Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem-cell trafficking in pregnancy. Lancet. 2004; 364:179–82. [PubMed: 15246731]
4. Koopmans M, Kremer Hovinga IC, Baelde HJ, Fernandes RJ, de Heer E, Bruijn JA, Bajema IM. Chimerism in kidneys, livers and hearts of normal women: implications for transplantation studies. Am J Transplant. 2005; 5:1495–502. [PubMed: 15888060]
5. Desai RG, Creger WP. Maternofetal passage of leukocytes and platelets in man. Blood. 1963; 21:665–73. [PubMed: 14027196]
6. Maloney S, Smith A, Furst DE, Myerson D, Rupert K, Evans PC, Nelson JL. Microchimerism of maternal origin persists into adult life. J Clin Invest. 1999; 104:41–7. [PubMed: 10393697]
7. Ariga H, Ohto H, Busch MP, Imamura S, Watson R, Reed W, Lee TH. Kinetics of fetal cellular and cell-free DNA in the maternal circulation during and after pregnancy: implications for noninvasive prenatal diagnosis. Transfusion. 2001; 41:1524–30. [PubMed: 11778067]
8. Lo YM, Lo ES, Watson N, Noakes L, Sargent IL, Thilaganathan B, Wainscoat JS. Twoway cell traffic between mother and fetus: biologic and clinical implications. Blood. 1996; 88:4390–5. [PubMed: 8943877]
9. Saadai P, Lee TH, Bautista G, Gonzales KD, Nijagal A, Busch MP, Kim CJ, Romero R, Lee H, Hirose S, Rand L, Miniati D, Farmer DL, MacKenzie TC. Alterations in maternal-fetal cellular trafficking after fetal surgery. J Pediatr Surg. 2012; 47:1089–94. [PubMed: 22703775] • Maternal microchimerism was increased in patients who underwent open fetal surgery for myelomeningocele compared to postnatal repair and term healthy controls. As preterm labor has also been associated with alterations in MFCT, understanding the effects of fetal intervention on this bidirectional passage of cells and whether these changes are causative in the onset of preterm labor may help identify new treatment strategies for pregnancy complications after fetal surgery.
10. Nijagal A, Wegorzewska M, Jarvis E, Le T, Tang Q, MacKenzie TC. Maternal T cells limit engraftment after in utero hematopoietic cell transplantation in mice. J Clin Invest. 2011; 121:582–92. [PubMed: 21245575]
11. Chen CP, Lee MY, Huang JP, Aplin JD, Wu YH, Hu CS, Chen PC, Li H, Hwang SM, Liu SH, Yang YC. Trafficking of multipotent mesenchymal stromal cells from maternal circulation through the placenta involves vascular endothelial growth factor receptor-1 and integrins. Stem Cells. 2008; 26:550–61. [PubMed: 17975225]
12. Holzgreve W, Ghezzi F, Di Naro E, Ganshirt D, Maymon E, Hahn S. Disturbed feto-maternal cell traffic in preeclampsia. Obstet Gynecol. 1998; 91:669–72. [PubMed: 9572208]
13. Bianchi DW, Farina A, Weber W, Delli-Bovi LC, Deriso M, Williams JM, Klinger KW. Significant fetal-maternal hemorrhage after termination of pregnancy: implications for development of fetal cell microchimerism. Am J Obstet Gynecol. 2001; 184:703–6. [PubMed: 11262475]
14. Berry SM, Hassan SS, Russell E, Kukuruga D, Land S, Kaplan J. Association of maternal histocompatibility at class II HLA loci with maternal microchimerism in the fetus. Pediatr Res. 2004; 56:73–8. [PubMed: 15128924]
15. Lambert NC, Evans PC, Hashizumi TL, Maloney S, Gooley T, Furst DE, Nelson JL. Cutting edge: persistent fetal microchimerism in T lymphocytes is associated with HLADQA1*0501: implications in autoimmunity. J Immunol. 2000; 164:5545–8. [PubMed: 10820227]
16. Roy E, Leduc M, Guegan S, Rachdi L, Kluger N, Scharfmann R, Aractingi S, Khosrotehrani K. Specific maternal microchimeric T cells targeting fetal antigens in beta cells predispose to autoimmune diabetes in the child. J Autoimmun. 2011; 36:253–62. [PubMed: 21414756]

17. Mold JE, Michaelsson J, Burt TD, Muench MO, Beckerman KP, Busch MP, Lee TH, Nixon DF, McCune JM. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science. 2008; 322:1562–5. [PubMed: 19056990]

18. Khosrotehrani K, Guegan S, Fraitag S, Oster M, de Prost Y, Bodemer C, Aractingi S. Presence of chimeric maternally derived keratinocytes in cutaneous inflammatory diseases of children: the example of pityriasis lichenoides. J Invest Dermatol. 2006; 126:345–8. [PubMed: 16374466]

19. Khosrotehrani K, Johnson KL, Cha DH, Salomon RN, Bianchi DW. Transfer of fetal cells with multilineage potential to maternal tissue. JAMA. 2004; 292:75–80. [PubMed: 15238593]

20. Stevens AM, Hermes HM, Rutledge JC, Buyon JP, Nelson JL. Myocardial-tissue-specific phenotype of maternal microchimerism in neonatal lupus congenital heart block. Lancet. 2003; 362:1617–23. [PubMed: 14630442]

21. Vanzyl B, Planas R, Ye Y, Foulis A, de Krijger RR, Vives-Pi M, Gillespie KM. Why are levels of maternal microchimerism higher in type 1 diabetes pancreas? Chimerism. 2010; 1:45–50. [PubMed: 21327046]

22. Cirello V, Perrino M, Colombo C, Muzza M, Filopanti M, Vicentini L, Beck-Peccoz P, Fugazzola L. Fetal cell microchimerism in papillary thyroid cancer: studies in peripheral blood and tissues. Int J Cancer. 2010; 126:2874–8. [PubMed: 19856309]

23. Gadi VK, Nelson JL. Fetal microchimerism in women with breast cancer. Cancer Res. 2007; 67:9035–8. [PubMed: 17909006]

24. Opiela SJ, Levy RB, Adkins B. Murine neonates develop vigorous in vivo cytotoxic and Th1/Th2 responses upon exposure to low doses of NIMA-like alloantigens. Blood. 2008; 112:1530–8. [PubMed: 18539903]

25. Dutta P, Molitor-Dart M, Bobadilla JL, Roenneburg DA, Yan Z, Torrealba JR, Burlingham WJ. Microchimerism is strongly correlated with tolerance to noninherited maternal antigens in mice. Blood. 2009; 114:3578–87. [PubMed: 19700665]

26. Rava RP, Srinivasan A, Sehnert AJ, Bianchi DW. Circulating Fetal Cell-Free DNA Fractions Differ in Autosomal Aneuploidies and Monosomy X. Clin Chem. 2013 • Massively parallel sequencing of cell-free DNA in maternal plasma was used to identify pregnancies with aneuploidies including trisomy 13, 18, 21, or Monosomy X. This has clinical implications for noninvasive prenatal testing for aneuploidy.

27. Farina A, Sekizawa A, Sugito Y, Iwasaki M, Jimbo M, Saito H, Okai T. Fetal DNA in maternal plasma as a screening variable for preeclampsia. A preliminary nonparametric analysis of detection rate in low-risk nonsymptomatic patients. Prenat Diagn. 2004; 24:83–6.

28. Jakobsen TR, Clausen FB, Rode L, Dziegiel MH, Tabor A. High levels of fetal DNA are associated with increased risk of spontaneous preterm delivery. Prenat Diagn. 2012; 32:840–5. [PubMed: 22711432]

29. Hirayama M, Azuma E, Ito T, Keida Y, Komada Y. A feasibility study on the prediction of acute graft-vs. host disease before hematopoietic stem cell transplantation based on fetomaternal tolerance. Chimerism. 2013; 4:84–6. • A novel method for predicting a tolerogenic efect of non-inherited maternal antigens using mixed lymphocyte reaction combined with enzyme-linked immunospot (MLR-eLiSpot) assay was applied in human cases. This test could be used to predict patients at risk for developing graft vs host disease after transplanation.

30. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol. 2004; 5:266–71. [PubMed: 14758358]

31. Erlebacher A, Vencato D, Price KA, Zhang D, Glimcher LH. Constraints in antigen presentation severely restrict T cell recognition of the allogeneic fetus. J Clin Invest. 2007; 117:1399–411. [PubMed: 17446933]

32. Nancy P, Tagliani E, Tay CS, Asp P, Levy DE, Erlebacher A. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface. Science. 2012; 336:1317–21. [PubMed: 22679098]

33. Owen RD, Wood HR, Foord AG, Sturgeon P, Baldwin LG. EVIDENCE FOR ACTIVELY ACQUIRED TOLERANCE TO Rh ANTIGENS. Proc Natl Acad Sci U S A. 1954; 40:420–4. [PubMed: 16589498]

34. Farina A, LeShane ES, Romero R, Gomez R, Chaiworapongsa T, Rizzo N, Bianchi DW. High levels of fetal cell-free DNA in maternal serum: a risk factor for spontaneous preterm delivery. Am J Obstet Gynecol. 2005; 193:421–5. [PubMed: 16098864]
35. Leung TN, Zhang J, Lau TK, Hjelm NM, Lo YM. Maternal plasma fetal DNA as a marker for preterm labour. Lancet. 1998; 352:1904–5. [PubMed: 9863792]
36. Al-Mufti R, Lees C, Albaiges G, Hambley H, Nicolaides KH. Fetal cells in maternal blood of pregnancies with severe fetal growth restriction. Hum Reprod. 2000; 15:218–21. [PubMed: 10611215]
37. Jakobsen TR, Clausen FB, Rode L, Dziegiel MH, Tabor A. Identifying mild and severe preeclampsia in asymptomatic pregnant women by levels of cell-free fetal DNA. Transfusion. 2013; 53:1956–64. [PubMed: 23320950] • Fetal cell free DNA measured in the second trimester was used to identify asymptomatic women at risk for developing preeclampsia. Investigators found that women with fetal cell-free fetal DNA levels >90th percentile were 8 times more likley to develop severe preeclampsia. This has implications for early diagnosis of pregnancy complications with the goal of initiating preventative measures or early treatment in order to decrease morbidity from the disease.
38. Stein W, Muller S, Gutensohn K, Emons G, Legler T. Cell-free fetal DNA and adverse outcome in low risk pregnancies. Eur J Obstet Gynecol Reprod Biol. 2013; 166:10–3. [PubMed: 23021026]
39. Fleck S, Bautista G, Keating SM, Lee TH, Keller RL, Moon-Grady AJ, Gonzales K, Norris PJ, Busch MP, Kim CJ, Romero R, Lee H, Miniati D, MacKenzie TC. Fetal production of growth factors and inflammatory mediators predicts pulmonary hypertension in congenital diaphragmatic hernia. Pediatr Res. 2013; 74:290–8. [PubMed: 23770923] • Fetuses with severe CDH were found to have increased levels of maternal microchimerism, and higher levels of inflammatory mediators in cord blood which increased with worsening severity of disease. 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.
40. Dan S, Wang W, Ren J, Li Y, Hu H, Xu Z, Lau TK, Xie J, Zhao W, Huang H, Xie J, Sun L, Zhang X, Wang W, Liao S, Qiang R, Cao J, Zhang Q, Zhou Y, Zhu H, Zhong M, Guo Y, Lin L, Gao Z, Yao H, Zhang H, Zhao L, Jiang F, Chen F, Jiang H, Li S, Li Y, Wang J, Wang J, Duan T, Su Y, Zhang X. Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors. Prenat Diagn. 2012; 32:1225–32. [PubMed: 23138752]
41. Sirichotiyakul S, Charoenkwan P, Sanguansermsri T. Prenatal diagnosis of homozygous alpha-thalassemia-1 by cell-free fetal DNA in maternal plasma. Prenat Diagn. 2012; 32:45–9. [PubMed: 22031039]
42. Wataganara T, Gratacos E, Jani J, Becker J, Lewi L, Sullivan LM, Bianchi DW, Deprest JA. Persistent elevation of cell-free fetal DNA levels in maternal plasma after selective laser coagulation of chorionic plate anastomoses in severe midgestational twin-twin transfusion syndrome. Am J Obstet Gynecol. 2005; 192:604–9. [PubMed: 15696010]
43. Tjoa ML, Jani J, Lewi L, Peter I, Wataganara T, Johnson KL, Bianchi DW, Deprest JA. Circulating cell-free fetal messenger RNA levels after fetoscopic interventions of complicated pregnancies. Am J Obstet Gynecol. 2006; 195:230–5. [PubMed: 16626602]
44. Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N, Tulipan NB, D'Alton ME, Farmer DL, M. Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011; 364:993–1004. [PubMed: 21306277]
45. Harrison MR, Keller RL, Hawgood SB, Kitterman JA, Sandberg PL, Farmer DL, Lee H, Filly RA, Farrell JA, Albanese CT. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. N Engl J Med. 2003; 349:1916–24. [PubMed: 14614166]
46. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med. 2004; 351:136–44. [PubMed: 15238624]

47. Wegorzewska M, Nijagal A, Wong R, Le T, Lescano N, Tang Q, MacKenzie TC. Fetal intervention increases maternal T cell awareness of the foreign conceptus and can lead to immune-mediated fetal demise. The Journal of Immunology. in press.
48. Khashan AS, Kenny LC, Laursen TM, Mahmood U, Mortensen PB, Henriksen TB, O'Donoghue K. Pregnancy and the risk of autoimmune disease. PLoS One. 2011; 6:e19658. [PubMed: 21611120]
49. Artlett CM, Smith JB, Jimenez SA. Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. N Engl J Med. 1998; 338:1186–91. [PubMed: 9554859]
50. Klintschar M, Immel UD, Kehlen A, Schwaiger P, Mustafa T, Mannweiler S, Regauer S, Kleiber M, Hoang-Vu C. Fetal microchimerism in Hashimoto's thyroiditis: a quantitative approach. Eur J Endocrinol. 2006; 154:237–41. [PubMed: 16452536]
51. Renne C, Ramos Lopez E, Steimle-Grauer SA, Ziolkowski P, Pani MA, Luther C, Holzer K, Encke A, Wahl RA, Bechstein WO, Usadel KH, Hansmann ML, Badenhoop K. Thyroid fetal male microchimerisms in mothers with thyroid disorders: presence of Y-chromosomal immunofluorescence in thyroid-infiltrating lymphocytes is more prevalent in Hashimoto's thyroiditis and Graves' disease than in follicular adenomas. J Clin Endocrinol Metab. 2004; 89:5810–4. [PubMed: 15531546]
52. Evans PC, Lambert N, Maloney S, Furst DE, Moore JM, Nelson JL. Long-term fetal microchimerism in peripheral blood mononuclear cell subsets in healthy women and women with scleroderma. Blood. 1999; 93:2033–7. [PubMed: 10068676]
53. Scaletti C, Vultaggio A, Bonifacio S, Emmi L, Torricelli F, Maggi E, Romagnani S, Piccinni MP. Th2-oriented profile of male offspring T cells present in women with systemic sclerosis and reactive with maternal major histocompatibility complex antigens. Arthritis Rheum. 2002; 46:445–50. [PubMed: 11840447]
54. Khosrotehrani K, Leduc M, Bachy V, Nguyen Huu S, Oster M, Abbas A, Uzan S, Aractingi S. Pregnancy allows the transfer and differentiation of fetal lymphoid progenitors into functional T and B cells in mothers. J Immunol. 2008; 180:889–97. [PubMed: 18178828]
55. Nguyen Huu S, Khosrotehrani K, Oster M, Moguelet P, Espie MJ, Aractingi S. Early phase of maternal skin carcinogenesis recruits long-term engrafted fetal cells. Int J Cancer. 2008; 123:2512–7. [PubMed: 18792101]
56. Zeng XX, Tan KH, Yeo A, Sasajala P, Tan X, Xiao ZC, Dawe G, Udolph G. Pregnancy-associated progenitor cells differentiate and mature into neurons in the maternal brain. Stem Cells Dev. 2010; 19:1819–30. [PubMed: 20707697]
57. Khosrotehrani K, Reyes RR, Johnson KL, Freeman RB, Salomon RN, Peter I, Stroh H, Guegan S, Bianchi DW. Fetal cells participate over time in the response to specific types of murine maternal hepatic injury. Hum Reprod. 2007; 22:654–61. [PubMed: 17074776]
58. Wang Y, Iwatani H, Ito T, Horimoto N, Yamato M, Matsui I, Imai E, Hori M. Fetal cells in mother rats contribute to the remodeling of liver and kidney after injury. Biochem Biophys Res Commun. 2004; 325:961–7. [PubMed: 15541383]
59. Sunami R, Komuro M, Yuminamochi T, Hoshi K, Hirata S. Fetal cell microchimerism develops through the migration of fetus-derived cells to the maternal organs early after implantation. J Reprod Immunol. 2010; 84:117–23. [PubMed: 20116109]
60. Seppanen E, Fisk NM, Khosrotehrani K. Pregnancy-acquired fetal progenitor cells. J Reprod Immunol. 2013; 97:27–35. [PubMed: 23432869]
61. Nelson JL, Gillespie KM, Lambert NC, Stevens AM, Loubiere LS, Rutledge JC, Leisenring WM, Erickson TD, Yan Z, Mullarkey ME, Boespflug ND, Bingley PJ, Gale EA. Maternal microchimerism in peripheral blood in type 1 diabetes and pancreatic islet beta cell microchimerism. Proc Natl Acad Sci U S A. 2007; 104:1637–42. [PubMed: 17244711]
62. Reed AM, Picornell YJ, Harwood A, Kredich DW. Chimerism in children with juvenile dermatomyositis. Lancet. 2000; 356:2156–7. [PubMed: 11191546]
63. Kobayashi H, Tamatani T, Tamura T, Kusafuka J, Yamataka A, Lane GJ, Kawasaki S, Ishizaki Y, Mizuta K, Kawarasaki H, Gittes GK. Maternal microchimerism in biliary atresia. J Pediatr Surg. 2007; 42:987–91. discussion 991. [PubMed: 17560207]

64. Kiefer AS, Lang TR, Hein MS, McNallan KT, Moir CR, Reed AM. Maternal microchimerism in Hirschsprung's disease. Am J Perinatol. 2012; 29:71–8. [PubMed: 22105432] • Investigators found increased numbers of maternal chimeric cells with an inflammtory phenotype in bowel of patients with Hirschsprung's disease and hypothesize that these cells may contribute to destruction of enteric neurons in this disease.

65. Lopez-Guisa JM, Howsmon R, Munro A, Blair KM, Fisher E, Hermes H, Zager R, Stevens AM. Chimeric maternal cells in offspring do not respond to renal injury, inflammatory or repair signals. Chimerism. 2011; 2:42–49. [PubMed: 21912718]

66. Billingham RE, Brent L, Medawar PB. Actively acquired tolerance of foreign cells. Nature. 1953; 172:603–6. [PubMed: 13099277]

67. Vernochet C, Caucheteux SM, Gendron MC, Wantyghem J, Kanellopoulos-Langevin C. Affinity-dependent alterations of mouse B cell development by noninherited maternal antigen. Biol Reprod. 2005; 72:460–9. [PubMed: 15469995]

68. Molitor-Dart ML, Andrassy J, Kwun J, Kayaoglu HA, Roenneburg DA, Haynes LD, Torrealba JR, Bobadilla JL, Sollinger HW, Knechtle SJ, Burlingham WJ. Developmental exposure to noninherited maternal antigens induces CD4+ T regulatory cells: relevance to mechanism of heart allograft tolerance. J Immunol. 2007; 179:6749–61. [PubMed: 17982065]

69. Stern M, Ruggeri L, Mancusi A, Bernardo ME, de Angelis C, Bucher C, Locatelli F, Aversa F, Velardi A. Survival after T cell-depleted haploidentical stem cell transplantation is improved using the mother as donor. Blood. 2008; 112:2990–5. [PubMed: 18492955]

70. Nijagal A, Fleck S, Hills NK, Feng S, Tang Q, Kang SM, Rosenthal P, MacKenzie TC. Decreased risk of graft failure with maternal liver transplantation in patients with biliary atresia. Am J Transplant. 2012; 12:409–19. [PubMed: 22221561] • Authors investigated 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. 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.

71. Burlingham WJ, Grailer AP, Heisey DM, Claas FH, Norman D, Mohanakumar T, Brennan DC, de Fijter H, van Gelder T, Pirsch JD, Sollinger HW, Bean MA. The effect of tolerance to noninherited maternal HLA antigens on the survival of renal transplants from sibling donors. N Engl J Med. 1998; 339:1657–64. [PubMed: 9834302]

72. van Rood JJ, Loberiza FR Jr. Zhang MJ, Oudshoorn M, Claas F, Cairo MS, Champlin RE, Gale RP, Ringden O, Hows JM, Horowitz MH. Effect of tolerance to noninherited maternal antigens on the occurrence of graft-versus-host disease after bone marrow transplantation from a parent or an HLA-haploidentical sibling. Blood. 2002; 99:1572–7. [PubMed: 11861270]

73. Opelz G. Analysis of the "NIMA effect" in renal transplantation. Collaborative Transplant Study. Clin Transpl. 1990:63–7. [PubMed: 2103176]

74. Panajotopoulos N, Ianhez LE, Neumann J, Sabbaga E, Kalil J. Immunological tolerance in human transplantation. The possible existence of a maternal effect. Transplantation. 1990; 50:443–5.

75. Okumura H, Yamaguchi M, Kotani T, Sugimori N, Sugimori C, Ozaki J, Kondo Y, Yamazaki H, Chuhjo T, Takami A, Ueda M, Ohtake S, Nakao S. Graft rejection and hyperacute graft-versus-host disease in stem cell transplantation from non-inherited maternal-antigen-complementary HLA-mismatched siblings. Eur J Haematol. 2007; 78:157–60. [PubMed: 17313562]

76. Muller SM, Ege M, Pottharst A, Schulz AS, Schwarz K, Friedrich W. Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: a study of 121 patients. Blood. 2001; 98:1847–51. [PubMed: 11535520]

77. Araki M, Hirayama M, Azuma E, Kumamoto T, Iwamoto S, Toyoda H, Ito M, Amano K, Komada Y. Prediction of reactivity to noninherited maternal antigen in MHC-mismatched, minor histocompatibility antigen-matched stem cell transplantation in a mouse model. J Immunol. 2010; 185:7739–45. [PubMed: 21078914]

78. Gadi VK. Fetal microchimerism in breast from women with and without breast cancer. Breast Cancer Res Treat. 2010; 121:241–4. [PubMed: 19768535]

79. O'Donoghue K, Sultan HA, Al-Allaf FA, Anderson JR, Wyatt-Ashmead J, Fisk NM. Microchimeric fetal cells cluster at sites of tissue injury in lung decades after pregnancy. Reprod Biomed Online. 2008; 16:382–90. [PubMed: 18339261]

80. Dubernard G, Aractingi S, Oster M, Rouzier R, Mathieu MC, Uzan S, Khosrotehrani K. Breast cancer stroma frequently recruits fetal derived cells during pregnancy. Breast Cancer Res. 2008; 10:R14. [PubMed: 18271969]

81. Cha D, Khosrotehrani K, Kim Y, Stroh H, Bianchi DW, Johnson KL. Cervical cancer and microchimerism. Obstet Gynecol. 2003; 102:774–81. [PubMed: 14551008]

82. Nguyen Huu S, Oster M, Avril MF, Boitier F, Mortier L, Richard MA, Kerob D, Maubec E, Souteyrand P, Moguelet P, Khosrotehrani K, Aractingi S. Fetal microchimeric cells participate in tumour angiogenesis in melanomas occurring during pregnancy. Am J Pathol. 2009; 174:630–7. [PubMed: 19147820]

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.