

# Chapter 2

## Feto-Maternal Cell Trafficking and Labor

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### Introduction

Maternal-fetal cellular trafficking (MFCT) is a well described phenomenon during pregnancy in which maternal cells migrate into the fetus and fetal cells migrate into the mother [1–5]. The specific mechanisms leading to such trafficking and its life-long consequences have fascinated scientists for decades and are still actively being investigated. For example, several groups have demonstrated an association between MFCT and both transplant tolerance and autoimmune disorders. Additionally, pregnancy complications have been shown to be associated with increased trafficking between the mother and fetus which are listed in Table 2.1. Innovative strategies to detect microchimerism have reinvigorated the interest in the field and will be outlined in this chapter. In this chapter, we will review implications of microchimerism, particularly as it relates to long-term consequences and pregnancy complications. Finally, we will explore the effects congenital abnormalities and fetal surgery have on maternal-fetal cellular trafficking.

### *Mechanisms of Cellular Trafficking*

Maternal microchimerism (MMc) refers to the presence of maternal cells within the fetus. This has been demonstrated by the presence of cells of maternal origin within the liver, spleen, thymus, thyroid, and skin of neonates [6], indicating the placenta

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**Table 2.1** Conditions associated with increased maternal fetal trafficking

Autoimmune processes
Diabetes mellitus-type I
Neonatal lupus congenital heart block
Multiple sclerosis
Hirschsprung’s disease
Autoimmune thyroiditis
Primary biliary cirrhosis
Systemic lupus erythematous
Pregnancy complication
Preeclampsia
Intrauterine fetal growth restriction
Preterm labor
Iatrogenic
Open fetal intervention
Laparoscopic fetal intervention
Congenital anomalies
Aneuploidy
Congenital diaphragmatic hernia

is not a perfect barrier as previously imagined. As MMc has been found in various organs well into adulthood, cells of maternal origin must possess the capacity to self renew [5]. Some postulate that MMc results from multipotent mesenchymal stromal cell migration across the placenta, which is governed by vascular endothelial growth factor A (VEGF-A) [7], a potent stimulator of hematopoietic stem cell migration [8]. In fact, the concentration of VEGF-A is higher in the fetal circulation compared to the maternal, which likely promotes its transplacental migration [9]. Additionally, in a mouse model, we demonstrated high levels of MMc in circulation at mid-gestation which decreases over time, such that it is undetectable at birth [10]. In this model, inflammatory stimuli during pregnancy, such as fetal intervention, led to changes in the number and type of cells that traffic, including maternal T, which usually does not cross over at baseline [10]. These results suggest that alterations in trafficking are not a result of general leakiness at the maternal-fetal interface, which is further supported by experiments showing that chemokine gene silencing limits T cell trafficking [11].

Fetal microchimerism (FMc), on the other hand, refers to the presence of fetal cells within maternal tissues and blood and can also persist for decades after delivery [2]. Similar to MMc, fetal cells have been found in multiple organs including the liver, kidney, heart, and bone marrow [12, 13], though the exact mechanism by which fetal cells migrate into the maternal circulation remains elusive. Fetal cell-free DNA (fDNA) has also been observed within the maternal circulation, which is released from the placental trophoblast layer lining the maternal-fetal interphase. Apoptosis and cell necrosis at this interphase leads to the release of fDNA into the maternal circulation [14, 15], the implications of which are actively being explored.

## ***Strategies to Detect Maternal-Fetal Cellular Trafficking***

Fetal microchimerism was first observed in 1893 when fetal trophoblast cells were observed in a lung specimen from a woman who suffered from eclampsia [16]. Several decades later, in 1963, maternal cells were identified in a cord blood sample using fluorescently labeled maternal leukocytes [17]. Since then, our understanding of MFCT has improved in large part from advances in techniques to distinguish mixed populations of cells.

In recent years, investigators have applied the common technique of gene amplification with polymerase chain reaction (PCR) to identify microchimerism in the context of pregnancy. It has become a useful tool to detect and quantify fetal DNA within the maternal circulation [3, 5, 18, 19]. This method is in large part restricted to gender mismatches in which primers to loci on the Y chromosome are used to distinguish fetal from maternal DNA [18, 20]. Using PCR amplification, fetal DNA can be detected circulating within the maternal serum in 80 % of normal pregnancies [21] and has been isolated as early as 4 weeks postconception [22, 23].

An alternative strategy is to compare non-shared HLA-DR or Insertion-Deletion alleles between the fetus and mother. To compare these allelic differences between cell populations, paired maternal and cord blood is analyzed using quantitative real-time polymerase chain reaction (qRT-PCR). Non-shared alleles between the two cell populations are termed informative alleles as they provide a means to distinguish one set of genetic material from another. In trauma patients who were transfused multiple units of allogeneic blood, Lee and colleagues compared 12 HLA-DR and 12 Insertion-Deletion alleles [24]. From this study, they found that at least 1 informative allele could be determined in 99.5 % of patients. Applied to MFCT, this strategy has been used to quantify the number of fetal cells in the maternal circulation (or vice versa) [25]. While informative, this strategy requires examination of both maternal and fetal blood and is therefore usually only applicable after birth.

MFCT is a particularly critical field of investigation as it has the potential to improve noninvasive detection of fetal anomalies. Currently, clinicians rely on second trimester sonographic imaging to identify fetuses at risk for aneuploidy and congenital anomalies. Positive screening is followed by invasive procedures such as amniocentesis and chorionic villus sampling for diagnosis. Despite a diagnostic accuracy of 98–99 % [26], these procedures carry a risk to both the fetus and mother [27]. Prenatal diagnosis that does not disrupt the maternal-fetal interface may be accomplished by identifying and analyzing fetal DNA within the maternal circulation. Several European countries including the Netherlands, Sweden, and Denmark have already implemented this strategy to determine fetal gender and Rhesus D status [28].

In mice, it is possible to evaluate the number and types of cells that traffic using flow cytometry [10], but this is not yet possible in humans unless the HLA type is known, [29] and antibodies to such cell markers exist. Alternatively, cells may be sorted into groups (T cells, B cells, etc.) prior to PCR sequencing, a technique that

has not yet been explored in pregnant woman. Currently, probing for fetal DNA is more feasible than isolating individual cells as the quantity of fetal DNA is much more than the number of fetal cells within the maternally circulating [15, 30]. Overcoming this barrier may help identify which cell populations are more influential during trafficking and whether particular populations are more prevalent in the setting of pregnancy complications.

### ***Tolerogenic and Immunogenic Consequences of Microchimerism***

Microchimerism can lead to a tolerogenic or immunogenic state. The presence of maternal cells in the fetus may play a role in fetal immune education and has been found to induce regulatory T cells to maternal antigen, which suppress the fetal immune response to the mother [29]. Tolerance to non-inherited maternal antigens has implications for transplantation tolerance later in life. For example, patients with biliary atresia, who have increased levels of MMc, have improved graft survival when they receive a maternal liver transplant compared to a paternal graft [31]. In acute leukemia, patient survival is increased and graft-versus-host disease is reduced when transplantation is with maternal stem cells [32, 33].

Conversely, microchimerism has been associated with autoimmune diseases in both mothers and children. Increased levels of MMc have been observed in childhood diseases, including diabetes mellitus-type I, neonatal lupus congenital heart block, multiple sclerosis [34], and Hirschsprung's disease [35]. Autoimmune diseases associated with FMc include systemic sclerosis in which fetal cells have been detected within both peripheral blood and skin lesions [36, 37], autoimmune thyroiditis, primary biliary cirrhosis, and systemic lupus erythematosus [38]. It is important to note that a causal relationship has not been established and the association with microchimerism may indicate that microchimeric cells proliferate in response to the disease process.

### ***Pregnancy Complications Associated with Cellular Trafficking***

Several independent investigators have found an association between increased FMc and pregnancy complications, including preeclampsia, intrauterine growth restriction (IUGR), and preterm labor [19, 39–46]. These observations may reflect a maternal immune response to fetal antigens, or may simply be a marker of the increased inflammatory milieu in the host. Understanding the mechanisms that promote increased cellular trafficking may lead to therapies to offset the development of preterm labor and other pregnancy complications.

## Preeclampsia

Preeclampsia is a significant cause of both fetal and maternal mortality during pregnancy [47] and is characterized by maternal hypertension and proteinuria after the 20th week of gestation [48]. The incidence ranges from 2 to 7 % in normal nulliparous females [49, 50], and increases to 18 % in those who have previously had preeclampsia [51]. Complications include placental abruption, renal failure, HELLP syndrome and even death.

The pathologic processes leading to preeclampsia are thought to occur at the location of the placenta, as histological examination of placentas in preeclamptic patients frequently shows infarction and sclerotic arterioles with poor remodeling of the uterine spiral arteries [52]. In addition, hypoxic changes and oxidative stress at the fetoplacental interface may lead to increased apoptosis and DNA released into the maternal circulation [53–57], particularly from the syncytiotrophoblast layer [58, 59].

Multiple groups have proposed an association between FMc and preeclampsia [60–66]. While some have found elevated level of maternally circulating fetal erythroblasts and placental syncytiotrophoblast microvesicles [67, 68], most studies have focused on increased levels of fDNA within the maternal circulation. Not only are levels elevated at delivery [64], but increased levels have been detected circulating within the maternal serum as early as the first trimester [65, 69]. Illanes and colleagues found that the quantity of maternal circulating fDNA measured between 11 and 14 weeks gestation directly correlated with the likelihood of developing preeclampsia [56], though other investigators have not found this association [70]. These conflicting observations warrant further investigation to not only standardize techniques but understand the process leading to fDNA release and how it may relate to the development of preeclampsia.

Maternal sampling for fDNA has been considered as a screening tool to predict preeclampsia. Preliminary results by Farina and colleagues found that increased levels of fDNA may be predictive in asymptomatic low risk patients during the second trimester [53]. They found that maternal serum levels of fDNA were 2.4-fold higher in mothers who developed preeclampsia compared to gestational age matched controls. As these are preliminary results, further studies are needed to determine the sensitivity of the assay as well as a cost analysis profile. If second trimester fDNA levels prove to be a useful screening tool, efforts may be focused towards monitoring patients at high-risk for developing preeclampsia or other complications associated with preeclampsia such as placental abruption, renal failure, and HELLP syndrome.

## Intrauterine Fetal Growth Restriction

Intrauterine growth restriction is another complication of pregnancy effecting 3–7 % of births worldwide. It is defined by fetal weight below the 10th percentile for a given gestational age and may result in respiratory distress syndrome,

intraventricular hemorrhage, necrotizing enterocolitis, and death. There are various underlying causes including both fetal (congenital abnormalities, chromosomal anomalies, and infection) and maternal (alcohol consumption, smoking, vascular disease, and malnutrition) origins. Like preeclampsia, IUGR may develop from abnormal placentation involving aberrant spiral artery development [57] with increased trophoblast cell apoptosis and necrosis as well as impaired oxygen and nutrient delivery to the fetus [71, 72].

While studies examining FMc in IUGR are limited and conflicting, some groups have found increased fetal erythroblasts and fDNA in maternal serum in cases of IUGR [39, 73], while others have not, despite using similar methods and patient populations [74, 75]. Conflicting results may be secondary to the various etiologies of IUGR. Perhaps maternal causes of IUGR, such as preeclampsia and vascular disease, result in abnormal placental development and trophoblast cell death, while fetal causes, such as aneuploidy and congenital abnormalities, do not significantly impact the placenta.

## **Preterm Labor**

Spontaneous preterm labor occurs in approximately 12 % of births and is the converging end-product of various pathological processes [76]. Causes include intra-uterine infections [77], placental vascular insufficiency [78, 79], uterine over-distention [80], and a shortened cervix [81, 82], resulting in the release of several cytokines and prostaglandins [83]. These inflammatory mediators promote the release of uterotonins which induce uterine contractions and proteases which result in cervical changes, culminating in preterm delivery [83].

Several groups have proposed an association between preterm labor and alterations in cellular trafficking [19, 42, 44]. For example, Leung and colleagues have implicated fDNA as a marker for preterm labor near the time of delivery [44]. The molecular pathway leading to labor in this population is unclear and further studies correlating cytokine and prostaglandin levels among patients with increased FMc may shed light into a more specific pathway. Although it is not clear whether these alterations are causally related to preterm birth, it has been suggested that increased fetal cell trafficking triggers the maternal immune response, which can induce labor [19].

Investigators have also directly explored the role of the maternal immune system in preterm labor. For example, Lee and colleagues demonstrated that women with circulating antibodies against fetal HLA class I or class II antigen, measured during the second trimester, were at increased risk for developing spontaneous preterm labor [84]. We recently found that MMc is also increased in mice undergoing preterm delivery as a result of LPS injection, with a particular increase in T cell trafficking if the fetuses are allogeneic to the mother [85]. Furthermore, we have seen that maternal T cells cause demise of allogeneic fetuses after fetal intervention, indicating the role of the maternal adaptive immune system in this pregnancy complication [86]. Taken together, preterm labor is a complex process that likely results

from multiple mechanisms, including increases in the quantity of FMc and, possibly, an immune response between the mother and the fetus.

## Fetal Surgery

Open fetal surgery was pioneered over 30 years ago and has since evolved with the advent of minimally invasive techniques. Fetal surgery has been shown to improve survival and long-term outcomes in disease processes such as twin-to-twin transfusion syndrome, myelomeningocele, and congenital diaphragmatic hernias [87–90]. However, fetal surgery often results in preterm delivery, which abrogates some of the benefits of the procedure. For example, a recent multi-center randomized control trial comparing the prenatal repair of myelomeningocele to standard postnatal repair, found that prenatal repair led to a reduced need for postnatal ventriculoperitoneal shunting as well as improved long term motor function and mental development [87] but frequently results in preterm delivery with a mean gestational age at delivery of 34.1 weeks compared to 37.3 in the standard postnatal control group.

Universal acceptance of fetal surgery for non-lethal congenital diseases has been hampered by the risk of pregnancy complications. These risks include preterm premature rupture of the membrane, placental abruption, uterine rupture, chorioamniotic separation, and preterm labor [87]. In fact, preterm delivery prior to 37 weeks gestation, even following minimally invasive procedures, exceeds 80 % [91, 92]. Since the latency period between the procedure and delivery typically ranges from 4 to 7 weeks [91, 92], it is possible that downstream events rather than the insult of the surgery itself leads to preterm labor. This observation led multiple groups to explore the effect of fetal intervention on MFCT [10, 25, 93, 94]. In a mouse model of fetal intervention, we reported that maternal cells traffic into the fetal circulation after fetal stem cell transplantation, with a particular increase in trafficking T cells in this context [10]. These cells have a functional consequence, in that they limit the stem cell engraftment into the fetus [10]. We have reported a similar findings in patients undergoing fetal surgery for the correction of myelomeningoceles: using PCR to genotype non-shared HLA-DR alleles between mother and fetus, we demonstrated increased trafficking of maternal cells within the fetal circulation following open fetal surgery for myelomeningocele repair [25]. These findings suggest that there is either increased trafficking of cells after fetal intervention or increased proliferation of trafficked cells in the inflammatory environment after fetal surgery. Interestingly, there was no increase in MMc if fetal intervention was performed at the time of birth, indicating that changes in microchimerism take some time to develop.

Increase in FMc during fetal surgery has been demonstrated in some studies, [94] but not others [25]. Following laser coagulation for twin-to-twin transfusion syndrome [94], increased fDNA was found with longer operative times, increased number of vessels ablated and demise of 1 twin [94]. However, a study measuring circulating mRNA following fetal intervention did not demonstrate a difference between those who underwent fetal intervention and age matched controls [93]. The

differences observed may reflect the challenge with detecting a very small pool of cells or genomic material within a large maternal blood volume. It is important to note that no study has proven a causal link between altered microchimerism and pregnancy complications. However, understanding the role of altered MFCT in the context of preterm labor and pregnancy complications may lead to treatments to abrogate such consequences.

### **Congenital Anomalies**

Maternal-fetal cellular trafficking may also be influenced by aneuploidy and congenital anomalies. For example, levels of FMc are significantly higher in mothers carrying fetuses with trisomy 21 [95] and lower in those with trisomy 18, 13, or monosomy X [96]. In a study analyzing cord blood samples from infants with a congenital diaphragmatic hernia, we found an increased number of maternal cells in the fetal circulation at the time of birth which increased with disease severity [97]. These findings suggest that the presence of fetal anomalies may influence trafficking, possibly secondary to an inflammatory response from fetal distress.

### **Conclusion**

In summary, there is striking evidence to suggest that pregnancy complications are associated with alterations in fetal microchimerism. The mechanisms leading to increased levels of trafficking remain a fascinating unanswered question in the field. Fetal and maternal inflammation and immune responses are likely critical players in this process and in the onset of pregnancy complications. New technologies will ideally unveil mechanistic pathways affected by MFCT and may provide targets for therapies to mitigate pregnancy complications. Beyond pregnancy, long-lived microchimerism may have additional consequences for tolerance and immunity in both the mother and her children.

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