

Emerging Questions in Materno-Fetal Microchimerism

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Abstract

Materno-fetal microchimerism is a common, life-long chimeric state first established by the exchange of small numbers of cells between the mother and the fetus during pregnancy. This apparently trivial phenomenon is now attracting attention due to its unexpected and profound implications in the immune system. For example, is the placenta really an immunological barrier? How do we balance the internal environment despite the existence of an immunological non-self? In this review, I will discuss the pros and cons of materno-fetal microchimerism for our immune system (e.g., tolerance, materno-fetal immune disease, tissue regeneration, etc.) and the unanswered, puzzling aspects of microchimerism from the immunological point of view.

We are all chimeras consisting of self and non-self cells

All of the billions of cells in our body come from a single fertilized egg. However, recent studies have revealed that cells from other people reside in our bodies. These are the cells of our immediate family members, our mother, twins, or our children in the case of parous women, exchanged during pregnancy. Surprisingly these cells are reported to last for more than a decade after birth [1]. Where are they located in our bodies? Various body organs and parts are known to possess non-self cells, including the skeletal muscles; heart; skin; lung; thyroid gland; digestive tube; liver; and even immunity-related organs such as the thymus, spleen, lymph nodes, peripheral blood, and bone marrow [2,3]. Even mouse brains have been found to carry the cells of their children [4-6].

A body consisting of cells from 2 or more genetically distinct populations is called a chimera. Since the number of cells in pregnancy-related chimera is relatively small (about 1 in 1000~10,000), the phenomenon is called "microchimerism" [7] (Figure 1). Meanwhile, despite their low frequency among our own cells, all people are considered to be in a microchimeric state, and parous women are considered to have cells of more than 3 different origins: their own cells, their mother's cells, and those of their children [2].

Why have these cells come under the spotlight in the field of immunology? This review will describe recent advances and emerging questions in this field.

How do microchimeric cells pass through the placenta?

Let us start with how microchimerism occurs. Although the precise timing of cell transfer remains to be clarified [8], microchimerism is established during pregnancy [9,10]. A major question is how these maternal and fetal cells migrated from one body to the other. During pregnancy, the risk of immunological conflict (especially an attack by the maternal immune system) is avoided by the placenta, which filters various substances including immune cells. However, based on recent reports, the concept of the placenta as an immunological barrier is now being challenged. That is, fetal and maternal cells cross the placenta and engraft with each other, resulting in microchimerism [4,11].

How do microchimeric cells become accepted by the host's immune system?

How do host immune systems live with these non-self cells? Although the precise mechanism is still under investigation [4,12,13], the condition of the mother's and infant's immune systems seem to affect the number of cells that are exchanged. One factor is the soundness of the immune systems of the mother and the fetus. For example, in infants with severe combined immunodeficiency disease (SCID), more cells migrate from the mother into the fetus [14]. Similar

results were reported in a mouse model. When the mother mouse was immunologically deficient (RAG^{-/-}), the mother accepted more fetal cells [15]. These findings show that absence of a functional immune system results in the exchange of a greater number of cells compared to when the immune systems are healthy. Another factor that affects the degree of microchimerism is the immunological compatibility between the mother and the fetus. Based on reports from Berry *et al.*, materno-fetal major histocompatibility complex (MHC) compatibility seems to favor acceptance of maternal cells [16], albeit this trend was not reproduced in a certain mouse model [17].

Together, these findings suggest that microchimeric cells are not cells that accidentally crossed the placenta, but are proportions of

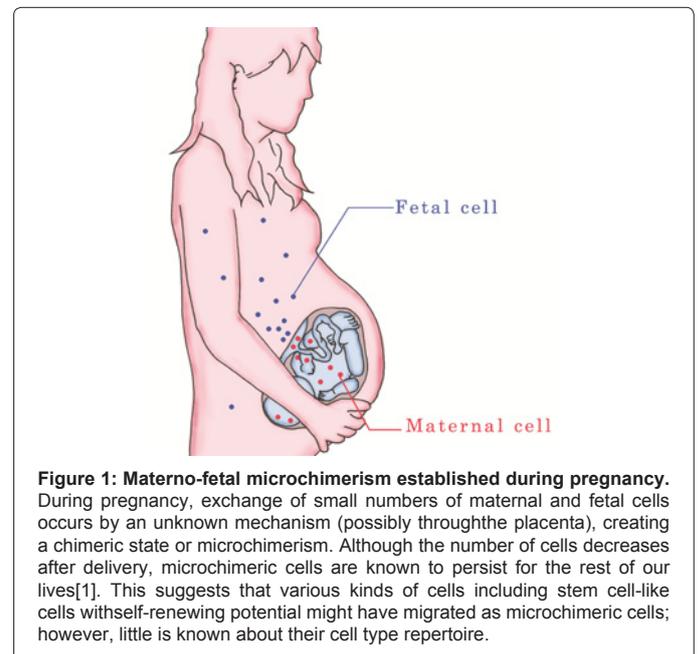


Figure 1: Materno-fetal microchimerism established during pregnancy. During pregnancy, exchange of small numbers of maternal and fetal cells occurs by an unknown mechanism (possibly through the placenta), creating a chimeric state or microchimerism. Although the number of cells decreases after delivery, microchimeric cells are known to persist for the rest of our lives [1]. This suggests that various kinds of cells including stem cell-like cells with self-renewing potential might have migrated as microchimeric cells; however, little is known about their cell type repertoire.

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the cells that migrated through the placenta and further survived the selective pressure of the host (maternal or fetal) immune system. This in turn provides us a new understanding of the placenta: rather than a strict cellular barrier, it can be regarded as a filter that allows a certain amount of cells to pass through.

What kinds of cells migrate through the placenta?

A puzzling aspect of microchimerism is that it can last for decades after pregnancy [1]. Some researchers have suggested that self-reproducing, undifferentiated stem cells might be involved [2,18]; these cells are called pregnancy-associated progenitor cells (PAPCs) [19]. In accordance with this, recent mouse studies revealed that PAPCs can differentiate into various cell types including neurons, astrocytes, oligodendrocytes, and macrophage-like cells [5]. PAPCs are expected to reside within certain stem cell niches to survive long periods, but the details of this hypothesis are still under investigation [20,21]. Apart from PAPCs, it is already known that immunologically mature maternal cells such as CD4+ and CD8+ cells are also detected in the diseased tissue of certain congenital diseases. This dramatizes once again the issue of microchimerism: how can microchimeric cells stay calm in host tissues even when they are immunologically functional?

How can non-self microchimeric cells colonize in the host?

After entering the host (mother or fetus), how can these cells colonize without being eliminated by the host immune system? In mice, microchimeric cells reside at an immunologically privileged site, the brain [5], but cells found in other organs cannot be explained by this idea. In late 2008, Mold *et al.* [22] published a paper in *Science*, showing that the fetal immune system is highly tolerance-inducible against alloantigens. Using 18–22 gestational week fetus-derived cells, they showed that the fetal environment is prone to induce regulatory T cells and selective low reactivity to maternal antigens [22]. In brief, it appears that the human fetus is genetically designed to accept or tolerate microchimeric maternal cells. And what is the situation in the mother? As in the fetus, tolerance also takes place on the maternal side, possibly lasting for long after the pregnancy. This idea was supported by an epidemiological study: during bone marrow grafting, maternal grafts had a lower occurrence of graft-versus-host (GvHD) disease in comparison to paternal grafts [23,24]. Complementary knowledge further supports the existence of tolerance in the mother. Experimentally reducing regulatory T cells in the circulation of pregnant mice leads to extensive influx of maternal immune cells into the fetus, causing lethal rejection of the fetus [25]. Immunological tolerance for each other is indeed induced in the mother and the fetus, supporting the view that tolerance permits the long survival of microchimeric cells.

Are they just leaky cells? Or do these cells have a physiological role?

In the field of obstetrics, microchimerism is drawing attention as a noninvasive, antenatal diagnostic tool, since the fetal cells can easily be obtained from maternal peripheral blood [2,44]. However, this is only an artificial role; what are the physiological roles? Recent studies reporting roles in tissue regeneration are accumulating. One case is from a parous woman with hepatitis C who achieved remission despite the fact that she had to interrupt treatment. Biopsy examination revealed that her liver contained thousands of XY cells, and these cells were morphologically indistinguishable from hepatocytes [45]. Another case study by Nelson *et al.* in 2007 reported a spleen from a type I diabetic male patient that contained XX cells that were expressing insulin peptides [39]. The patient did not have a history of organ transplantation, suggesting that these cells originated from his mother.

These studies seem to support the regenerative roles of microchimeric cells; however, is it possible that these cells were just bystanders that happened to encounter regenerating tissues? Several studies in mice have clearly shown that this is unlikely, and further provided evidence that microchimeric cells are actively accumulating at regenerating tissues [5,46]. Importantly, experimentally damaged brain regions had 6 times more fetal cells than uninjured regions [5], and the frequency of fetal cells was up to 10 in 1000, suggesting that these cells are actively involved in tissue regeneration. To put it plainly, mother and fetus each facilitate the health of the other.

Another advantage of materno-fetal microchimerism is the graft-versus-tumor (GvT) effect [47]. Supporting evidence includes the fact that patients with breast cancer are reported to have lower numbers of fetal microchimeric cells (fMCs), and parous women have a lower occurrence of malignant cancer [48,49]. This circumstantial evidence, however, could be due to the changes in hormonal balance associated with pregnancy, and are rather indirect effects of microchimerism. Meanwhile, activated haploidentical peripheral blood stem cell transplantation donated by parents or children to patients with advanced-stage chemotherapy-refractory solid tumors lends support to the idea. Patients who have a higher number of microchimeric cells before PBSC transplantation have longer survival times and better therapeutic response [50]. These studies might indicate the high GvT potential of microchimeric cells, which are immunologically non-self. Further studies are needed to clarify the advantageous roles of microchimeric cells.

Can immunological conflict be caused by microchimerism?

Given that microchimeric cells have a potential to attack cancer cells in the host, why do they not attack normal cells in the host? Several reports suggest that this indeed occurs in certain conditions. Infants with SCID have a larger number of maternal cells in their bodies. In fact, about 16% of these infants have severe GvHD-like symptoms in their skin and liver [14], indicating that maternal cells do have the potential to attack fetal cells.

Furthermore, autoimmune diseases like scleroderma are associated with larger numbers of fetal microchimeric cells compared to healthy individuals, and accumulating reports are now challenging the understanding of these diseases as fundamentally autoimmune in nature [2,19]. This is also the case in diseases in children. Some of the inflammatory diseases such as juvenile dermatomyositis and biliary atresia (BA) are associated with larger numbers of maternal microchimeric cells [32,38,51,52]. BA is a nonhereditary, rare disease (about 1 in 10,000 births) that is associated with chronic, progressive liver problems. Surprisingly, we have found that the diseased tissue of BA patients had 20 XX cells in 1,000 XY fetal cells on average, and this is 10 times higher than that in normal controls. In addition, these XX cells contained a certain amount of CD8+ cells [32].

Several studies have reported maternally derived immune cells in certain kinds of congenital diseases [32,51,52]. The biggest issue is whether these cells are playing major roles in the pathogenesis of infant diseases. What makes this issue complicated is that these diseases are basically inflammatory diseases, which raises the possibility that increased numbers of maternal microchimeric cells are merely secondary products that have been stimulated to proliferate by fetal immune reactions and have nothing to do with pathogenesis. However, important circumstantial evidence refutes this possibility. The number of maternal microchimeric cells increases when the mother and the fetus have higher MHC compatibility, and diseases suspected to involve MHC indeed have a higher ratio of MHC-compatible mother-child

pairs [26,27,33]. These reports suggest that the diseases suspected to involve MMc indeed have biased genetic combinations to receive more maternal cells. We have proposed this hypothetical etiopathogenesis as materno-fetal immune disease, at the prospect of integrating the knowledge of rare but similar diseases [32,53]. However, it has to be noted that no study has yet clarified that MHC compatibility or microchimerism *per se* is sufficient to cause these diseases.

Is microchimerism a programmed cell migration to maintain pregnancy?

As describe above, studies reporting the possible effects of materno-fetal microchimerism are accumulating (Table 1). However, are we really sure that these effects are not merely byproducts caused

Possible negative effects	Possible positive effects
Scleroderma [2,3,26]	Beta cell regeneration in type I diabetes [39]
Systemic lupus erythematosus [27,28]	Rheumatoid arthritis [40,41]
Multiple sclerosis [2]	Prevention of breast cancer [42]
Primary biliary cirrhosis [29]	Tolerance in hematopoietic stem cell transplantation [43]
Sjogren syndrome [30,31]	
Biliary atresia [32,33]	
Grave disease [34]	
Hashimoto thyroiditis [35]	
Juvenile dermatomyositis [36]	
Fetal loss [37]	
Neonatal lupus congenital heart block[38]	

Table 1: Materno-fetal microchimerism established during pregnancy.

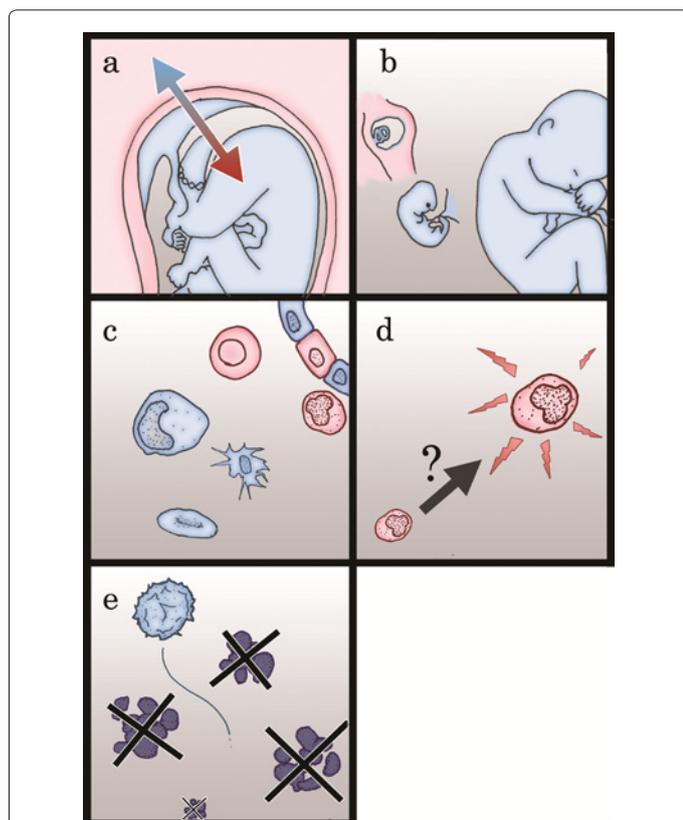


Figure 2: Materno-fetal microchimerism established during pregnancy. During pregnancy, exchange of small numbers of maternal and fetal cells occurs by an unknown mechanism (possibly through the placenta), creating a chimeric state or microchimerism. Although the number of cells decreases after delivery, microchimeric cells are known to persist for the rest of our lives[1]. This suggests that various kinds of cells including stem cell-like cells with self-renewing potential might have migrated as microchimeric cells; however, little is known about their cell type repertoire.

by the abnormal conditions of microchimeric cells? In other words, does microchimerism have certain physiological roles? Although the answers remain to be found, reports in obstetrics raise intriguing possibilities. Highly shared MHC between couples positively correlates with higher risk of recurrent pregnancy loss [54,55,56], suggesting that pregnancy tends to produce various MHC progenies by nature.

Given that MHC compatibility correlates with higher ratio of microchimerism [16], it would be worth validating the physiological role of microchimerism in maintaining pregnancy.

Emerging questions in immunology

Many questions concerning microchimerism and immunology remain to be clarified (Figure 2). After all, the greatest question is whether pregnancy-associated microchimerism is a boon or a bane. For example, there are cases in which pregnancy ameliorates rheumatoid arthritis, and importantly, the degree of amelioration correlates with fetal microchimeric cells [2]. On the other hand, fMCs are proposed to be involved in the etiopathogenesis of scleroderma on the basis of reports that patients with scleroderma have more fMCs [2]. One reasonable interpretation of these contradictory findings would be that microchimerism could act as both a boon and a bane, depending on the situation, just as our immune system does. Consequently, how is this watershed determined? Why are some people afflicted with various troubles caused by microchimerism, even though all of us have microchimeric cells in our body? Going further, even among people with negative effects, such as GvHD-like inflammation, why is this inflammation restricted to certain organs or tissues? Further studies, especially with well-controlled animal experiments, would provide important clues to these questions.

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