Placenta 60 (2017) 130–133

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Microchimerism: Defining and redefining the prepregnancy context – A review

H.S. Gammill [a, b, *], W.E. Harrington [c]

[a] Department of Obstetrics and Gynecology, University of Washington, United States
[b] Clinical Research Division, Fred Hutchinson Cancer Research Center, United States
[c] Department of Pediatrics, University of Washington and Seattle Children's Hospital, United States

ARTICLE INFO

Article history:
Received 25 April 2017
Received in revised form
27 July 2017
Accepted 29 August 2017

Keywords:
Microchimerism
Maternal-fetal exchange
Reproductive immunology
Preeclampsia
Placental malaria

ABSTRACT

Bidirectional transplacental exchange characterizes human pregnancy. Cells exchanged between mother and fetus can durably persist as microchimerism and may have both short- and long-term consequences for the recipient. The amount, type, and persistence of microchimerism are influenced by obstetric characteristics, pregnancy complications, exposures to infection, and other factors. A reproductive-aged woman enters pregnancy harboring previously acquired microchimeric "grafts," which may influence her preconception health and her subsequent pregnancy outcomes. Many questions remain to be answered about microchimerism with broad-ranging implications. This review will summarize key aspects of this field of research and propose important questions to be addressed moving forward.

1. Broadening the definition of self

Microchimerism (Mc) is defined as the presence of a small amount of foreign genetic material in an individual. Natural acquisition of cellular Mc occurs during human pregnancy through bidirectional transplacental exchange, allowing multigenerational sources of Mc to exist and interact within an individual [1].

During pregnancy, fetal cells transfer to the mother (termed fetal Mc, FMc), and maternal cells transfer to the fetus (termed maternal Mc, MMc). MMc in the fetus can durably persist through birth and maturation, with potential to influence health in neonatal life, childhood, and into adulthood. Persistence of MMc can continue into reproductive life. For a woman, or "proband," who can subsequently acquire FMc from her own pregnancies, Mc previously acquired from the proband's own mother (for clarity when discussing several generations referred to as the "mother of the proband Mc" or MP-Mc) or from her prior pregnancies has the potential to interact with new FMc [2]. Acquired FMc can also persist and has the potential to influence a woman's health in the years after pregnancy. The specific impact of FMc on the mother likely depends on several factors including immunogenetic relationships [1] and specific alleles carried by the Mc [3]. In addition, the role of FMc clearly depends on context, as described in detail by Boddy et al., who used an evolutionary framework to predict FMc function considering the relative cooperative versus conflicting interests of mother and offspring in chronological and tissue-specific contexts [4]. An example of a disease in which FMc appears to be a consistent risk factor is systemic sclerosis [5]. On the other hand, FMc has been found to consistently associate with protection from breast cancer [6].

Natural acquisition of Mc through maternal-fetal exchange and its persistence may impact all stages of life, from fetal development through post-reproductive health and aging. Coexistence and allotolerance of potentially several sources of Mc within an individual brings into question simple definitions of self. Thus, the concept of a single individual's genetic and immunologic makeup becomes more complex.

2. MMc: shaping the immune system beginning in fetal life

Clues about the potential impact of MMc on the fetus and offspring can be gleaned from detection patterns over time and across tissues and cell types. MMc has been detected in the fetus as early as the second trimester, with detection in widespread tissues and cell subsets, including CD45$^+$ leukocytes as a whole, as well as CD3$^+$, CD19$^+$, CD11b+, and CD34$^+$ cell subsets [7–12]. Prior to

* Corresponding author. Department of Obstetrics and Gynecology, University of Washington, United States.
E-mail address: hgammill@uw.edu (H.S. Gammill).

http://dx.doi.org/10.1016/j.placenta.2017.08.071
0143-4004/

delivery, detection has been demonstrated in whole cord blood (from cordocentesis specimens), as well as in circulating $CD8^+$ and $CD34^+$ cell subsets [9,10]. At the time of delivery, studies have demonstrated detection of maternal cellular Mc in 40–70% of umbilical cord blood samples [7,8]. In a recent study, detection of MMc in cord blood was demonstrated in both memory and naïve T cells, B cells, NK cells, and monocytes, with particularly high concentrations in memory T cells [13]. There is limited data on the mechanism of transfer, but data for a humanized rat model found that the trafficking of maternal cells into the fetus was dependent upon integrin-mediated adhesion to the syncytiotrophoblast and a VEGF gradient across the placenta [14]. The detection pattern of MMc in cord blood cell subsets may have implications for the offspring and may also influence outcomes in the therapeutic context of cord blood transplantation [15].

During childhood, MMc persists and has been demonstrated in peripheral blood and tissues, including liver, pancreas, lung, kidney, bladder, skin, spleen, heart, thymus, and thyroid [16,17]. Later, most adults continue to harbor MMc. One study of adult men and women (mean age 25, max age 49) demonstrated that 55% of subjects had detectable maternal cellular Mc in peripheral blood mononuclear cells [18]. Detection varies by cell subset, with 14–40% of subjects having demonstrable MMc in T cells, B cells, monocytes, NK cells, or granulocytes [18–20]. In reproductive years, MP-Mc is detectable in normal pregnancy, especially during the third trimester yet, interestingly, is absent in the pregnancy complication preeclampsia [2].

Our understanding of MMc is also informed by observations in animal models and humans that illustrate its function and, specifically, its importance in development of immune tolerance. Though a detailed discussion of the immunology of Mc is beyond the scope of this review, the impact of exposure to Mc during fetal immune development is unique. In 1953, Billingham and Medawar demonstrated that mice exposed to specific antigens during fetal life developed durable acquired tolerance to those antigens [21]. A year later, a study by Owen showed that Rh negative women whose mothers are Rh positive are more likely to be tolerant of an Rh positive fetus, compared with Rh negative women whose mothers are also Rh negative. This epidemiologic observation supported the hypothesis that exposure to maternal Rh antigens in utero conferred durable tolerance, resulting in protection from future sensitization for Rh negative women during their own pregnancies [22]. At least one mechanism through which in utero exposure to foreign antigens, including maternal antigens, confers specific and lasting tolerance was illustrated elegantly by Mold and McCune who demonstrated the development of maternal-specific regulatory T cells during fetal life [11]. Acquisition of MMc in fetal life allows for fetal exposure to maternal antigens not genetically inherited by the fetus, termed "non-inherited maternal antigens, or NIMA," which usually results in development of NIMA-specific fetal tolerance, similar to allotolerance in the context of transplantation. The natural consequences of durable tolerance to NIMA on reproduction remain incompletely understood. However, tolerance to NIMA has been shown to be relevant to transplantation outcomes [23,24], dependent on persistence of MMc in offspring [12] and possibly related to MMc-derived extracellular vesicles [25], and likely relevant to next-generation pregnancy outcomes [26].

3. Does pregnancy change the nature of Mc?

Many epidemiologic observations suggest that pregnancy history influences subsequent post-reproductive disease risk. Both parity itself, and particular pregnancy complications such as preeclampsia, are associated with risk of and protection from conditions such as cardiovascular disease. Mc may be a contributing factor to these observed relationships. For this to be the case, we would expect the pattern of Mc harbored by adult women to vary according to their pregnancy history. In fact, in post-reproductive women, higher parity is associated with lower detection of MMc, perhaps reflecting a replacement of previously acquired MMc with newly acquired fetal grafts [27]. FMc may also be acquired during pregnancy loss – both miscarriage and induced abortion [28]. In one study, years after pregnancy, induced abortion was associated with the highest detection of FMc, compared with delivery or miscarriage [29].

Many questions remain about the ways in which Mc harbored by a woman can be altered by pregnancy outcome. Does previously-acquired MMc actively influence pregnancy outcomes? Do pregnancy complications change the composition of acquired FMc? Do pregnancy complications influence the ways in which previously acquired and newly acquired grafts interact? As supported by the observations of Van Rood et al., MMc in cord blood may confer additional graft-versus-leukemia protection after cord blood transplantation [15]; how can these data inform our understanding of naturally acquired Mc?

Pregnancy loss, both miscarriage and abortion, may play a particularly important role, given its association with higher rates of durable persistence, as well as the overrepresentation of genetically abnormal fetuses associated with these outcomes. Are there particular implications of aneuploid or otherwise genetically abnormal Mc, for example?

Another pregnancy complication of interest is preeclampsia, which has been shown to be associated with higher concentrations of fetal cellular Mc [30] and is also known to be associated with post-reproductive risk of cardiovascular disease. In preeclampsia, are there phenotypic differences in the FMc that is acquired? Or are there differences in the maternal response to acquired fetal cells? Is a role played by other, previously acquired Mc grafts, including MP-Mc?

4. Global example: placental malaria and MMc in the offspring

Consideration of infectious disease may provide a hypothetical framework with which to understand the evolutionary benefit of Mc and the complex intergenerational interactions it brings. A recent study of MMc in the setting of placental malaria offers some insights [31]. Placental malaria refers to the sequestration of *Plasmodium falciparum*-infected red blood cells in the placental intervillous spaces. This sequestration is associated with an inflammatory infiltrate of mononuclear cells and poor clinical outcomes in the mother, fetus, and infant [32]. The researchers found that placental malaria, was associated with higher levels of MMc in cord blood at the time of delivery, and in particular, inflammatory placental malaria was associated with the highest levels of MMc. Placental malaria has also been associated with disruptions in VEGF signaling, and the researchers found that level of maternal soluble FMS-like tyrosine kinase-1 (sFlt-1) – the soluble receptor of VEGF – predicted level of cord blood MMc. They hypothesize that maternal sFlt-1 may bind to maternal VEGF, accentuating the VEGF gradient across the placenta, and increasing the trafficking of maternal cells. It is unknown whether placental malaria and its associated inflammation alters the types of maternal cells acquired by the fetus.

In the same study, the presence of MMc in cord blood predicted a higher likelihood of malaria infection during early childhood. Interestingly, however, when infected with malaria, offspring with MMc in the cord blood had a lower risk of developing symptoms or requiring hospitalization, resulting in protection from malarial disease. These data suggest that intergenerational immune interactions may influence offspring susceptibility to infection and

that MMc may confer an advantage in malaria endemic settings.

Certainly, the relationships between maternal malaria, Mc, pregnancy outcomes, and offspring outcomes are complex, and they may vary by maternal age and parity [33]. Insofar as this complexity mirrors many observations in reproductive epidemiology, placental malaria may represent a model through which to better understand the biology of Mc exchange, persistence, and function. For example, placental malaria has also been associated with alterations in placental angiogenic factors, like sFlt-1, and with particular maternal/fetal Flt-1 genotypes. These factors play a role in pregnancy complications such as preeclampsia, suggesting that evolutionary pressures on placental function related to malaria may have broad-ranging consequences on reproduction and post-reproductive disease [34].

5. Conclusion

In summary, during fetal life, individuals acquire Mc from their mothers, with potential for durable persistence and immunologic consequences. For a woman, who can be exposed to additional sources of Mc from subsequent pregnancies, acquired grafts may reflect both her own in utero development and her reproductive history. Mc grafts harbored by a woman prior to a pregnancy have potential to influence preconception health and reproductive outcomes. Mc from a woman's mother differs fundamentally from that acquired from her fetus, and FMc likely varies by pregnancy outcome. Evolutionary pressures on this process are likely influenced by infection with additional consequences for non-infectious disease. Many questions remain to be answered, with broad implications for the fields of immunology, infectious disease, transplantation, and reproductive science.

Conflict of interest statement

No author has a conflict of interest related to this manuscript.

Acknowledgements

This work was supported by the National Institutes of Health (K08 HD067221 and T32 HD007233) and the Thrasher Research Fund. The funding sources had no role in the writing of the manuscript nor in the decision to submit the article for publication.

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