Perspective

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Proangiogenic Macrophage Development in Human Prenatal Stage: A Key Element in Maternal-Fetal Medicine Puzzle

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Introduction

Macrophages, a major immune cell type constituting the human innate immune system, are involved in various physiological processes, such as tissue development, remodeling, homeostasis, and repair, crucial for maintaining normal growth and development of embryos/fetuses.[1–3] Influenced by their cellular origin and specific tissue environments, macrophages exhibit a diverse range of phenotypes.[4–7] Among these subtypes, perivascular macrophages are strategically located on or near the abluminal surface of blood vessels, contributing significantly to essential functions at the interface between tissues and blood.[7–9]

Our recently published study in *Cell* has presented a developmental atlas of the human prenatal immune system. The study involved the collection of nearly 300,000 immune cells from 19 tissues spanning 18 gestational time points, ranging from postconceptional 4 to 26 weeks, using single-cell transcriptome sequencing analysis.[10] This study has yielded new insights into the differentiation, spatial distribution, functional traits, and transcriptional regulation mechanisms of distinct macrophage subtypes during human prenatal development. These findings illuminate the intricate processes underlying macrophage development in the prenatal stage. Notably, our research has identified two novel macrophage subtypes, including proangiogenic macrophages (PraMs), demonstrating a unique capability to promote angiogenesis. The distribution of PraM cells across various tissues underscores their crucial role in the development and maintenance of blood vessels during the prenatal stage. These findings not only enhance our comprehension of immune system development but also carry implications for prospective therapeutic interventions aimed at addressing macrophage-related disorders in maternal-fetal medicine.

Proangiogenic macrophages and embryonic/fetal development

During embryogenesis, the formation of vasculature involves two distinct but interconnected processes: vasculogenesis and angiogenesis.[11–13] Vasculogenesis is a process of de novo formation of blood vessels in which endothelial cells differentiated from angioblasts assemble to form primitive vascular structures and then establish the initial vascular network in the developing embryo/fetus.[11–13] Angiogenesis refers to the sprouting and outgrowth of endothelial cells from existing blood vessels, which then proliferate and differentiate to form new capillaries, veins, and arteries.[11–13] The coordination and collaboration between vasculogenesis and angiogenesis create an intricate network of functional blood vessels that provide oxygen and nutrients to developing tissues and organs, supporting the overall growth and development of the embryo.

Macrophages could be a key factor in maintaining the normal development of fetal/embryonic vasculature. Based on the studies in rodents, there are long-suspected but not well-understood macrophages that support the formation of blood vessels during embryonic/fetal development.[14] In humans, we have identified PraMs, which expressed a proangiogenic signature, including *TNF*, *CD83*, and *CXCL8*, in different tissues/organs. At postconceptional 4 weeks, yolk sac–derived macrophage progenitors are able to differentiate into a precursor of PraMs in the yolk sac and progressively give rise to PraMs (Fig. 1). During this process, the proangiogenic signal increases accompanied by the gradual formation of vasculature in the embryo/fetus. Throughout the duration of the gestation, in addition to the construction of the vascular system of the embryo/fetus itself, the formation of the vascular network in the placenta that sustains the growth and development of the embryo/fetus is equally vital. Once the establishment of the placental vascular system is obstructed, it may lead to placental dysfunction, ultimately affecting the optimal development of the fetus. Therefore, ensuring the proper establishment and functionality of the placental vascular system is also of utmost importance to promote healthy fetal development.

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Possible clinical implications

Fetal growth restriction

Fetal growth restriction (FGR) refers to the fetus being of abnormal size and not reaching its genetic growth potential in utero, which is clinically defined as the birth weight of the fetus is being less than the 10th percentile of normal weight for the gestational age.[15] Fetal growth restriction is associated with the occurrence of low birth weight, which causes more than 2 million neonatal deaths every year worldwide.[16] The etiologies related to FGR are complicated, and poor placental function is one of the pathophysiological factors underlying FGR.[17–23] After implantation of the zygote into the endometrium, the trophoblast differentiates into the syncytiotrophoblast (outer layer) and the cytotrophoblast (inner layer of cells), which further form chorionic villi extending into the uterine tissue and later become the embryonic/fetal portion of the placenta.[24] Blood vessels start to form within the chorionic villi. Initially, these blood vessels are of embryonic/fetal origin, but they will eventually connect with the maternal blood supply.[25–27] Several studies indicated that placental macrophage abnormalities–mediated deficient trophoblast invasion can result in placental ischemia and hypoxia, triggering a series of events that lead to FGR.[28,29] On the other hand, congenital macrophage-related vascular malformations occurring within the fetus may also hinder the proper circulation of blood, leading to a diminished delivery of essential nutrients and oxygen to the developing fetus. This, in turn, exacerbates the risk of FGR and its associated complications.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy, including most commonly known gestational hypertension and preeclampsia, are a group of common medical complications in pregnancy and account for a leading cause of maternal and neonatal mortality and morbidity.[30] Although the exact causes related to preeclampsia remain unclear, aberrant placental angiogenesis induced by a combination of insufficient trophoblast invasion, poor placental oxygen extraction, antiangiogenic factors, endothelial dysfunction, and oxidative stress could be the determinants resulting in the development of preeclampsia.[31] A previous study has found increased numbers of macrophages around the spiral arteries in women with preeclampsia.[32] However, the exact role of this macrophage in placental angiogenesis and function is uncertain. Moreover, the characteristics of fetal PraMs and how they interact with other immune cells in hypertensive disorders of pregnancy are also worth further investigation.

Spontaneous preterm labor

Spontaneous preterm labor (PTL) is a significant global health issue, responsible for a high rate of perinatal morbidity and mortality.[33] The majority of complications occur in pregnancies that end before the 34th week of gestation, which accounts for approximately 2% of all pregnancies.[34] The incidence of various complications, such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and even mortality, is closely linked to the gestational age at which the birth occurs.[35] Impaired placentation has been identified as one of the processes associated with spontaneous PTL.[36] In a mouse model of PTL, the administration of an angiogenic factor angiopoietin-2 resulted in a shortened period to delivery, which was partly achieved by disrupting fetal angiogenesis, which is associated with the loss of proper blood flow to the developing embryo.[37] In humans, a recent study has shown an association of single-nucleotide polymorphisms

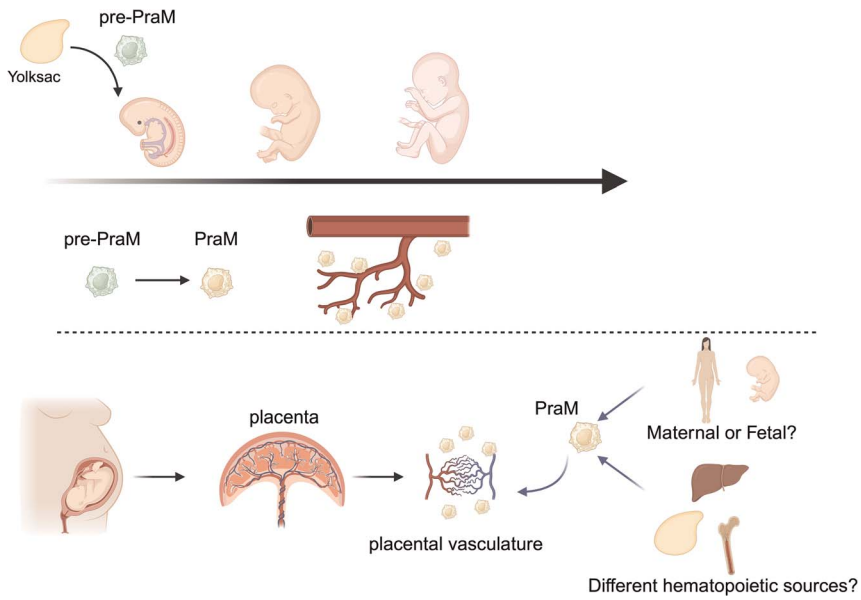

Figure 1. The pre-PraM originates from the yolk sac and, with the development of embryo/fetus, progressively differentiates into PraM, the mature state, in the various organs, during which the proangiogenic signal of PraMs is also augmenting to accomplish the construction of vascular network in the body. During the development of the embryo/fetus, the placenta is a vital organ for exchanging maternal and fetal circulation, which is subject to the vasculature in the placenta. PraMs may play a key role in the formation and normal function of the vasculature in the placenta. Besides, it remains to be determined whether PraMs from either maternal or fetal sources, and from different hematopoietic sources, has the same effects in the formation of the placental vasculature. Pre-PraM: Precursor of proangiogenic macrophages. The figure created with BioRender.com.

from angiogenesis-related genes with spontaneous PTL.[38] These findings indicate that abnormal angiogenesis may play a role in women experiencing spontaneous PTL. Nevertheless, the mechanisms by which fetal PraMs regulate angiogenesis and their impact on fetal development in this group of women are still unknown.

Future directions

In addition to exploring the role of fetal PraMs in adverse pregnancy outcomes in well-designed clinical studies, it is also of interest that the placental macrophages are reportedly associated with the construction of vasculature in the placenta,[39,40] which most likely corresponds to the PraMs identified. Therefore, exploring the PraMs in the placenta may offer a potential direction for understanding the underlying causes of some pregnancy-related diseases. However, it is worth noting that as the important organ mediating communication between maternal and embryonic/fetal circulation, the placenta contains the maternal macrophages as well as fetal macrophages. Whether both maternal and fetal macrophages exhibit similar functions also needs further investigation. On the other hand, the PraMs from the different sites may have distinct hematopoietic origins,[41] and such differences may lead to subtle changes in angiogenesis and vasculogenesis regulation in the placenta. This means that more efforts need to be made to distinguish the different types of macrophages, which could be one of the possible prenatal intervention targets in the future.

Conclusion

Understanding the role of prenatal PraMs in promoting angiogenesis and vasculogenesis in the fetus and placenta can help better comprehend the pathogenesis of adverse pregnancy outcomes. Furthermore, the investigation into the origins of PraMs from different sites highlights the importance of considering the heterogeneity of these cells. In conclusion, the study of prenatal PraMs emerges as a crucial piece of the puzzle and provides insights into the field of maternal-fetal medicine. It also offers promising directions for future research and interventions aimed at improving maternal and fetal health.

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Conflicts of Interest

None.

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