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The Effect of Pregnancy on Production of Maternal Endogenous Hematopoietic Stem Cells

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Summary

Fetal microchimerism refers to the presence of fetal cells in maternal blood and tissues during pregnancy. This microchimerism may result from trafficking of fetal and maternal blood across the placenta during pregnancy. Physiological changes in the maternal blood cellular milieu are also recognized during pregnancy and in the early post partum period. Earlier studies showed that maternal blood contains CD34⁺ hematopoietic stem cells (HSCs) that bear paternal genetic markers or male phenotype, suggesting that these cells circulated to the mother from male fetuses during pregnancy. Other studies showed that these maternal HSCs have significantly lower expansion potential than their fetal counterparts. We have recently shown increased percentages of CD34⁺ HSCs in peripheral blood of pregnant and parous women. Herein, we hypothesize that pregnancy stimulates the production of endogenous CD34⁺ HSCs of maternal origin, a phenomenon which potentially could favor post partum regenerative capacity.

Introduction

Maternal fetal microchimerism refers to the presence of bidirectional trafficking of cells from different origins within the maternal circulation. Detection of cells of fetal and placental origin in maternal blood during and after pregnancy has been well documented over the past half century.¹ This was illustrated by detection of trophoblast-like cells and Y chromosome-carrying fetal leukocytes in maternal blood after delivery.^{1,2} Bianchi et al have reported that male progenitor cells (CD34⁺ and CD34⁺ CD38⁺) could be detected in maternal circulation for several decades after pregnancy.^{3,4} It has been suggested that primitive cells detected in the maternal blood have significant impact on the state of fetal tolerance^{5,6}, as well as on the future development of autoimmune disease in multiparous women.⁷ Fetal progenitor cells have also been suggested to contribute to regeneration of damaged maternal tissue.^{8,9}

Data from ongoing research in our laboratory show that primitive CD34⁺ stem cells circulate in maternal blood of pregnant and parous women. While the concept of maternal-fetal trafficking supports the detection of these primitive stem cells in maternal tissues, many questions on the source of these cells, how they reached maternal circulation and where they home in maternal tissues remain to be answered. The effect of pregnancy on the immune modulation of maternal homeostasis has been shown by several investigators in animal models

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and in human studies.¹⁰ We propose that this modified maternal homeostasis includes increased stem cell production by maternal organs (bone marrow) in response to pregnancy-related signals.

Hypothesis

We hypothesize that pregnancy-related signals stimulate endogenous mobilization of CD34⁺ hematopoietic stem cells into maternal blood. We propose that while fetal maternal chimerism contributes to the increase in circulating CD34⁺ HSCs in the pregnant and post partum period, a population of primitive CD34⁺ progenitors is produced from maternal bone marrow. Increased maternal CD34⁺ cells maybe induced by interaction with umbilical cord blood cells (UCB).

Discussion

The use of stem cell therapy has the potential for treatment of many fatal diseases. One of the most promising types of adult stem cells for purposes of regenerative therapy is the hematopoietic stem cell. CD34⁺ HSCs have been effectively used for the treatment of blood malignancies such as lymphomas, leukemia and aplastic anemia.^{11,12} The proposed mechanisms of function of stem cells include cell replacement, modulation of immune responses and production of growth and trophic factors. While the issue of transdifferentiation of stem cells has been the subject of much debate^{13,14}, increased production of endogenous stem cells able to initiate tissue regeneration has been suggested as a mechanism for repair.¹⁵

Pregnancy is an exemplary physiological condition in which a state of microchimerism between maternal and fetal stem cells can be evaluated. Despite the placental barrier, there is significant evidence that fetal cells and biomarkers can be detected in maternal blood during pregnancy and for several decades after delivery.¹⁶ However, it has also been shown that exposure of adult HSCs to human umbilical cord blood stem cells *in vitro* culture conditions promotes expansion and differentiation of HSCs.^{17,18} This supports the hypothesis that exposure of maternal stem cells to fetal cells promotes their expansion. Furthermore, data from heterochronic parabiosis experiments showed that exposure of old stem cells to young microenvironments restores stem cell functions. Connecting the circulation of old and young animals increased aged hepatocyte proliferation and restored the cEBP-alpha complex to levels observed in young animals.¹⁹

Herein, we propose that exposure of maternal marrow and blood to fetal cells during pregnancy stimulates endogenous production and/or expansion of the maternal CD34⁺ stem cell pool. Previous reports showing that blood from pregnant and parous women contains larger numbers of CD34⁺ cells compared to nulliparous women hypothesized that these primitive stem cells were of fetal origin. However, other studies showed significant functional differences between CD34⁺ stem cells isolated from maternal compared to fetal blood. When co-cultured with feeder cells, fetal hematopoietic progenitor cells could be expanded four times more than their maternal counterparts.²⁰

To test our hypothesis that these CD34⁺ primitive cells are of maternal origin, CD34⁺ cells isolated from maternal blood will be sorted using FACSria three-laser cytometer (Becton Dickinson), and genetic typing using PCR will be applied to the sorted cells. Colony formation on methyl cellulose culture medium supplemented with hematopoietic growth factors will be used to determine number of hematopoietic colonies. The number of colonies in culture media indicates the enrichment of HSC population within a cell preparation. Diverse number of colonies and differentiation potential will be interpreted to reflect different origin of the CD34⁺ populations.

Experiments in mice by Kim et al. showed that the endodermal transcription factor Sox17 was required for stem cell function of HSCs from fetal but not from adult origin.²¹ Lack of expression of Sox17 will be used to further provide evidence for the maternal origin of HSCs. It is noteworthy that that CD34⁺ cells in maternal blood in our experiments were found to express some embryonic markers such as Oct-4 and SSEA4 (unpublished data). However, it remains to be determined whether the presence of these embryonic markers denotes fetal or maternal origin.

We and others have shown that fetal human umbilical cord blood (HUCB) mesenchymal stem cells promote hematopoiesis *in vitro*.^{17,18,21} Other experiments will be done to determine quantitative and qualitative analysis of hematopoietic cell expansion and differentiation after incubation of maternal blood stem cells and fetal blood stem cells with HUCB-derived feeder cells. Experiments in which GFP (green fluorescent protein)-labeled cord blood cells are mixed with maternal blood can show whether there is bidirectional expansion of CD34⁺ cells of both fetal and maternal origin.

Pregnancy results in immune modulation and altered blood homeostasis due to several factors. Immune endocrine changes in pregnancy are associated with upregulation of the protective innate immune system. Signals triggered by injury include upregulation of neutrophil function, C-reactive protein and other acute phase proteins. The same signals that trigger upregulation of the immune system may result in mobilization of HSCs from the bone marrow of pregnant women into the circulation to replenish the increased need for immune cells. Increased maternal endogenous stem cell production could also favor post partum regenerative capacity.

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