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Timing and regulation of hematopoietic stem cell colonization of the human fetal bone marrow by endothelial and CAR stromal cells during pregnancy

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The bone marrow (BM) contains the major reservoir of immature and maturing hematopoietic and immune cells throughout adult life while also harboring most hematopoietic stem and progenitor cells (HSPCs). BM-retained hematopoietic stem cells (HSCs) are mostly maintained in a quiescent, non-motile mode. A small fraction of BM-retained HSPC daily proliferate, differentiate, and migrate to the circulation, to replenish the blood with new immature and maturing blood and (all) immune (both myeloid and lymphoid) cells with a finite life span.[1] The anti-coagulation and anti-inflammatory receptor EPCR is also functionally expressed by primitive BM-retained HSCs which are endowed with the highest competitive long-term repopulation potential (LT-HSC). Only BM-retained, quiescent EPCR-positive LT-HSCs are protected from DNA damaging insults including clinical chemotherapy and radiation treatments. Primitive EPCR-positive LT-HSC chemotherapy resistance requires the CXCL12-CXCR4 axis that also regulates HSC quiescence, cell cycle, and directional migration as well as the aPC/EPCR/PAR1 axis.[2,3] The chemokine CXCL12 is highly expressed by many BM endothelial and stromal cells types including HSC niche supporting osteoprogenitor cells termed CXCL12 abundant reticular cells (CAR cells), while primitive EPCR-positive fetal liver and adult BM HSC functionally express its major receptor CXCR4.[4]

Most functional HSC studies involve mice experimental preclinical models as well as results obtained from clinical BM transplantation protocols.

During fetal development, HSCs migrate from the fetal liver to the fetal BM and spleen for their lodgment and repopulation. Stem cell homing to the BM during development and in functional experimental transplantation assays including with human HSC in transplanted immune deficient mice is CXCL12/CXCR4-dependent.[5,6]

The precise timepoint of HSC colonization of the human fetal BM and spleen during pregnancy, as well as the identity of BM stromal niche cells and ligand–receptor interactions which regulate human BM HSC lodgment during fetal development are poorly understood.

The group of Zheng et al[7] have recently reported on the emergence of HSC in the human fetal BM and spleen and their landscape microenvironment during pregnancy by single-cell RNAseq analysis. This work revealed that functional, human fetal LT-HSC as assayed in transplanted immune deficient mice do not emerge before week 12 post conception. By careful examination of various types of fetal BM stromal and endothelial cells during weeks 10–14 post conception and their transcriptome, this study revealed that fetal BM CAR-like cells endowed with the high levels of CXCL12 production together with fetal endothelial cells which also highly express CXCL12 are the major LT-HSC niche supporting cells. Interestingly, the human fetal spleen was not repopulated with functional human LT-HSC before week 14 post conception, revealing that fetal BM is superior in providing critical signals for LT-HSC homing and lodgment over the fetal spleen. Importantly, self-renewing human CD146 positive osteoprogenitor CAR-like cells were detected in adult human BM and were found to provide a niche for adult human LT-HSC as well as in a miniature human bone implanted in immune deficient mice.[8]

In conclusion, this study provides evidence for the first functional fetal BM LT-HSC as well as their BM supporting microenvironment and niches.

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