

Placenta Is a Niche for Hematopoietic Stem Cells

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Hematopoietic cells develop in the embryo in several anatomical locations. Coordinated activities of the different hematopoietic sites ensure both rapid production of differentiated blood cells for the embryo's immediate needs and establishment of a large pool of undifferentiated hematopoietic stem cells (HSCs). However, the origin of HSCs is not fully resolved, and little is known about how the different fetal hematopoietic microenvironments direct the genesis, maturation and expansion of HSCs.

We have reassessed the anatomical distribution of HSCs during mouse development and discovered a previously unknown HSC reservoir in the placenta. Collagenase treated placentas and known hematopoietic organs from E10.5-18.5 embryos (CD45.1/45.2) were transplanted in limiting dilutions into irradiated CD45.2 adult hosts with CD45.1 support BM cells. Our results showed that the midgestation mouse placenta harbors a large pool of HSCs that possess functional properties of authentic adult-type HSCs by providing long-term, multi-lineage reconstitution and exhibiting self-renewal capacity upon serial transplantation. Placental HSC activity starts in parallel with the AGM region (E10.5-11.0), before HSCs are found in circulation or have colonized the fetal liver. The placental HSC pool expands until E12.5-13.5 contains >15-fold more HSCs than the AGM and the yolk sac. The expansion of the CD34⁺c-kit⁺ HSC pool in the placenta occurs during the time when the fetal liver HSC reservoir begins to grow. Interestingly, hematopoietic expansion in the placenta favors HSCs over clonogenic progenitors (17-fold vs. 2-fold expansion at E11.5-12.5) and is not accompanied with myeloerythroid differentiation, as in the fetal liver. HSC activity in the placenta declines after a few days, while HSCs in the fetal liver and blood continue to increase. The unique kinetics and magnitude of placental HSC activity suggest that the placenta plays an important role in the establishment of the definitive HSC pool during development. As the placenta is directly upstream of the fetal liver in umbilical circulation, it is likely that placental HSCs are a major source of the adult type HSCs that colonize the fetal liver.

To define the anatomical origin and localization of placental HSCs, knock-in mice that express GFP from regulatory elements of *runx1*, a transcription factor that is expressed in all developing HSCs, are analyzed. Future studies will focus on defining the microenvironmental signals that support HSC development in the placenta. If the stem cell-promoting properties of the placental niche can be harnessed *in vitro* to support HSC formation, maturation and/or expansion in culture, these assets may greatly improve hematopoietic stem cell-based therapies in the future.

(Gekas et al. *Developmental Cell*. 2005;8:365-375.)