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The fetal-to-adult hematopoietic stem cell transition and its role in childhood hematopoietic malignancies

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Abstract

As with most organ systems that undergo continuous generation and maturation during the transition from fetal to adult life, the hematopoietic and immune systems also experience dynamic changes. Such changes lead to many unique features in blood cell function and immune responses in early childhood. The blood cells and immune cells in neonates are a mixture of fetal and adult origin due to the co-existence of both fetal and adult types of hematopoietic stem cells (HSCs) and progenitor cells (HPCs). Fetal blood and immune cells gradually diminish during maturation of the infant and are almost completely replaced by adult types of cells by 3 to 4 weeks after birth in mice. Such features in early childhood are associated with unique features of hematopoietic and immune diseases, such as leukemia, at these developmental stages. Therefore, understanding the cellular and molecular mechanisms by which hematopoietic and immune changes occur throughout ontogeny will provide useful information for the study and treatment of pediatric blood and immune diseases. In this review, we summarize the most recent studies on hematopoietic initiation during early embryonic development, the expansion of both fetal and adult types of HSCs and HPCs in the fetal liver and fetal bone marrow stages, and the shift from fetal-to-adult hematopoiesis/immunity during neonatal/infant development. We also discuss the contributions of fetal types of HSCs/HPCs to childhood leukemias.

Graphical Abstract

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Authors' contributions

Ryan Mack and Lei Zhang drafted the first version of this review. All authors contributed to the writing of this manuscript. Peter Breslin did the final editing. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing financial or professional interests.

Declarations

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Consent to participate

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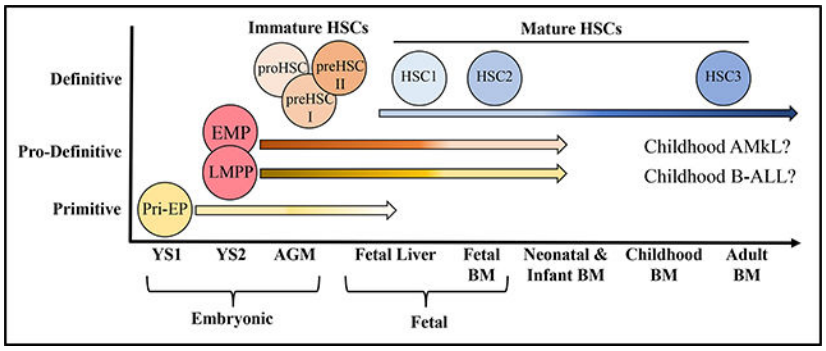

Keywords

fetal; neonatal; infant; hematopoiesis; leukemia

Introduction.

Hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) persist in a fetal phenotype until 2–3 weeks of age in mice.[1–3] Compared to adult HSCs, fetal and neonatal HSCs exhibit markedly different properties, including differences in surface markers, proliferative state, repopulation/self-renewal capabilities, gene expression, and differentiation activities.[2, 4, 5] Fetal/neonatal HSCs are highly proliferative with relatively high repopulation/self-renewal capabilities, while adult HSCs are quiescent with respect to the cell cycle (G_0 phase) with reduced repopulation/self-renewal capabilities. Fetal liver (FL) HSCs display faster hematopoietic regeneration and outcompete the production of HSCs from adult bone marrow (BM) cells in irradiated recipients.[6–8] Fetal HSCs display an erythroid differentiation bias, possess a distinct potential for innate-like lymphocytes (such as B1a, V$\gamma3^+$ $\gamma\delta$-T and innate lymphoid cells) and produce smaller sized and lower ploidy megakaryocytes (Mks) [9, 10], while adult HSCs show more balanced differentiation, produce larger sized/higher ploidy Mks and lack potential to become innate-like lymphocytes. The erythroid bias of fetal/neonatal HSC/HPCs is due to the slower kinetics of erythropoietin (EPO)-induced differentiation.[11] In addition, fetal/neonatal T/B lymphocytes show reduced or deviant responses to antigenic stimulation compared to adult counterparts. Furthermore, fetal HSCs are resistant to many leukemic oncogenes detected in adult cases of leukemia, which might explain the different frequency of various leukemia subtypes in neonates/infants compared to adults [12–15]. Both HSC-intrinsic and environmental mechanisms have been proposed to explain such distinct properties of fetal and adult HSCs. Therefore, a better understanding of the cellular and molecular mechanisms by which the dynamic hematopoietic changes occur will provide a blueprint for the study of pediatric blood and immune disorders, as well as strategies potential for these disorders.

Most early studies consider adult HSCs/HPCs to be uniformly derived from definitive (adult-type) hematopoiesis in the para-aortic splanchnopleural/AGM region. These studies suggested a dynamic maturation theory of adult-type HSCs/HPCs during the fetal-to-adult hematopoietic transition. However, prior to definitive hematopoiesis within the AGM, at least 2 more waves of fetal type hematopoiesis are generated from the yolk sac (YS). Studies

suggested that both fetal and adult types of HSCs/HPCs migrate to and expand in the FL and subsequently in the fetal BM. The hematopoietic and immune cells in the fetal stage are primarily produced by fetal types of HSCs/HPCs, which are then gradually diminished and replaced by cells produced by adult-type HSCs/HPCs during later fetal and early postnatal development. Many types of fetal hematopoietic cells, including fetal HSCs and HPCs, are present in neonatal and infant BM, which might contribute to hematopoiesis and immunity at multiple stages. Therefore, the fetal-to-adult hematopoietic transition is more likely a combination of the fetal-type to adult-type shift and gradual HSC/HPC maturation. In this review, we discuss the multiple waves of hematopoietic generation during early embryonic development and the blood/immune cell contributions of these waves to fetal, neonatal and adult stages. We specifically focus on the dynamic changes of fetal and adult types of HSCs/HPCs during the fetal-to-adult hematopoietic transition and discuss their potential roles in the pathogenesis of pediatric blood and immune diseases.

It needs to be mentioned that most of our current knowledge of fetal-to-adult hematopoietic transition is primarily drawn from the studies of mouse models. Nevertheless, hematopoietic development is conserved across vertebrates, and thus most of the results obtained from animal studies have been confirmed in humans. Therefore, we will mainly focus on studies involving mouse models and will extend our discussion to humans when there are notable differences between mouse and human.[16, 17] As there are many cell populations and developmental stages discussed, a summary of HSC and HPC phenotypes is listed in Table 1.

Multiple waves of hematopoietic initiation during embryonic development.

At least three consecutive overlapping waves of hematopoietic generation have been identified during embryonic development.[18, 19] The first wave, called primitive hematopoiesis, is generated directly from the mesoderm in the YS blood islands on embryonic day (E) 7.5 for mice and E17 for humans in a Runx1/Myb-independent manner. HPCs produced at this stage are called primitive erythroid progenitors (pri-EPs), defined as $CD41^{+}Kit^{+}Sca1^{-}$, which produce red blood cells (RBCs), macrophages (Mφ) and megakaryocytes (Mks) but no lymphocytes.[20] RBCs produced by pri-EPs are large, nucleated cells that express a specific pattern of embryonic globin chains: εy- and βH1- in mice and ζ- and ε- in humans.[21] Distinct from Mφ produced by adult HPCs, pri-EPs produce Mφ without monocytic intermediates. Platelets produced by pri-EPs are larger in size compared to adult BM-derived platelets.[22]

The second wave, called pro-definitive (or transient-definitive) hematopoiesis, arises from Wnt-responsive hemogenic endothelial cells (ECs)($CD31^{+}TIE^{+}CD45^{-}CD41^{-}Runx1^{+}$) in the YS around E8.5 for mice in a Flk-1 and Scl-dependent, but Myb-independent, fashion.[19, 23–26] The HPCs generated during this wave are termed erythro-myeloid progenitors (EMPs), defined as $CD45^{low}CD41^{+}Kit^{+}AA4.1^{+}CD16/32^{+}Sca1^{-}$. Shortly after generation, EMPs migrate to the FL and can differentiate into erythrocytes, Mks, Mφ, innate immune cells (NK cells, ILCs and mast cells), and other myeloid lineages such as neutrophils but have minimal conventional T/B lymphocyte potential. Transplantation studies suggested that EMPs lack self-renewal and long-term hematopoietic engraftment capacity,[18, 19, 23,

26–32] EMPs can contribute to the erythrocyte compartment for more than 20 days upon transplantation.[19] While these EMP-derived RBCs resemble adult RBCs, they express fetal globin βH1- (or γ-).[33] Recently, $CD45^+CD34^+CD44^+$ YS-derived myeloid-biased progenitors, a type of EMP-like cell in the human with RBC, Mk, Mφ and mast cell differentiation potential, have been described.[34–36]

In addition to generating EMPs, the YS also serves as an initial source of T and B lymphoid progenitors.[24, 37, 38] $Lin^-Kit^+Rag1\text{-}GFP^+Flt3^+IL7R\alpha^+$ lymphomyeloid progenitors (LMPs) have been identified in the E9.5 YS. Most LMPs also express colony stimulating factor 1 (CSF1) receptor and thrombopoietin (THPO) receptor. LMPs have both lymphoid (including canonical B2/T lymphocytes and innate B1a/dermal γδ T cells) and myeloid differentiation potential but lack megakaryocytic and erythroid potential. LMPs have been proposed to be the first progenitors to seed the developing thymus.[39] Phenotypically, LMPs might be the developmentally restricted HSCs (drHSCs) described by Forsberg,[40] which share many features of the epigenetic and transcriptional regulatory landscape with adult lymphoid-primed multipotent progenitors (LMPPs).[41] However, the exact interrelationships among EMPs, LMPs and drHSCs need to be determined. Several early studies also identified common primitive-definitive precursors, multipotent lympho-myeloid progenitors, myeloid-restricted progenitors, and multipotent progenitors in E8.5–9.5 YS, suggesting heterogeneity of the multipotent differentiation potential of YS HPCs.[25, 42–44] These studies suggested that common primitive-definitive precursors might produce multipotent lympho-myeloid, myeloid-restricted progenitors and EMPs to form a differentiation hierarchy.

The third wave of blood cell formation is called definitive hematopoiesis and emerges during E8.5-E11.5 for mice and 3–5 post-conception weeks (PCW) for humans in the major arteries in the para-aortic splanchnopleural/AGM region in a nitric oxide- and Notch1-Runx1-Gata2 axis-dependent manner.[45–52] The HPCs produced during this wave are referred to as immature HSC (imHSCs) and they can transform into multi-lineage functional HSCs in the FL environment or in proper *in vitro* culture conditions.[53, 54] Before colonization of the FL, imHSCs undergo quick maturation steps from pro-HSCs at as early as E9.5, through pre-HSC I at E10.5, and then pre-HSC II at E11.5.[55, 56] Endothelial protein C receptor expression could enrich all the HSCs in the E11.5 AGM region.[19] Functional transplantation study demonstrated a dramatic expansion of the imHSC pool during these maturation steps, from 5 cells at early E10 to 50 cells by late E10.5.[57] The majority (85%) of HSCs in the E11.0 and E11.5 AGM were lymphoid-biased γ-subtype and the remaining 15% were balanced β-subtype.[58] However, clonal fate-mapping experiments estimated that 600–700 HSC clones in mice and ~30 HSC clones in zebrafish contribute to life-long hematopoiesis.[59–61] This suggests that the numbers of imHSCs are significantly under-estimated from previous studies using functional assays. More effective assays are urgently needed in order to accurately examine the numbers of functional imHSCs.

In addition, colony-forming HPCs and functional HSCs have been identified within the vascular labyrinth region of mice at E9.5 and E10.5–11.0 in humans. HSCs in the placenta are expand by ~20-fold between E11.5–12.5, diminish by E13.5, and completely disappear by E15.5.[62–66] These studies suggest that the placenta serves as a major niche for HSC

expansion. The emergence of HSCs in the placental vasculature can be detected in the absence of circulation, suggesting a *de novo* source of hematopoietic generation that is independent of YS and AGM hematopoiesis.[62, 64, 67] Placental HSCs colonize the FL on E11.5 and their diminishment in the placenta is coincides with FL HSC expansion. The emergence of placental HSCs during early embryonic development (~6 PCW) in humans suggests that this mechanism is developmentally conserved. Placental HSCs possess the classical $CD34^{med}c\text{-}kit^{hi}$ fetal HSC surface phenotype, similar to FL HSCs. However, it remains unknown what contribution placenta-derived HSCs make to the adult HSC pool.

The role of YS HPCs to fetal, infant and adult hematopoiesis.

Pri-EPs generated in YS at E7.5 are expanded and maintained there until E10.5. These pri-EPs produce nucleated RBCs and highly proliferative Mks for platelets that support embryonic growth up until E15.5.[53, 54, 68] In addition, pri-EPs also produce primitive Mφ progenitors starting at E7.5 in the YS. After the onset of circulation, primitive Mφ progenitors predominantly migrate into the brain for self-renewal and lifetime maintenance of microglial cells in a PU.1 and Irf8-dependent manner (Figure 1A).[18, 69, 70] Thus, before the 2^{nd} wave of YS hematopoiesis was identified, it was believed that YS hematopoiesis was transient and only supported fetal hematopoiesis for short time in order to bridge the gap to HSC activity. However, after the identification of 2^{nd} wave YS hematopoiesis, recent studies demonstrated that EMPs and LMPs generated in the YS can support hematopoiesis and immunity for embryonic development at least up-to birth. Fate-mapping studies demonstrated that many types of EMP- and LMP-derived cells can be sustained even in adult tissues over the long term.[4, 46, 71] Figure 1B.

Shortly after generation in YS, both EMPs and LMPs colonize the FL starting on E10.5, which is earlier than that of AGM imHSCs (starting on E11.5, see in below).[57] Therefore, it is likely that EMPs and LMPs establish the first wave of hematopoiesis in the FL.[72] EMPs are also increased 3-fold from E10.5 to E11.5, at which time they are 25 times more numerous in the FL than in E8.5 YS.[73] The early stages of FL hematopoiesis are dominated by the erythroid lineage, while lymphoid and myeloid lineages are increased at later stages.[74] At E13.5, the largest FL population is nucleated erythrocytes, but after E14.5 more mature enucleated erythroid cells are found within the vessels.[75] Most of the hematopoietic cells express the pan-hematopoietic marker CD45; however, primitive erythroid cells at this stage of FL development are $CD45^{-}$.[76] A recent study demonstrated that during FL hematopoiesis, a large population of erythroid progenitors (EPs) are produced by EMPs, which comprise >70% of $CD45^{-}Ter119^{-}$ cells (>10% of FL cells) at E14.5. Similar to observations in mice, EPs in human FL also do not express CD45 at stages ranging from 7 to 17 weeks after conception.[35] The FL also provides a unique microenvironment for the expansion of EMP-produced megakaryocytic progenitors (MkPs).[77] This study suggests that AGM-derived HSCs do not contribute to erythropoiesis or megakaryopoiesis up until birth, but that these processes are primarily dependent upon EMP-derived EPs and MkPs. Mechanistically, it was found that EMP-derived EPs require 10-fold lower concentrations of erythropoietin, related to the low EPO microenvironment of the FL, than AGM-derived HSC counterparts for efficient erythrocyte production. As

a consequence, EMP-derived EPs efficiently outcompete AGM HSC progeny and sustain erythropoiesis throughout murine embryonic life.[78, 79]

LMPs have been identified in FL at E10.5, expand during E11.5-E14.5 in FL, and colonize fetal BM on E16.5.[24] Such cells phenotypically and functionally resemble the drHSCs defined by Forsberg's lab. LMPs/drHSCs contribute to tissue-residual innate immune cells such as B1a cells (primarily inhabiting the peritoneal and pleural cavities), epidermal γδT cells (predominantly expressing T cell receptor with a Vγ5Vδ1 allele), NK cells, innate lymphoid cells (including ILCs 1, 2, and 3) and mast cells during later embryonic development as well as for a short time after birth. Consistently, drHSCs can still be detected in BM 2 weeks after birth. A serial transplantation study demonstrated that drHSCs are capable of self-renewal and long-term multi-lineage reconstitutive capacity with a lymphoid bias. In addition, drHSCs can produce B1a and γδT lymphocytes. The contribution of EMPs to tissue-residual innate immune cells such as B1a cells, epidermal γδT cells (predominantly express T cell receptor with a Vγ5Vδ1 allele), NK cells, ILCs and mast cells is still being debated. [1, 8, 79, 80]

Pre-Mφ are present in YS from E8.5, where they proliferate and then access to bloodstream to migrate towards the embryonic tissues, peaking around E10.5. The traffic of such cells is dramatically decreased after E12.5 and disappears after E14.5.[81] In embryonic tissues, the pre-Mφs produce an M2-like non-inflammatory phenotype of tissue-resident Mφs. Such Mφs not only help to clear up the dead cells but also produce cytokines to stimulate tissue growth. During embryonic development, YS-derived Mφs play a critical role in the emergence of AGM HSCs and the organogenesis of many embryonic organs including kidney, testis, myocardial vascular network, endocardial valvular tissues, coronary and skull. [15, 17, 20, 82–86] Genetic depletion of YS-derived Mφs in the early embryo impairs timely hematopoietic colonization and morphogenesis of many organs. Most importantly, such tissue-resident Mφs have self-renewal capacity which can persist in the adult tissues throughout life, such as Kupffer cells in liver, Langerhans cells in the epidermis, alveolar Mφ in the lungs, and microglia in the brain.[28, 53, 69, 70, 73] These tissue-resident Mφs not only mediate immune responses but are also involved in wound healing and tissue repair.

In summary, the major functions of these two early waves of YS hematopoiesis are to produce: 1) circulating RBCs for gas exchange during the early and later embryonic development;[79] 2) platelets to maintain hemostasis; 3) Mφ to clean up apoptotic cells for tissue/organ generation and remodeling; 4) inflammatory signaling for definitive HSC emergence[80, 82]; and 5) tissue-resident Mφ in adults for tissue regeneration and repair. Although pri-EPs and EMPs (as well as their progeny) can be detected in adult BM tissue (7–20%, dependent the techniques used),[71, 73, 83] future studies will need to determine if and how these varieties of HPCs produced in the YS contribute to neonatal and adult hematopoietic systems.

The role of AGM imHSCs in fetal, infant and adult hematopoiesis.

Spatiotemporal analysis and genetic fate mapping of developmental HSCs demonstrate that adult BM hematopoiesis is primarily derived from imHSCs generated within the AGM.[4,

46] imHSCs do not have long-term multi-lineage hematopoietic reconstitutive capacity.[52, 87] After generation, imHSCs first colonize the FL and then the spleen and BM, where these cells undergo several maturation changes until they become quiescent HSCs in the adult BM niche 3–4 weeks after birth. Figure 2.

The first step of HSC maturation is the imHSC-to-functional HSC transformation which occurs in FL between E11.5-E12.5 to obtain long-term multi-lineage hematopoietic reconstitutive capacity. ImHSCs colonize FL at E11.5 (~5–6 PCW in humans). Fully functional HSCs can be detected at E12.5 (6 PCW for human) in FL.[57] Transplantation study demonstrated that the number of HSCs is expanded ~38 times from their original number (from E11.5-E14.5), peaking at around E14 for mice and E140 for humans. The phenotypes of HSCs in the FL are $Lin^{-}Sca\text{-}1^{+}Mac\text{-}1^{low}CD201^{+}$ on E12 and $CD45^{+}CD150^{+}CD48^{-}$ $CD201^{+}$ after E14.[8, 84][85] The 2nd step of HSC maturation is a gradual and uncoordinated epigenetic and transcriptional reprogramming to obtain most adult HSC properties which starts on E18.5, shortly after fetal BM colonization. [15] The 3rd step of HSC maturation is to acquire cell cycle quiescence 3–4 weeks after birth, which coincides with diminishment of fetal-type hematopoietic properties.[86, 88, 89]

The generation and maturation process of HSCs during embryonic and neonatal development are primarily stimulated by inflammatory cytokines, which is correlated with niche environmental changes. Interferon (IFN)-γ, interleukin (IL)-3, and tumor necrosis factor produced by Mφ are important for imHSC emergence in the AGM.[80, 82, 90–93] Together with Scf-Kit signaling, IFNα is required for the imHSC-to-HSC transformation event during early FL hematopoiesis, the 1st step in HSC maturation.[90, 92] At E18.5, IFNα and IFNβ produced by epidermal Mφs stimulate the 2nd stage of maturation by promoting the differentiation of HSCs and expansion of HPCs.[15] The 3rd step in HSC maturation might be controlled by Cebpα and Ash1-mediated transcriptional and epigenetic programs and regulated by the Pten-Akt-mTor signaling pathway.[86, 88, 89] This signaling promotes cell cycle quiescence of HSCs and may be initiated by chronic type I IFN stimulation.[94–96] Interestingly, such maturation steps do not always correlate to micro-environmental changes. For example, the most significant environmental challenge that HSCs face are oxidative stress, nutritional stress, and microbial infection immediately after birth. Such stresses induce shifts in glucose and glutamine metabolism, mitochondrial activation, and redox production in HSCs. HSCs are protected from such stresses by Atg5-dependent autophagy during the first 5–7 days after birth, but are adapted to such challenges by P7.[97, 98]

Transition of HSC niche from AGM, FL to fetal BM.

Specific signals promoting the chemoattraction of EMPs, LMPs and imHSCs to FL are still unclear. It most likely that EMPs, LMPs and imHSCs circulate in the peripheral blood (PB) and are passively retained in FL through adhesive factor–mediated cell-extracellular matrix (ECM) and cell-cell contacts, including a number of integrins (such as β1-integrin CD29 and α2b-integrin CD41),[99, 100] VE-Cadherin/CD144, glycosylphosphatidylinositol-anchored surface protein-GPI-80, together with ItgaM-CD11b. [101–103] Seminal studies demonstrated that HPCs lacking β1-integrin were unable to

colonize the FL[99, 104], while the chemokine C-X-C Motif Chemokine Ligand 12 (CXCL12) produced by FL ECs is an important factor for retaining HSCs in FL, but not for its initial colonization.[105, 106]

FL provides the first niche for HSC maturation and expansion.[2, 3, 5, 107, 108] In FL, several types of cells have been proposed to directly contact with HSCs and promote HSC maturation and expansion; these include desmin^{+} stellate cells, DLK1^{+} or CD3^{+}DLK1^{+}SCF^{+} hepatocyte progenitors.[105, 109] Such cells promote HSC expansion and maturation by producing several supportive hematopoietic cytokines such as KIT ligand (KITL), THPO, α-fetoprotein, insulin growth factor 2 (IGF2), angiopoietin-like 2 (Angptl2) and Angpt3 [105, 110–113], extracellular matrix proteins including vascular cell adhesion protein 1, fibronectin1, vitronectin1, Laminin-b1 and Laminin-c1,[114] as well as an essential fatty acid docosahexaenoic acid.[115] Detailed imaging studies suggested that EPCR^{+} HSCs in FL are localized around the Lyve-1^{+} sinusoidal network, [116] while CD150^{+}CD48^{-}Sca1^{+}CD11b^{+}CD45^{+} CD41^{-}Lin^{-} DAPI^{-} HSCs[84] are found closely associated with the Nestin^{+}NG2^{+} pericytes of portal vessels, suggesting that both the peri-sinusoidal network and peri-arterial stromal cells might be niches for FL HSCs. [117, 118] Nestin^{+}NG2^{+} mesenchymal stromal cells are required for HSC expansion by producing KITL, Angptl2, and IGF2 and other HSC factors. Selective elimination of Nestin^{+}NG2^{+} pericytes leads to a modest reduction in HSCs numbers and HSC proliferative.[117] In addition, DLK^{+} hepatoblasts produce KITL, FLT3 ligand, IGF2, Angpt3, Angptl2, Wnt family growth factors, Ephrin2a, CSF1, EPO, CXCL12, and IL-6. DLK^{+} hepatoblasts can support HSC expansion for ~20-fold within 3 weeks of co-culture [119]. Moreover, p75NTR^{+} FL hepatic stellate cells express a range of hematopoietic cytokines, such as CSF1, IGF2, THPO, KITL, EPO, IGF1, IL-1, FLT3 ligand and Oncostatin M.[110] Furthermore, bile acids, the active components of bile from the maternal and FL hepatocytes, contribute to FL HSC expansion through repressing unfolded/misfolded protein accumulation and inhibiting endoplasmic reticulum stress.[120] A most recent study demonstrated that KITL is primarily expressed by hepatic stellate and endothelial cells which create perisinusoidal vascular niche for HSCs in FL. Specific deletion of KITL from both endothelial and hepatic stellate cells in FL results in nearly complete loss of HSCs [121]. A summary of HSC niche cells at various developmental time points, as well as the factors each secretes, can be found in Table 2.

Fetal BM colonization of HSCs and HPCs occurs around at E16.5–17.5 for mice and 10–12 PCW for human and this becomes the dominant site of hematopoiesis going forward.[122] The HSC migration from FL to the BM is mediated by different cytokines, ECM signals and adhesion molecules (e.g., CXCL12, SCF, cadherins, integrins).[123] MMP9 produced by neutrophils promotes the release of HSCs from their FL niche by remodeling ECM. [124] And then HSCs migrate to fetal BM niche in response to the chemotaxis of several key BM environmental signals including CXCL12, VEGF, Slit, and SCF. After reaching fetal BM, HSCs are retained within the niche by several adhesive matrix proteins such as collagen, N-cadherin, VCAM, selectins and fibronectin.[106, 123, 125] The adhesive niche factors promote HSC survival by stimulating survival signaling such as the Wave-2/c-Abl pathway.[126, 127] Osterix^{+} primitive and definitive stromal progenitors play critical roles in BM niche formation during BM development.[128] *Osx*$^{-/-}$ fetal BM fails to generate

the HSC niche due to defects in endochondral ossification, osteolineage stromal cells, and osteopontin, secreting which play important roles in the regulation of HSC quiescence and homing.[129–131]

The transition of fetal-to-adult blood cells.

The fetal-to-adult transition of HSCs/HPCs is evident by the transition of mature blood and immune cells. Significant differences are observed between fetal and adult blood and immune cells.

Fetal-to-adult B cell transition.

The major changes of B lymphopoiesis during the fetal-to-adult transition include the loss of potential of $CD5^+$ B1a B cell production, the gain of IL-7/thymic stromal-derived lymphopoietin (TSLP)-dependent IgD^{high} B2 cell growth, and fetal-to-adult B cell receptor shift.[1, 132–134] B-1a cells are innate immune cells which reside in the peritoneal and pleural cavities. B-2 cells mediate a canonical adaptive immune by producing antibodies in a T cell-dependent fashion, while B-1a cells execute important roles in the first line of defense against microbial infection by producing IgM type of stereotypic natural antibodies in a T cell-independent manner.[135–137] Such B1 to B2 type shift of the B lymphopoiesis is associated with the fetal to adult type shift of B cell progenitors.[138]

In mice, although the progenitors for B-1 B cells are still debated, it is accepted that B-1a cells are primarily produced by fetal types of HSCs/HPCs. Different from the B cell progenitor cells derived from AGM HSCs/HPCs in FL which primarily produce B-2 lymphocytes [88], the B progenitor cells derived from YS HSCs/HPCs in FL have a strong tendency toward differentiation into B-1a B lymphocytes.[9, 43, 139] It was suggested that YS LMPs produce $AA4.1^+CD19^+B220^{lo/-}$ B-1 cell progenitor cells peak in the FL. Such progenitor cells are maintained in the BM and spleen during fetal development and the first 2 weeks after birth, and then diminish in adulthood.[9, 10, 140–142] The dynamic changes in B-1 progenitor cells is closely associated with the dynamic change of drHSCs.[1, 132] The development of B-1 cells is IL-7/TSLP-independent, while the development of B2 cells absolutely requires IL-7/TSLP. This might explain the IL-7/TSLP-independent B lymphopoiesis during fetal and 2 weeks after birth, as observed in knockout mouse studies [143, 144].

In humans, just as is observed in mice, fetal HSCs/HPCs have the potential to produce B-1 B-cells, which might be associated with the fetal types of B cell progenitors. Transcriptomic data suggests that an LMP equivalent is also present in human YS.[35] In addition to adult types of B cell progenitors such as $CD34^+CD19^+CD10^+$ ProB progenitors, two fetal types of B cell progenitors, $CD34^+IL7R^+CD19^-CD10^-$ oligo-potent early lymphoid progenitors (ELPs) and $CD34^+CD19^+CD10^-$ uni-lineage pre-ProB, were identified in FL and fetal BM.[145–149] Biologically ELPs are potentially analogous cells of human LMPs.[148–150] Functional study demonstrated that ELPs are upstream of pro-preB cells, which then give rise to proB cells. The onset of B cell lymphopoiesis in FL was demonstrated by the detection of ELPs at 6 PCW, as well as pre-proB and proB progenitors at 7 PCW. Pre-proB and proB cells account for ~2.5% and ~8% of FL $CD34^+$ cells, respectively, at 7 PCW. Both

progenitors are significantly expanded in fetal BM. Approximately 20% and 11% of fetal BM $CD34^+$ cells are pre-proB-progenitors and proB-progenitors, respectively, at 11 PCW. ProB-progenitors are expanded further to >30% of $CD34^+$ cells in fetal BM during the latter part of the second trimester. In adult BM, proB- account for ~14% $CD34^+$ cells. However, both fetal-types of B progenitors ELP and pre-proB can be detected in cord blood and early postnatal but are diminished during the postnatal-to-adult transition.[146, 148] Single cell RNAseq study suggests the presence of $IL7R^+$ ELPs in human YS [35], however whether ELPs and pre-pro-B cells are originated from YS or AGM need to be determined.

Fetal-to-adult T cell transition.

The major change in T lymphopoiesis during the fetal-to-adult transition is the gain of adaptive immune responsiveness. Fetal and neonatal T cells exhibit innate-like functions. In contrast to adult T cells which express a higher avidity TCR (T cell receptor) and produce more conventional cytokines (IFN-γ or IL-4 and IL-13) after clonal proliferation and differentiation, naive T cells from the fetus/neonate express Toll-like receptors, complement receptors, and NK cell receptors, as well as a more peptide-promiscuous TCR (such as dermal γδTCR). Following TCR stimulation, fetal/neonatal T cells rapidly produce IL-8, which is consistent with their more broadly reactive nature. Compared to adult T lymphocytes, fetal $CD4^+$ T cells exhibit enhanced proliferation, and preferentially become regulatory T cells (Tregs) or a Th2 phenotype in response to foreign antigen induction. As a result, fetal $CD4^+$ T cells are immune tolerant.[151, 152] Fetal $CD8^+$ T cells exhibit an enhanced capacity to proliferate and give rise to more short-lived effectors after infection, whereas adult $CD8^+$ T cells respond with slower kinetics but give rise to more memory $CD8^+$ T cells.[153] Studies demonstrated that fetal and adult T cells are distinct populations that arise from separate populations of HPCs that are present at different stages of development.[153] In addition, neonatal T cells are transcriptionally shifted to a more effector-like state early in life by developmentally regulated miRNAs.[154] Expression analyses reveal heterogeneous responsiveness of fetal lymphoid progenitors to Notch signaling [155, 156].

Transition of fetal to adult megakaryopoiesis.

Mks derived from EMPs form colonies more rapidly than those derived from adult BM, and mature more rapidly than adult-derived Mks.[22, 157] Compared to their adult counterparts, neonatal MkPs are hyperproliferative and generate 10-fold more Mks. In addition, neonatal Mks show a ten-fold higher proliferative rate compared to adult Mks. Due to the unique uncoupling of proliferation, polyploidization, and cytoplasmic maturation in neonatal Mks, large numbers of fetal/neonatal Mks are smaller and have lower ploidy than their adult counterparts, thus producing fewer pre-platelets than adult Mks.[158] Although relatively high THPO plasma levels are detected in fetuses and neonates compared to adults, the differences between neonatal and adult Mks are primarily due to the intrinsic differences of fetal and adult MkPs. Compared to adult MkPs, neonatal MkPs are more sensitive to THPO *in vitro*. Thus, the rapid proliferation of MkPs and Mks during fetal and neonatal phases might compensate for the lower production of MkPs from HSPCs. Interestingly, newborn mice are less responsive to THPO-receptor-agonist treatment compared to adult mice *in vivo*, as evidenced by the observation that neonatal Mks increase in numbers but

not in size.[159] Neonatal platelets are hyporeactive to platelet agonists such as collagen, thrombin, adenosine 5′-diphosphate and thromboxane due to enhanced primary hemostasis, such as higher hematocrit values, higher von Willebrand factor (vWF) concentrations, and a predominance of ultra-long vWF polymers. [160, 161] In addition, fetal platelets have low levels of integrin-activating proteins and P-selectin (CD62P), and do not readily associate with neutrophils *in vitro* and *in vivo*.[162] The developmental alteration of MkPs and Mks from FL to early postnatal BM indicate a graded influence of ontogenic stage. Such ontogenic changes of MkPs-Mks-platelets are regulated by the dynamic alteration of *Lin28b-Let-7b* which negatively regulates the expression of platelet P-selectin.[163] Most importantly, such ontogenic features of neonatal HPCs and MkPs play a critical role in the pathogenesis of several fetal Mk disorders, including a transient myeloproliferative disorder (TMD) with Down Syndrome (DS) and *Gata-1* mutations as well as acute megakaryocytic type (AMkL) with or without DS.

Transition of fetal to adult erythropoiesis.

Compared to adult HSCs/HPCs, FL HSCs/HPCs display erythroid bias as demonstrated by producing a significantly higher ratio of megakaryocyte-erythroid progenitors/granulocyte-monocyte progenitors and erythroid progenitors/granulocyte progenitors.[164] Such differentiation bias is primarily due to the HSC intrinsic property with minimal contribution from microenvironments. In addition, the proliferation of FL EPs is significantly higher than that of adult EPs. However, FL EPs exhibited delayed differentiation kinetics compared to adult EPs. As a consequence, fetal EPs produce increased number of both burst-forming units and colony-forming units [11]. In addition, there are 3 major differences between fetal and adult mature red blood cells (RBCs)[11]: 1) Fetal RBCs express γ-globin throughout fetal life and are silenced after birth due to the 2nd wave of globin switching (γ to β). About 98% of hemoglobin (Hb) in fetal RBCs is HbF (α2γ2 globins), while about 95% of Hb in adults is HbA (α2β2 globins); 2) Fetal PB contains a large number of nucleated RBCs, which are rare in adult PB;[165] and 3) Compared to adult RBCs, the volume of fetal and neonatal RBC was 21% larger.[166]

Distinct regulatory machinery of fetal and adult HSCs.

The different requirements of genes for the self-renewal, survival and differentiation of fetal and adult HSCs indicates that they are regulated by distinct mechanisms. Studies suggested that the *Lin28b-Let7* axis and transcription factor Sox17 are selectively required for the function and identities of fetal HSCs, while Gfi-1, Tel/Etv6 and Bmi-1 are selectively required for the survival and self-renewal of adult HSCs. Lin28b and Sox17 are highly expressed in fetal HSCs and are repressed in adult HSCs. Mice with *Tie2-Cre* mediated *Sox17* deletion in ECs die at E12.5 due to the lack of the 2nd and 3rd waves of hematopoiesis, suggesting that Sox17 is required for the generation of these 2 waves of hematopoiesis. Mice with polyI:C-induced *Sox17* deletion at postnatal day 2 (P2), P4 and P6 die due to BM failure within 15 days; however, adult mice with induced deletion of *Sox17* are completely normal.[167] Lin28b overexpression in adult BM HSCs induces fetal HSC identities as demonstrated by the reactivation of γ fetal globin genes in RBCs and ability to generate B1a and innate-like γδ T cells.[6] Lin28b plays such a role by repressing Let7 to

de-repress an array of oncogenes including *Myc*, *Ras*, *Blimp1*, *Arid3A* and *Hmga2*.[6, 7, 35, 138, 168, 169] These studies suggest that Lin28b and Sox17 may act as master regulators of developmentally-timed changes in HSC programs and HSC self-renewal potential.[167] However, the knockout of many other genes selectively cause hematopoietic defects in certain stages of development. Reorganizing these genes based on developmental stages provides explanations for the gene requirements of each hematopoietic wave.

The 1st wave of hematopoiesis initiates directly from YS mesoderm. During the 2nd (YS) and 3rd waves (AGM) of hematopoiesis, HPCs are produced by specialized ECs called hemangioblasts through a program called the endothelial-to-hematopoietic transition. After generation, HPCs undergo maturation and expansion to generate blood cells and immune cells to fulfill the demands of development. The HPCs generated in the 1st and 2nd waves primarily provide blood support from E10.5-E15.5 and E15.5-P0, respectively, while HPCs generated in the 3 wave provide blood and immune cell supports for all of postnatal life. The ontogeny of HPCs produced in all 3 waves is controlled by dynamic transcriptional and epigenetic landscapes and is stimulated by microenvironment signaling.[170–172] For example, it was found that regulation of the epigenetic landscape by determination of topologically-associating domain boundaries is controlled by transcription factors TCF3 and MAFB in fetal HSCs, but by transcription factors NR4A1 and GATA3 in adult HSCs.[173] Thus, the genes required for proliferation, differentiation and survival of the 3 waves of HSCs/HPCs might not be the same. One can determine the genes that are required for each wave of hematopoiesis through various Cre-mediated knockout systems targeting different developmental stages.

Sox2^{Cre} mediates gene deletion specifically in the epiblast; *VEC*^{Cre} and *Tie2*^{Cre} mediate gene deletion in hemogenic ECs and hemogenic precursors; *Vav*^{Cre} mediates gene deletion in almost all HSCs/HPCs in YS, AGM and FL. *Mx1*^{Cre} mediates gene deletion in HSCs and HPCs as well as hepatocytes any time after polyI:C induction, while *Rosa26*^{CreERT} mediates gene deletion in all tissue cells any time after 4-hydroxytamoxifen induction. By crossing conditional knock-out animals with such *Cre* lines, the roles of many genes in HPC generation in YS and AGM, HPC maturation, proliferation, differentiation and survival in FL and BM have been studied. In Figure 3, mice with either germline or HEC deletion of any of the genes in group 1, including *Scl1, Runx1, Ezh2, Chd1, β-catenin, Notch1, Gata2* or *Sox17,* failed to generate both the 2nd and 3rd waves of hematopoiesis and died before E15.5, suggesting that such genes are required for the endothelial-to-hematopoietic transition.[174] Mice with *Vav*^{Cre}-mediated deletion of *Gata2, Meis1, Myb, Myc, Pu.1, Erg*, or *Lis1* (Group 2) died between E12.5-E16.5 due to impaired FL hematopoiesis, suggesting that these genes are required for maturation, proliferation, differentiation survival or self-renewal/maintenance of HSCs/HPCs from both the 2nd and 3rd waves of hematopoiesis. Mice with *Vav*^{Cre}-mediated deletion of *Moz, Mof, Satb1, Rae28, Mel18, Eed, Suz12, Prdm16* or *Lsd1* (Group 3) died perinatally or shortly after birth due to impaired fetal BM hematopoiesis. Although FL hematopoiesis can sufficiently support embryonic development in such genetic knock-out mice, HSCs in FL have functional defects, suggesting that these genes are required for maturation, proliferation, differentiation survival and/or self-renewal/maintenance of the HSCs that are generated from the 3rd wave of hematopoiesis. Interestingly, all Group 1 genes (except for *Gata2* which also belongs to Group 2) are not

required for the expansion and maintenance of either FL or adult BM HSCs and HPCs. All Group 2 genes are required for the proliferation, self-renewal, and maintenance of fetal HPCs and adult HSCs, while all group 3 genes are required for the self-renewal and maintenance of adult HSCs. In addition, only *Atg5* and *Sox17* have been assessed by inducing deletion immediately after birth. Although neither of these genes is required in adult HSCs, induced deletion of either *Atg5* or *Sox17* between P0-P7 causes severe defects in HSCs. It was suggested that Atg5-mediated autophagy is required to protect HSCs from stresses during early postnatal life, including oxidative stress, nutritional stress, and microbial infection. Future study will be needed to determine whether Sox17 is also required for the proliferation, self-renewal, and maintenance of fetal HPCs by using the Vav^{Cre} -mediated deletion method.

5. Fetal origin of pediatric leukemia.

Pediatric leukemia presents before 14 years of age. Based on age of onset, pediatric leukemia can be further divided into neonatal leukemia (< 1 month) infant leukemia (1 month to 1 year), and childhood leukemia (1 to 14 years). Studies suggests that the leukemic subtypes and characteristics among neonates, infants and adults are associated with the ontogenic changes of HSCs and HPCs.[13, 14, 175] For example, the high incidence of AMkL and B-ALL in fetal stages might be associated with the transient existence of platelet-biased HSCs and lymphoid-biased drHSCs, respectively. Convincing evidence demonstrated that most pediatric leukemias originate before birth. However, it has not been determined from which of the 3 waves of hematopoiesis these leukemic cells originate. The unique features of pediatric leukemia suggest that at least some may originate from the earlier YS hematopoiesis rather than the 3rd wave of AGM hematopoiesis.[149, 176–185] Understanding the ontology of fetal hematopoiesis is of particular interest in understanding the pathogenesis of childhood blood disorders.

Distinct genetic abnormalities of pediatric and adult leukemia due to the different response of fetal/neonatal HSCs/HPCs and adult HSCs/HPCs to leukemic oncogenes.

As opposed to leukemia in adults and elderly patients, which are dominated by acute myeloid leukemia (AML), childhood leukemias are primarily of the acute lymphoblastic type (ALL > 85%) and AMkL with fewer AML cases.[186] Among ALL cases, ~85% are B cell ALL (B-ALL) and 15% are T cell ALL (T-ALL). The peak incidence of B-ALL is 2–6 years of age, while T-ALL and AML show a relatively constant incidence throughout childhood.

The genetic abnormalities in pediatric leukemia are different from those in adult leukemia. In ALL, Bcr-Abl and Ph-like mutations are most commonly detected in adults while hyperdiploidy and several chromosomal translocations, including t(12;21), t(1;19) and t(17;19), are most common in childhood. Such translocations lead to fusions of *ETV6-RUNX1*, *TCF3-PBX1* and *TCF3-HLF* genes respectively. In AML, mixed lineage leukemia (*MLL*) gene rearrangements (*MLL-r*) and *GATA1* mutations (such as *GATA1s* mutation) are common in infant and early childhood but rare in adults[187–189], while mutations in *FLT3*, *NPM1*, *DNMT3A*, *TET2* and *IDH1* are all common in adults but rare in infancy and

early childhood.[190, 191] Such differences in genetic abnormalities between pediatric and adult leukemia are primarily attributable to the different responses of fetal/neonatal and adult HSCs/HPCs to stimulation of leukemic oncogenes. [12–15]

Transgenic overexpression and animal model studies demonstrated that fetal/neonatal HSCs/HPCs are resistant to genetic transcriptions induced by some adult types of leukemic oncogenes, while adult HSCs/HPCs are resistant to genetic transcriptions induced by some pediatric types of leukemic oncogenes [12–15]. Consequently, some of the pediatric types of oncogenes preferentially induce leukemia when expressed in fetal/neonatal stages while some of the adult types of oncogenes preferentially induce leukemia when expressed in adult HSCs/HPCs. For example: 1) FLT3-ITD induces the expression of a significant panel of genes in adult HSCs/HPCs but does not do so in fetal and neonatal HSCs/HPCs. FLT3-ITD can only induce leukemia development when expressed in adult HSCs/HPCs, while fetal and neonatal HSCs/HPCs are resistant to FLT3-ITD-induced leukemic transformation. A recent study suggests that IFNα-induced HSC maturation and HPC expansion are required for FLT3-ITD-induced leukemia development. Fetal and neonatal HSCs/HPCs lack of such IFNα-induced maturation and expansion.[14, 15] 2) Gata1s induces the expression of megakaryocytic genes and represses erythroid genes in fetal HSCs/HPCs but fails to do so in adult HSCs/HPCs. As a consequence, Gata1s induces a TMD in mice only when overexpressed in fetal/neonatal HSCs/HPCs. Gata1s does so by stimulating fetal HSCs/HPCs to produce significantly more $CD41^{lo}AChE^{-}$ immature megakaryoblasts and $CD71^{+}Ter119^{lo}$ immature pro-erythroblasts. However, Gata1s failed to do so in adult BM HSCs/HPCs[12]; 3) MLL-ENL preferentially induces a significant panel of gene expression in neonatal HSCs/HPCs but does not do so in adult HSCs/HPCs. Thus, MLL-ENL overexpression drives highly efficient leukemic initiation in neonatal HSCs/HPCs but is poorly efficient in doing so in adult HPSCs.[13] Interestingly, some oncogenes induce different types of leukemia in fetal and adult HSCs/HPCs. For example, ETO2-GLIS2 induces the activities of key transcription factors, including ERG, SPI1, GATA1, and CEBPα, in neonatal HSCs/HPCs that are different in adult HSCs/HPCs. ETO2-GLIS2 in fetal HSCs/HPCs induces rapid AMkL development whereas expression in adult BM HSCs/HPCs results in no AMkL types of AML with long latency.[175]

Fetal origin of pediatric leukemia.

Approximately 70–80% of infant ALL are associated with *MLL-r*. The most common genetic abnormality in B-ALL in early childhood (<5 years) is the *ETV6-RUNX1* fusion. Other common types of genetic abnormalities in childhood B-ALL include hyperdiploidy, TCF3-PBX1, TCF3-HLF, and BCR-ABL1. B-ALL with these genetic abnormalities occurs relatively constantly throughout childhood. See Figure 4. All of these chromosomal translocations and alterations in chromosome numbers detected in pediatric leukemias are the primary genetic events. Studies of leukemia patients in monozygotic twins and detection of genetic abnormalities in newborns and their cord blood suggested that most of these genetic abnormalities are *intra-utero* in origin. The prenatal origin of pediatric leukemias has been demonstrated in ALL with MLL-r, ETV6-RUNX1, TCF3-PBX1, BCR-ABL1 and hyperdiploidy. [192]

AMkL is characterized by expression of megakaryocytic lineage markers (*e.*g., CD41, CD42, and CD61).[193] The majority of AMkL cases are diagnosed in early childhood (<4 years) (Figure 4), and most are DS-associated, related trisomy 21.[194, 195] Approximately 10–30% of DS neonates are born with a TMD. Among them, 20–30% progress to AMkL with a few cases developing into ALL by 4 years of age. Nonsense mutations in exon 2 of *GATA1* lead to production of a short form of *GATA1* (GATA1s) and loss of the long form of GATA1; these occur in approximately 90% of DS-TMD and DS-AMkL cases. Such mutations are the only somatic mutations seen in TMD in most instances. During progression of DS-TMD to DS-AMkL, 2–5 additional mutations are found to have occurred. The remaining AMkL develop without DS and are called non-DS AMkL. The most frequently observed chromosomal translocations in non-DS-AMkL are *RBM15-MKL1, ETO2-GLIS2, KAT6A-CREBBP and NUP98-KDM5A.*[196–198] *GATA1s* mutations and chromosomal translocations can be detected in newborns, also suggesting that these originate in fetal life.

MLL-r in infant ALL can always be detected before birth. In most infant ALL cases, MLL-r is the only driver mutation, indicating that *MLL-r* alone is sufficient to induce leukemia in infants.[187] To further support this notion, it was found almost all neonates harboring *MLL-r* developed leukemia within one year. In some cases, ALL is diagnosed immediately after birth. For monozygotic twins, if one develops MLL-r leukemia the other twin always also develops leukemia. There are no healthy *MLL-r* carrier cases reported. However, with ETV6-RUNX1 and TCF3-PBX1, significantly higher frequencies of such fusions can be detected in the PB and/or cord blood of healthy newborns. Depending on the sensitivity of the assays used, *ETV6-RUNX1* fusions can be detected in 0.01–5% of newborns, hundreds of times higher than patients with *ETV6-RUNX1 ALL.*[177–184] *TCF3-PBX1* fusion can be detected in ~0.6% of healthy newborns, also hundreds of times higher than the incidence of *TCF3-PBX1* ALL cases.[185] This suggests that either *ETV6-RUNX1* or *TCF3-PBX1* alone induces only a pre-leukemic clone and is therefore insufficient to induce leukemia development.[199, 200] Secondary genetic events are absolutely required for full-blown ALL in such cases. The fact that a majority of healthy carriers of *ETV6-RUNX1* or *TCF3-PBX1* do not develop leukemia during their lifetimes suggests that *ETV6-RUNX1*$^{+}$ or *TCF3-PBX1*$^{+}$ clones are diminished early in life, just as numbers of drHSCs diminish during the early neonatal period. Such might be the same for hyperdiploidy and some cases of BCR-ABL1. Recent studies suggest that all of these above mentioned genetic abnormalities are primary events. Certain stress conditions such as infections or abnormal T cell/NK cell immune responses are required to induce the pre-leukemic lesions by promoting the clonal evolution of mutant HSCs/HPCs.[200–204] Further additional genetic events are absolutely required for full-blown leukemia to develop.[177, 178, 184, 205–207] Currently, it is unknown whether all these primary genetic abnormalities originate *in utero* or whether some of them can be acquired after birth, specifically for these later onset cases.

Spontaneous regression of leukemia in neonates and infants.

A distinctive feature of neonatal and infant leukemia is the occurrence of spontaneous regression in some cases. The TMD in DS often resolves spontaneously within the first 3 months of life.[208] Spontaneous regression is also frequently observed in neonatal and

infant leukemia cases associated with t(8;16)/KAT6A-CREBBP, especially leukemia cutis. In addition, spontaneous regression has been reported in juvenile chronic myelomonocytic leukemia cases involving *RAS* signaling pathway mutations, such as active mutations of PTPN11 gene.[209] PTPN11 gene mutations are the cause of Noonan syndrome, which increases the risk of developing juvenile chronic myelomonocytic in early childhood. However, the propensity for leukemia development in those with Noonan syndrome declines to baseline later in life despite the persistence of the congenital genetic abnormalities. Two mechanisms have been proposed to explain the spontaneous regression of neonatal/infant leukemia: 1) the nature of the mutant cells. Many of the pediatric leukemias are initiated and propagated in certain types of HPCs that have limited self-renewal capacity such as drHSCs. Such mutant HPCs subsequently differentiate or die in the postnatal microenvironment if the oncogenes failed to induce self-renewal. 2) The changes in the hematopoietic microenvironment from the FL to postnatal BM. The postnatal BM cannot support mutant fetal cell growth due to the absence of certain factors, which remain to be determined.

6. Prospective

Primitive hematopoiesis in YS and definitive hematopoiesis in the AGM region have been well-documented by many earlier studies. Based on these studies, it was suggested that primitive hematopoiesis only supports a short period of blood cell production during early embryonic development and is then replaced by definitive hematopoiesis. Thus, it was believed that all adult hematopoietic cells and immune cells and all hematopoietic disorders are initiated from definitive hematopoiesis. However, since the identification of pre-definitive hematopoiesis in YS (the 2^{nd} wave of hematopoiesis), such a concept must be questioned. As with the 1^{st} and 3^{rd} waves of hematopoiesis, the 2^{nd} wave of hematopoiesis is conserved in all mammals. In mice, the 2^{nd} wave of hematopoiesis provides blood and immune support for fetal development at least up to birth. HSCs/HPCs derived from the 2^{nd} wave of hematopoiesis can still be detected in BM during the first 2 weeks of postnatal life and are completely replaced by HSCs/HPCs derived from the 3^{rd} wave by 3–4 weeks of age in mice. The contribution of HSCs/HPCs derived from the 2^{nd} wave of hematopoiesis to tissue resident Mφ and innate immune cells is well-documented. However, the contribution of this wave of hematopoiesis to other types of blood cells and immune cells in adult is largely unknown. In addition, although HPCs that biologically and functionally similar to EMPs and LMPs have been identified in human FL and fetal BM, [35] the contribution of such HPCs to pediatric leukemia has been suggested, whether such HPCs are true analogues of EMPs and LMPs need to be determined.

Compared to adult ALL, the outcomes for pediatric ALL patients have significantly improved over the last 3 decades owing to the combination of improved chemotherapy and supportive therapy.[210, 211] Currently, 5 year overall survival (OS) in children with ALL is >90%, and the cure rate is approaching 90%.[212] However, ALL in infants and neonates are associated with extremely poor treatment outcomes with only ~60% 5 year OS and <40% cure rate, mostly due to primary chemotherapy refractory disease and/or early relapse.[213, 214] Such disparate outcomes have been primarily attributed to the differences in

genetic abnormalities. [215] However, there is increased evidence suggesting that pediatric leukemias outcomes are associated with the developmental origins of leukemic cells.[216]

Several subtypes of childhood B-ALL have been shown to arise *in utero* including those characterized by *KMT2A-r*, *ETV6-RUNX1*, *BCR-ABL*, *TCF3-PBX1* or *TCF3-ZNF384* gene fusions and hyperdiploid ALL. MLL-r infant ALL blasts share many of the biologic properties with fetal type of B cell progenitors, pre-proB, as demonstrated by studies of immunophenotypic profiles as well as transcriptomic and IgH rearrangement patterns. As is true for as pre-proB progenitors, *MLL-r* infant ALL blasts typically carry immunoglobulin loci with rearranged D-JH but not VH-to-DJH segments, fail to express CD10, and express myeloid and stem cell gene programs.[148] In contrast, blast cells from most childhood-ALL share many biological properties with more mature $CD19^{+}CD10^{+}$ adult types of B-progenitors such as proB-progenitors. However, less is known about the “pre-leukemic” cells within which first-hit events occur. Human modeling data showed that a small portion of $CD34^{+}CD38^{-}CD19^{+}$ cells present in both infant and childhood ALL patients which cells have leukemia stem cell properties. However the primary rearrangements probably occur at the earliest stage in $CD34^{+}CD19^{-}IL\text{-}7R^{+}$ ELPs [176], a kind of cell population shares the biological phenotype with fetal LMPs/drHSCs in mice [149]. The disappearance of pre-leukemic clones observed in most individuals during early infant development suggests that they may be derived from developmentally restricted types of cells [177–185]. Confirmation of the leukemic cell of origin is fundamental to identification and understanding of the cellular and molecular mechanisms that underlie leukemogenesis. Future studies need to determine whether pediatric ALL originates from YS LMPs/drHSCs, while infant/neonatal AMkL originate from YS EMPs.

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Availability of data and material

This is not applicable for this review.

Abbreviations

AGM	Aorta-mesonephros-gonad
Angptl2	Angiopoietin-like 2
AMkL	Acute megakaryocytic type
AML	Acute myeloid leukemia
ALL	Acute lymphoblastic type
BM	Bone marrow
CSF1	Colony-stimulating factor 1

CXCL12	C-X-C Motif Chemokine Ligand 12
drHSCs	Developmentally-restricted HSCs
DS	Down Syndrome
E	Embryonic day
ECs	Endothelial cells
EPO	Erythropoietin
EMPs	Erythro-myeloid progenitors
ECM	Extracellular matrix
FL	Fetal liver
HSCs	Hematopoietic stem cells
HPCs	Hematopoietic progenitor cells
Hb	Hemoglobin
imHSCs	Immature HSC
IGF2	Insulin-like growth factor 2
IL	Interleukin
IFN	Interferon
KITL	KIT ligand
LMPs	Lympho-myeloid progenitors
Mφ	Macrophages
Mks	Megakaryocytes
MLL	Mixed lineage leukemia
ELPs	Early lymphoid progenitors
PB	Peripheral blood
PCW	Post-conception weeks
pri-Eps	Primitive erythroid progenitors
RBCs	Red blood cells
THPO	Thrombopoietin
TSLP	Thymic stromal-derived lymphopoietin
TMD	Transient myeloproliferative disorder

vWF	von Willebrand factor
YS	Yolk Sac

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Key points:

1. Hematopoiesis undergoes dynamic alterations during fetal-to-neonatal and neonatal-to-adult transitions.
2. Both fetal and adult types of HSCs and HPCs exist in fetuses and neonates.
3. The fetal types of HSCs and HPCs are expanded in fetal liver and fetal bone marrow, and diminish during neonatal-to-adult transition.
4. Adult types of HSCs and HPCs undergo dynamic and gradual maturation in bone marrow during perinatal-to-adult transition.
5. Almost all neonatal and infant leukemias originate from the fetal stage and have a poor prognosis.
6. Most subtypes of leukemia in childhood are also of fetal origin but have a more favorable prognosis.

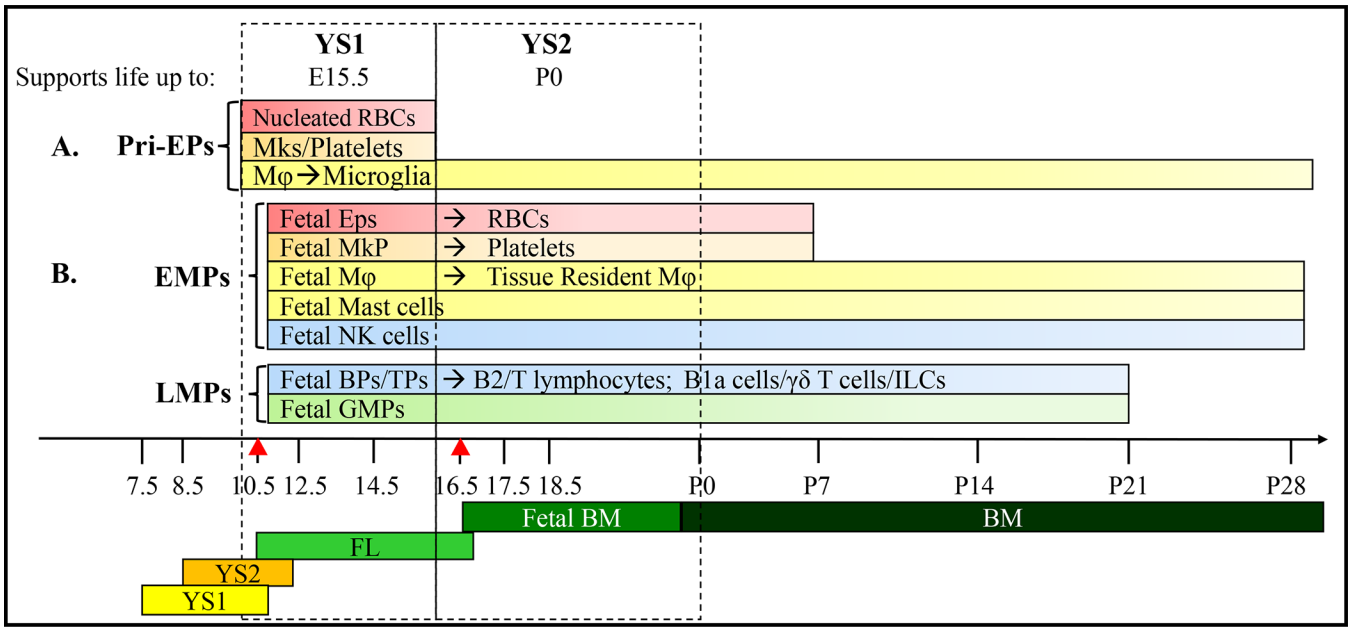

Figure 1. The contribution of 2 waves of YS hematopoiesis to embryonic and postnatal blood/ immune cells.

A. The 1st wave of YS hematopoiesis (YS1) is initiated on E7.5. pri-HSCs generated in this wave primarily produce nucleated RBCs and Mks/platelets to support embryonic survival up to E15.5. In addition, Mφ produced in this wave generate microglia in the brain for the remainder of life. **B.** The 2nd wave of YS hematopoiesis (YS2) starts on E8.5. EMPs and LMPs generated in this wave migrate to FL and then fetal BM to produce RBCs, platelets, innate immune cells and granulocytes. This wave of hematopoiesis can support the survival of the embryo up until birth. In addition, Mφ and innate immune cells infiltrate the embryo's tissues and renew themselves, maintaining tissue resident Mφ and immune cells for the remainder of life.

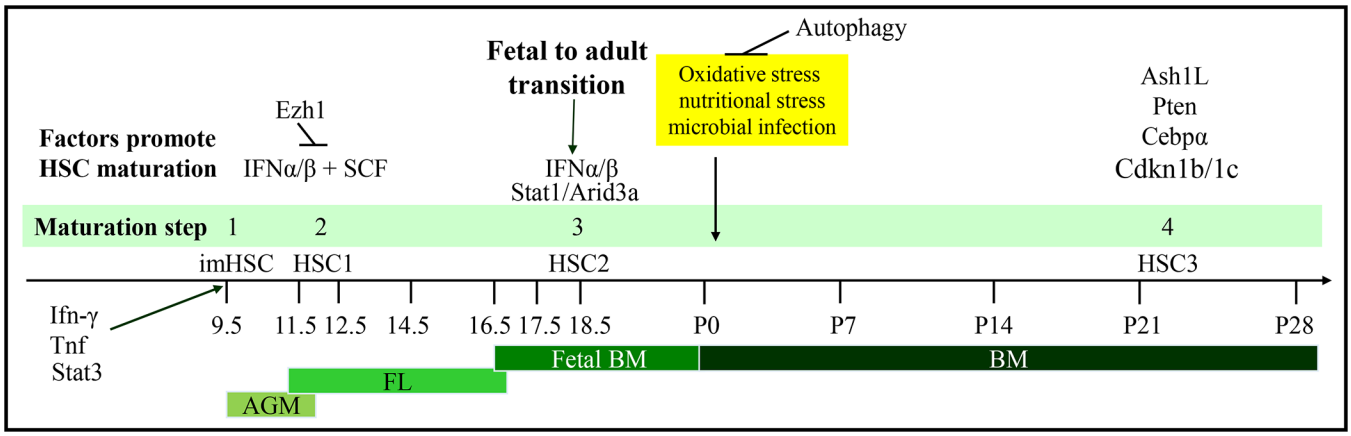

Figure 2. Maturation of AGM hematopoiesis during embryonic, postnatal and adult life.

Definitive hematopoiesis is initiated in the AGM region at E9.5. imHSCs generated at this wave of hematopoiesis migrate to FL at E10.5, to fetal BM at E16.5, and finally are maintained in adult BM for lifetime hematopoiesis. During this process, imHSCs undergo multiple steps of maturation. First, inflammatory cytokines such as IFN and the hematopoietic cytokine SCF stimulate imHSCs to develop self-renewal and hematopoietic engraftment capacities to become functional HSCs (HSC1) in FL. HSC1 proliferate and expand in FL before colonizing fetal bone marrow. Starting at E18.5, stimulated by IFNs, HSC1 in BM gradually transition to adult HSCs (HSC2) by losing their fetal features and gaining adult HSC characteristics. The full fetal-to-adult maturation of HSCs is completed at approximately 3 weeks postnatal, at which time the majority of HSCs become quiescent in the cell cycle. Ash1L, Pten and Cebpα might be responsible for this quiescent state through regulation Cdkn1b and Cdkn1c expression, which are negative regulators of the cell cycle. Although the major environmental challenges of HSCs occur immediately after birth, HSCs are protected from such challenges by autophagy.

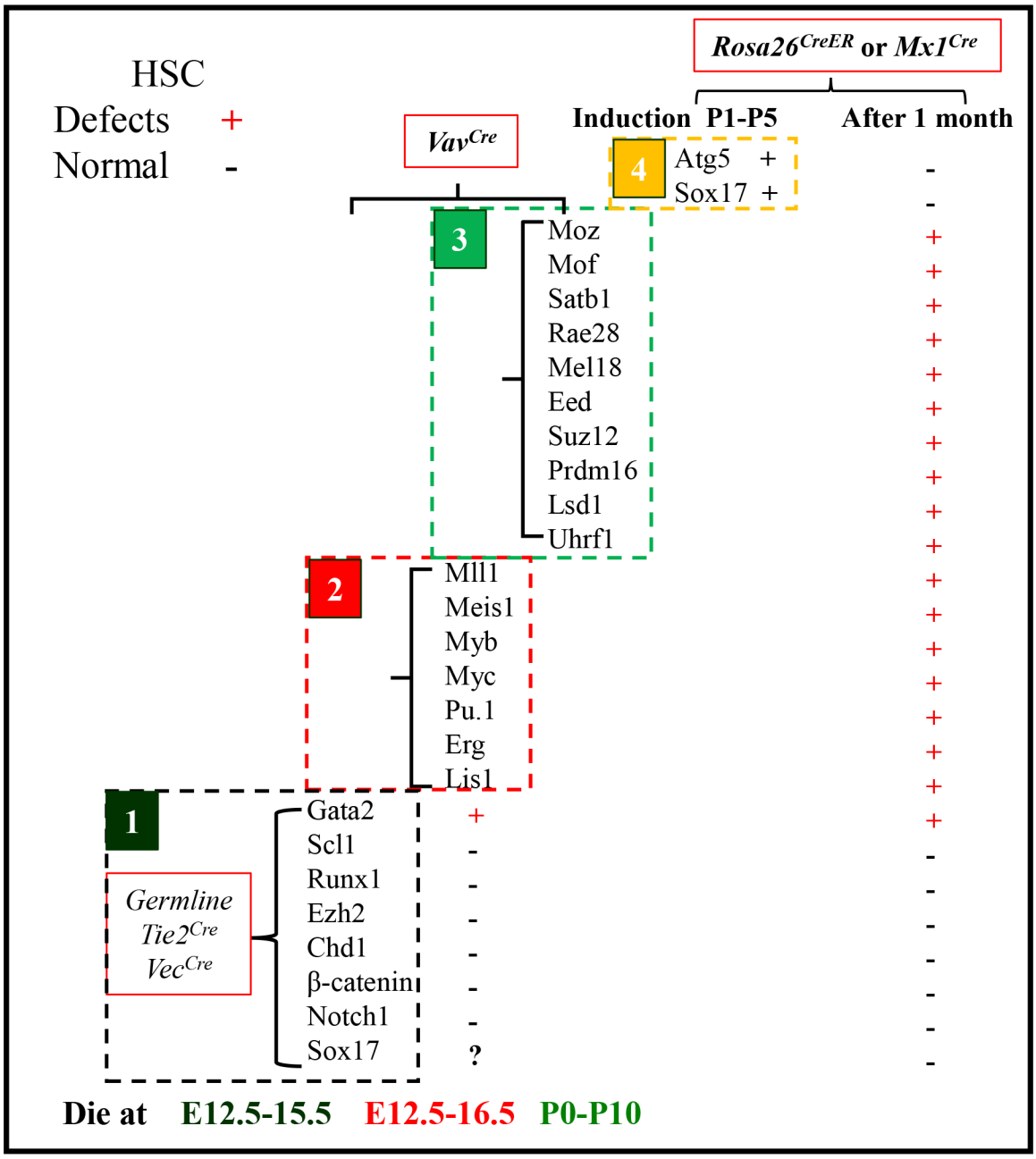

Figure 3. Genes required for the generation, maturation and maintenance of HSCs as demonstrated by knock-out mouse studies.

VEC^{Cre}-mediated gene deletion in hemogenic ECs. *Tie2*^{Cre} mediates gene deletion in hemogenic precursors of hematopoietic and endothelial lineages including the majority of ECs and a subset of HCs. *Vav*^{Cre} mediates gene deletion in FL HSCs/HPCs. *Mx1*^{Cre} mediates gene deletion in HSCs/HPCs and hepatocytes and time post polyI:C induction. *Rosa26*$^{Cre\text{-}ERT}$ mediates gene deletion in all types of tissue cells after 4-hydroxytamoxifen induction. Genes in Group 1 are not necessary for the generation of the 1st wave of YS hematopoiesis but are required for the generation of the 2nd wave of YS hematopoiesis and AGM hematopoiesis. Genes in Group 2 are not necessary for hematopoietic initiation

but are required for maturation, proliferation, differentiation survival and/or self-renewal/maintenance of HSCs/HPCs from both the 2nd and 3rd waves of hematopoiesis. Genes in Group 3 are only required for the maturation, proliferation, differentiation, survival, and/or self-renewal/maintenance of the functional HSCs that are generated from the 3rd wave of hematopoiesis. (+) indicates severe defects in HSCs/HPCs after deletion of the indicated gene. (−) indicates normal hematopoiesis after deletion of the indicated gene.

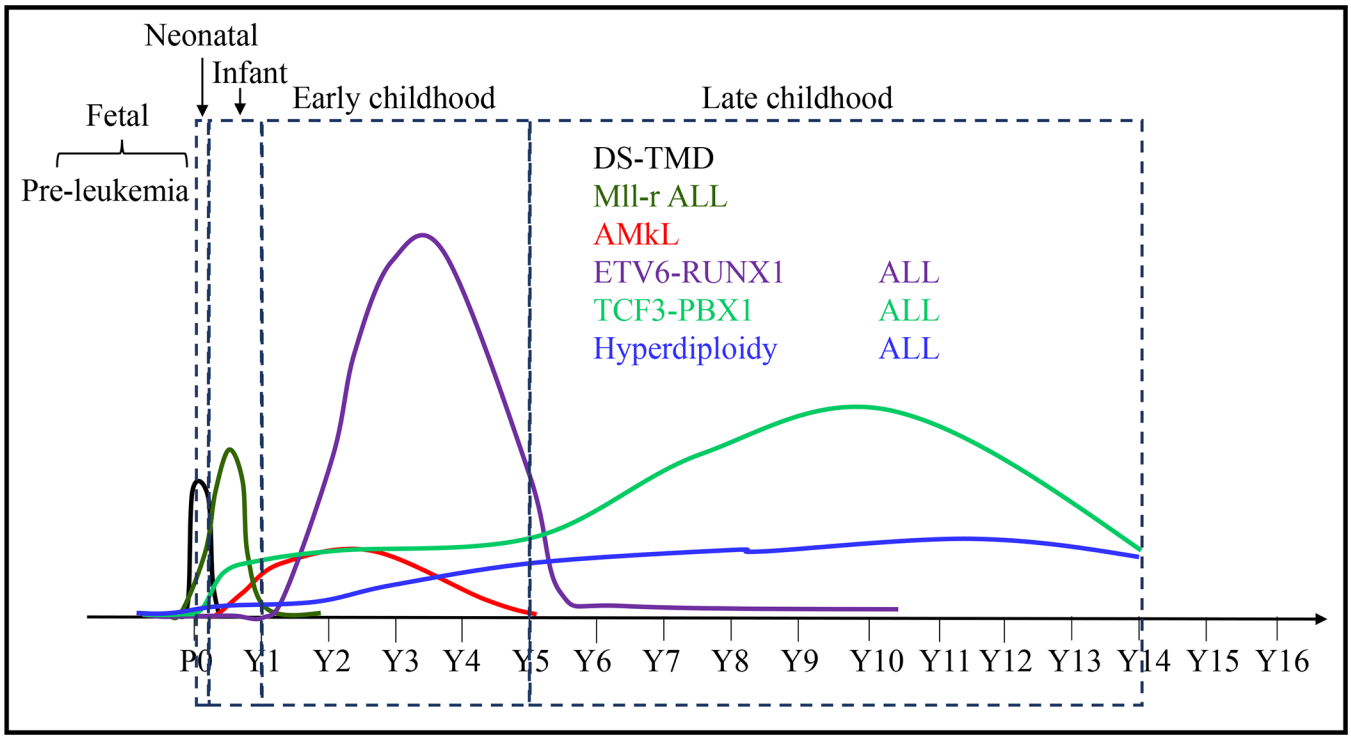

Figure 4. Almost all infant/neonatal leukemias and most of childhood leukemias originate from infant.

Almost all primary genetic abnormalities can be detected in fetal HSCs/HPCs, suggesting a fetal stage of pre-leukemia development. The different peaks of leukemia onsets induced by distinct genetic abnormalities are determined by: 1) efficiency of leukemia induction capacity of the primary genetic abnormalities; 2) the occurrence time of the secondary genetic abnormalities. For examples, Gata1s or MLL-r alone is sufficient to induce TMD or ALL development respectively, explaining the early onset peaks of DS-TMD and ALL in neonatal and infant. Secondary genetic mutations are required for the leukemia onsets induced by other primary genetic abnormalities, explaining the latter onset peaks of childhood AMkL and ALL.

Table 1.

Phenotypes of HSCs and HPCs during fetal development

Development Stage	Cell Population	Phenotype
E7.5–10.5 YS	Primitive Erythroid Progenitor (Pri-EP)	$CD41^{+}Kit^{+}Sca1^{-}$
E8 YS	Pre-Macrophage (Mφ)	$CD45^{+}CX3CR1^{+}$
E8.5 YS	Hemogenic Endothelial cells (ECs)	$CD31^{+}TIE^{+}CD45^{-}CD41^{-}Runx1^{+}$
E8.5–9.5 YS FL, FBM and Neonatal BM	Erythro-Myeloid Progenitor (EMP)	$CD45^{low}CD41^{+}Kit^{+}AA4.1^{+}CD16/32^{+}Sca1^{-}$ $CD45^{+}CD34^{+}CD44^{+}$ (H)
E9.5 YS FL, FBM and Neonatal BM	Lympho-Myeloid Progenitor (LMP)	$Lin^{-}Kit^{+}$Rag1-$GFP^{+}Flt3^{+}IL7R\alpha$ in YS, also $Csf1r^{+}ThpoR^{+}$ $CD45^{+}KIT^{+}$ $FLT3^{+}IL7R\alpha^{+}$ in FL
E9.5 YS FL, FBM and Neonatal BM	Developmentally-Restricted HSC (drHSC)	$Lin^{-}Sca1^{+}Kit^{+}CD150^{low}Flt3^{+}IL7R\alpha^{+}$ $Rag1^{+}$
Adult BM	Lymphoid-Primed Multipotent Progenitor (LMPP)	$Lin^{-}Sca1^{+}Kit^{+}CD150^{low}Flt3^{hi}Rag1^{+}$
E8.5–9.5 YS	Common Primitive-Definitive Precursor (CPDP)	$CD45^{-}CD41^{+}AA4.1^{-}Kit^{med}$
E8.5–9.5 YS	Multipotent Lympho-Myeloid Progenitor (MLMP)	$CD45^{+}Kit^{high}AA4.1^{+}CD41^{+}$
E8.5–9.5 YS	Multipotent Progenitors in YS	$CD43^{+}KIT^{high}Sca1^{+}CD11A^{-}$
E8.5–9.5 YS	Myeloid-Restricted Progenitor	$CD45^{+}$ $Kit^{high}AA4.1^{-}CD41^{+}$
FL	Erythroid Progenitors (EP)	$CD45^{-}Kit^{+}Ter119^{-}$
E9.5–12.5 Placenta	Placenta HSCs	$CD34^{med}$c-kit^{hi}
AGM E9.5 E10.5 E11.5	**imHSCs** pro-HSCs pre-HSC I pre-HSC II	$VEC^{+}CD41^{lo}CD43^{-}CD45^{-}$ at as early VEC^{+} $CD31^{+}CD41^{lo}CD43^{+}CD45^{-}$ $VEC^{+}CD31^{+}CD41^{lo}$ $CD43^{+}CD45^{+}$, $PROCR^{+}$
E12 FL E14 FL FL	HSCs HSCs HSCs	$Lin^{-}Sca\text{-}1^{+}Mac\text{-}1^{low}CD201^{+}$ $CD45^{+}CD150^{+}CD48^{-}$ $CD201^{+}$ $CD150^{+}CD48^{-}Sca1^{+}CD11b^{+}CD45^{+}$ $CD41^{-}Lin^{-}$ $DAPI^{-}$
FL and FBM	B-1 Cell Progenitor Cells (mouse)	$AA4.1^{+}CD19^{+}B220^{lo/-}$
FL and Fetal BM (Human)	**Adult Type** B cell Progenitors **Fetal Type** Early Lymphoid Progenitors (ELPs)-Mouse LMP Equivalent Pre-ProB	$CD34^{+}CD19^{+}CD10^{+}$ $CD34^{+}IL7R^{+}CD19^{-}CD10^{-}$ $CD34^{+}CD19^{+}CD10^{+}$

Table 2.

HSC niches during development

Development Stage	Niche Cells	Hematopoietic Supporting Factors
AGM	Mesenchymal Cells Mφ	Notch1 and Wnt, IFN-γ, IL-3, TNF, IFNα and IFNβ
FL	Endothelial cells[121, 217] Desmin^{+} Stellate Cells[114, 121] p75NTR^{+} Stellate Cells[110] Dlk1^{+} or CD3^{+}DLK1^{+}SCF^{+} Hepatocyte Progenitors[105, 109, 111, 112, 120, 121] Lyve-1^{+} Sinusoidal Network Nestin^{+}NG2^{+} Pericytes of Portal vessels[117] Neutrophils	CXCL12, KITL, WNT5A IL-3, IL-6, CSFs and EPO CSF1, IGF2, THCO, KITL, EPO, IGF1, IL-1, FLT3 Ligand and Oncostatin M KITL, IGF2, Angpt2, Angpt3, THPO, CXCL12, α-fetoprotein, bile acids, VCAM1, Fibronectin1, Vitronectin1, Laminin-b1 and Laminin-c1, DHA Undefined factor(s) maintain slow cycling state of HSCs KITL, Angptl2, and IGF2 MMP9 for HSCs release from FL
Fetal BM	Osterix^{+} Stromal Progenitors[128–130]	CXCL12, Osteopontin, VEGF, Slit, and SCF, Collagen, N-cadherin, VCAM, Selectins, Fibronectin, Integrins