SnapShot: Hematopoiesis

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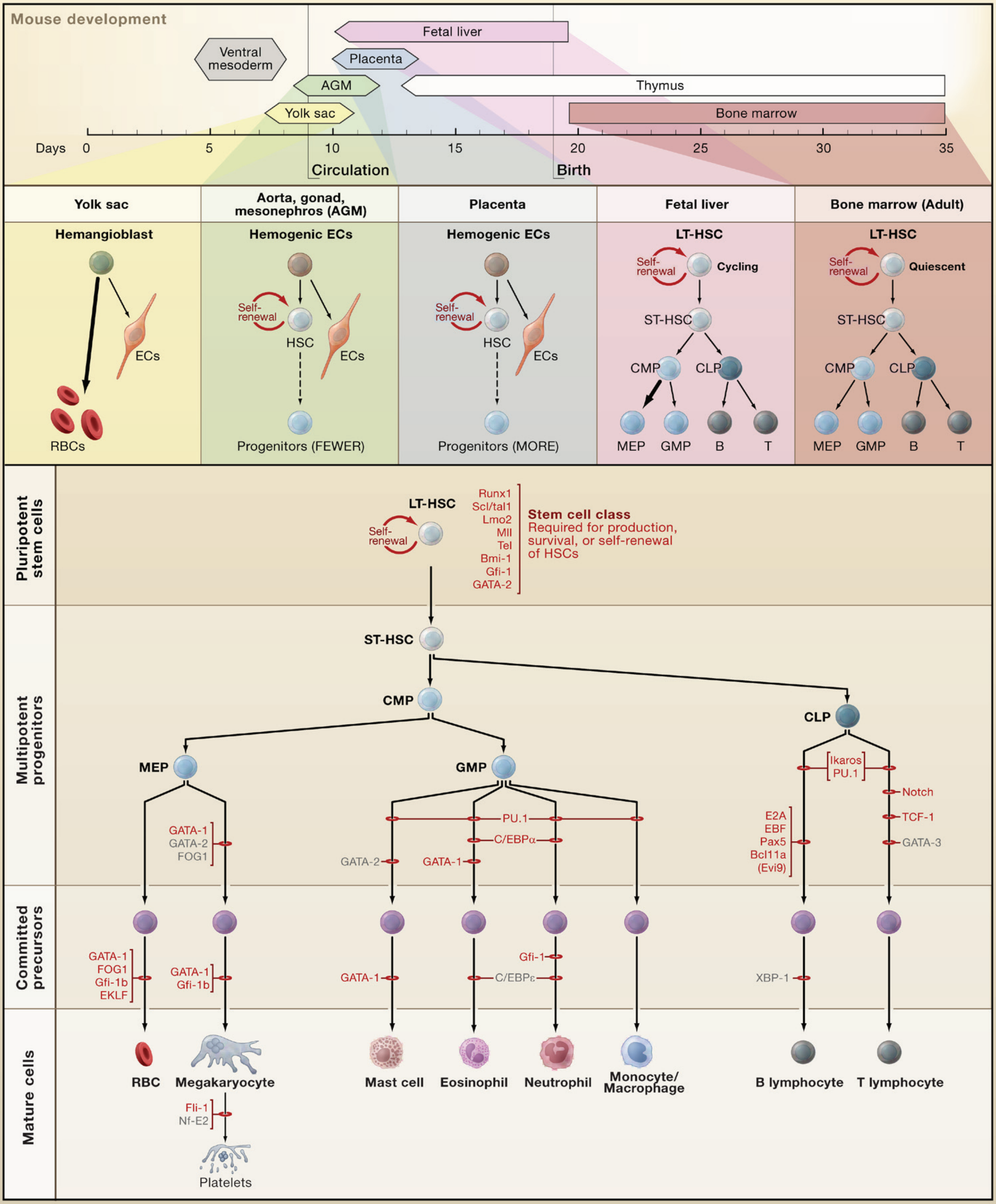

 See online version for legend, abbreviations, and references.

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Cell

The upper panel depicts the stages of hematopoiesis in the mouse. Hematopoietic stem cells (HSCs) are derived from ventral mesoderm, and the sequential sites of hematopoiesis during development include the yolk sac, an area surrounding the dorsal aorta termed the aorta-gonad mesonephros (AGM) region, the fetal liver, placenta, and finally the bone marrow. The properties of HSCs in each site differ, presumably reflecting diverse niches that support HSC expansion and/or differentiation and intrinsic characteristics of HSCs at each stage.

The initial wave of blood production in the mammalian yolk sac is termed "primitive." The primary function for primitive hematopoiesis is production of red blood cells (RBCs) that facilitate tissue oxygenation as the embryo undergoes rapid growth. The hemangioblast of the yolk sac is proposed to give rise to both blood and endothelial cells (ECs). The next region of hematopoiesis is the AGM. It has been proposed that the AGM forms hemogenic ECs in the ventral wall of the aorta that bud off HSCs. Significant numbers of HSCs are also found in the mouse placenta. Placental HSCs could arise through de novo generation or colonization upon circulation, or both. The relative contribution of each of the above sites to the final pool of adult HSCs remains largely unknown. Subsequent definitive hematopoiesis involves the colonization of the fetal liver, thymus, spleen, and ultimately the bone marrow. In definitive hematopoiesis, long-term HSCs (LT-HSCs) give rise to short-term HSCs (ST-HSCs). ST-HSCs produce common myeloid progenitors (CMPs) and common lymphoid progenitors (CLPs). CLPs are the source of committed precursors of B and T lymphocytes, whereas CMPs give rise to megakaryocyte/erythroid progenitors (MEPs) and granulocyte/macrophage progenitors (GMPs). GMPs give rise to the committed precursors of mast cells, eosinophils, neutrophils, and macrophages.

The transcription factors that govern hematopoiesis in the mammals are depicted in the lower panel. The stages at which hematopoietic development is blocked in the absence of a given transcription factor, as determined through conventional gene knockouts, are indicated by red loops. The factors depicted in red have been associated with oncogenesis. Those factors in black have not yet been found translocated or mutated in human/mouse hematologic malignancies. Among the transcription factors required for HSC production, survival, or self-renewal are MLL (for mixed lineage-leukemia gene), Runx1, TEL/ETV6, SCL/tal1, and LMO2. These genes account in toto for the majority of known leukemia-associated translocations in patients. In these instances, the translocations either deregulate expression of the locus, as in the case of *SCL/tal1* and *LMO2* in T cell acute leukemias, or generate chimeric fusion proteins, as in myeloid and lymphoid leukemias associated with *MLL*, *Runx1*, and *TEL/ETV6*. In the absence of SCL/tal1 and its associated protein partner, LMO2, no blood cells are generated. Within the primitive system at the yolk sac stage, SCL/tal1 and LMO2 are thought to function within the hemangioblast to specify a blood rather than a vascular fate. The genes encoding MLL and Runx1 proteins are essential for generation of HSCs within the AGM (and possibly at other sites). In the absence of *Runx1*, no hematopoietic clusters (representing presumptive HSCs) form in the dorsal aorta in mice. Other factors appear to have more lineage-restricted roles and some, such as *PU.1*, *Gfi-1*, and *C/EBP*α, are important in both HSCs and for the differentiation of specific lineages.

Abbreviations

ECs, endothelial cells; RBCs, red blood cells; LT-HSC, long-term hematopoietic stem cell; ST-HSC, short-term hematopoietic stem cell; CMP, common myeloid progenitor; CLP, common lymphoid progenitor; MEP, megakaryocyte/erythroid progenitor; GMP, granulocyte/macrophage progenitor.

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