Mouse Hematopoietic Stem and Progenitor Cell Phenotypes and Frequencies

HSPC Compartment	Sub-Population	Properties	Lineage Potential	Approximate Frequency in Young Whole BM (Unless Otherwise Noted)	HSPC Markers																					
					Ly6c	Sca1 (Ly6A/E)	T1/ST2 (IL-33R)	CD16/32 (FcγR II/III)	CD27	CD34	CD41	CD43	CD48	CD90 (Thy1)	CD93 (AA4.1)	CD105 (Endoglin)	CD110 (c-mpl)	CD115 (M-CSF R)	CD117 (c-Kit)	CD123 (IL3Rα)	CD127 (IL7Rα)	CD135 (Flk2/Flt3)	CD150	CD229	CD244	Lin[a]
Multipotent Stem Cells	LT-HSC[1-37]	Serially engraftable, self-renewing progenitor cells capable of providing long-term (> 16 weeks) reconstitution in primary transplant recipients. Refined purification strategies can isolate populations with LT-HSC purity as high as 67%. Most protocols report a purity of 20 - 50%. Cells actively efflux Hoeschst 33342 and Rhodamine 123 fluorescent dyes. Subpopulations express ESAM1 and EPCR (CD201) and do not express CD49b.	Multilineage	0.0005 - 0.05%		+			-	-		+	-	lo	-	+	+		+		-	-	+	+/-	-	-
	IT-HSC[38]	A distinct sub-class from short-term HSCs, IT-HSCs persist for 6 - 8 months post-transplantation before becoming extinct. Cells actively efflux Rhodamine 123 and express CD49b.	Multilineage	0.1 - 0.2% of Lin⁻Sca1⁺c-Kit⁺ cells		+				lo			-						+			lo	+			-
Multipotent Progenitor Cells	ST-HSC[1,8,18,19,21,29,31,33,34,39]	Limited capability for self-renewal. These cells give rise to transient multilineage reconstitution, which peaks at 4 - 6 weeks post-transplantation, with myelopoiesis declining to negligible levels after 10 - 16 weeks. Subpopulations express ESAM1.	Multilineage	0.0006 - 0.03%		+			+	+	lo		-	lo					+		-	+	-	+/-	+/-	-
	MPP[32-34,40,41]	Limited engraftment with no capability for self-renewal. Several subsets have been defined that are biased to lymphoid, granulocyte-macrophage, megakaryocyte, or erythroid lineages. Subpopulations heterogeneously express ESAM1 and VCAM (CD106).	Multilineage	Represent 5 - 75% of Lin⁻Sca1⁺c-Kit⁺ cells		+			+	+	+		+	-			+		+	+	-	+	+/-			-
	LMPP[18,34,42,43]	Short-term (~6 weeks) reconstitution in irradiated hosts. 25% of the brightest Flt3⁺ LSKs are lymphoid-biased, possessing T, B, and NK cell potential. Cells express low levels of ESAM1. Subpopulations express CD44.	Mostly lymphoid	0.06%		+				+	lo		+				-		+	+	+	hi	-			-
Oligopotent Progenitor Cells	CMP[44-46]	Generate a mixture of myeloid cell types (GEMM/GM/G/E/Meg/Mac) as well as DCs in vitro. Very low B cell differentiation potential. CMPs give rise to GMPs and MEPs. Radioprotective.	Myeloid	0.2%		-		lo		int	+					-	+		+				-			-
	GMP/PreGM[44,45,49,50]	Give rise to granulocytes, macrophages, and DCs. Not radioprotective.	Granulocyte-macrophage and DCs	0.4% or ~17% of Lin⁻Sca1⁻c-Kit⁺ progenitor cells		-		hi		+	-					-			+	+			-			-
	MEP/PreMegE[34,44,47-51]	Give rise to megakaryocytic or erythroid colonies, or a mixture of both colony types. Generate a large number of CFU-S8 colonies at a frequency of ~0.1%. Produce reticulocytes in vitro. Express EPO receptor. Radioprotective.	Megakaryocytic-erythroid	0.1% or ~7.4% of Lin⁻Sca1⁻c-Kit⁺ progenitor cells		-		-/lo		-/lo	-/lo					lo			+	-			-			-
	CLP[60-64]	Give rise to T, B, NK cells, DC, and ILC progenitor cells. Do not express B220 and Ly6d. Express CD44.	Lymphoid and DCs	0.01%		int			+					-	-				int		+	+				-
	EILP[65]	Give rise to all NK cells, ILCs, and DCs, but not T or B cells. Identified using a TCF-1 knock-in reporter.	NK cells, ILCs, and DCs	0.07%		lo								-					lo		-	lo				-
	ETP/DN[72-84]	Early thymic progenitor cells. Similar subpopulations identified in blood and bone marrow. ETPs are a subset of DN1 thymocytes. ETPs possess T, B, NK cell, DC, granulocyte, and macrophage potential. Express CD24 and CD44.	Mostly T cells	~0.01% of total thymocytes		+			hi					lo	+				+		-/lo	+				-
Lineage-Restricted Progenitor Cells	MkP[48-50]	Generate megakaryocytic colonies. Transient in vivo generation of platelets.	Megakaryocytic	0.01% or ~1.5% of Lin⁻Sca1⁻c-Kit⁺ progenitor cells		-		-/lo		-/lo	hi					lo	+		+		-	-	+			-
	PreCFU-E (EP)[49,50]	Generate erythoid colonies. In vivo production of reticulocytes. Low radioprotective capacity. Express receptors for EPO and transferrin.	Erythroid	~2.4% of Lin⁻Sca1⁻c-Kit⁺ cells		-		-/lo			-/lo					hi			+			-	+			-
	CFU-E (EP)[49-51]	Generate single-cluster erythroblasts. Express receptors for EPO and transferrin. Not radioprotective.	Erythroid	~8.6% of Lin⁻Sca1⁻c-Kit⁺ cells		-		-/lo			-/lo					hi			+	-	-	-	-			-
	cMoP[52]	Exclusively produce monocytes in culture and, upon in vivo adoptive transfer, able to generate monocytes and macrophages. Identified using a CX3CR1 knock-in reporter.	Restricted to the monocyte lineage	~0.39%	+													+	+			-				-
	NP[53]	Derived from oligopotent Lin⁻Sca1⁻c-Kit⁺CD34⁺FcγRII/III⁺Ly6C⁻ GMPs. Highly enriched for neutrophil-producing granulocytic progenitor cells.	Mostly neutrophils	~22.5% of GMPs	+	-		+		+								lo	+							-
	BMCP[54]	Derived from β7[lo] GMPs, these clonal bipotent progenitor cells, present only in the spleen, give rise to basophils and mast cells. Reconstitute mucosal and connective tissue mast cells. Do not express FcεR1α.	Basophils and mast cells	0.005% of total spleen cells			lo	+		+				+					+							-
	MCP[54-56]	Monopotent progenitor cells that exclusively generate mast cells in vitro and in vivo. Found in the intestine and bone marrow, the latter being highly enriched for MCPs. Lineage relationships unclear with GMPs, CMPs, and MPPs being able to generate mast cells. Express low levels of FcεR1α.	Mast cells	0.01% of all CD45⁺ intestinal hematopoietic cells	-	-	+	+	-	+									+							-
	BaP[54]	Differentiate exclusively into basophils. Express high levels of FcεR1α.	Basophils	0.06%			lo			+				-					-							-
	EoP[57]	Derived from HSCs, CMPs, and GMPs. Represent an important in vivo intermediate in eosinophil development that specifically responds to helminth infection.	Eosinophils	0.05%		-				+									lo							-
	CDP[58,59]	Also known as pro-DCs; produce all DC types in vitro and in vivo.	Mostly cDCs and pDCs	0.1%	-			lo				+						+	int		-	+				-
	CHILP[66]	Differentiate into all ILC subsets, including LTi cells, but not NK cells. Identified using a Id2 knock-in reporter. Express integrin α4β7.	ILCs	0.002%		lo	lo		+						-				+		+	-			+	-
	ILCP[67]	Give rise to all ILC subsets but not LTi cells. Identified by a PLZF knock-in reporter. Do not express CD161 and CD335. Express integrin α4β7.	ILC1, ILC2 and ILC3	PLZF[hi] population represents ~5% of Lin⁻IL-7Rα⁺c-Kit⁺α4β7[hi] cells		-	-							+					+		+					-
	pre-NKP[68,69]	NK-restricted precursor cells. Developmental intermediate between CLPs and NKPs. Similar in phenotype and function to pre-pro NKPa cells. Express CD314. Do not express CD161 and CD335.	NK cells	0.001%					+										lo		+	-		+		-
	NKP[69-71]	NK-restricted precursor cells. Developmental intermediate between pre-NKPs and iNK cells. Express CD314. Do not express CD49b, CD161, and CD335.	NK cells	< 0.001%					+					+					lo		+	-		+		-
	BLP[62]	The earliest lineage-restricted progenitor cells committed to B cell development. Express low levels of B220 but not CD19. Express high levels of Ly6d.	Mostly B cells	~50% of CLPs		+			+	+									lo/int		+	+				-

Key

+	Expressed on all or most cells
hi	Highly expressed on most cells
int	Intermediately expressed on all or most cells
lo	Lowly expressed on all or most cells
+/-	Heterogenously expressed in cell population
lo/int	Lowly or intermediately expressed on all or most cells
-/lo	Not expressed or lowly expressed on all or most cells
-	Not expressed on all or most cells
a	Lineage markers include combinations of the following: CD2, CD3, CD4, CD5, CD8, CD11b (Mac1), CD11c, CD19, B220, Gr1, IgM, Ly1, Ly6G, MHC class II, NK1.1, TCRβ, TCRδ, TCRγδ, Ter119, and 7-4.
	Not known/Not applicable

Abbreviations

BaP: basophil progenitor; BLP: B lymphoid progenitor; BMCP: basophil-mast cell progenitor; cDC: conventional dendritic cell; CDP: common dendritic cell progenitor; CFU-E: colony-forming unit – erythroid; CFU-S8: colony-forming unit – spleen at day 8; CHILP: common helper-like innate lymphoid precursor; CLP: common lymphoid progenitor; CMP: common myeloid progenitor; cMoP: common monocyte progenitor; DC: dendritic cell; DN: double negative; EILP: early innate lymphoid progenitor; EoP: eosinophil progenitor; EP: erythroid progenitor; ETP: early thymic progenitor; G: granulocyte; GEMM: granulocyte, erythrocyte, megakaryocyte, monocyte; GM: granulocyte-monocyte; GMP: granulocyte-monocyte progenitor; HSC: hematopoietic stem cell; HSPC: hematopoietic stem and progenitor cell; Id2: inhibitor of DNA binding 2; ILC: innate lymphoid cell; ILCP: innate lymphoid cell progenitor; iNK: immature NK; IT-HSC: intermediate-term hematopoietic stem cell; Lin: lineage; LMPP: lymphoid-primed multipotent progenitor; LSK: Lin⁻Sca1⁺c-Kit⁺; LT-HSC: long-term hematopoietic stem cell; LTi: lymphoid tissue inducer; Mac: macrophage; MCP: mast cell progenitor; Meg: megakaryocyte; MEP: megakaryocyte-erythroid progenitor; MkP: megakaryocyte progenitor; Mono/Mφ: monocyte/macrophage; MPP: multipotent progenitor; NK: natural killer; NKP: natural killer progenitor; NP: neutrophil progenitor; pDC: plasmacytoid dendritic cell; PreCFU-E: pre-colony-forming unit – erythroid; Pre-GM: pre-granulocyte-monocyte; PreMegE: pre-megakaryocyte-erythroid; RBC: red blood cell; ST-HSC: short-term hematopoietic stem cell.

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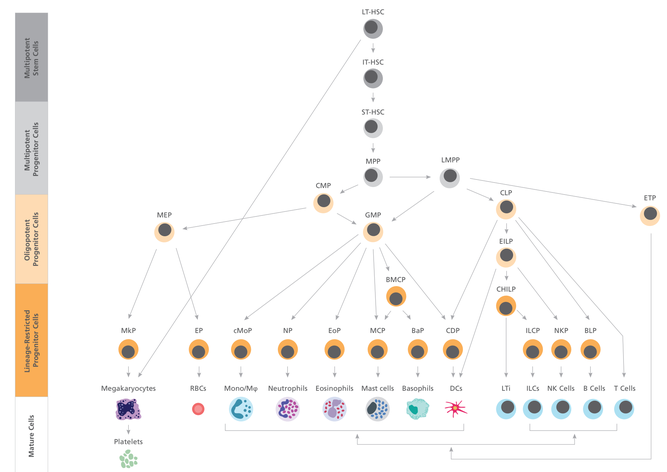
Hematopoietic Stem and Progenitor Cell Subset Hierarchy



Model of mouse hematopoiesis and inferred trajectories (arrows) of HSPC differentiation leading to the production of mature blood cells. The overarching concept of this model suggests that HSC populations, which reside at the apex of a hierarchical organization of cellular relationships, give rise to several discrete intermediate progenitor populations including multipotent, oligopotent, and lineage-restricted progenitor cells. Whilst this simplified model assumes homogeneity in HSPC populations, and thus an equal ability to produce all blood cells, single cell transplantation assays as well as transcriptional profiling have revealed significant heterogeneity within subpopulations that are intrinsically biased toward the generation of certain blood lineages. For example, differentiation of HSCs to platelets may not involve transitioning to CMP or MEP intermediates and can be achieved directly via megakaryocyte-primed HSCs. It must be highlighted that models of HSPC development are continually evolving, with the current consensus indicating that step-wise commitment of HSPCs from one intermediate to the other, as traditionally depicted, may not be representative of the situation in vivo. Rather, cell intrinsic and extrinsic inputs may guide HSC development along a continuum with cells gradually differentiating and passing through a small set of intermediate stages. Definition of acronyms can be found under "Abbreviations" below the table.

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