



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

501. HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

New Insights into Hematopoietic Redefinition and New Paradigms in Hematopoietic Hierarchy Roadmap

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The definition of hematopoietic progenitor cells (HPCs) has not been standardized. Surface markers are insufficient to capture the entire differentiation stages of progenitor cells and reflect the dynamic differentiation mechanisms underlying hematopoiesis. Deciphering the hematopoiesis mechanism that underlies progenitor cells definition and fate decision are critical to understanding fundamental questions of hematopoietic lineage commitment.

Here, we redefined the entire spectrum of adult hematopoietic progenitors, and recovered the critical transcript factors (TFs) in lineages fate decision, and reaffirmed the lineage commitment model of HPCs by a comprehensive transcriptome. The progenitor lineages were accurately redefined with unique makers and transcription factors by unsupervised dimensionality reduction and clustering, which subverted the conventional definition of HPCs (Table 1). The expression characteristics of TFs, such as GATA1, KLF1, PRDM1, and MAFB, presented enormous capacity to define the entire spectrum of HPCs.

The transcriptional atlas showed that original hematopoietic progenitors were simultaneously primed into lymphoid, neutrophils, and megakaryocytic-erythroid progenitor cell types in the initial differentiation stage and thereafter matured into different hematopoietic lineages (Figure 1). The common intermediate progenitor stage was not observed among myeloid lineages, indicating the absence of a common myeloid progenitor during the lineage commitment. Our transcriptional atlas revealed the major fate decision factors in each branch among hematopoietic hierarchy formation (Table 1). Several fate decision factors were identified, including GATA2, TESPA1, and MYB of myeloid progenitors and HOXA9, HOPX, and TSC22D1 of lymphoid progenitors. Through the sequential activation/deactivation of TFs, synergism with key receptor genes, and signal activation, the original progenitor cells were primed and differentiated into various progenitors. The expression and activation characteristics of fate decision TFs faithfully reflect the mechanisms underlying hematopoietic lineage commitment.

A hematopoietic hierarchy roadmap was reaffirmed. Our reaffirmed hematopoietic hierarchy validated that the megakaryocytic-erythroid lineage process is continuous, while the lymphoid lineage process is more likely a discrete stepwise progression with distinct lineage-committed populations during hematopoiesis, opening a new perspective on hematopoiesis (Figure 1). Our study revealed that the original progenitors of basophils, eosinophils, and neutrophils differed. Plasma progenitor cells were first identified and defined, and the rearrangements of IGHV, IGKV, and IGLV genes were already existed and occurred during the progenitor state of plasma cells.

In summary, our transcriptional atlas of HPCs provides an accurate definition, hierarchy, and biological insights into hematopoiesis and lineage commitment. Our study opens up numerous possibilities for precise and controlled progenitor cell differentiation, facilitating research development in regenerative medicine and disease treatment.

Disclosures No relevant conflicts of interest to declare.

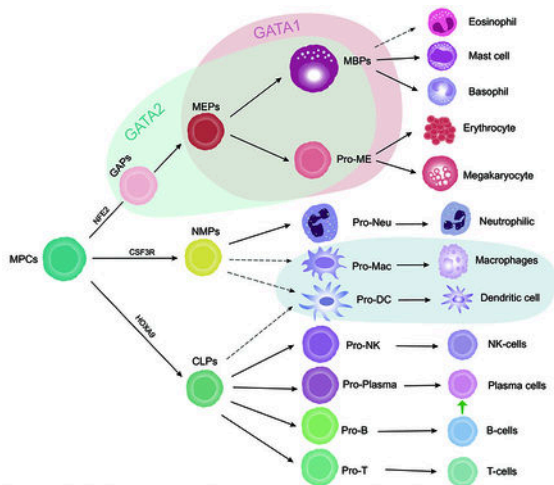


Figure 1. Redefinition of hematopoietic progenitor cell redefined hematopoietic hierarchy

Table 1. The specific marker genes and fate decision genes (partly) of all re-defined subgroups

Redefined Progenitors	Marker genes and fate decision genes (partly)	TFs	Negative
CLP (Common lymphoid progenitors)	SF3B2, HOPX, HOXA9, RUNX2, LTB, IGHD, DNIT7, MME, CCR7	HOPX, HOXA9	GATA1
Pro-NK (Progenitor of NK cell)	GNLY, NKG7, CD347, CCL5, FCGR3A, PRF1, G2M4, CD1E, CD7, HOPX	HOPX	IL7R
Pro-Plasma (Progenitor of Plasma cell)	CD27, IGKC, IGHA1, SLAMF7, CD79A, CD79B, PRDM1, IRF4, CD15	PRDM1, IRF4	MS4A1, FCER2
Pro-T (Progenitor of T Cell)	TCF7, IL7R, GATA3, KLRB1, CD1E, CD1D, CD7, CD347, LTB, DDIT4	TCF7, GATA3	GNLY, FCGR3A
Pro-B (Progenitor of B Cell)	CD19, MS4A1, FCER2, CD79A, CD79B, IGHM, PAX5, VPREB3, CD24	PAX5	CD27
Lineages of Megakaryocyte-erythrocyte	GATA1, KLF1, GATA2, ZBTB16, TAL1, TESPA1, MYB, CD64, ITGA2B	GATA1, ZBTB16, TAL1	SF3B2, HOPX
GMPs (GATA gene-controlled progenitors)	GATA2, NFE2, LYL1, MYB, SLC40A1, TESPA1, CSF3R	GATA2, NFE2	GATA1, KLF1
Pro-ME (Megakaryocyte-erythrocyte progenitor)	HBD, CDT1, MCM2, MCM4, MCM3, CDCA7, CD64, TYMS	CD64	MS4A2, MS4A3
MBPs (mast cell and basophil progenitors)	TPSAB1, LMO4, HDC, MS4A2, TPSB2, MS4A3, KIT, HPD6, CLC, PRO2	LMO4, CD64	HBD
Eosinophil (Progenitor of Eosinophil)	CLC, HDC, RFLNB, ETV6	ETV6	MS4A2
NMPs (neutrophilic and monocyte progenitors)	CSF3R, MPO, S100A10, C1QTNF4, NPDC1, MYB, CD64, CDCA7, CEBPA	MYB, CD64, CEBPA	GATA2
Pro-Mac (Progenitor of Macrophages)	EGR1, SP11, KLF4, FCGR3A, CSF1R, CD68, CD66, ITGAX, CEBPA, MAFB	SP11, CEBPB, MAFB	CLEC9A
Pro-DC (Progenitor of DCs)	CLEC9A, ANPEP, THBD, IRF3, KLF4, CD68, CD66, ITGAX, SLAMF7, BCL6	IRF3	FCGR3A, CSF1R

Figure 1

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