

**All Hematopoietic Cells Develop from Hematopoietic Stem Cells through Flk2/Flt3-Positive Progenitor Cells.**

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**Public Summary:**

This publication defines the pathways of differentiation as blood stem cells give rise to mature blood cells.

**Scientific Abstract:**

While it is clear that a single hematopoietic stem cell (HSC) is capable of giving rise to all other hematopoietic cell types, the differentiation paths beyond HSC remain controversial. Contradictory reports on the lineage potential of progenitor populations have questioned their physiological contribution of progenitor populations to multilineage differentiation. Here, we established a lineage tracing mouse model that enabled direct assessment of differentiation pathways in vivo. We provide definitive evidence that differentiation into all hematopoietic lineages, including megakaryocyte/erythroid cell types, involves Flk2-expressing non-self-renewing progenitors. A Flk2<sup>+</sup> stage was used during steady-state hematopoiesis, after irradiation-induced stress and upon HSC transplantation. In contrast, HSC origin and maintenance do not include a Flk2<sup>+</sup> stage. These data demonstrate that HSC specification and maintenance are Flk2 independent, and that hematopoietic lineage separation occurs downstream of Flk2 upregulation.

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