

Foxo3a is essential for maintenance of the hematopoietic stem cell pool.

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Hematopoietic stem cells (HSCs) are maintained in an undifferentiated quiescent state within a bone marrow niche. Here we show that Foxo3a, a forkhead transcription factor that acts downstream of the PTEN/PI3K/Akt pathway, is critical for HSC self-renewal. We generated gene-targeted Foxo3a(-/-) mice and showed that, although the proliferation and differentiation of Foxo3a(-/-) hematopoietic progenitors were normal, the number of colony-forming cells present in long-term cocultures of Foxo3a(-/-) bone marrow cells and stromal cells was reduced. The ability of Foxo3a(-/-) HSCs to support long-term reconstitution of hematopoiesis in a competitive transplantation assay was also impaired. Foxo3a(-/-) HSCs also showed increased phosphorylation of p38MAPK, an elevation of ROS, defective maintenance of quiescence, and heightened sensitivity to cell-cycle-specific myelotoxic injury. Finally, HSC frequencies were significantly decreased in aged Foxo3a(-/-) mice compared to the littermate controls. Our results demonstrate that Foxo3a plays a pivotal role in maintaining the HSC pool.

