In Vivo Rescue of the Hematopoietic Niche by Induced Pluripotent Stem Cells

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Mesenchymal progenitors and cells of the osteoblast lineage play critical roles in supporting bone marrow hematopoiesis, and cells at specific stages of differentiation contribute to distinct hematopoietic niches. For example, mesenchymal stem cells support hematopoietic stem cells, while osteoprogenitors are crucial for the differentiation of B cell precursors. However, understanding the molecular mechanisms underlying these stage-specific contributions is limited by the inability to prospectively harvest defined mesenchymal populations in large numbers. Induced pluripotent stem (iPS) cells, like embryonic stem (ES) cells, are capable of self-renewal and differentiation into cell types of all three germ layers. Our goal is to use iPS technology to enrich for defined populations along the osteoblast lineage, and to evaluate their distinct roles in supporting hematopoiesis in vivo. To assess the osteogenic potential of iPS cells in vivo, we have employed a model of skeletal complementation. Mouse embryos lacking Runx2, a transcription factor required for differentiation of bone-forming osteoblasts, display a failure of osteoblast differentiation, absence of bone formation, and lack a hematopoietic bone marrow. We have introduced wild-type ROSA-YFP iPS cells into Runx2 null blastocysts and assessed YFP^+ cell contribution by whole-mount fluorescence and histological analysis. We observed the presence of YFP^+ iPS cells in resulting chimeric embryos, with partial skeletal formation that increases in proportion to iPS contribution. Furthermore, these iPS cells were associated with areas of mineralization and restored bone marrow hematopoiesis. In a second model, targeted ablation of osteoblasts with dipheria toxin in chimeric embryos harboring wild-type iPS cells revealed grossly normal skeletal morphology in embryos where iPS contribution exceeds 30%. In summary, iPS cells can undergo osteogenic differentiation in vitro and partially reconstitute an osteoblast-deficient skeleton with hematopoietic marrow in vivo. Further investigation using genetically modified iPS cells with stage-specific fluorescent reporters will enable us to investigate the individual contributions of mesenchymal progenitors, osteoprogenitors, and maturing osteoblasts to distinct hematopoietic niches in vivo.