

Hematopoietic cells and osteoblasts are derived from a common marrow progenitor after bone marrow transplantation

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Bone and bone marrow are closely aligned physiologic compartments, suggesting that these tissues may represent a single functional unit with a common bone marrow progenitor that gives rise to both osteoblasts and hematopoietic cells. Although reports of multilineage engraftment by a single marrow-derived stem cell support this idea, more recent evidence has challenged claims of stem cell transdifferentiation and therefore the existence of a multipotent hematopoietic/osteogenic progenitor cell. Using a repopulation assay in mice, we show here that gene-marked, transplantable marrow cells from the plastic-nonadherent population can generate both functional osteoblasts/osteocytes and hematopoietic cells. Fluorescent *in situ* hybridization for the X and Y chromosomes and karyotype analysis of cultured osteoblasts confirmed the donor origin of these cells and excluded their generation by a fusion process. Molecular analysis demonstrated a common retroviral integration site in clonogenic hematopoietic cells and osteoprogenitors from each of seven animals studied, establishing a shared clonal origin for these ostensibly independent cell types. Our findings indicate that the bone marrow contains a primitive cell able to generate both the hematopoietic and osteocytic lineages. Its isolation and characterization may suggest novel treatments for genetic bone diseases and bone injuries.

donor osteoblast engraftment was demonstrated after transplantation of unmanipulated bone marrow (14), but the percentage of such engraftment could not be improved by transplanting as many as 5×10^6 isolated plastic-adherent marrow stromal cells per kg of body weight, a cell number that greatly exceeds the marrow stromal cell content of unmanipulated marrow (15). One interpretation of these observations is that cells other than those in the adherent population, where mesenchymal stem cells are thought to reside (3), are potent transplantable progenitors of osteoblasts, consistent with laboratory studies showing that nonadherent cells can give rise to bone (12, 13, 16). We tested this prediction in a murine transplantation model by using gene-marked bone marrow cells and retroviral integration site-specific PCR analysis.

Methods

Transduction and Transplantation of Marrow Cells. Bone marrow was flushed from the dissected femurs and tibiae of FVB/N mice (The Jackson Laboratory), and the isolated adherent marrow cells were transduced with a GFP-expressing retroviral vector (multiplicity of infection, ≈ 5) as described (17). In separate studies, nonadherent marrow cells, isolated from a 5-day *ex vivo* culture in which adherent cells stuck to the plastic dish, were transduced with the same GFP-expressing retroviral vector