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Plasticity of hematopoietic stem cells

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A B S T R A C T

Almost two decades ago, a number of cell culture and preclinical transplantation studies suggested the striking concept of the tissue-reconstituting ability of hematopoietic stem cells (HSCs). While this heralded an exciting time of radically new therapies for disorders of many organs and tissues, the concept was soon mired by controversy and remained dormant. This chapter provides a brief review of evidence for HSC plasticity including our findings based on single HSC transplantation in mouse. These studies strongly support the concept that HSCs are pluripotent and may be the source for the majority, if not all, of the cell types in our body.

Introduction

Almost two decades ago, a number of cell culture and preclinical transplantation studies suggested a radically new concept of the tissue-reconstituting ability of hematopoietic stem cells (HSCs). While this concept (often referred to as HSC plasticity) heralded an exciting time of new therapeutic approaches for disorders of many organs and tissues, the concept was soon mired in controversy. We reasoned that only single HSC transplantation would provide definitive information about HSC plasticity.

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Single HSC transplantation

One reason for the controversy was the paper [1] and review [2] from a Stanford group that negated the plasticity strongly. However, as Theise et al. [3] pointed out in their rebuttal, there is ambiguity about the levels of hematopoietic engraftment in the paper from the Stanford group. Studies of HSC plasticity require use of mice exhibiting high-level, hematopoietic engraftment from single HSCs. In order to generate such mice efficiently, we combined single cell deposition of bone marrow (BM) cells that are highly enriched for HSCs with short-term (1 week) cell culture [4,5]. The use of short-term cell culture takes advantage of the known cell-cycle dormancy of steady state HSCs. As donors of the BM cells, we used mice that had been genetically engineered to ubiquitously express enhanced green fluorescent protein (EGFP) [6]. BM cells that had been highly enriched for HSCs by fluorescence-activated cell sorting (FACS) were individually deposited into each of 96-well culture plates and cultured for 1 week in the presence of Steel factor (SF; c-kit ligand) and interleukin-11 or a combination of SF and granulocyte colony-stimulating factor (G-CSF). Because the majority of HSCs in steady state BM do not begin cell division until a few days after initiation of the cell culture [5], transplantation of clones consisting of 20 or fewer cells after 1 week of incubation significantly raised the efficiency of generating mice with high-level multi-lineage engraftment [4,5]. Two months to one year after transplantation, only mice revealing higher than 50% multi-lineage hematopoietic engraftment were selected for analyses of tissue reconstitution. An example of hematopoietic engraftment seen in such mice is presented in Fig. 1. This experimental approach uncovered an HSC origin of connective tissues including fibroblasts/myofibroblasts, adipocytes, and osteo-chondrocytes.

HSC origin of fibroblasts/myofibroblasts

Fibroblasts and myofibroblasts confer the structural integrity of the tissues and organs and support the proliferation and differentiation of other cell classes, thus playing an important role in the steady state physiology of many tissues. Tissue fibroblasts are also important in many pathological processes. For example, fibroblasts can be activated to become myofibroblasts and exert contractile force to reduce the size of the wound. Uncontrolled proliferation and/or activation of these cells, however, may result in tissue fibrosis, often with dire consequences. In addition to the ubiquitous type of fibroblasts, there are a number of myofibroblasts with defined tissue-specific functions. For example, glomerular mesangial cells in the kidney, hepatic stellate cells, and pericytes are contractile and function as regulators of blood flow [7,8].

As summarized in a review [9], we discovered, in the first series of single HSC transplantation studies, that many types of fibroblasts/myofibroblasts, including glomerular mesangial cells of the kidney [4], brain microglial cells and perivascular cells [10], tumor-associated fibroblasts/myofibroblasts [11], inner ear fibrocytes [12], and the fibroblasts/myofibroblasts in the adult heart valves [13] are derived from HSCs via non-fusion mechanisms. Subsequently, investigators in other laboratories, also using the single HSC transplantation, reported that fibroblasts/myofibroblasts seen at the site of myocardial infarction [14] and hepatic stellate cells [15] are also derived from HSCs. These findings strongly suggest that all fibroblasts/myofibroblasts in our body are derived from HSCs.

HSC origin of adipocytes

Since fibroblasts and adipocytes are closely associated as members of mesenchymal tissues, we next tested the hypothesis that HSCs also generate adipocytes [16]. In order to enhance neo-adipogenesis, we fed rosiglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-ϒ) agonist, to clonally engrafted mice. Adipose tissues from all mice showed $EGFP^+$ adipocytes that stained positive for leptin, perilipin, and fatty acid binding protein 4. Addition of rosiglitazone to the diet significantly enhanced the number of the $EGFP^+$ adipocytes. $EGFP^+$ adipocytes were detected in both white and brown adipose tissues. Interestingly $EGFP^+$ adipocytes were found in small clusters as though they originated from precursors. Fig. 2 presents sections from white and brown adipose tissues containing the $EGFP^+$ adipocytes. We also carried out cell culture studies of BM cells from mice engrafted with single HSCs. When FACS-sorted $EGFP^+$ BM cells were cultured under adipogenic conditions, all of the cultured cells