Mobilization of Bone Marrow-Derived Progenitors

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Abstract Bone marrow (BM) is a source of various stem and progenitor cells in the adult, and it is able to regenerate a variety of tissues following transplantation. In the 1970s the first BM stem cells identified were hematopoietic stem cells (HSCs). HSCs have the potential to differentiate into all myeloid (including erythroid) and lymphoid cell lineages in vitro and reconstitute the entire hematopoietic and immune systems following transplantation in vivo. More recently, nonhematopoietic stem and progenitor cells have been identified that can differentiate into other cell types such as endothelial progenitor cells (EPCs), contributing to the neovascularization of tumors as well as ischemic tissues, and mesenchymal stem cells (MSCs), which are able to differentiate into many cells of ectodermal, endodermal, and mesodermal origins in vitro as well as in vivo. Following adequate stimulation, stem and progenitor cells can be forced out of the BM to circulate into the peripheral blood, a phenomenon called “mobilization.” This chapter reviews the molecular mechanisms behind mobilization and how these have led to the various strategies employed to mobilize BM-derived stem and progenitor cells in experimental and clinical settings. Mobilization of HSCs will be reviewed first, as it has been best-explored—being used extensively in clinics to transplant large numbers of HSCs to rescue cancer patients requiring hematopoietic reconstitution—and provides a paradigm that can be generalized to the mobilization of other types of BM-derived stem and progenitor cells in order to repair other tissues.

Keywords Mobilization · Hematopoietic stem cells · Endothelial progenitor cells · Mesenchymal stem cells · Transplantation · Tissue repair

1 Introduction

In the adult, bone marrow (BM) is a source of various stem and progenitor cells that are able to regenerate a variety of tissues following transplantation. Schofield identified the first BM stem cells, which were hematopoietic stem cells (HSCs) (Schofield 1970). HSCs have the potential to differentiate into all myeloid (including erythroid) and lymphoid cell lineages in vitro and reconstitute the entire hematopoietic and immune systems following transplantation in vivo. More recently, nonhematopoietic stem and progenitor cells have been identified that can differentiate into other cell types such as endothelial progenitor cells (EPCs), contributing to the neovascularization of tumors as well as ischemic tissues (Asahara et al. 1999), and mesenchymal stem cells (MSCs), which are able to differentiate into many cells of ectodermal, endodermal, and mesodermal origins (such as adipocytes, chondrocytes, osteoblasts, hepatocytes, neurons, myocytes, and endothelial and epithelial cells) in vitro as well as in vivo (Sale and Storb 1983; Barry et al. 1999, 2001; Devine et al. 2001; Dennis and Charbord 2002).

In steady-state conditions in adult mammals, most HSCs, EPCs, and MSCs reside in the BM, with a few HSCs (Wright et al. 2001; Abkowitz et al. 2003) and EPCs (Lin et al. 2000) circulating in the peripheral blood; circulating MSCs are usually not detectable (Lazarus et al. 1997; Wexler et al. 2003). For this reason, the stem and progenitor cells used to be isolated by BM aspiration for subsequent transplantation into patients requiring immune and hematopoieti-