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The great migration of bone marrow-derived stem cells toward the ischemic brain: Therapeutic implications for stroke and other neurological disorders

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ABSTRACT

Accumulating laboratory studies have implicated the mobilization of bone marrow (BM)-derived stem cells in brain plasticity and stroke therapy. This mobilization of bone cells to the brain is an essential concept in regenerative medicine. Over the past ten years, mounting data have shown the ability of bone marrow-derived stem cells to mobilize from BM to the peripheral blood (PB) and eventually enter the injured brain. This homing action is exemplified in BM stem cell mobilization following ischemic brain injury. Various BM-derived cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs) and very small embryonic-like cells (VSELs) have been demonstrated to exert therapeutic benefits in stroke. Here, we discuss the current status of these BM-derived stem cells in stroke therapy, with emphasis on possible cellular and molecular mechanisms of action that mediate the cells' beneficial effects in the ischemic brain. When possible, we also discuss the relevance of this therapeutic regimen in other central nervous system (CNS) disorders.

Contents

Abbreviations: BM, bone marrow; PB, peripheral blood; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells; EPCs, endothelial progenitor stem cells; VSELs, very small embryonic-like stem cells; BBB, blood brain barrier; SDF-1, stromal derived factor-1; CNS, central nervous system; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; CB, cord blood; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; VEGFR2, vascular endothelial growth factor receptor 2; IGF-1, insulin growth factor-1; IBZ, ischemia border zone; SVZ, subventricular zone; SGZ, subgranular zone; MCAo, middle cerebral artery occlusion; GDNF, glial cell line-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; NT3, neurotrophin-3; Cx43, connexin-43; UCB, umbilical cord blood; PSC, progenitor stem cells.

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1. Introduction

Increasing evidence supports the capability of bone marrow (BM)-derived cells to mobilize from the marrow to the peripheral blood (PB) and home the injured tissue/organ. This homing action is exemplified in BM stem cell mobilization following ischemic brain injury. This article will review the accumulating laboratory supporting evidence of the ostensible feasibility to induce the therapeutic mobilization of transplanted BM stem cells for brain plasticity and remodeling following a stroke. There have been studies published involving similar research into the mobilization of BM-derived cells; however, where one paper has focused on malignancies and cancer, this paper is novel in its focus on CNS-disorders and stroke therapy (Hess and Allan, 2011).

Heterogeneous populations of stem and progenitor cells are found in the bone marrow (Herzog et al., 2003). The more developed research pertains to hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Additionally, endothelial progenitor cells (EPCs) and very small embryonic-like stem cells (VSELs) have also been isolated from the BM (Fig. 1). Previous reports have discussed in vitro differentiation of BM-derived stem cells into neurons following exposure to various inducing regimens (Munoz-Elias et al., 2003), and their secretion of growth factors critical for neuronal survival (Hara et al., 2008; Hess and Borlongan, 2008a,b). Interest in these stem cells as donors has increased as researchers look to use the BM-derived cells as therapy for neurological disorders, such as stroke. Although the concepts discussed here are derived primarily from stroke studies, they have a broad significance in treating other CNS diseases. BM-derived stem cells have been used in the laboratory as a potential therapeutic for various CNS disorders, such as epilepsy (Venturin et al., 2011), Parkinson's disease (Khoo et al., 2011a), and Alzheimer's disease (Nikolic et al., 2008).

Stroke is a major cause of death in the US and around the world. Over the last decade, stem cell therapy has shown promise as an experimental treatment for stroke (Borlongan et al., 2008; Chopp et al., 2009; "Stem Cell Therapies", 2009). The first clinical trial occurred in 1998 (Kondziolka et al., 2000; Meltzer et al., 2001; Nelson et al., 2002). Recently, there has been an increase in cell-based therapy clinical trials for stroke patients.

There are distinct therapeutic advantages in stroke to use a minimally invasive intra-arterial or intravenous transplantation. However, this peripheral route of cell injection requires mobilization of the cells and their secreted products proximal to the site of injury in order to induce brain plasticity and remodeling. A better understanding of mechanisms underlying the homing of cells from the periphery to the ischemic brain is likely to aid in optimizing cell therapy for stroke. Stem cells can be mobilized from various niches within the body. A stem cell niche is any microenvironment where stem cells reside. Various stem cell phenotypes are found within different niches. For example, neural stem cells are found in the dentate gyrus and subventricular zone of the brain, whereas HSCs can be found in the BM. Here, the specific (sometimes overlapping) mobilization pathways mediating the homing of HSCs, MSCs, EPCs and VSELs from BM (and other stem cell niches) to the intravascular space and into the ischemic brain are explored.

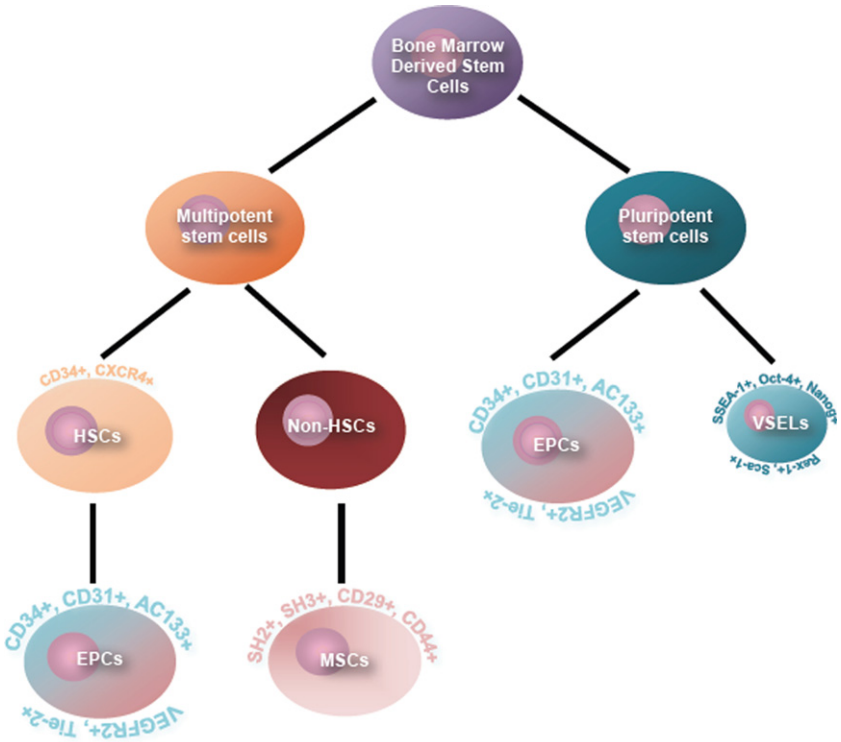

Fig. 1. Bone marrow-derived stem cells. Schematic diagram shows subsets of bone marrow-derived stem cells, including HSCs, MSCs, EPCs, and VSELs, which have been examined in the laboratory and are rapidly being translated into clinical applications as efficacious stem cell source for transplantation therapy in stroke.