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Bone-marrow cell therapy induces differentiation of radial glia-like cells and rescues the number of oligodendrocyte progenitors in the subventricular zone after global cerebral ischemia

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Abstract The subventricular zone (SVZ) is recognized as one of the neurogenic regions in the adult mammalian central nervous system and the presence of cells that share similar characteristics with developmental radial glia, the radial glia-like cells (RGLCs) has been demonstrated in this region. In this study, we investigated whether and how SVZ cells respond to global ischemia and/or to the intravenous transplant of bone-marrow mononuclear cells (BMMCs). Adult rats were subjected to bilateral common carotid ligation (BCCL) and after 1 day 2×10^7 BMMCs or saline injection. The BMMC transplant stimulated a transitory increase in the proliferation of SVZ cells in the BCCL group. We observed a significant increase in the number of RGLCs 3 days after ischemia, in both BCCL and BCCL + BMMC groups. However, this increase persisted in the subsequent days only in BCCL animals that received the transplant. BMMC transplantation also inhibits the reduction of NG2-positive oligodendrocyte progenitors in the SVZ observed in the

Abbreviations: RGLCs, radial glia-like cells; BCCL, bilateral common carotid ligation; BMMCs, bone-marrow mononuclear cells.

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BCCL group. Interestingly, brain-derived neurotrophic factor (BDNF) expression was up-regulated in the SVZ in the treated animals, but not in the other groups. These data thus suggest that BMMC transplantation modulates the phenotype of RGLCs/progenitors in the SVZ and could have a protective role after ischemia.

Introduction

Radial glia cells play important roles in neuronal migration and neurogenesis during development (Kriegstein and Alvarez-Buylla, 2009; Malatesta et al., 2003; Noctor et al., 2001). These cells have their cell bodies in the ventricular zone, and radial processes extending to the pial surface. By the end of the developmental period, most of the radial glia cells differentiate into astrocytes (Alves et al., 2002; Levitt and Rakic, 1980; Mission et al., 1991; Voigt, 1989). During development, radial glia cells correspond to the neural stem cells (NSCs), since they are able to proliferate, self-renew, and also differentiate into neurons, astrocytes and oligodendrocytes (Anthony et al., 2004; Costa et al., 2010; Merkle et al., 2004; Noctor et al., 2001, 2002; Spassky et al., 2005). It has also been shown that radial glia cells originate resident NSCs in the subventricular zone (SVZ) in the adult brain (Merkle et al., 2004). There are two regions in the mammalian brain where neurogenesis persists during adulthood: the SVZ, around the lateral ventricles (LV); and the subgranular layer (SGL) of the hippocampal dentate gyrus (DG) (Gage, 2000; Gage et al., 1998; Kaplan and Bell, 1984; Kriegstein and Alvarez-Buylla, 2009; Lois and Alvarez-Buylla, 1993).

Recently, we and others demonstrated that cells with astroglial characteristics and radial processes are still present in specific regions of the adult brain. These cells are termed radial glia-like cells (RGLCs) and they are present in the SVZ and in the SGL (Alvarez-Buylla et al., 2002; Gubert et al., 2009; Shapiro et al., 2005; Sundholm-Peters et al., 2004). In the SVZ, we have shown that RGLCs can be identified by their radial morphology, with the cell body in the SVZ and long processes extending to the striatum. These cells express vimentin, nestin, astrocyte-specific glutamate transporter (GLAST) and Pax6, well-known markers of radial glia cells during development (Gubert et al., 2009), and similarly to these cells, they seem to have NSC characteristics in the SVZ (Gubert et al., 2009; Mirzadeh et al., 2008).

Several groups have studied the response of NSCs to injury or neurodegenerative diseases. In pathological conditions that cause neuronal death, such as cerebral ischemia, epilepsy or traumatic brain injury, neurogenesis increases in the SVZ and in the SGL (Barkho and Zhao, 2011; Dash et al., 2001; Kokaia et al., 2006; Li et al., 2002; Liu et al., 1998). In these conditions, the newly formed neurons are attracted and migrate to the lesion site (Arvidsson et al., 2002; Jin et al., 2003; Kokaia et al., 2006; Parent et al., 2002; Zhang et al., 2001). After an injury that affects glial cells such as oligodendrocytes, a similar response is observed; NSC proliferation increases and newly formed oligodendrocyte progenitors migrate to the lesion (Gonzalez-Perez and Alvarez-Buylla, 2011; Menn et al., 2006; Picard-Riera et al., 2002). However, even though the endogenous NSCs respond to injuries, this increase in proliferation is insufficient to replace a significant number of the lost cells. In an attempt to regenerate or protect neural cells after injury, several research groups are testing therapies with stem cells in animal models and humans (Barbosa da Fonseca et al., 2009, 2010; Friedrich et al., 2012; Pimentel-Coelho and Mendez-Otero, 2010; Rost et al., 2012; Thwaites et al., 2012). One of the sources of stem cells used is bone marrow, and several studies using animal models of neurological diseases have shown that these cells can attenuate the functional loss after an injury to the nervous system (de Vasconcelos Dos Santos et al., 2010; Giraldi-Guimaraes et al., 2012; Li et al., 2006; Ribeiro-Resende et al., 2009; Vasconcelos-Dos-Santos et al., 2012; Zaverucha-do-Valle et al., 2011).

Although the mechanisms involved in the therapeutic effects described above are still subject to debate, it is accepted that these cells migrate to the lesion area and probably release neuroprotective and/or trophic factors that may have neuroprotective and/or neuroregenerative functions. In this respect, several studies have demonstrated that bone-marrow therapy reduces cell death, glial scar formation, microglial activation and inflammation, protects the tissue against insult, and also stimulates axonal growth (Costa-Ferro et al., 2012; de Vasconcelos Dos Santos et al., 2010; Li et al., 2005; Ohtaki et al., 2008; Ribeiro-Resende et al., 2009; Schwarting et al., 2008; Zaverucha-do-Valle et al., 2011). It has also been demonstrated that bone-marrow therapy increases the proliferation of NSCs in the SVZ and SGL (Chen et al., 2003; Kan et al., 2011), and some growth factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) or fibroblast growth factor-2 (FGF-2) have been found to be related to this event (Cao et al., 2004; Craig et al., 1996; Doetsch et al., 2002; Sun et al., 2009). In addition, infusion of growth factors could also increase the number of RGLCs in the SVZ of adult mice (Gregg and Weiss, 2003).

In the present study, we subjected adult rats to chronic cerebral hypoperfusion, a model of global cerebral ischemia that decreases the cerebral blood flow to about 25 to 94% of the normal levels (Tsuchiya et al., 1992) and causes damage mainly in the white matter (Kurumatani et al., 1998; Wakita et al., 2002). We investigated if in this model of moderate brain injury, intravenously injected bone-marrow cells migrate to the brain and have any effect on the SVZ, an important NSC niche in the adult brain.

Materials and methods

Animals

Adult (3–5 month-old) male Lister hooded rats were obtained from our breeding colony. All experiments were performed in