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Cell based therapies for ischemic stroke: From basic science to bedside

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ABSTRACT

Cell therapy is emerging as a viable therapy to restore neurological function after stroke. Many types of stem/progenitor cells from different sources have been explored for their feasibility and efficacy for the treatment of stroke. Transplanted cells not only have the potential to replace the lost circuitry, but also produce growth and trophic factors, or stimulate the release of such factors from host brain cells, thereby enhancing endogenous brain repair processes. Although stem/progenitor cells have shown a promising role in ischemic stroke in experimental studies as well as initial clinical pilot studies, cellular therapy is still at an early stage in humans. Many critical issues need to be addressed including the therapeutic time window, cell type selection, delivery route, and *in vivo* monitoring of their migration pattern. This review attempts to provide a comprehensive synopsis of preclinical evidence and clinical experience of various donor cell types, their restorative mechanisms, delivery routes, imaging strategies, future prospects and challenges for translating cell therapies as a neurorestorative regimen in clinical applications.

Contents

Abbreviations: Ang-1, angiopoietin-1; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMSCs, bone marrow stromal cells; CNS, central nervous system; CXCR4, chemokine (C-X-C motif) receptor 4; ESCs, embryonic stem cells; GDNF, glial cell-derived neurotrophic factor; GFP, green fluorescent protein; GRID, gadolinium rhodaminedextran; GVHD, graft-*versus*-host disease; HGF, hepatocyte growth factor; HLA, human leukocyte antigen; hMSCs, human mesenchymal stem cells; HUCBCs, human umbilical cord blood cells; IA, intra-arterial; IBZ, ischemic boundary zone; IC, intracerebral; IGF-1, insulin-like growth factor 1; iPSCs, induced pluripotent stem cells; IV, intravenous; LGE, lateral ganglionic eminence; MCAO, middle cerebral artery occlusion; MCP-1, monocyte chemotactic protein-1; miRNA, microRNA; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; MSCs, mesenchymal stem cells; NGF, nerve growth factor; NIHSS, National Institutes of Health Stroke Scale; NIR, near-infrared; NPCs, neural progenitor cells; NSCs, neural stem cells; PD-MSCs, placenta-derived mesenchymal stem cells; PlGF, placental growth factor; RMS, rostral migratory stream; SDF-1, stromal-derived factor 1; SPIO, superparamagnetic iron oxide; STEPS, Stem Cell Therapy as an Emerging Paradigm for Stroke; SVZ, subventricular zone; tPA, tissue plasminogen activator; UCMSCs, umbilical cord mesenchymal stem cells; VEGF, vascular endothelial growth factor.

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1. Introduction

Stroke remains a worldwide health burden, causing high morbidity, mortality, and costs to health care (Feigin et al., 2009; Johnston et al., 2009), and is the primary cause of serious long-term disability in the United States, leading to $38.6 billion in direct and indirect costs in 2009 (Go et al., 2013). Ischemic stroke accounts for over 80% of the total number of strokes. Currently the only validated therapy for ischemic stroke is thrombolysis, which must be administered within 4.5 h after onset (Del Zoppo et al., 2009). Due to its narrow therapeutic time window and the concern of hemorrhagic complication, thrombolysis is still not used regularly (Liu, 2012). Approximately 5% of stroke patients benefit from reperfusion therapies, and even so, only 10% of the stroke survivors return to independent living. In this context, development of neurorestorative therapies to improve neurological deficits after ischemic stroke is a great challenge for both bench scientists and clinical investigators.

After decades of research focused on acute neuroprotection and the failure of produce much in the way of tangible results (Ginsberg, 2008; Fisher, 2011), the Stroke Progress Review Group has identified neurorestoration as a major priority for stroke research (Grotta et al., 2008). Cell therapy is emerging as a viable neurorestorative therapy for stroke (Zhang and Chopp, 2009). A paucity of studies was reported in previous decades, yet the past 5 years have witnessed a remarkable surge in publications on this topic. Based on these reports, this review attempts to provide a comprehensive synopsis of preclinical evidence and clinical experience using various donor cell types, their restorative mechanisms, delivery methods, imaging strategies, future prospects and challenges for translating cell therapies as neurorestorative therapy for stroke in clinical applications.

2. Restorative mechanisms of cell-based therapies

In this section, we discuss the potential mechanisms of cell-based therapy-induced neurorestorative effects after stroke, which includes cell replacement, enhanced trophic/regenerative support from transplanted cells, immunomodulation, and stimulation of endogenous brain repair processes (such as angiogenesis, arteriogenesis, neurogenesis, synaptogenesis and white matter remodeling).

2.1. Cell replacement

The initial goal of stem cell transplantation was to reconstruct the disrupted cytoarchitecture of stroke-damaged tissue. However, the context of stroke is a complex entity, which would require the survival of grafted cells in an inhospitable environment that includes inflammatory reactions, necrotic cell leakage and glial scar formation (Buhnemann et al., 2006). For stem/progenitor cell therapy, usually several million cells are transplanted into stroke animals. Once locally or systematically injected, stem/progenitor cells exhibit a certain degree of targeted migration toward the damaged regions (*i.e.* pathotropism) (De Feo et al., 2012). Implanted stem/progenitor cells can follow the gradients of chemoattractants, including vascular cell adhesion molecule 1 (VCAM-1), stromal-derived factor 1 (SDF-1), monocyte chemotactic protein-1 (MCP-1), chemokine (C-C motif) ligand 2 (CCL2), and other cytokines that aid in the localization to the damaged central nervous system (CNS) parenchyma (Guzman et al., 2008c). By quantitative estimation, approximately 1/3 of the locally injected cells migrate to the focal infarct area (Kelly et al., 2004; Darsalia et al., 2007). Contralateral parenchymal grafting yielded similar migration efficiency along the corpus callosum (Modo et al., 2002c; Veizovic et al., 2001). However, upon intravascular delivery, as expected, significantly fewer (1–10%) exogenous cells arrive to the lesion area (Li et al., 2001b, 2002).

Among these migrated cells, one may ask, how many will integrate into the lost circuits? Many groups have reported variable numbers of grafted cells differentiating into mature neurons. The success of attaining a mature neuronal phenotype appears to depend on the source of the stem cells: 34–60% of neural stem cells (NSCs) (Takagi et al., 2005; Darsalia et al., 2007; Ishibashi et al., 2004), 40–66% of induced pluripotent stem cells (iPSCs) (Oki et al., 2012; Jensen et al., 2013), 30% of embryonic stem cells (ESCs) (Buhnemann et al., 2006), and 2–20% of mesenchymal stem cells (MSCs) (Chen et al., 2001a, 2001b) differentiated into neurons expressing mature or immature neuronal markers like NeuN, HuD, and MAP2. A 1-year follow-up study demonstrated

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