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Review article

Stem cell transplantation therapy for multifaceted therapeutic benefits after stroke

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ABSTRACT

One of the exciting advances in modern medicine and life science is cell-based neurovascular regeneration of damaged brain tissues and repair of neuronal structures. The progress in stem cell biology and creation of adult induced pluripotent stem (iPS) cells has significantly improved basic and pre-clinical research in disease mechanisms and generated enthusiasm for potential applications in the treatment of central nervous system (CNS) diseases including stroke. Endogenous neural stem cells and cultured stem cells are capable of self-renewal and give rise to virtually all types of cells essential for the makeup of neuronal structures. Meanwhile, stem cells and neural progenitor cells are well-known for their potential for trophic support after transplantation into the ischemic brain. Thus, stem cell-based therapies provide an attractive future for protecting and repairing damaged brain tissues after injury and in various disease states. Moreover, basic research on naïve and differentiated stem cells including iPS cells has markedly improved our understanding of cellular and molecular mechanisms of neurological disorders, and provides a platform for the discovery of novel drug targets. The latest advances indicate that combinatorial approaches using cell based therapy with additional treatments such as protective reagents, preconditioning strategies and rehabilitation therapy can significantly improve therapeutic benefits. In this review, we will discuss the characteristics of cell therapy in different ischemic models and the application of stem cells and progenitor cells as regenerative medicine for the treatment of stroke.

Contents

Abbreviation: Ang 1, angiopoietin 1; BI, barthel index; bFGF, basic fibroblast growth factor; BBB, blood brain barrier; BMSCs, bone marrow stem cells; BDNF, brain-derived neurotrophic factors; CRABP, cellular RA-binding proteins; ChR2, channelrhodopsin-2; CXCR4, chemokine receptor type 4; CSF-1, colony-stimulating factor-1; CCA, common carotid artery; DCX, doublecortin; EEG, electroencephalography; ET-1, endothelin-1; ECs, embryonal carcinomas; EB, embryonic bodies; ES, embryonic stem; EGF, epidermal growth factor; EPO, erythropoieti; ECA, external carotid artery; GRID, gadolinium-rhodamine dextran; GDNF, glial cell-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; G-CSF, granulocyte-colony stimulating factor; HuD, hu protein D; HLA, human leukocyte antigen; HIE, hypoxic-ischemic encephalopathy; HP, hypoxia preconditioned; iPScells, induced pluripotent stem cells; IV, injected intravenously; INF-γ, interferon gamma; ICH, intracranial hemorrhage; LIF, leukemia inhibitory factor; LCBF, local cerebral blood flow; MRI, magnetic resonance imaging; MHC, major histocompatibility; MSCs, mesenchymal stem cells; MMP-2, metalloproteinase 2; MCA, middle cerebral artery; mRS, modified Rankin Scale; MS, multiple sclerosis; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Score; NGF, nerve growth factor; ARNT, nuclear translocator; PBMCs, peripheral blood mononuclear cells; OPCs, oligodendrocyte progenitors; OGD, oxygen-glucose deprivation; RA, retinoic acid; RMS, rostral migratory stream; SCF, stem cell factor; SGZ, subgranular zone; SVZ, subventricular zone; SPF, survival-promoting factors; t-PA, tissue plasminogen activator; TBI, traumatic brain injury; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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1. Introduction

Stem cell therapy has been considered in basic and clinical stroke research fields to be a promising regenerative medical treatment and a more promising approach for brain injury induced by different types of strokes. Stem cells (either endogenous neural stem cells or induced pluripotent stem cells *e.g.* iPS cells) have the potential of replacing damaged cells in the brain. Cell replacement strategies have been proposed and tested in many stroke models across decades of research in animal models. In addition, multipotent and pluripotent stem cells have shown beneficial paracrine effects, which can reduce cell death and provide growth/trophic support to host cells and regenerative activities in the host brain.

Induction of iPS cells from somatic cells (*e.g.* fibroblasts) with transcriptional factors (Oct-3/4, Sox-2, c-Myc and Klf-4) has shown promising translational potential. Similar to embryonic stem (ES) cells, iPS cells can be expanded *in vitro* and induced into neurospheres, neural progenitors, and mature neurons. Neuronally-differentiating ES/iPS cells and ES/iPS-derived neural progenitors have been extensively tested in transplantation therapies for the treatment of stroke, traumatic brain injury (TBI), spinal cord injury (SCI) and neurodegenerative diseases. It is generally agreed that transplanted cells may provide morphological and functional benefits via multiple mechanisms including, but not limited to, cell replacement, trophic support, immunosuppression/anti-inflammation, stimulation of endogenous signaling for neural plasticity and regeneration, and regulatory interactions with endogenous cells such as astrocytes and oligodendrocytes (Horie et al., 2015; McDonald and Howard, 2002; Volpe et al., 2016; Yu et al., 2013). Based on promising results and better understanding on the therapeutic mechanisms, translational studies and clinical trials using stem cells including mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs), adipose-derived stem cells (ASCs), iPS cells, and many others are being tested for clinical applications.

In this review, we will focus on neural progenitor cells derived from ES, adult brain and iPS cells, and widely tested MSCs. Their mechanism of action and beneficial effects after stroke in animal models and human studies will be reviewed. Regarding transplantation therapy, we will discuss the efforts to improve the survival, neuronal differentiation and therapeutic potential of transplanted cells, post-transplantation cell distribution, and effects related to repairing the neurovascular unit. Cell delivery methods will be discussed highlighting the recent advances in non-invasive intranasal delivery of cells. We will also introduce functional and behavioral improvements after stem cell transplantation therapy.

1.1. Regenerative medicine for the treatment of stroke

Stroke is the fifth leading cause of death and the number one cause of disability in the adult population in the United States (Mozaffarian et al., 2015). With an average of one victim every 40 s, almost 795,000 individuals experience a stroke every year in the United States, accounting for approximately one out of every 18 deaths (Mozaffarian et al., 2015; Roger et al., 2012). Of all stroke cases, 87% are ischemic in nature and the rest are hemorrhagic. In ischemic stroke, a clot occludes a brain vessel (most commonly the middle cerebral artery or its branches) and blood flow to the brain region supplied by that vessel is ceased, causing a cascade of pathological events associated with energy failure, acidosis, excessive glutamate release, elevated intracellular Ca^{2+} levels, generation of free radicals (especially after reperfusion), blood-brain-barrier (BBB) disruption, inflammation and eventually massive excitotoxic cell death composed of necrosis, apoptosis, autophagy and likely concurrent mixed forms of cell death involving hybrid mechanisms (Durukan and Tatlisumak, 2007; Li et al., 2013a; Puyal et al., 2013; Wei et al., 2004; Xiao et al., 2002). Hemorrhagic stroke, on the other hand, occurs when a blood vessel ruptures in the brain leading to intracranial hemorrhage (ICH) (Ferro, 2006). ICH, with the associated edema, makes the outcome