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Review

Review of transplantation of neural stem/progenitor cells for spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is a debilitating condition often resulting in paralysis, yet currently there is no effective treatment. Stem cell transplantation is a promising therapeutic strategy for promoting tissue repair after SCI. Stem cells offer a renewable source of cells with inherent plasticity for tissue regeneration. Neural stem/progenitor cells (NSPCs) are multipotent cells that self-renew and are committed to the neural lineage, and thus, they are especially suited to SCI repair. NSPCs may differentiate into neural cells after transplantation into the injured spinal cord, replacing lost or damaged cells, providing trophic support, restoring connectivity, and facilitating regeneration. Here, we review experimental studies and considerations for clinical translation of NSPC transplantation for SCI.

Contents

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1. SCI

1.1. Epidemiology

Over one million North Americans suffer from paralysis caused by SCI (One Degree, 2010). The primary causes of traumatic SCI are motor vehicle crashes, falls, violence, sports and recreational injuries, and work-related traumatic injuries (Chen et al., 2013). Most SCI patients are young adults and older adults, the latter primarily involving falls (Furlan and Fehlings, 2009; Pickett et al., 2006; Sekhon and Fehlings, 2001). The highest incidence of traumatic injury is to individuals in the age range of 20–29 and also those over 70 years of age (Farry and Baxter, 2010). Each complete SCI costs society millions of dollars for medical costs and lost earnings in addition to the great personal loss to the victims and their families (Garcia-Altes et al., 2012).

1.2. Pathophysiology

Traumatic injury to the spinal cord, such as compression, contusion, or laceration, disrupts motor, sensory and/or autonomic functions at the site of injury and below. Permanent disability including paralysis, loss of sensation, neuropathic pain, and bowel and bladder dysfunction can occur depending on the level and severity of the SCI (Bunge, 1994; Hulsebosch, 2005; Tator, 1995). Damage from the primary mechanical trauma causes local edema, hemorrhage, necrosis, and laceration of tissue. Subsequently, a series of secondary events (Fig. 1) is initiated including further swelling, blood flow constriction, vasospasm, inflammation, excitotoxicity, lipid peroxidation, free radical production, ischemia, apoptosis, demyelination, and neurotransmitter and electrolyte disturbances (Fehlings and Sekhon, 2001; Hagg and Oudega, 2006; Hulsebosch, 2002; Mothe and Tator, 2012; Snyder and Teng, 2012). The most common types of injuries in humans are contusion or impact/compression of the spinal cord following a fracture-dislocation of the vertebral column or burst fracture (Tator, 1995). Experimental rat models of contusion, compression, and crush SCI reflect the pathophysiology of human SCI (Basso et al., 1996; Behrmann et al., 1994; Constantini and Young, 1994; Tator and Poon, 2009). Substantial tissue loss occurs after major SCI and this results in a fluid-filled cavity in the center of the cord at the site of injury that may even enlarge over time resulting in further tissue damage. Inhibitory molecules are upregulated around the injury site and a glial scar forms resulting in a physical and chemical barrier to regeneration. Interestingly, there is usually some tissue preservation in the subpial region containing demyelinated axons (Bunge et al., 1993), and remyelination of these axons is one of the targets for therapeutic approaches (Table 1).

1.3. Current treatment of clinical SCI

Treatment for SCI patients involves operative decompression for any persisting compression of the spinal cord, stabilization and fusion of unstable injuries, management of secondary complications, and rehabilitation. Although medical and surgical care has improved the overall outcome of SCI patients, no effective treatment currently exists for the major neurological deficits after SCI. Drugs such as methylprednisolone are no longer widely used due to limited efficacy and significant side effects (Bracken et al., 1997; Fehlings and Sekhon, 2001; Hurlbert and Hamilton, 2008). However, currently there are several promising neuroprotective agents being investigated in ongoing clinical trials (Kwon et al., 2011; Tator et al., 2012). The goal of neuroprotective treatments is to reduce cell death and attenuate mechanisms of secondary injury. However, to maximize neurological recovery it is important to not only minimize the extent of the SCI but also to promote regeneration and tissue repair. Stem cell transplantation is a promising treatment strategy for promoting repair of the spinal cord. Stem cell therapy offers several highly attractive potential mechanisms for spinal cord repair, such as replacement of damaged neuronal and glial cells, remyelination of spared axons, restoration of neuronal circuitry, enhanced preservation of host neuronal and glial cells, increased expression of beneficial neurotrophins/cytokines by transplanted or host cells, promotion of angiogenesis, bridging of cysts or cavities, reduced inflammation and gliosis, stimulation of endogenous precursor cells, and creation of a favorable environment for plasticity and axonal regeneration (Fig. 2) (Mothe and Tator, 2012). Although various cell types have been transplanted into the injured spinal cord, including Schwann cells, olfactory ensheathing glia, activated macrophages, skin-derived precursors, mesenchymal stem cells, and oligodendrocyte progenitor cells (reviewed in Fehlings and Vawda, 2011; Mothe and Tator, 2012; Sahni and Kessler, 2010; Tetzlaff et al., 2011; Thomas and Moon, 2011; Wright et al., 2010), the focus of the present review is focused on the transplantation of neural stem/progenitor cells (NSPCs) and their advantages and limitations for SCI.

2. Neural stem/progenitor cells (NSPCs)

2.1. NSPCs from the rodent brain and spinal cord

NSPCs are multipotent cells that self-renew, readily expand in vitro, and are committed to the neural lineage. Twenty years ago, Reynolds and Weiss first reported the isolation of neural stem cells from the adult mouse brain using a culture system known as the neurosphere assay (Reynolds and Weiss, 1992) that is now widely used. This involves culturing dissociated CNS tissue in a chemically defined serum-free medium supplemented with specific mitogenic growth factors, such as epidermal growth factor (EGF) and basic fibroblast growth factor (FGF2). These factors select for the neural stem/progenitor cell populations that form colonies of undifferentiated cells called neurospheres. NSPCs are typically cultured as neurospheres in suspension culture but can also be cultured as a monolayer on an adherent substrate. During the selection process, the majority of differentiated cell types die within a few days of culture, and then the NSPCs are subcultured to expand the pool of neural stem cells. NSPCs consist primarily of progenitor cells and a small percentage of stem cells. The multipotent stem cells self-renew and generate daughter cells that differentiate into neurons, oligodendrocytes, and astrocytes. In contrast, progenitor cells are more restricted, with a limited proliferative capacity and differentiation potential. These cells are collectively referred to as NSPCs which consist primarily of progenitor cells and a small percentage of stem cells.

Both the fetal and adult brains contain NSPCs (Gage, 2000; McKay, 1997). NSPCs are found within specific niches including the subventricular zone lining the lateral ventricles of the forebrain (Chiasson et al., 1999; Gritti et al., 1996; Morshead et al., 1994; Reynolds and Weiss, 1992), the dentate gyrus of the hippocampus (Palmer et al., 1997) and the periventricular region of the spinal cord (Weiss et al., 1996). Multipotent, self-renewing NSPCs can be generated from the adult spinal cord when the cultured tissue includes the periventricular region containing the central canal (Kulbatski et al., 2007; Martens et al., 2002; Mothe et al., 2011a). NSPCs in general are advantageous for transplantation because they can be readily expanded and they self-renew, and unlike other types of stem cells, NSPCs are inherently specified along the neural lineage. NSPCs can be induced to produce enriched populations of glial or neuronal progenitors by incubation with specific exogenous factors in vitro or modifications in cell culture techniques. For

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