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Review

Stem cell based therapies for spinal cord injury

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ABSTRACT

Treatment of spinal cord injury has always been a challenge for clinical practitioners and scientists. The development in stem cell based therapies has brought new hopes to patients with spinal cord injuries. In the last a few decades, a variety of stem cells have been used to treat spinal cord injury in animal experiments and some clinical trials. However, there are many technical and ethical challenges to overcome before this novel therapeutic method can be widely applied in clinical practice. With further research in pluripotent stem cells and combined application of genetic and tissue engineering techniques, stem cell based therapies are bond to play increasingly important role in the management of spinal cord injuries.

Contents

1. Background

Spinal cord injury (SCI) is one of the most severe complications of spine injuries. 15–40/million people suffer from SCI each year, WHO estimates only 250,000 to 500,000 people suffer SCI each year, including approximately 12,000 cases in the United States. (Mortazavi et al., 2015; One Degree, 2009). The common causes of

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SCI include vehicle accidents, falls, sports and other trauma, infections and tumors. The majority of SCI victims are young patients, who are at the prime of their working age (Tator, 1995). Those injuries not only affect the physical and psychological well-being of those patients, but also bring huge economic burden to their families. In the United States, the social economic lose due to SCI is 8 billion dollars each year. Thus the prevention of SCI and treatment after SCI is an important health care issue.

In the current literature, several methods have been described to be effective in the treatment of SCI. However, none of those methods were efficient enough to gain any functional recovery after the injury (Kwon et al., 2010). The major challenge in the treatment of SCI is achieving axonal regeneration and rewiring the spinal cord, which was thought to be impossible until Aguayo et al. (David and Aguayo, 1981) described that central nervous system axons can grow into the peripheral nerve grafts in the early 1980s. Strong proliferation and differentiation potential of stem cells made stem cell transplantation technique possible to replace the injured neurons, modulate the microenvironment, facilitate axonal regeneration and bridge the spinal cord. In this paper, we review the possible mechanisms of stem cell based therapies for SCI, the types of stem cells that can be used for such purpose, the optimal time for stem cell transplantation, different ways to transplant the cells, new trends in stem cell based therapies as well as the problems to solve before using this technique widely in clinical practice.

2. Possible mechanisms of stem cell based therapies for SCI

Although it is not absolutely clear, stem cell based therapies for SCI mainly work through several mechanisms.

2.1. Replacing the damaged neurons in the spinal cord

After being transplanted, stem cells can differentiate into neurons and gliocytes, make new connections with the host neurons, and rebuild the neuronal circuit in the spinal cord (Stenudd et al., 2014).

2.2. Protecting the host neurons and preventing apoptosis

It has been proven that stem cell transplantation after SCI can down-regulate the expression of genes related to inflammation and apoptosis, and up-regulate the genes with neuron-protective effect, and protect the spinal neurons from secondary changes after the injury (Oliveri et al., 2014).

2.3. Promoting axonal regeneration and synapses formation

After transplantation, stem cells interact with the surrounding tissues and produce extracellular matrix as well as several neurotropic factors such as brain derived neurotropic factors, neural growth factor, vascular endothelial growth factor, this changes the microenvironment in the injury site and accelerate the growth of neural axons. The interneurons differentiated from transplanted stem cells can sprout axons and bridge the spinal cord proximal and distal to the site of injury (De Feo et al., 2012; Dalous et al., 2012).

2.4. Promoting myelin formation around the remaining and newly grown neural axons

The transplanted stem cells can differentiate into oligodendrocytes and gliocytes, which can promote the formation of myelin and functional recovery in patients with SCI (Cusimano et al., 2012; Yang et al., 2013; Lu et al., 2014a).

3. The types of stem cells that have been used for the treatment of SCI

A variety of stem cells have been reported to be efficient in the repair of SCI, including neural stem cells, embryonic stem cells, bone marrow mesenchymal stem cells, adipose derived mesenchymal stem cells, umbilical cord blood stem cells, umbilical cord Wharton jelly stem cells, induced pluripotent stem cells, adipose derived mesenchymal stem cells (Table 1).

3.1. Neural stem cells

In 1992, Reynolds and Weiss (1992) successfully cultivated neuronal stem cells from mammals by “neurosphere” method, a series of studies since then proved that neural stem cells can be used to promote functional recovery after SCI (Ao et al., 2007; Lu et al., 2014b; Tuszynski et al., 2014). Although this method is easy to carry out and but neural stem cells inside the neurosphere could easily die or differentiate because they could not get enough support from the nutrient composition and the differentiation inhibitory factors in the culture medium. Another well- known method to generate neuronal stem cells is the monolayer method established by Prof Austin Smith in Cambridge Stem Cell Institute (Pollard et al., 2006). This method significantly increases the area of each cell exposed to the culture medium, and provides enough nutritional support to those cells, but requires strict control of the culturing conditions. It has been reported that a combination of those two methods can be applied to harvest large number of neural stem cells with high purity (Dao-Fang et al., 2009).

3.2. Mesenchymal stem cells

Mesenchymal stem cells such as bone marrow stem cells, umbilical cord stem cells and stem cells originated from blood or skin tissues have been applied for the treatment of spinal cord injury (Parr et al., 2007). Cell surface markers can be used to identify meschenchymal stem cells. For example, the typical fractions of mouse MSCs in bone marrow identified by cell sorter are PDGFRα+/CD51+ fraction (Pinho et al., 2013), and those of human MSCs are Stro-1+/SSEA-4+/CD271+/CD146+ (Bianco, 2014). Although the stem cells supposedly differentiate into neural and glial cells to directly participate in bridging the spinal cord, the current literature is controversial on the ability of mesenchymal stem cells differentiating into neurons (Meletis and Frise ín, 2003). However, still most studies evaluating mesenchymal stem cells transplantation for SCI report significantly approved functional recovery in the test subjects. The most likely explanation is that those cells indirectly promote axonal regeneration after SCI by modifying the microenvironment by secreting neurotropic factors and cytokines.

The most commonly used mesenchymal stem cells for the treatment of SCI is bone marrow stem cells. Osaka et al. used mesenchymal stem cells derived from bone marrow to treat rat models of contusive spinal cord injury and found that it significantly improved functional outcome (Osaka et al., 2010). Sasaki et al. (2001) found that bone marrow mesenchymal stem cells can be used to repair spinal axons and myelin sheath. Attar et al. (2011) used bone marrow mesenchymal stem cells in clinical trial and none of the patients showed adverse reactions. In the year 2000, Zuk and Safford et al. (Zuk, 2001; Safford et al., 2002) extracted adipose derived mesenchymal stem cells and proved that it can be differentiated into neurons in vivo. Adipose derived mesenchymal stem cells can be easily extracted and cultivated in large numbers, genetically modified and differentiated into neural stem cells. Since the stem cells are extracted from the fat tissue of the patient, there are no ethical concerns regarding its clinical application. However,