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Bone marrow mesenchymal stem cells (BMSCs) improved functional recovery of spinal cord injury partly by promoting axonal regeneration

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ABSTRACT

Spinal cord injury (SCI) disrupts the spinal cord and results in the loss of sensory and motor function below the lesion site. The treatment of SCI became a challenge because the injured neurons fail to axon regenerate and repair after injury. Promoting axonal regeneration plays a key role in the treatment strategies for SCI. It would meet the goal of reconstruction the injured spinal cord and improving the functional recovery. Bone marrow mesenchymal stem cells (BMSCs) are attractive therapeutic potential cell sources for SCI, and it could rebuild the injured spinal cord through neuroprotection, neural regeneration and remyelinating. Evidence has demonstrated that BMSCs play important roles in mediating axon regeneration, and glial scar formation after SCI in animal experiments and some clinical trials. We reviewed the role of BMSCs in regulating axon regeneration and glial scar formation after SCI. BMSCs based therapies may provide a therapeutic potential for the injured spinal cord by promoting axonal regeneration and repair.

Contents

1. Introduction

Spinal cord injury (SCI) is a severe disease with a variety of pathogenic factors which lead to spinal cord structure and functional injury, finally resulting in the loss of voluntary movements and sensation below the damaged plane (Tran and Silver, 2015). SCI is also the enormous economic burden on the patients, their families, and the society. About 40–80 persons are suffering from spinal cord injury per million people every year in the world (Noonan et al., 2012). Epidemiological data showed that about three million people are living with traumatic SCI worldwide, and nearly 133–226 thousand incident cases were reported, globally in 2007 (Lee et al., 2014). The age of the SCI has increased from 28.7 years old in the 1970s to 42.2 during 2010–2014, which is noted for both sexes, all races, and all etiologies except acts of violence according to the survey of the United States (Chen et al., 2016). Current treatments for SCI are insufficient and cause severe side effects while the new therapy for SCI is urgently needed.

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SCI has two major injury mechanisms including the primary and the secondary injury. Primary injury occurs quickly within a short time after injury (generally considered within 4 h), of which the effect is irreversible and the deformation and tearing of tissues caused by external forces directly. Then the neuronal axis is destroyed, starting from the damaged part to both sides. In a word, the primary injury could be divided into neural destroying and vascular structures injury (Sinescu et al., 2010). The secondary injury takes place in a few minutes to several days after the primary injury. It accompanied with a series of intracellular metabolisms, such as inflammatory cell infiltration, neurons apoptosis, and necrosis. The secondary injury caused by the tissue damage is even more severe compared with the primary injury (Fig. 1). After SCI, the blood-brain barrier (BBB) is disrupted, and an influx of inflammatory cells occurs, with the increased expression of matrix metalloproteinases (MMPs). Then the inflammatory cells, along with other resident microglia, produced generating toxic molecules, such as free oxygen, nitrosyl–derived radicals, MMPs, cytokines, and chemokines (Sinescu et al., 2010). It induced cell and neuron death more in the tissues surrounding the original injury site in turn (Wright et al., 2011). Subsequently, macrophages would clear the tissue debris at the lesion site, leading to the scar tissues filling with fluid-filled cysts. It could inhibit the regenerative sprouting of the lesion spinal cord by secreting the scar-associated neurite growth-inhibitory molecules (the chondroitin sulfate proteoglycans) (Schwab, 2002). At the same time, with the role of neurotoxic excitatory amino acids, oxygen free radical formation and calcium overload, furthermore resulting in the death of neurons and other cells.

Spinal cord injury destroys the nerve conduction pathway, leading to the loss of movement and sensory function below the injured plane, resulting in severe dysfunction and badly influenced the patient's life and psychology. Therefore, the ultimate goal of SCI treatment is to reconstruct the injured spinal cord and improve the motor, sensory and autonomic function (Lu, 2017). However, Nogo, a molecule expressed by myelin, the glial scars, and chondroitin sulfate proteoglycans (CSPGs) would be obstacles for the adult central nervous system (CNS) regeneration (Young, 2014). Adult central nervous system (CNS) regeneration needs neurons to survive in the damaged site, initiate new axonal growth, and ultimately establish new synaptic connections (Hao and Collins, 2017). There are five steps of the axon regeneration: retrograde signal transduction from the site of injury, entry of the signal into the nucleus, transcription and translation of the molecules essential for axon growth, axon growth itself, and synapse formation (Sakamoto and Kadomatsu, 2017). Therefore, the two main obstacles of the axonal regeneration for spinal cord repair are the diminished growth capacity of the adult neurons and the presence of inhibitory molecules in the scar at the lesion (Wu et al., 2015). An ideal treatment for spinal cord injury is to improve the two obstacles. Stem cell transplantation therapy represents an attractive alternative, especially for the treatment of patients suffering from SCI. The previous studies reported that bone marrow mesenchymal stem cells (BMSCs) secreted trophic factors that improved axonal regeneration and reduced cavity formation. Therefore, BMSCs could promote the intrinsic ability of the spinal cord to regeneration (Ide et al., 2016).

2. BMSCs and SCI

BMSCs are the most abundant cells in bone marrow, existing in the body connective tissue and organ stroma. BMSCs are still hematopoietic and functional support cells in the bone marrow. The characters of low immunogenic–no unique surface markers help BMSCs easily elude the immune surveillance (Zhang et al., 2015). Many studies have shown that BMSCs play an important role in the regulation of hematopoietic stem and progenitor cells (HSPCs) by different signal pathways, for example, the Cxcl12–Cxcr4 axis, the key HSPC maintenance chemokine, Rac GTPases, and Wnt signaling (Garcia-Garcia et al., 2015). The experiments showed that BMSCs could improve the motor function recovery by up-regulating vascular endothelial growth factor (VEGF) mRNA expression and increasing angiogenesis in the spinal cord after SCI in rats (Yu et al., 2011). Another study indicated that BMSCs co-transplantation could double the number of functional, donor-derived Hematopoietic stem cells, and significantly reduce clinically relevant side

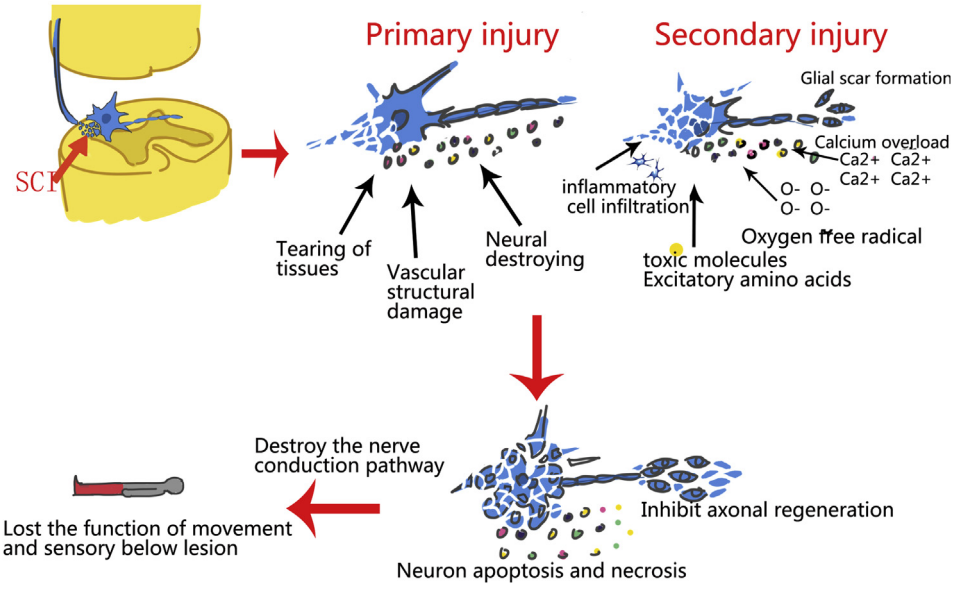

Fig. 1. Two major injury mechanisms of spinal cord injury. SCI could divide into two major injury mechanisms: The primary injury occurs for tearing of tissues, vascular structures injury and neural destroying; The secondary injury caused by inflammatory cell infiltration, neurotoxic excitatory amino acids, oxygen free radical formation, calcium overload and the glial scar formation. Then SCI induced neuron apoptosis and necrosis and inhibition of axonal regeneration.