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Review

An update on application of nanotechnology and stem cells in spinal cord injury regeneration

Kazem Nejati-Koshki[a], Yousef Mortazavi[a,b,*], Younes Pilehvar-Soltanahmadi[c,d], Sumit Sheoran[d], Nosratollah Zarghami[a,c,e,f,**]

[a] Department of Medical Biotechnology and Nanotechnology, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[b] Cancer Gene Therapy Research Center, Zanjan University of Medical Sciences, Zanjan, Iran
[c] Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Australian Regenerative Medicine Institute, Monash University, Clayton 3800, Victoria, Australia
[e] Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Council for Development of Stem Cells Sciences and Technologies, Tehran, Iran

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ABSTRACT

Spinal cord injury (SCI) is damage to the spinal cord that leads to sudden loss of motor and autonomic function and sensory under the level of the injury. The pathophysiological advancement of SCI is divided into two categories: primary injury and secondary injury. Due to the loss of motor, sensory, or cognitive function, a patient's quality of life is likely reduced and places a great burden on society in order to supply health care costs. Therefore, it is important to develop suitable therapeutic strategies for SCI therapy. Nano biomedical systems and stem cell based therapy have the potential to provide new therapeutic availability and efficacy over conventional medicine. Due to their unique properties, nanomaterials and mesenchymal stem cells can be used to offer efficient treatments. Nanoparticles have a potential to deliver therapeutic molecules to the target tissue of interest, reducing side effects of untargeted therapies in unwanted areas. Mesenchymal stem cells (MSCs) can reduce activating inflammation responses that lead to cell death and promote functional recovery and cell growth. We review recent uses of nanomaterials and stem cells in regeneration of SCI.

Contents

Abbreviations: SCI, spinal cord injury; MSCs, mesenchymal stem cells; BBB, blood brain barrier; MP, methylprednisolone; NASCIS, national acute spinal cord injury study; PLGA, poly lactic-co-glycolic acid; iNOS, inducible nitric-oxide synthase; PEG, polyethylene glycol; PHEMA-MMA, poly (2-hydroxyethyl methacrylate-co-methyl methacrylate); LMTs, lipid microtubules; ECM, extracellular matrix; PGFs, based glass fibers; EGFR, epidermal growth factor receptor; NPC, neural progenitor cell; PLLA, poly-L-lactic acid; FDA, Food and Drug Administration; EMA, European Medicines Agency; Shh, sonic hedgehog; CDK, cyclin-dependent kinase; MAIs, myelin-associated inhibitors; CSPGs, chondroitin sulfate proteoglycans; ChABC, chondroitinase ABC; PMMA, polymethylmethacrylate; SPIONPs, superparamagnetic iron oxide nanoparticles; MCP, monocyte chemoattractant protein; BDNF, brain-derived neurotrophic factor; GDNF, glial cell-derived neurotrophic factor; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; CREB, cAMP responsive element binding protein; MNTS, multineurotrophin.

* Corresponding author at: Department of Medical Biotechnology and Nanotechnology, Faculty of Medicine, Zanjan University of Medical Sciences, P.O. Box: 14115-111, Zanjan, Iran.
** Corresponding author at: Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Golgasht Street, 51664 Tabriz, Iran.
E-mail addresses: youmort@yahoo.com (Y. Mortazavi), zarghami@tbzmed.ac.ir (N. Zarghami).

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1. Introduction

1.1. Spinal cord injury

Spinal cord injury (SCI) is a destroying condition that leads to sudden loss of motor and autonomic function and sensory under the level of the injury. The number of people in around the world who suffer a SCI is estimated to be between 250,000 and 500,000 every year [1,2]. The majority of spinal cord injuries are due to penetrating bullet wounds and other forms of violence, vehicular accidents, and sports accidents and falls. The loss of sensory and motor capabilities and obtain devastating neurological deficits results from two major pathophysiological events: the initial physical injury and the subsequent secondary injury that initiated by the initial trauma [3]. The primary injury is acute and caused by mechanical forces such as compression and displacement that can physically rupture cell membranes and blood vessels and destroy a lot of local neurons and glia [4]. The primary mechanical injury induces a cascade of chemical reactions and biological events leading to a secondary injury that occurs in the hours following the initial injury (Fig. 1). These secondary injury processes cause oxidative damage by activated radical oxygen, calcium-mediated damage by calcium ion influx, immune reactions, apoptosis, hemorrhage, inflammation, edema and more tissue damage resulting in axonal degeneration, demyelination and cavitation at the site of injury [5]. In addition to, SCI leading to the formation of a glial scar causes raised neuron and oligodendrocyte cell death that result in up-regulation of axonal growth inhibitory factors with in injury site [6]. Therefore, can to arrange SCI as a multi-factorial disease. By reducing the quality of life in patient due to the loss of motor, sensory or cognitive function, developing of suitable therapeutic strategies for SCI therapy is important.

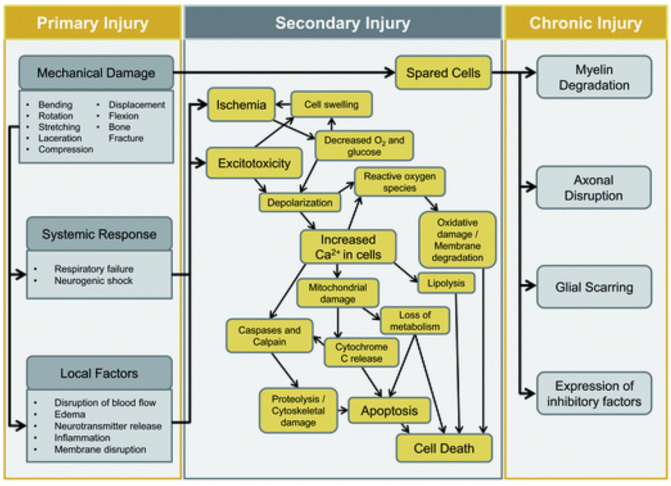

Fig. 1. Progression of primary injury and secondary injury [81].

1.2. Application of nanotechnology for treatment of SCI

Nanomaterials due to their unique benefits can be used to solve current therapeutic limitations. They can be used as nano-carriers that have the capacity to increase the bioavailability of drugs by targeted delivery into injury site and expanded circulation times [7]. In addition to, nano-carriers due to their size can cross borders like the blood brain barrier (BBB) and cell membrane walls simply. Nanomaterials can also help axonal regeneration in order to reinstitute conduction in injured spinal cords by advancement axonal re-growth [8]. Scaffolds constituted of nanomaterials can be used to imitate the natural cell microenvironment [9]. In recent years, nanotechnology for the treatment of SCI have gained an inordinate progress which is mentioned in following sections below.

1.3. Methylprednisolone delivery by nanoparticles

One of the of treatment options for SCI is the use of methylprednisolone (MP) which is a synthetic cortico-steroid and used in high dose (30 mg/kg bolus injection followed by a 5.4 mg/kg/h infusion over 23 h) to suppress the immune system, decreasing inflammation surrounding the injury site. The National Acute Spinal Cord Injury Study II (NASCIS II) exhibited that methylprednisolone given during the first 8 h following an initial SCI injury can improve neurologic recovery and decrease neurological deficits after SCI in humans [10,11]. The use of systemic high-dose methylprednisolone in acute SCI causes adverse side effects including gastric bleeding, sepsis, pneumonia, wound infections, and acute cortico-steroid myopathy accompanied by only moderate improvements in neurological recovery [12]. The most of the adverse side effects of methylprednisolone treatment are related to the systemic high dosage and associated toxicity. Therefore, we require a targeted delivery of methylprednisolone at injury site to increase the bioavailability and avoid any adverse side effects. In 2009, Kim and colleagues examined the nanoparticle-mediated site-specific MP delivery onto the injured spinal cord to overcome the side effects of systemic high-dose perfusion while significantly intensification delivery productivity. They used poly lactic-co-glycolic acid (PLGA)-based MP loaded nanoparticles (MP-NPs) carrying 1/20th of the common clinical dose of MP locally delivered at the site of injury in a dorsal over-hemisection model of SCI and reported that locally delivered significantly decreased the responsiveness of pro-apoptotic proteins such as Calpain, iNOS, and Bax, and increased responsiveness of anti-apoptotic protein such as Bcl-2 at the injury site when compared with the control treatments. Therefore, they suggested that locally delivery of MP-NP can minimize the side effects associated with high-dose MP systemic dosage, while maximizing the therapeutic effectiveness of MP for treating a spinal cord injury [13].

In other study Chavatal and colleagues have developed a minimally invasive hydrogel-nanoparticle drug delivery system that consists of a thermo reversible agarose gel as a carrier for MP that is encapsulated in biodegradable PLGA based nanoparticles