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Cell Therapy; A New and Safe Strategy for the Treatment of Spinal Cord Injury: A Review

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Abstract

Background: Spinal cord injury is a progressive process that initially causes abnormal nerve connections. Following spinal cord injury, the spinal cord is impaired after which cell death and apoptosis occurs. Primary damage happens in the spinal cord due to the demyelization of the large axons. Cell therapy is among the new strategies that have been considered for the treatment of neural injuries in recent years.

Aim: In this narrative review article, we discuss "Cell Therapy" as a new and safe strategy for the treatment of spinal cord injury. we are going to explain the epidemiological and pathophysiological aspects of spinal cord injuries (SCI) as well as SCI experimental and clinical stem cell strategies.

Conclusion: There are several promising advancements and findings in the field of stem cell biology and cell reprogramming, with the aim of treating patients with SCI via stem cell therapy. We reviewed critical issues for clinical translation and we also provided a commentary on recent developments such as termination of the first human embryonic stem cell transplantation trial in human SCI.

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Introduction

Spinal cord injuries (SCIs) account for approximately 10% of injuries to the nervous system. Although these injuries are not usually severe, they have devastating effects on social, psychological, and medical dimensions of one's life for a long time or even until the end of their life (1).

Spinal cord injury arises from various causes including crashes, hard sports and occupational injuries, inflammatory processes, and discopathies. In Iran, about 50,000 people live with spinal cord injury, of whom 2,100 are veterans of war (2). Spinal cord injuries are usually caused by severe mechanical trauma to the spinal cord, causing cardiovascular problems, venous thrombosis, osteoporosis, pressure ulcers, and neuropathic disorders. These injuries cause brain blood dysfunction and lead to the release of inflammatory factors and subsequent activation of the glial cells that ultimately cause spinal cord necrosis (3).

The inflammation process initially begins with the introduction of lymphocytes, neutrophils, and monocytes to the site of the lesion. These cells destroy digestive remnants and remove dead cells. The cascade of inflammation ultimately results in cyclic activation of cytokine and chemo-like inflammatory factors that cause apoptosis, demyelination, loss of axons, and degeneration (4).

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The inflammatory cells destroy the spinal cord through secreting the matrix metalloproteinase to the site of the lesion [5]. On the other hand, macrophages result in neuronal regeneration and spinal cord repair via phagocytosis and release of protective cytokines such as FGF, NGF, and NT3 (6). When the spinal cord injury occurs, oligodendrocytes act faster than all other cells. They promote apoptosis and necrosis and cause myelin to disappear in both ascending and descending pathways.

The exact mechanism of apoptosis of oligodendrocytes is still not fully understood. FAS receptor, which is located on the surface of oligodendrocytes, is activated through the FAG ligand by microglial cells and triggers the apoptotic cascade (7,8). After an injury to oligodendrocytes, some inhibitory factors, including OMGp, MAG, Nogo-A, which are secreted by these cells, inhibit axonal growth (9, 10). The next target is the neurons whose axons are thinned and achromatized.

The transmission of the nerve signal becomes disturbed and it loses the ability to guide neuronal impulses. Several means have been proposed to interfere in this process including reintroduction of myelin by stem cells the use of neurotrophic enriched stem cells. The factors, secreted from these cells, constitute the basis for their role in providing faster recovery, though the simultaneous use of more than one method known as combination therapy may be more effective.

In cell therapy, various cellular sources are used for myelination, where the cell therapy strategy for a particular disease, to a great extent, depends on the complexity of the anomaly. Nowadays, cell therapy is considered an important strategy in restorative medicine. In tissue engineering, cells are definitely the most important part of the reconstruction and repair of the patient's tissue. The decisive factor is the need for reliable cellular resources, from multi-power cells that can be captured at a low death rate, plus a precise control while well-placing the cells in the target tissue.

Pathophysiology

The spinal cord injury consists of primary and secondary phases. In the first stage, motor, sensory, and autonomic functions become impaired while in the second stage, sequential events and molecular cascades happen at the site of the lesion, leading to inflammation, production of free radicals, necrosis, apoptosis, and astrogliosis.

Damaging factors are divided into two groups: a) Factors of external origin such as sudden and severe blows, driving accidents, falling, birth-related injuries, bullet injuries, and injuries caused by exercise; b) Factors of internal origin such as cerebrovascular accidents, spinal cord tumors, infections, myelitis, vascular disorders, degenerative changes, hematoma, rupture of disc, molybdenum scoliosis, spinal cord fluid disorders, and spinal cord inflammation (11, 12).

Types of spinal cord injury

Spinal cord injuries are divided according to the type of lesion and the degree of involvement. The degree of injury to the spinal cord is different given the severity and type of injury. The lesions created in the spinal cord are classified as follows: a) Concussion which causes mild nervous symptoms and develops after several hours; b) Contusion that leads to edema and surface hemorrhage of the spinal cord; and c) Compression which is associated with severe edema and ischemia leading to necrosis.

This type of lesion may be permanent or slowly resolved after a while. Complete spinal cord injury results in permanent destruction of all physiological activities of the spinal cord below the site of the lesion. This lesion may be caused by wounding back, rotating and compressing the spinal cord (14).

Spinal cord injury stages

Acute: Symptoms include vascular pathological changes and changes in blood

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pressure in the grey region of the lesion area. It begins immediately after the trauma and lasts for several hours (15). Due to the effect of free radicals, the capillary and vascular walls of the perinatal region become defective. With the destruction of the vascular wall, a pathway opens for the movement of blood cells.

Subacute: As bleeding continues in the spinal cord, more cells die and the number of cytoplasmic reticulations increases in microglia cells. They express molecules such as antigens I and II and C3 receptor plus macrophages activator markers. Astrocytes grow larger than usual and activate the opioid and lysozyme enzymes (16).

Chronic: A few days after the spinal cord injury, a cystic area appears at the site of the lesion. This cyst is usually connected to the central canal and is full of cerebrospinal fluid (CSF). Macrophages are not present anymore. A week after injury, scar tissue which is a dense network of cytoplasmic astrocytes appears in the region. The inflammatory cells and meningeal cells participate in the development of this network. The resulting destruction of myelin causes a blockage in the transmission of sensory and motor data. The rate of myelin destruction is very important for estimating the prognosis of spinal cord injury (17).

Cell therapy

Recently, cell therapy has been considered as an important means in the repair of spinal cord injury in the secondary phase. Although the multifactorial treatment process should not be overlooked in medical treatments and rehabilitation activities, stem cells are new candidates for this process. These cells are the most important part of the reconstruction and repair of the patient's tissue (18). There are different types of stem cells which come from different sources and have various applications in the treatment of spinal cord injury. Various cells have been used for transplantation in demyelinated models of spinal cord injury. They include oligodendrocytes or their precursors (19), Schwann cells (20), olfactory plating cells, and adult or induced pluripotent stem cells (21). Nevertheless, the possibility of differentiating into unwanted cells, tumor formation, executive and ethical issues, social intolerance (22), and most importantly, the possibility of triggering inflammatory and immunological responses have limited the use of these methods (23).

Bone marrow stromal stem cells

By examining different cellular sources for transplantation, it is clear that fetal stem cell transplantation is not a suitable method for the treatment of neurodegenerative diseases. In addition to achievement of non-consistent results, there are ethical and executive issues in their use (23).

Observations suggest that Bone marrow stromal stem cells (BMSCs) in rats and humans retain the ability to differentiate into non-mesenchymal derivatives including neurons. There are several recent reports about the application of BMSCs for creating neuronal cells such as neurons and astrocytes both in vitro and in vivo. These results, coupled with the limitations of the use of embryonic stem cells and the limited availability of adult stem cells in therapeutic applications, have added value to the importance of further research on the use of BMSCs. Bone marrow mesenchymal cells (MSCs) are now considered as a source of adult stem cells for the treatment of neurological diseases, and research in this field has become widespread. These cells are mainly used in two general forms for transplantation in the lesions. A team of researchers introduced these cells into a diseased animal without induction. The researchers found that BMSCs had the ability to differentiate into glial and neuronal cells in vivo; after direct injection of these undifferentiated cells in the brain and the ventricles, they still survived and expressed some glial and neuronal markers (24,25,26). Note that recent studies have shown that BMSC cells are able to secrete most of the neurotropic

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factors, such as BDNF, NT3, NGF, CNTF, etc. In this case, it seems that these cells are superior to be used as neuron prophylactic cells and a means for nerve injury repairs (27). BMSCs transplanted through the intra-spinal injection into the hemisection SCI in rats can engage in reinsertion of parts of the demineralized spinal cord and improve the movement (28).

Neural stem cells

Neural stem cells (NSCs) are found mainly in the epidermal regions of the ventricles and the central canal of the spinal cord (28). They express a developmental marker of neuroepithelial cells (29). Nestin is by far the best marker for in vivo neuro-proliferative neuronal cells, although it is difficult to trace in vivo (30, 31). These cells are multiplicative and integrate BrdU into their DNA. BrdU is an open thymidine analog which can be replaced in cellular phase S; as such, its traceability reflects the presence of proliferating cells (32).

Recent studies have suggested that stem cells of the sub-ventricular regions can be activated in response to various pathological signals such as trauma, ischemia, inflammation, neurodegeneration, and loss of myelin (33). These NSCs can relocate from their natural path to the injury region and become converted into a particular cell phenotype (34). Stereotypically derived NSCs can be in the form of a sphere called Induced Indoor 10 hours post induction. Then after 1 hour, they move towards each other and form a perfect globe after one day (35). Several studies have shown that NSCs are able to migrate to areas affected by the injury and convert into oligodendrocyte in a variety of animal models (36).

Oligodendrocyte

Identification of the origin and development of the oligodendrocytes is important to understand the demyelination and re-myelination processes (37). According to the recapitulation hypothesis, the repair process involves the re-use of similar programs that occur during the developmental process (38). The purpose of regenerative therapies is to re-initiate myelination and prevent the formation of bare axons, which is functionless (37). Repeated myelination is essential for the survival of the exons and their activity (39).

The central nervous system of the adult population has the capacity for re-myelination in response to a myelin-breaking event, but the newly formed myelin usually lacks the appropriate thickness and length (37). The surviving oligodendrocytes at the site of the lesion are not able to make myelin (40). Myelin is also made by oligodendrocytes that extend throughout the brain and the spinal cord, and replenish in response to the loss of myelin. After migration, they fill the demyelinate region. In healthy adults, the oligodendrocytes in the white matter form fixed populations that are rarely divided and do not participate in the oligodendrocyte replacement period and are often silent. However, these cells are activated in response to injury and begin to proliferate (41).

Inflammatory environments in spinal cord injuries induce apoptosis of oligodendrocyte precursor cells (42). FAS receptor, which is located on the oligodendrocyte surface, is activated by FAG ligand via microglial activation cell and triggers apoptotic cascade (7). Myelin lesions in spinal cord injuries inhibit the process of myelination and axonal regeneration by expressing myelin proteins such as Nogo, MAG, and MOG, which are collectively referred to as myelin inhibitory factors (43). A number of studies have reported that re-myelination could occur as a result of the transplantation of oligodendroglia cells, Schwann cells, olfactory epithelial cells, and various types of stem cells and their derivatives (44). In contrast to other studies, it has been shown that in demyelinated models, endogenous oligodendrocytes or oligodendrocytes that are implicated in re-myelination are not functional (33,34). Studies suggest that a real improvement in the

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functioning of the spinal cord myelination may be achieved through reinsertion of healthy axons. Studies have also shown that oligodendrocytes derived from ESC cells can mimic the non-adult CNS ones (35).

Adipose stem cells

The adipose stem cells (ADSC) in the culture medium are similar to fibroblastic cells and stromal cells of the bone marrow. ADSC have the ability to differentiate into cells with mesodermal tissue origins, such as fatty, cartilage, bone, and other cells. They also can transdifferentiate into neural cells. Research has shown that direct injection of ADSC into SCI models transforms these cells to neuronal cells. These cells improved the symptoms in the models by secreting growth factors and cytokines (44).

Neurotrophic factors

Neurogolins constitute a family of growth factors including NGF, NDF, HRG, PDGF, and bFGF. Neurogolins interfere with the growth and differentiation of various histological groups including epithelial, oligodendrocyte and Schwann cells. Recent findings highlight the major roles of neurogolins and their receptors in regulating cell numbers and determining the fate of the cell during cell therapy. These molecules also account for the growth of oligodendrocyte cells. It seems that GGFs are unique among growth factors as they can determine the fate of oligodendrocytes and glial cells (45).

Schwann cells

Schwann cells are the glial protective cells of the peripheral nervous system, which are responsible for making myelin around the axons. These cells are responsible for the regeneration of axons and re-myelination after injury. Schwann cell implantation into the damaged spinal cord produces Neurotrophins and leads to neuron survival as well as growth of the exons. These cells were the first to be used in the treatment of spinal cord injury. Zamini et al observed Schwann cells derived from mesenchymal stem cells. They injected them into a spinal cord hemisection model and reported improved motor function in experimental rats (46,47).

Conclusion

Results have suggested that cell therapy is one of the best ways to treat spinal cord injury in the future and is one of the best sources of stem cells for this adult stem cell process which is free from tumorigenicity and immunization.

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Conflicts of Interest

The Authors declare no conflicts of interest.

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