Administration of Olfactory Ensheathing Cells to Relieve the Symptoms of Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a challenging issue for scientists and clinicians. Thus far, no treatments capable of relieving symptoms associated with neuronal loss and functional defects have been developed. However, stem cell therapy has demonstrated considerable promise in overcoming neuronal cell death and glial scarring in the area of damage associated with SCI. A number of studies have demonstrated the therapeutic advantages and clinical applicability of olfactory ensheathing cells (OECs) in neurodegenerative disorders. This review focuses on the potential benefits of OECs in an SCI animal model and examines partial successes that have been achieved in human clinical trials. We also discuss methods that could further enhance the therapeutic efficacy of these efforts, such as modifying the extracellular matrix to ensure appropriate differentiation and prolong the survival of transplanted cells; and further in situ altering of the spinal cord niche to facilitate the completely therapy of OECs in SCI.

Keywords: Spinal cord injury; Olfactory ensheathing cell; Niche; Extracellular matrix

Introduction

Between 10,000 and 14,000 spinal cord injury (SCI) are reported every year in the United States [1], and medical treatments that deal with acute SCI and subsequent complications are extremely expensive. Following the occurrence of SCI, there is a therapeutic window in which the devastating outcomes of secondary injury can be improved [2]. Therapeutic schemes implemented in response to SCI can be divided into two categories: 1) prevention or amelioration of secondary injury and 2) regenerative intervention. At present, there are no therapeutic methods capable of promoting the complete recovery of neurological damage resulting from SCI. Nonetheless, several research teams have reported limited recoveries through the transplantation of pluripotent cells; therefore, stem cells are being widely studied to develop strategies for the regenerative treatment of SCI [3].

Neuronal cell death is the major pathogenetic mechanism of various neurological disorders, including SCI disorder; therefore, stem cell therapy is a promising strategy to replace injured cells through regeneration [4]. The effectiveness of transplanting embryonic stem cells in patients suffering from neurodegenerative disorders, such as Parkinson’s [5], Huntington’s [6], and SCI has been investigated [7]. However, logistical and ethical considerations have presented challenges to further therapeutic developments in this area, raising the clinical applicability of autologous stem cells [8]. Peripheral stem cells (PSCs) can be isolated from various tissues, such as bone marrow, adipose tissue, umbilical cord blood, muscles, corneal stroma, tooth buds, and nasal mucosa, thereby providing an alternative source for use in transplantation medicine [9,10]. The preparation of autologous stem cells may be an appropriate strategy for clinical applications, as there is no need for in vitro extension and because these cells can be cultured in serum free conditions [11].

Various strategies have been developed for the treatment of animals with SCI, such as adding growth factors [12], providing peripheral nerve or embryonic tissue [13], and transplanting Schwann cells [14]. Recent studies have shown that olfactory ensheathing cells (OECs) have therapeutic potential to enhance axonal restoration and repair in demyelinating-related disorders [15,16]. Previous researchers have further highlighted the therapeutic potential of OECs in neurodegenerative disorders including SCI; however, the mechanisms underlying neural regeneration have yet to be elucidated [16,17]. This review presents information currently available on SCI and OECs, summarizes the potential therapeutic effects of OECs in SCI animal models and human clinical trials, and discusses various potential molecular mechanisms.

OECs

OECs are found in the olfactory bulb and olfactory mucosa in the vicinity of the lamina propria. In animal neurodegenerative disorders, they are believed to induce neurotrophic effects similar to those of Schwann cells [18]. The olfactory mucosa are stimulated by a variety of external environmental variables. As a result, they are under perpetual

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threat of damage and constantly being repaired. Nonetheless, the fact that the sense of smell is rarely lost throughout this process of injury and repair can be attributed to the constant regeneration of olfactory nerve cells [19]. More specifically, the olfactory mucosa is constantly renewed through OECs which are capable of supporting neurogenesis throughout life [20,21]. Nerve cells projected from the nasal mucosa are directed to olfactory nerves associated with the central nervous system [22].

As demonstrated in previous studies, the olfactory mucosa includes unmyelinated olfactory nerve fibers with OECs and sheet-like processes of olfactory nerve fibroblasts [23,24]. The OECs enable the growth of axons from the neurons of the olfactory mucosa to reinnervate the olfactory bulb and in turn form synapses in the brain [17]. The neuroregenerative ability OECs through axonal outgrowth has shown promise in the treatment of SCI in relevant animal models [25]. Furthermore, a number of investigations have shown that OECs can play an important role in the recovery of bladder function and phrenic nerve activity following SCI [3]. This makes OECs a useful type of pluripotent cell for transplantation, capable of facilitating nerve regeneration in SCI patients.

**SCI**

The spinal cord contains neuronal cell bodies and serves as a conduit connecting motor and sensory information, which is necessary for neurotransmission between the brain and the body [26]. In component of spinal cord include neuron cells and the axon of long nerve fibers [27]. Axonal conduction follows either a downward or upward path, carrying signals to and from the brain [28]. Most axonal pathways are insulated by a white sheath called myelin, otherwise known as white matter. Neuronal trees have branches called dendrites, which receive signals from other nerve cells, constitute gray matter, located in the center of the spinal disc as a butterfly shaped region.

SCI refers to spinal cord damage and is more commonly caused by trauma than disease [29]. Traumatic injuries to the vertebral columns often result from accidents, such as motor vehicle mishaps, falls, acts of violence, and recreational injuries. SCI may also be caused by infection or inflammation in the region of the spinal tissue, as well as polio, spina bifida, transverse myelitis, and multiple sclerosis [30]. If damage occurs longitudinally across the spinal tract, SCI can lead to the loss of nerve function [31]. Without effective treatment, the neurological deficits of SCI can have long-term effects for the patient, the family, and society as a whole [32].

**OEC application in SCI treatment**

The traditional view that the central nervous system injury due to poor intrinsic and extrinsic environmental regeneration inhibition, resulting in damage axons cannot regenerate [33]. Recent discoveries have moved the transplantation of OECs to the forefront of SCI treatments [34]. OECs have attracted considerable attention because the unique nature of these cells can promote nerve regeneration and the recovery of nerve function in the spinal cord. Besides, transplantation of OECs into the injured spinal cord display an excellent regenerative effects mediated through reorganize the glial scar, remyelinate axons and stimulate blood vessel formation [35]. According to the results of behavioral examinations, OEC transplantation can provide considerable improvement in functional recovery following SCI (Table 1) [36-48]. Use of OECs transplantation obtained axonal regeneration, although it looks mildly progressive, might provide an adequate foundation for the functional benefits [38].

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Type</th>
<th>Model</th>
<th>Symptom improvement</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI relevant [38]</td>
<td>Primarily cultured rat OECs</td>
<td>T8 spinal cord crush injury</td>
<td>Significant improve BBB scores after OECs transplantation</td>
<td>Combined with chondroitinase ABC</td>
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<td></td>
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<td>Reduced gross area of necrosis</td>
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<td>SCI relevant [37]</td>
<td>GDNF modified OECs</td>
<td>Thoracic spinal cord transection injury</td>
<td>Lots of confused and disorderly regenerated axons</td>
<td>Combined with axonal growth inhibiting protein antibody (IN-1)</td>
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<td></td>
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<td>Restored motor activity</td>
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<td>Improve survival and regeneration of the injured axons</td>
</tr>
<tr>
<td>SCI relevant [38]</td>
<td>OECs were isolated from the olfactory bulbs of adult rats</td>
<td>Spinal cord transection at T9</td>
<td>Improved hindlimb locomotor function</td>
<td>Combined with neural stem cells</td>
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<td></td>
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<td>New nerve fibers across the injured region</td>
</tr>
<tr>
<td>SCI relevant [39]</td>
<td>Primarily cultured rat OECs</td>
<td>C4 hemisection in adult rats</td>
<td>Enhanced axonal growth nor prevented retrograde cell death</td>
<td>OECs were transplanted into the lateral funiculus at 1 mm rostral and caudal to the transection site</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Support neuronal survival and regeneration after spinal cord injury</td>
</tr>
<tr>
<td>SCI relevant [40]</td>
<td>Human OECs</td>
<td>lateral T8 hemisection of the spinal cord</td>
<td>Motor functions steadily increased</td>
<td>involvement together with Schwann cells into remyelination of regenerating axons</td>
</tr>
<tr>
<td>SCI relevant [41]</td>
<td>Primarily cultured rat OECs</td>
<td>T4 spinal cord transection</td>
<td>Reduce duration of autonomic dysreflexia</td>
<td></td>
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</tbody>
</table>
Molecular Signalling

The molecular mechanisms involved in the treatment of OECs have been investigated with regard to neurotrophins, extracellular matrices, ligands, transcriptional coactivators, and other factors [18]. Neurotrophins have demonstrated benefits in prolonging the survival of neurons and axonal expansion. Many neurotrophins secreted from hOECs/ONFs, such as BDNF [47], VEGF [49] and GDNF [50], have been studied extensively to determine whether they play a role in facilitating cerebral plasticity and improving functional rehabilitation in SCI animal models. In recent reports, stromal cells have been used to derive factor-1. Its receptor, CXCR4 (SDF-1/CXCR4), has been shown to provide generalized trophic support to neuronal cells and also have therapeutic potential in relevant animal models. This chemokine is a potent chemo-attractant for hematopoietic stem cells that are constitutively expressed by peripheral tissue [17].

Table 1: OECs applications upon SCI in the past few years.

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<tr>
<th>SCI relevant</th>
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<tr>
<td>SCI relevant [42]</td>
<td>Primarily cultured rat OECs</td>
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<td>SCI relevant [44]</td>
<td>embryonic, neonatal, and adult rats OECs</td>
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<td>SCI relevant [43]</td>
<td>Rat SCI models were created with cushion forces</td>
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<td>SCI relevant [46]</td>
<td>Improvement of hindlimb function</td>
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<td>SCI relevant [49]</td>
<td>To search the optimal donor age for OEC associated remyelination</td>
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<td>SCI relevant [50]</td>
<td>Improvement in spinal cord transmission and activity of lower extremity muscles</td>
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<td>SCI relevant [51]</td>
<td>Improved substantial sensation and motor activity</td>
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<td>SCI relevant [52]</td>
<td>No serious complications postoperatively or during the follow-up period</td>
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<td>SCI relevant [53]</td>
<td>Improved in their ASIA sensory neurological scores</td>
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<td>Abbreviation: BBB (Basso, Beattie, and Bresnahan), T8 (Thoracic 8), C4 (Cervical 4), ASIA (American Spinal Injury Association)</td>
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Future Expectations

For more effective therapeutic potentials of the extracellular matrix (ECM) approach has been deemed a suitable method to control the fate of stem cells, prolong cell survival, and promote differentiation into neuronal precursors [51,52]. Research has indicated that ECM, such as functional three-dimensional scaffolds and microenvironment factors assembled into a matrix, are correlated with neuron-like cells differentiation [53]. In addition, cells cultured in vitro in ECM have demonstrated the ability to perform the standard functions of neuron cells and also have therapeutic potential in relevant animal models. These findings support the applicability of the ECM cultured cells in the treatment of SCI.

The ECM can be remodeled to create a niche that controls the differentiation outcomes and inhibits undifferentiated transplanted cells. Thus, directly programming endogenous stem cells into tissue-specific lineages may be an achievable goal [54]. The alteration of ECM in situ has demonstrated considerable potential to increase the survival and differentiation rate of transplanted cells, thereby enhancing the effectiveness of cell-based therapies [55,56]. A finely defined microenvironment is likely able to provide endogenous undifferentiated stem cells (including transplanted undifferentiated stem cells) with a suitable niche for differentiation [57]. Autologous hematopoietic stem cells (HSCs) are known to exist in bone marrow and have the capacity to differentiate into most cell lines. However, they rarely end up in peripheral tissue, where endogenous PSCs are already scarce [58]. Additionally, granulocyte colony-stimulating factors (GCSFs) are widely applied to mobilize HSCs in many types of treatments. Thus, therapies combining the use of GCSFs could be adopted to transport HSCs to tissues requiring treatment [59,60]. Other studies have demonstrated that the combination of defined
transcription factors has the ability to convert somatic cells directly into functional nerve cells and does not require iPSCs cells fate, to reduce tumorigenic potential [61]. In summary, in situ alteration of the extracellular matrix to direct the programming/reprogramming of endogenous cells is a promising method for the treatment of SCI.

References


