Animal experiments and clinical application of olfactory ensheathing cell transplantation for treatment of spinal cord injury*

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Abstract

BACKGROUND: The olfactory epithelium can still generate new neurons after arresting its growth and development in the human body. Axons can still be generated and pass through peripheral tissue to reach the olfactory bulb. Thus, olfactory cells have been widely used in the repair of spinal cord injury.

OBJECTIVE: Using animal experiments in conjunction with a clinical study of olfactory ensheathing cells, this paper was designed to clarify the function and application prospects of olfactory ensheathing cells, as well as the existing problems with their application.

RETRIEVAL STRATEGY: Using the terms “olfactory ensheathing cells, spinal cord injury”, we retrieved manuscripts published from January 1990 to June 2007. The languages were limited to English and Chinese. Inclusion criteria: studies addressing the characteristics, basic study, clinical application and prospects of olfactory ensheathing cells; studies that were recently published or were published in high-impact journals. Exclusion criteria: repetitive studies.

LITERATURE EVALUATION: The included 29 manuscripts were primarily clinical or basic experimental studies.

DATA SYNTHESIS: Following spinal cord injury, spinal neurons die, neurotrophic factors are lacking, and the existing glial scar and cavities hinder axonal growth. One method to repair spinal cord injury is to interfere with the above-mentioned factors based on animal experiments. Myelination and axonal regeneration are the keys to spinal cord injury therapy. Olfactory ensheathing cells can secrete several neurotrophic factors, inhibit horizontal cell reactions, have noticeable neuroprotective effects, and possess a very strong reproductive activity, so they have many advantages in the fields of cell transplantation and gene therapy. However, there still exist many questions and uncertainties, such as the best time window and dose, as well as complications of olfactory ensheathing cell transplantation; precise mechanism of action after olfactory ensheathing cell transplantation; the number and length of growing axons as well as whether axonal growth is consistent with spinal cord recovery after olfactory ensheathing cell transplantation; and the long-term curative effect of olfactory ensheathing cells transplanted into spinal cord injury patients.

CONCLUSION: Both animal experiments and clinical application have demonstrated that olfactory ensheathing cell transplantation helps spinal neurofunctional recovery, but the mechanism of action requires further investigation.

Key Words: olfactory ensheathing cells; spinal cord injury; review literature

INTRODUCTION

It is generally thought that after central nervous system injury, injured axons cannot regenerate due to poor regeneration capacity and inhibition from the external environment. However, recent studies have shown that, after spinal cord injury, some methods to change the local environment following spinal cord injury can promote the repair and regeneration of injured nerves and recover partial neural function of the spinal cord. Among these methods, olfactory ensheathing cell transplantation is considered to be the most promising method for treatment of the spinal cord.

Olfactory ensheathing cells originate from the olfactory basement membrane, are distributed in the olfactory bulb and olfactory nerve, exist and migrate to peripheral and central nerves [1]. Olfactory ensheathing cells, which are a kind of glial cells, can help olfactory neuronal axonal growth and regeneration. More and more animal models have shown that olfactory ensheathing cells transplanted into injured spinal cord can speed up spinal cord recovery [2]. Human olfactory epithelium possesses a life-long regeneration capacity [3]. Renewal of olfactory neurons is a regulatory process in which many factors participate [4]. The source of new sensory neural stem cells remains unclear. But sensory neural stem cells are thought of as a basic olfactory epithelial...
Olfactory ensheathing cells possess characteristics similar to Schwann cells and horizontal cells, the former in particular. They also have two distinct characteristics: olfactory ensheathing cells exist in peripheral nerves (like Schwann cells) and central nerves (like horizontal cells). They help axonal growth like Schwann cells and possess the capacity to survive in the central nervous system like horizontal cells. The olfactory mucosa also has life-long regeneration capacity. Such regeneration is a high-performance regulatory process, in which olfactory ensheathing cells participate, but the precise mechanism remains unclear. These two characteristics make olfactory ensheathing cells the best choice for nerve repair. Olfactory ensheathing cells express many molecules related to cell adhesion and axonal growth, on the cell membrane, such as L1, polysialylated neural cell adhesion molecule, neural cell adhesion molecule, laminin, and fibronectin, which regulate olfactory nerve axonal prolongation, as well as glia 2-derived nexin and S100, which promote neural growth. Olfactory ensheathing cells also can secrete different kinds of neurotrophic factors, such as platelet-derived growth factors, neuropeptide Y, and S100. At present, olfactory ensheathing cells have been widely used in various spinal cord injury models, such as, spinal cord transection, semi-section, spinal tract injury and spinal cord demyelination. Li et al. reported that animal models of acute spinal cord injury could be developed by abscising the unilateral corticospinal tract of the rat cervical cord. A purified olfactory ensheathing cell suspension was then injected into the injured region. Three to ten weeks later, they found that a regenerated corticospinal tract passed through the injured region and bridged across the distal spinal cord; at the same time, rat forelimbs recovered slightly. Li et al. also reported that, under the condition of precise location, animal models of corticospinal tract impairment at the adult rat C1,2 segment could be developed by electrical lesioning; thus, all of the tissues in the center of spinal cord could be precisely damaged. After lesioning, an olfactory ensheathing cell suspension well cultured was immediately transplanted into the spinal cord injury region. In the first week after transplantation, it was found that the abscised corticospinal tract axon sprouted towards the original axonal direction, and small varicosities appeared before small axons. In the third week after transplantation, regenerated axons were encased by phosphosphingolipid and arranged in a tract. Axons extended through injured region and re-entered the distal corticospinal tract. Imaizumi et al. showed that, under the condition of neural demyelination, olfactory ensheathing cells could help neural myelination and speed up neuroelectrophysiological conduction. Chen et al. co-cultured spinal cord dorsal neurons and olfactory ensheathing cells and found that olfactory ensheathing cells could noticeably promote embryonic dorsal neurite growth. These results demonstrated that olfactory ensheathing cell transplantation might promote the regeneration of injured fibers in the ascending conducting pathway and the descending propriospinal tract, both of which originate from spinal cord dorsal neurons, following spinal cord injury. Olfactory ensheathing cells possess migratory function along with regenerated axons, and can be conformed in the central nervous system to form a scaffold bridge and then pass.
that the corticospinal tract grew noticeably [23]. These results
spastic palsy improved, and histological sections revealed
that the electrophysiological indices of rat two hindlimbs and
comparison with a control group. The results demonstrated
Others reported that they dissected a rat T8 segment,
conduction velocities were faster than those of normal axons,
axons were encased by medullary sheaths, and their
migrated to a rat recipient neuronal axon. All regenerated
into the transverse region of the rat spinal dorsal lateral
comprising 222 patients with complete injury and 78 patients
reach the olfactory bulb. Based on this, olfactory cells have
and development in the human body, and the axons could
been investigated. It was shown that the olfactory epithelium
ensheathing cells in the repair of animal spinal cord have
was milder in the transplantation group compared with the
control group, indicating the inhibitory effect of olfactory
ensheathing cells on apoptosis after spinal cord injury. Inmaizumi et al [24] transplanted olfactory ensheathing cells into the transverse region of the rat spinal dorsal lateral funiculus, and demonstrated that impulse conduction could be detected in the injured area by electrophysiological methods. Cell labeling confirmed that the transplanted cells migrated to a rat recipient neuronal axon. All regenerated axons were ensheathed by medullary sheaths, and their conduction velocities were faster than those of normal axons, although their number was limited. Lu et al [25] reported that olfactory ensheathing cells, which were acquired from the nasal mucosa and transplanted into transverse sections of rat spinal cord, could promote functional recovery from acute and delayed spinal cord injury. This characteristic is significant for spinal cord functional recovery.

Clinical application of olfactory ensheathing cell transplantation for treatment of spinal cord injury

Huang et al [7] reported the first clinical study to use olfactory ensheathing cell transplantation for treatment of spinal cord injury. They removed the olfactory bulbs from aborted fetuses aged over 4 months old, performed a series of processing, culture and purification, and transplanted the cells into 23 patients with advanced spinal cord injury. The results demonstrated that spinal neural functions improved to a remarkable extent. Sensation were markedly improved following transplantation. Motor function, light touch and pain sensation were markedly improved after transplantation. Prior to transplantation, there were 222 patients graded A on the ASIA scale; after transplantation, 38 were graded B, and 46 were graded C. These results demonstrated that embryonic olfactory ensheathing cell transplantation could induce recovery of neurological function in patients with advanced spinal cord injury. Zheng et al [12] performed exploratory studies on the culture, selection of transplantation method and site, transplantation dose, and post-transplantation complication processing of olfactory ensheathing cells, and acquired good clinical therapeutic effects. At present, the primary questions about human embryonic cell transplantation used in clinical practice focus on cell source, post-transplantation adverse reactions, transplantation effects, and operative procedure. Olfactory ensheathing cells have primarily been obtained from neonatal olfactory bulbs [26]. They have also been acquired from the cranial bases of corpses or patients themselves. In addition, they have been obtained from pigs [24]. These sources of olfactory ensheathing cells cannot be widely supported. At present, in China, olfactory ensheathing cells are primarily acquired from the natal mucosa of patients themselves and the olfactory bulbs of 4-6-month-old embryos. Olfactory ensheathing cells obtained from patients are few in number and can be easily polluted, so they are hardly used in clinical practice. Based on the family planning policy in China and abiding by the ethics principles of embryonic stem cell study, most of the olfactory ensheathing cells currently used in clinical practice in China are primarily acquired from aborted 4–6-month-old embryos (donated voluntarily). With research progress in somatic cell culture for stem cells, there will be better ways to obtain olfactory ensheathing cells. The potential risks of olfactory cell transplantation include the risk of the operation itself and the biotic safety of cells. Chen et al [27] followed up 171 patients who underwent olfactory ensheathing cell transplantation for treatment of spinal cord injury for 3 years. No new spinal cord injury, tumor or neoplasm growths were found. These findings indicated that olfactory ensheathing cell transplantation is safe.

SIGNIFICANCE OF AND PROSPECTS FOR OLFATORY ENSHEATHING CELL TRANSPLANTATION FOR THE TREATMENT OF SPINAL CORD INJURY

Olfactory ensheathing cell transplantation for the repair of spinal cord injury is still in the initial stage, and the mechanism of action requires further investigation. Through the use of electrophysiological and anatomical methods, it was found that number of regenerated axons is not completely positively related to functional reconstruction effects [28]. How to induce axonal growth and establish functional synaptic association will be a key topic for future study. Gene therapy is a hot topic in current studies, as it can enhance repair following spinal cord injury, but it also has some adverse effects. At present, adenovirus is a most commonly used gene transfection tool. Adenovirus is replication defective and has no self-replication capability in the cells, but it can cause central and peripheral inflammations and immune reactions in vivo [9,29]. In addition, the long-term effects of transgenic cell transplantation and
whether or not tumorigenesis occurs require long-term repeated experiments and observation. Nevertheless, olfactory ensheathing cell transplantation is still a promising method for the repair of spinal cord injury.

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