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Review

Progress in the study of stem cell transplantation for the repair of spinal cord injury

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Abstract: Spinal cord injury is a critical medical emergency that severely jeopardizes human health. Such injuries can cause lifelong paralysis and lead to various complications, including death, and there are often tremendous economic and emotional burdens placed on the society and family. Therefore, the study of spinal cord injury repair has important significance. The use of stem cell transplantation to repair spinal cord injury has been the focus and cause of difficulty in studies of spinal cord injury repair in recent years. However, there are numerous types of stem cells, diverse cell transplantation methods and different injury models that often cause confusion for investigators. The goal of this paper is to review the studies of spinal cord injury repair with various stem cells and summarize the bottleneck of stem cell transplantation for spinal cord injury repair to reveal the future direction of stem cell transplantation studies for spinal cord injury repair.

Keywords: spinal cord injury, stem cell, cell transplantation.

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Introduction

Spinal cord injury is a severe trauma of the central nervous system (CNS) that frequently results in irreversible loss of sensory and motor functions. These injuries mainly present as a complete loss of sensory-motor function below the location of injury as well as incontinence, with worldwide characteristics of high incidence, high morbidity, high cost and early onset. Each year, an average of 15 to 40 people out of every one million has a spinal cord injury worldwide [1]. Based on our previous epidemiological studies from 2004 to 2008 in Tianjin China, 869 patients were treated for traumatic spinal cord injury [2, 3] in first-class hospitals, and the incidence rate of such injuries is rising year by year.

In recent years, a deeper understanding of the pathophysiological process of spinal cord injury has produced progress in the treatment of spinal cord injury as a result of various therapies, such as surgical decompression, omental transplantation, drug therapy, local freezing, physical rehabilitation and application of enzymes to inhibit connective tissue scarring [4-8]. Although these methods can alleviate the pathological changes resulting from spinal cord injury to a certain extent, they have not achieved a satisfactory clinical outcome, and most patients with spinal cord injury still have different levels of sensory, motor and autonomic dysfunction.

In recent years, stem cell transplantation for the repair of spinal cord injury has become a popular focus of research. Stem cells exhibit a self-renewal capacity and pluripotency; in addition, they can continuously proliferate to maintain their number and differentiate into mature functional cells. These properties allow stem cells to become new methods of repairing spinal cord injury; therefore, they have clinical significance and good application prospects. Therefore, this paper will review stem cell transplantation for spinal cord repair.

The Pathogenesis of Spinal Cord Injury

The most common type of spinal cord injury is caused by acute pressure on the spinal segments, and the mechanical trauma from such injuries causes tissue necrosis, edema, hemorrhage and vasospasm and results in local decreased blood flow and swelling. Secondary pathophysiological responses include ischemia, apoptosis, water and electrolyte imbalance, lipid peroxidation, free radical production and inflammation. Eventually, a large liquefaction chamber or multiple small cysts are formed at the center of the damaged spinal cord segment. After spinal cord damage, the extracellular matrix is secreted by local astrocytes, macrophages and other cells, and highly expressed inhibitory molecules form a glial scar that act as a physicochemical barrier to prevent the regeneration of nerve tissue [9-10].

The pathogenesis of spinal cord injury is extremely complex and involves multiple systems.

1) Blood vessels: after spinal cord injury, the blood vessels that are directly damaged can spasm and lead to reduced blood transportation capability, resulting in local tissue ischemia, hypoxia and necrosis;

2) catecholamine accumulation: after spinal cord injury, a large amount of neurotransmitters, such as histamine and catecholamine, are accumulated in tissues, and these neurotransmitters act on the vascular smooth muscle receptors in the spinal cord, which leads to vascular spasms and tissue ischemia, hypoxia and necrosis;

3) calcium accumulation in spinal cord nerve cells: after spinal cord injury, edema causes reduced blood transportation capability in tissues and leads to even greater edema, and this cycle results in nerve cell necrosis;

4) free radicals: the spinal cord nerve cell membrane is enriched in unsaturated fatty acids that are vulnerable to attack by free radicals, and after spinal cord injury, the resistance to free radicals is significantly reduced. The attack of free radicals causes lipid peroxidation and results in tissue damage [11-13].

Regarding the pathophysiological mechanisms of spinal cord injury, the local microenvironment changes are an important factor that leads to failures in regenerating the nervous system. The local microenvironment changes after spinal cord injury include the following: 1) nerve cell death and spinal cord barrier breakdown, which causes an imbalance of spinal cord internal environments; 2) expression of multiple inhibitory factors on the surface of the cells after injury; 3) appearance of local cytotoxic substances that cause ischemia-reperfusion injury; 4) dramatic proliferation of reactive glial cells, formation of glial scars and regeneration inhibitory molecules that prevent axonal regeneration and crossing of the damaged zone [14-17].

Stem Cell Transplantation for Spinal Cord Injury

Stem cells are self-renewing and non-specific pluripotent. Their ability to differentiate and renew occurs through the growth of tissues and organs. Under certain conditions, stem cells can differentiate into cells that have different morphologies and functions; furthermore, they can be divided into three categories: totipotent stem cells, which are derived from the inner cell mass of the embryo or embryonic germ cells of early embryonic primordial germ cells, such as embryonic stem cells, which can differentiate into all types of cells within the body; pluripotent stem cells, which can produce more than two types of differentiated cells; and multipotent stem cells, which can only differentiate into a single type of cell. The second and the third types of stem cells exist in adult tissue and are also called adult stem cells; they include neural stem cells, muscle stem cells, mesenchymal stem cells and epidermal stem cells.

The adult CNS has long been thought to have a limited ability to self-repair after injury because dead neurons cannot be replaced by new neurons that are self-generated by the CNS or by neighboring neurons. However, in recent years, a number of stem cell transplantation studies have determined that it is possible to repair damaged nervous system cells through stem cell transplantation. Currently, the stem cells that are available mainly include neural stem cells, bone marrow mesenchymal stem cells, umbilical cord blood stem cells, induced pluripotent stem cells and embryonic stem cells [18].

Neural stem cells

Neural stem cells (NSCs) are stem cells that can differentiate into neurons, astrocytes and oligodendrocytes, have self-renewal capabilities and can produce other types of cells other through asymmetric division to provide large amounts of cells for brain tissue. The characteristics of NSCs can be summarized as follows: capable of generating nerve tissue in the nervous system; capable of self-renewal; capable of generating new cells through asymmetric cell division.

To date, investigators have reported that NSCs occur in most of the regions of the CNS in mammalian embryos, including the cerebral cortex, lateral ventricle, subependyma, hippocampus, striatum and other areas, and NSCs also occur in the cerebral cortex, dentate gyrus, subependyma, striatum, central canal of the spinal cord and olfactory bulb of adult animals. Decades ago, investigators were successful in transplanting human NSCs into spinal cord injury animal models and found that NSCs could survive and the motor functions of injured animals could be partially restored; therefore, the efficacy of neural stem cell transplantation to repair spinal cord injuries was confirmed. However, the massive death of transplanted NSCs is still a problem, and it is considered to be related to a series of pro-inflammatory cytokines that induce apoptosis, extensive demyelination and axonal destruction. Subsequently, scientists made extensive attempts to avoid such phenomena and improve the efficacy of transplantation. The most recent studies have shown that early inhibition of local tumor necrosis factor α (TNF-α) expression can enhance the survival of transplanted NSCs[19], thereby promoting the repair efficacy of cell transplantation. In addition, investigators have shown that during the transplantation of NSCs, a certain threshold number of neural stem/progenitor cells (NSPCs) should be grafted into the epicenter segment instead of to rostral and caudal sites to avoid damaging sites that are adjacent to the lesion during the injection procedure.

Bone marrow mesenchymal stem cells

Mesenchymal stem cells (MSCs) are pluripotent stem cells derived from the embryonic mesoderm during early embryo development, and their name is derived from their ability to differentiate into mesenchymal cells. MSCs are non-hematopoietic stem cells in the bone marrow of adult animals or humans, and they have the properties of pluripotent stem cells that can differentiate into a variety of cell types; in addi§tion, they can be converted to NSCs and differentiate into cells of the nervous system. MSCs can be obtained from many sources and are easily extracted, isolated, purified and propagated in vitro; moreover, self-transplantation is not subject to ethics controversies and rejection problems. Investigators have reported that after transplantation, MSCs migrate locally, and the nerve cells differentiated from MSCs can reactively secrete various neurotrophic factors and growth factors that have neuroprotective functions and promote local microvascular regeneration, nerve regeneration and reconstruction, resulting in the repair of the injured spinal cord. Investigators have also reported that local transplantation of MSCs can significantly improve the neurological functions of rats with spinal cord injuries. The most recent studies have shown that the mechanism of spinal cord injury repair by MSC transplantation is related to the transplanted cells significantly inhibiting the expression of TNFα, interleukin (IL)-4, IL-1β, IL-2, IL-6 and IL-12 and other inflammatory factors at the injury site and up-regulating the expression of macrophage inflammatory proteins (MIP)-1α and the chemokine regulated upon activation, normal T-cell expressed and secreted (RANTES), which provides a good internal environment for nerve regeneration. In addition, to

further improve the efficacy of MSC transplantation, Gransee et al. generated MSCs with a high expression of brain-derived neurotrophic factor (BDNF) through transfection and used them on rats with spinal cord injury, and the results showed that these enhanced MSCs had an improved efficacy compared with traditional MSCs [20].

Umbilical cord blood stem cells

Umbilical cord blood stem cells (UCB-STs) include the early hematopoietic stem cells in human umbilical cord blood. UCB-STs are more primitive than adult bone marrow stem cells and have an increased ability to proliferate and differentiate. When cultured in vitro, UCB-STs are better than bone marrow stem cells in both proliferation ability and survival time, and sources of UCB-STs are broader. Under different experimental conditions, UCB-STs have the potential to differentiate into various mesodermal cells, including nerve cells. Barring ethical and other issues, UCB-STs are expected to become potential seed cells for stem cell transplantation repair therapy. Furthermore, UCB-STs have low immune function and stronger regenerative capability, and because they are immature, they have a lower rejection rate after transplantation.

It is reported that when cultured mononuclear cells isolated from human umbilical cord blood were transplanted into newborn rat brains, not only did the UCB-STs survive in the neonatal rat brain and differentiate into different glial cells and neurons, but they were also able to express specific marker of glial cells and neurons. Umbilical cord blood mesenchymal stem cells can differentiate into glial cells and neurons and secrete various neurotrophic factors that promote the regeneration of residual nerve cells and axons at the spinal cord stump to allow them to cross the glial scar area.

According to our previous studies, the mechanism behind the UCB-STs' ability to promoting axonal regeneration is dependent on two aspects: 1) UCB-ST transplantation can affect the injured local nerve cell signaling system, thereby inhibiting neuronal apoptosis and protecting nerve tissue; 2) transplanted UCB-STs can locally secrete neurotrophic factors, such as glial cell-derived neurotrophic factor and vascular endothelial growth factor, thereby promoting axonal regeneration. All of these factors play important roles in spinal cord injury repair. Recent studies have shown that in a rat spinal cord ischemia model, local injection of a certain concentration of UCB-STs can significantly improve rat motor function compared to that of the control group [21].

Embryonic stem cells

Embryonic stem cells (ESCs) are diploid cells derived from the inner cell mass of early mammalian embryos, and they have the ability to proliferate long-term without differentiation. Under certain conditions, ESCs can differentiate into tissues and cells from three mesoderms. Because the inner cell mass can develop into a complete individual, these cells are considered to have developmental totipotency. When the inner cell mass is cultured on culture plates and passaged for research, they are called ESCs. ESCs have multipotent differentiation capabilities, and they function mainly through repairing damaged axons to form an integral neural circuit. Currently, gene-transfected ESC transplantation is a focus of research, and there have been reports that cell adhesion factor 11 and mammalian achaete scute homolog-1 (MASH1) transfected ESCs have been used to repair spinal cord injury. Recent studies have shown that the use of NSCs clonally derived from ESCs for spinal cord injury repair provide much better results than does traditional ESC transplantation. However, current studies have indicated that the prospect of clinical application of ESCs is not optimistic because of the following reasons: 1) the research subjects for spinal cord injury repair using ESC transplantation are limited to rodents, and there are no reports in primate animal models; therefore, it is difficult to evaluate the safety and effectiveness of the procedure for humans; 2) the mechanism of ESC proliferation and differentiation requires further study, and ESC differentiation are affected by local microenvironments, which might be significantly altered after spinal cord injury compared with the microenvironment of a normal body; therefore, directed differentiation is difficult to achieve; 3) there is a risk of forming teratomas after ESC implantation; and 4) there are ethical constraints [22].

Induced pluripotent stem cells

The application of ESCs is hindered because of their limited source and ethical constraints, whereas adult stem cells also have unavoidable issues related to the difficulty of obtaining the cells, limited proliferation and limited directional differentiation.

Induced pluripotent stem cells (iPSCs) refer to differentiated mature somatic cells that are reprogrammed to return to a pluripotent state. The biggest advantage of iPSCs is the ease of obtaining seed cells; for example, skin tissue cells from spinal cord injury patients can be reprogrammed and induced to differentiate, and these cells are then transplanted. In 2006, the Takahashi and Yamanaka group in Japan reprogrammed mouse fibroblasts using a retrovirus and obtained pluripotent stem cells that had the potential for multi-differentiation [23].

Recent studies have shown that both ESCs and iPSCs have similar morphological characteristics, pluripotency, and self-renewal and gene expression properties. However, compared with ESCs, a low percentage of NSPCs that are obtained from the directional induction of iPSCs tends to differentiate into neural lineages. Therefore, the development of an effective neural lineage-oriented induction program is important for the clinical application of iPSCs. Experiments have shown an increased incidence of cancer after transplantation of iPSC-derived neurons into the CNS, and this may be a result of the sustained expression of transcription factors during reprogramming, which tends to increase the occurrence of teratomas. Investigators have improved the reprogramming scheme using adenoviral transposons or direct protein transduction. When necessary, transcription factors are introduced to achieve reprogramming and reduce the tumorigenic rate of the cloned offspring of iPSCs. Nori et al. transplanted human iPSC-derived neurospheres that had been pre-selected for safety to repair mouse spinal cord injury, and the results showed that mouse motor function was significantly recovered. Synapses were formed between the transplanted cells and host cells, and the expression of neurotrophic factors was increased; in addition, axon regeneration, myelin formation and angiogenesis were obvious without tumor formation [24]. Recent studies have also shown that the use of induced human pluripotent stem cells to repair adult rat spinal cord injury has significant efficacy. The iPSCs survived and differentiated into neurons and glia, and tens of thousands of axons were extended from the lesion site over virtually the entire length of the rat CNS. However, investigators have reported that teratoma formation was detected when unsafe

iPSCs derived from neurospheres were transplanted in animal experiments, and the experimental animals quickly lost motor function. Therefore, the safety of iPSC transplantation requires further study.

Issues Faced by Clinical Applications of Transplanted Stem Cells in the Repair of Spinal Cord Injury

Currently, the issues faced by stem cell transplantation therapy are mainly related to the cell source, ethics, morality, related legal issues, tumorigenesis, neuropathic pain and immune rejection response. Limited cell sources hinder the application of human embryonic stem cells and NSCs. Although MSCs can be used for autologous transplantation without requiring immunosuppressive drugs, they require 2-4 weeks of in vitro culture, purification and amplification and cannot be used for acute spinal cord therapy; in addition, MSC components are difficult to control because of restrictions in the cultivation factors. Studies have shown that after neural stem cell transplantation, cells might differentiate into other cell types, over-proliferate and migrate, resulting in corresponding complications; for example, cell aggregation during migration and growth can cause thrombosis in small blood vessels and capillaries, which can lead to cerebrospinal fluid circulation disorders or stroke. The risk of tumorigenesis must be considered when stem cell therapy is used to repair spinal cord injuries or any other disorders. Although this risk can be lowered after embryonic stem cells differentiate into NSCs, it cannot be completely ruled out, and the formation of brain tumors after neural stem cell transplantation has been reported. Therefore, studies on the differentiation and directional migration of transplanted stem cells will remain a popular and important research topic for future stem cell transplantation [25].

In addition, complications caused by stem cell transplantation should not be ignored, and neuropathic pain is one of the complications. Reports have shown that although the hindlimb function has a certain degree of recovery in a spinal cord injury rat model after neural stem cell transplantation, the forelimb shows a phenomenon of hyperalgesia. Histological results suggest that the transplanted NSCs mainly differentiate into star-shaped glial cells, and this leads to limb hyperalgesia after transplantation. Because some stem cell transplantations are allogeneic, the long-term use of steroids or immunosuppressive agents is unavoidable and may result in severe adverse reactions and an increased incidence rate of infections and malignancies [26]. Therefore, these complications cannot be ignored when attempting to increase the efficiency of transplantation and differentiation.

In the research for iPSCs, investigators have confirmed that some inherent DNA damage occurs in iPSCs that are derived from reprogrammed adult somatic cells, and the effects of these differences on the human body require further study. In addition, the criteria used to evaluate the success of stem cell transplantation remain controversial [27], which limits the clinical application of iPSCs.

Prospects

Spinal cord injury research has been an important focus of neuroscience research, and stem cell transplantation in experimental animal models in recent years has generated exciting results and appears to be an attractive prospect. However, to achieve the goal of clinical treatment, there are still too many issues that must be addressed. Therefore, realizing clinical stem cell transplantation therapy for spinal cord injury may not occur for some time. By reviewing current studies, we determined that the major bottlenecks are as follows: 1) current results have been obtained in rodent animal models, which cannot fully represent human systems; therefore, such results must be confirmed in primates and human; 2) the selection of target genes and vectors in gene therapy requires better solutions for the preparation, transplantation and survival of cells, a time period of continuous expression and immunogenicity of the effective engineered cells; 3) the problem of inducing stem cells to differentiate according to the directions required for spinal cord repair and promoting axon regeneration to form functional bridges must be solved; 4) there are limited numbers, lengths and types of regenerated axons in various methods, and issues related to the accurate docking with the remote end must be solved; clinical studies have found that the growth and differentiation of stem cells in vivo cannot be controlled and regulated; in addition, there is a statistical uncertainty of the control group and evaluation criteria, and the selection of the time and method for transplantation has not been standardized in clinical applications; and 5) there is a paucity of data related to nervous system complications during animal experiments, with most of the studies only using the survival rate of the experimental subjects as the evaluation criteria.

Because of the complexity of the spinal cord, single therapeutic interventions cannot solve all of the problems related to spinal injury. Therefore, although cell transplantation can provide a bridge to support the secretion of growth factors and execute substitutions, perform multiple roles in spinal cord injury, and cover all of the aspects related to spinal cord injury repair, there is still an increasing number of investigators who have emphasized comprehensive interventions with multiple therapies, including stem cell transplantation. Thus, spinal cord injury therapies, including stem cell transplantation, require further studies. In summary, stem cell transplantation studies have provided new and innovative ideas for spinal cord injury treatment that have theoretical significance and clinical value. However, the various problems reported in cell transplantation studies require continued investigation. We believe that with further studies, significant breakthroughs will be made in spinal cord injury treatment.

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Conflict of interest

There are no potential conflict of interests and financial activities related to the present paper to disclose.

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