# Clinical and gene therapy progress of acute spinal cord injury

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**Abstract:** Acute spinal cord injury (ASCI) refers to the symptoms of sensory, motor dysfunction and defecation disorder in the parts below the level of spinal cord injury after the spinal cord is injured by various factors, which seriously affects the quality of life of the patient. ASCI is a common severe disabling disease in the field of neuroscience. Although the clinical treatment of spinal cord injury has made great progress, compared with the development of theoretical research, its clinical research progress is still insufficient. The most commonly used treatment methods at this stage are surgery and high-dose hormone pulse therapy. According to recent studies, the technology of in situ regeneration of neurons has received widespread attention and development due to its unique advantages of avoiding immune rejection of exogenous cell transplantation, risk of tumor formation, and in situ transformation of scar glial cells into neurons is expected to become a new therapeutic intervention for spinal cord injury.

**Keywords:** Spinal cord injury ； Clinical treatment ； Nerve regeneration

## Introduction

Acute spinal cord injury (ASCI) refers to the spinal cord injury caused by various violent factors that directly or indirectly act on the injury site below the level of the injured spinal cord segment, making the sensory and motor functions damaged below the level of this segment. Such as limb muscle strength, dystonia, bladder, rectal sphincter function loss and other corresponding clinical symptoms[1]. Common factors of violence include traffic accidents, falling, sports injuries, etc. Among all kinds of spinal cord injuries, the most severe injury to human neurological function is complete transection, which will lead to the complete loss of neural pathways in the injured segment plane. According to the epidemiological studies conducted by the World Health Organization (WHO) and European and American countries, the annual incidence of acute spinal cord injury worldwide is between 133,000 and 226,000 cases.[2]. China and the United States are the high incidence of spinal cord injury countries (more than 40 per million people per year), the United States per million people per year the incidence of spinal cord injury can reach 40~50 people, domestic especially economically developed areas, such as Beijing, Shanghai, Guangzhou and other places, per million people per year the incidence of spinal cord injury can reach 50~60 people[3]. Patients with SCI not only endure great pain physiologically and psychologically, but also suffer from a long period of treatment, care and rehabilitation, causing heavy economic burden to the patients' families and society.

Acute spinal cord injury (ASCI) induces a series of complex pathophysiological changes, including axonal degeneration, neuron loss and reactive glial hyperplasia. The glial scar finally formed by reactive astrocytes has long existed at the injury site and hinders axonal regeneration, resulting in no improvement of clinical symptoms in our patient.[4]. The pathological process includes two intertwined stages: primary injury and secondary injury. Secondary injury is more serious than primary injury in terms of irreversible damage to the spinal cord, which is also the main research direction of SCI treatment at present.[5, 6]. Current therapeutic strategies for acute spinal cord injury include early surgical decompression and fixation, enhancement of mean arterial blood pressure (MAP) with vasopressors to improve spinal cord perfusion, and glucocorticoid drug shock therapy. However, there are still many controversial areas, including the optimal timing of surgical intervention, the advantages and disadvantages of early and delayed decompression results, and the use of glucocorticoids[7-9]. How to restore the injured spinal cord neurological function

is still a major medical challenge, and there is no significant breakthrough in drugs or technology for the treatment of paralysis after SCI in China and abroad.[5, 10, 11]. The treatment research of SCI has therefore become a major problem facing the medical community today.

### I. Surgical treatment

After acute spinal cord injury, continuous mechanical compression causes spinal cord microcirculation disorder, leading to ischemia and further expansion of the injury area. Therefore, surgical treatment is mainly through epidural decompression, relieve the compression of bony structures, intervertebral discs and ligaments on the spinal cord, and reduce spinal cord pressure, so as to achieve the purpose of improving the local microenvironment and promoting neurological recovery.[11]. Therapeutic methods to improve spinal cord injury include decompression and surgery to stabilize the spinal cord. At present, there are three common types of epidural decompression: anterior, posterior and combined anterior and posterior approaches. Anterior approach surgery needs to expose blood vessels and nerves, which has relatively high surgical risk, and has the disadvantages of incomplete decompression of spinal cord injury with unstable posterior column structure and poor overall effect; The combined anterior-posterior approach surgery can alleviate the anterior-posterior compression of the spinal cord and achieve more complete spinal cord decompression, but the surgical trauma is larger, and the patient's tolerance is poorer. Posterior approaches, which are less invasive and allow for procedures such as intradural decompression, are by far the most common and mature approaches to surgery[12]. Early surgical decompression plays a role in incomplete spinal cord injury, but its repair for complete spinal cord injury resulting in dyskinesia due to obvious compression is extremely limited.[13]. The main objectives of surgical treatment are spinal cord decompression and the maintenance of spinal stability. Too much emphasis on the reduction and compression treatment of complete spinal cord injury, which will destroy the stability of the spine, often leads to the pyogenic results after surgery.

### II. Drug treatment

1. High dose hormone shock

Methylprednisolone (MP) is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of SCI. According to the research results of National Society for Spinal Cord Injury (NASCIS), high dose of MP can relieve secondary injury of spinal cord clearly within 8h after injury[14]. The mechanism of MP has not been fully recognized so far, but the research shows that it at least includes the following aspects. MP can counteract the secondary inflammatory reaction and play a protective role in the para-spinal cord tissue. Reduce lipid peroxidation; Relieve local edema; Promote the increase in the content of protective factors, nutritional factors and regeneration promoting factors such as sulfuric acid for autonerves[15], thereby reducing further damage to neurons at the damage site. However, there are risks such as gastrointestinal bleeding, significantly increased incidence of respiratory tract and urinary tract infections in the application of MP, and the degree of benefit for patients is still controversial[16-18].

2. Ganglioside

Total monosialotetrahexosyl gangliosides (Trisialoganglioside-GT1b) are sialic acid-containing glycosphingolipids that are widely distributed on mammalian cell membranes. Gangliosides have the effect of protecting the enzyme activity of proton pump of cell membrane in vivo, such as Ca+-ATP pump and Na+-K+-ATP pump. It can also enhance the activity of nerve growth factor (NGF) by mediating its production, thus forming new neural networks.[19]Gangliosides were once considered the most likely substitutes for glucocorticoids. Studies in recent years have shown that the drug, in combination with glucocorticoids, has a significant promoting effect on the recovery of motor and sensory function in patients with acute spinal cord injury[20]. However, some researchers have pointed out that the use of gangliosides significantly increases the risk of systemic allergic reactions and Guillain-Barré syndrome in patients[21]It is considered that this therapy should not be used as a routine regimen, and the feasibility of using gangliosides for ASCI needs further investigation.[15, 22].

3. Calcium channel antagonists

At present, many experts and researchers try to use calcium ion channel antagonists to prevent the internal flow of calcium ions and alleviate the development of secondary spinal cord injury. Nimodipine (0.05mg/kg) is commonly used in clinic, but it can cause the decrease of mean arterial pressure, so it must be used carefully. Studies have reported that the combined use of dextran and ATP can increase blood flow in the spinal cord and maintain blood pressure at the same time, thus promoting the recovery of spinal cord function.[23]. However, some studies have also pointed out that the effect of calcium channel antagonists on SCI is not clear, and they may easily lead to unstable blood pressure

and other adverse reactions.[24], continuous attention should be paid to the hemodynamic state of the patient during application.

**III. Assisted treatment**

1. Hyperbaric oxygen treatment

Hyperbaric oxygen therapy can not only reduce the inflammatory response in secondary spinal cord injury, but also promote the recovery of neurological function. The treatment mainly increases arterial partial pressure of oxygen to increase blood oxygen content of central nervous system and accelerate aerobic metabolism of local neurons, thereby promoting motor nerve regeneration.[25]. Second, hyperbaric oxygen can effectively accelerate blood flow velocity and inhibit coagulation system. It can make that blood become dilute on one hand, the blood flow speed is accelerated, the gas exchange quantity is increase, on the other hand can make fibrinogen dissolve speed is increased, reduce the danger of thrombosis[12]. Hyperbaric oxygen therapy plays a significant role in improving the hypoxic environment and blood circulation of the damaged spinal cord tissue, and can effectively promote the recovery of contusion and transverse injury of the spinal cord.

2. Electroacupuncture treatment

The main mechanism of EA in the treatment of SCI is to stimulate nerve cells and reduce the secretion of inflammatory cells and molecules at the same time, in order to reduce the local inflammatory response and oxidative stress, and promote the functional recovery of nerve cells. Secondly, EA can inhibit the overactivation of astrocytes and reduce the formation of glial scars, which has a certain effect on the neurological reconstruction, axonal regeneration and recanalization of nerve conduction pathways after injury[26, 27].

**IV. In-situ nerve regeneration treatment**

Regenerating neurons in situ refers to the use of active factors of nerve regeneration to inhibit the molecular effects of secondary damage to the nervous system and avoid further aggravation of the injury. At the same time, it can promote the regeneration of nerve cells in the body, make the glial cells that originally hinder the neural pathway transform into successful neurons in situ, and induce the growth and maturation of new nerve cell axons and establish new synaptic connection with target tissue, thus forming a complete neuronal synaptic response step by step.[28]. Compared with the traditional nerve repair technology, the advantages of this technology can effectively avoid the risks of immunologic rejection and tumorigenesis brought by the transplantation of exogenous cells, and it does not need to invest a large amount of money to establish a stem cell bank[29]. Second, the glial cells in scar at the injury site are just the important factors that hinder the reaction of neural pathway, and the in-situ conversion technology can skillfully convert this unfavorable factor into regenerated neurons. Therefore, this technology has received extensive attention in recent years and has gradually shown broad application prospects.

During development, the central nervous system (CNS) produces the right number and type of neurons and glial cells at the right location and time to form functional neural circuits. In the embryonic central nervous system, different types of neurons and glial cells are produced by pluripotent progenitor cells after undergoing precisely designed time-identity transformation (i.e., time-dependent changes in their identities). Transcription factors of the pre-basic helix-loop-helix (bHLH) family are factors that determine the fate, transformation, and differentiation of nerve cells, ensuring that the body produces an appropriate number of specific neurons and glial cell types[30]. Neurod1 is mainly expressed in the nervous system at late development and can play a transformation role through a variety of ways. It is closely related to the terminal differentiation, maturation and survival of neurons. It is an important member of the transcription factors of BHLH family.[31], plays a key role in the formation of the whole central system[32]. Studies have shown that the expression of NeuroD1 can reprogram cultured human cortical astrocytes into functional neurons[33]. Related studies have shown that in the animal model of spinal cord injury caused by puncture or contusion, after in-situ injection of AAV-NeuroD1 gene with lentivirus as the carrier at a distance of 1 mm from the injury site for treatment, NeuroD1 can be found to efficiently convert reactive astrocytes into spinal dorsal horn neurons in situ (about 95%)[34]. Notably, regenerated neurons can form functional synaptic connections with other neurons, indicating that these converted new neurons can be integrated with proprioception neurons into a complete spinal neural circuit. Reprogrammed neurons may form a "neuronal relay" that transmits information at the site of injury. At the same time, the in vivo reprogramming of NeuroD1 can supplement the proprioceptive spinal neurons lost during the injury, to promote the reconstruction of local neuronal circuits, which is necessary for functional recovery after SCI. In addition, NeuroD1-mediated regenerative gene therapy has a long intervention window that directly converts astrocytes into neurons in both the early (10 days) and late (4 months) stages of injury[35]. These results

indicate that in situ nerve regeneration based on NeuroD1 transcription factor has been applied in animal models of spinal cord injury and some progress has been made, which may provide a new treatment for SCI.

**V. prospects and perspectives**

In summary, despite the continuous improvement of current medical level, various surgical methods for spinal cord injury have been quite mature. Other medical and physical treatments are also improving, but the prognosis of patients with severe spinal cord injury is still unsatisfactory. Effective treatment of spinal cord injury is still a medical problem, which needs to be solved urgently. At present, nerve regeneration technology has shown great advantages, so the central nervous in situ regeneration technology has been tried to be used for the treatment of stroke, brain tumors, brain trauma, parkinson's disease, alzheimer's disease, huntington's disease, retinopathy and spinal cord injury and other central nervous system diseases[35-37]. With the deepening of research, this technique has great potential as a new treatment for spinal cord injury. However, there are still some problems to be solved at this stage, including selection of transcription factor vectors, concentration control, and injection method, which are also technically limited to animal research. It is believed that nerve regeneration technology can be further developed in the near future for the benefit of mankind.

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