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ORIGINAL ARTICLE

Mitochondrial Dysfunction in Spinal Cord Injury: Current Understanding and Emerging Treatment Strategies

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Abstract:
This review discusses the challenging task of functional recovery in spinal cord injury patients. To investigate new advances in spinal cord injury, current basic and clinical experiments have validated the mechanisms and various therapeutic strategies for spinal cord injury. This article comprehensively elucidates the pathophysiology, mitochondrial changes and recent treatment advancements in acute spinal cord injury, providing new research directions and treatment approaches for spinal cord injury.
Keywords: Epidemiology, Pathophysiology, Mitochondria in Spinal Cord Injury, Treatment of Spinal Cord Injury

I. Epidemiology

Spinal Cord Injury (SCI) denotes the transient or enduring functional alterations resulting from damage to the spinal cord. In the United Kingdom, the annual incidence of spinal cord injury stands at 19 cases per million population. Epidemiological data from the United States reveal a noteworthy shift in the average age at SCI diagnosis, rising from 28 years in the 1970s to 43 years. The susceptibility to SCI across distinct age cohorts gradually equalizes. Concurrently, the male demographic continues to predominate in SCI cases, with approximately four-fifths of traumatic SCIs occurring in males within the United States. On a global scale, SCI has emerged as a substantive health hazard that demands meticulous attention and cannot be dismissed.[1; 2; 3].

Spinal cord injuries are classified into traumatic and non-traumatic. The main causative factor for spinal cord injury is trauma, with non-fracture dislocation of the cervical spine commonly resulting from situations such as motor vehicle accidents, sports injuries, falls and wrestling[4]. The primary causes of spinal cord injury vary depending on age, with children often experiencing accidental injuries during physical activities, adults being more susceptible to falls from heights and sports-related accidents, and the elderly primarily suffering from spinal cord injury due to falls [5; 6; 7]. Non-traumatic spinal cord injury occurs during acute or chronic diseases, such as tumour infections. In traumatic spinal cord injury, the primary injury damages cells and triggers a complex cascade of secondary injury that cyclically produces neuronal and glial cell death, ischemia, and inflammation, leading to permanent Neurological impairment.

II. Spinal Cord Injury Pathophysiological Changes

The pathophysiological changes in SCI can be divided into primary and secondary injury, with oxidative stress and ischaemia-reperfusion injury being the main mechanisms.

(1) Vascular Damage and Ischemia

Patients with SCI are particularly susceptible to

systemic hypotension due to volume depletion, neurogenic shock, and bradycardia[8; 9]. Primary injuries usually damage major blood vessels, such as the anterior spinal artery. Ischemia and necrosis trigger inflammatory processes such as activation of microglia, recruitment of immune cells, and secretion of pro-inflammatory cytokines such as tumour necrosis factor (TNF) α and interleukin (IL)-β[10].

(2) Inflammation

SCI widely causes neuroinflammation and triggers multi-organ systemic reactions, causing damage to the lungs, kidneys, and liver[11; 12]. The inflammatory process of SCI is complex, and the degree of damage depends on its duration and time. The inflammatory response after spinal cord injury involves various cellular components, such as microglia, neutrophils, and macrophages, as well as molecular components, such as cytokines, prostaglandins, and the complement system. After SCI, the complement is activated almost immediately, then increases locally within one day and persists long-term[13]. Inhibition of the complement system is beneficial during the acute phase of SCI (<7 days). Likewise, cellular components of inflammation are activated early after SCI. Particularly for microglia, induction of IL-1β expression in a mouse model of SCI showed activation of local resident microglia five minutes after injury[14]. Microglial activation can also be detected in humans at the earliest time points studied. Activated microglia secrete IL-1α and IL-1β, promoting the infiltration of leukocytes into the lesion [15].

(3) Oxidative Stress

Oxidative stress is a significant mechanism of secondary neuronal damage following spinal cord injury. It involves neutrophil infiltration, increased secretion of proteases, generation of abundant oxidative intermediates, and adverse effects caused by free radicals[16]. The primary free radicals in the body are derived from oxygen and nitrogen, collectively known as reactive oxygen species (ROS), including O_2^-, OH^-, and H_2O_2. Mitochondrial energy metabolism and NADPH oxidase are the primary sources of O_2^-. Under oxidative stress conditions, spinal cord neurons may experience mitochondrial damage, leading to mitochondrial and cellular apoptosis and autophagy [17]. Studies have shown a significant increase in intracellular levels of oxygen free radicals in spinal cord cells at 4 hours post-spinal cord injury compared to the control group[18]. The excessive generation of oxygen free radicals leads to oxidative stress, which disrupts the integrity of the lipid bilayer through lipid peroxidation, reduces the fluidity of the mitochondrial membrane in the injured segment of the spinal cord, increases permeability, decreases Na^+-K^+-ATPase activity, and subsequently impairs cellular energy metabolism in the affected cells[1; 19; 20]

(4) Ischemia-Reperfusion Injury

After the long-term relief of compression in spinal cord injury, when blood flow is restored to the spinal cord, irreversible neuronal death termed ischemic-reperfusion injury occurs. This is the second most common type of injury in spinal cord injury. Ischemia-reperfusion injury increases mitochondrial permeability alterations in mitochondrial dynamics and triggers cellular apoptosis[21; 22]. Some studies have indicated that modulating the mitochondrial-dependent pathway can reduce cell apoptosis after ischemic reperfusion injury and provide neuroprotection for spinal cord neurons[23].

In conclusion, oxidative stress and ischemia-reperfusion injury are significant pathophysiological changes in spinal cord injury. However, mitochondrial abnormalities and dysfunction accompany both of them, so mitochondrial abnormalities in spinal cord injury are the focus of research.

III. Mitochondrial Changes after Spinal Cord Injury

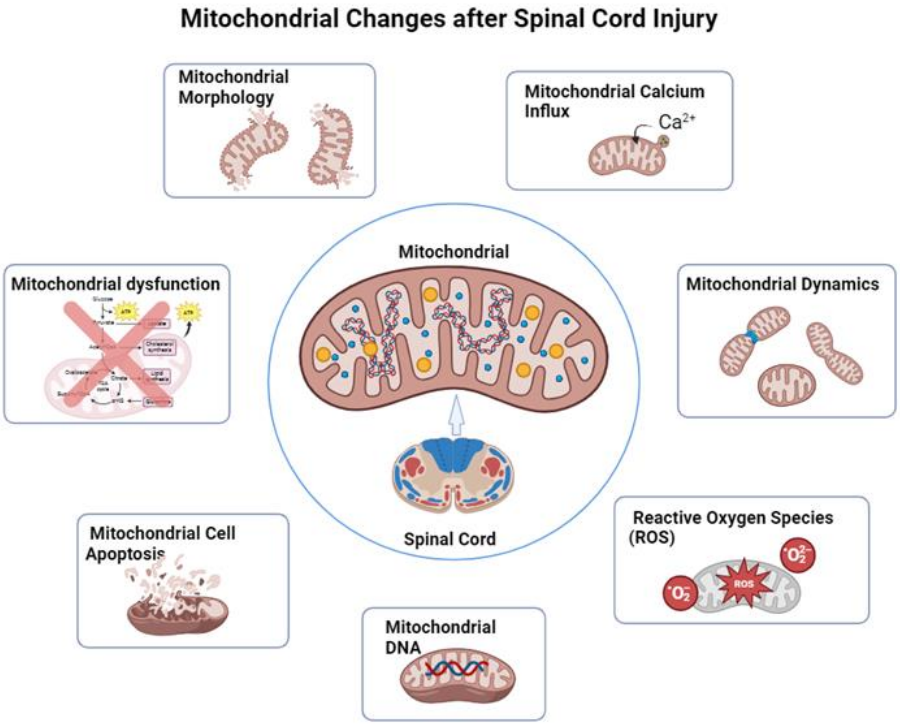

Figure 1. Mitochondrial Changes after Spinal Cord

As shown in Figure 1, after spinal cord injury, mitochondrial function may undergo changes that can affect the functionality of spinal cord neurons, regulation of immune responses, axonal regeneration, and the self-renewal and differentiation processes of neural stem cells. Mitochondria are the primary sites for cellular energy production, and their function is not only related to energy metabolism but also involves various critical biological processes such as cell apoptosis and oxidative stress. Therefore, mitochondrial changes following spinal cord injury can potentially impact the recovery and treatment of spinal cord injury[24]. This chapter focuses on the pathological processes involved in mitochondria in SCI.

(1) Mitochondrial Morphology

When SCi occurs, the morphology of mitochondria will undergo significant changes[25]. Transmission electron microscopy studies have revealed significant changes in mitochondrial morphology in spinal cord cells at early stages of injury. The mitochondria exhibit irregular shapes, increased volume, disorganized cristae arrangement, and possible membrane rupture. At 4 to 8 hours post-injury, significant enlargement of mitochondria and disorganized or swollen cristae can be observed. From 2 to 24 hours, mitochondrial cristae become disordered, the mitochondrial membrane ruptures and vacuolization may occur[26].

(2) Mitochondrial Calcium Influx

Alterations in calcium homeostasis within mitochondria are another critical indicator. Calcium ions are essential second messengers in the cytoplasm, mitochondria, and endoplasmic reticulum[27]. Mitochondria are involved in the cellular tricarboxylic acid cycle and energy metabolism, influencing ATP synthesis. After spinal cord injury, substances, including calcium ions, enter the mitochondria, resulting in ion concentration imbalances between the inside and outside of the mitochondria. This concentration gradient causes an influx of water into the mitochondria, leading to mitochondrial swelling. Changes in the mitochondrial permeability transition pore (mPTP) also affect the permeability of the mitochondrial membrane, reducing the activity of Na^+-K^+-ATPase and cytochrome oxidase, damaging the normal function of membrane receptors, and inhibiting mitochondrial energy metabolism[28; 29]

(3) Mitochondrial dysfunction

The standard mitochondrial membrane potential (MMP) is an essential indicator of mitochondrial function, crucial for mitochondrial oxidative

phosphorylation and ATP synthesis. The mitochondrial permeability transition pore (mPTP) regulates mitochondrial energy metabolism, cell apoptosis, and cell necrosis. Under physiological conditions, the mPTP remains inactive, maintaining low permeability of the mitochondrial inner membrane, essential for maintaining MMP and ion gradients inside and outside the membrane, crucial for mitochondrial energy synthesis.

(4) Changes in Mitochondrial Dynamics

Mitochondrial dynamics involve fission, fusion, transport, and cristae remodelling, playing essential roles in genetics, substance exchange, oxidative phosphorylation, ATP supply, and cell cycle. Damaged mitochondria are primarily eliminated through mitochondrial autophagy to maintain cellular metabolism and renewal[30]. The mitochondrial membrane potential is closely associated with mitochondrial dynamics, and a decrease in membrane potential can lead to various cellular changes such as cytochrome C release, altered mitochondrial permeability, and changes in the Bcl-2 protein family, ultimately leading to mitochondrial and cellular apoptosis. Studies have shown that the expression of mitochondrial fusion protein one gradually increases after spinal cord injury, peaking at 8 hours post-injury and decreasing to the lowest level after 24 hours, while the expression of mitochondrial fission protein 1 shows the opposite trend[31].

(5) Mitochondrial Cell Apoptosis

Based on the above factors, mitochondria will undergo apoptosis. The Bcl-2 family of proteins is a critical regulatory factor in mitochondrial apoptosis, located in the outer mitochondrial membrane, nuclear envelope, and endoplasmic reticulum membrane. Bcl-2 inhibits mitochondrial apoptosis and cell death signalling pathways[32]. The Bcl-2 family includes numerous members such as Bax, Bcl-x, Bak, Bad, Mcl-1, GRS, and others [33]. Bax is a pro-apoptotic protein that promotes mitochondrial apoptosis, and increased expression of Bax in cells indicates cell death[34]. Some pharmacological treatments for spinal cord injury aim to alter the ratio of Bcl-2 to Bax. Examples include mangiferin, ginsenoside Rb1, neurotrophin-3, and Ginkgo biloba extract [35; 36; 37].

(6) Mitochondrial Reactive Oxygen Species (ROS)

Mitochondrial reactive oxygen species refer to the active oxygen molecules generated within the mitochondria, primarily including superoxide anion (O_2^-), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2). Under normal physiological conditions, low levels of ROS within cells can be signalling molecules involved in cellular regulation. However, ROS production within the mitochondria increases rapidly during tissue injury, damaging the mitochondria itself.

Antioxidants mainly originate from the cell membrane, mitochondria, peroxisomes, and the NADPH oxidase complex within the endoplasmic reticulum. Mitochondria are crucial organelles that convert energy into a usable form for cells known as ATP through oxidative phosphorylation. When the spinal cord is injured, changes in the morphology of cellular mitochondria occur, resulting in limited energy synthesis and accelerating secondary spinal cord damage[38].

Substantial evidence suggests that generating oxygen-free radicals plays a significant role in the secondary damage process following primary mechanical brain or spinal cord injuries. In damaged neural tissues, oxidative damage induced by oxygen free radicals primarily manifests as lipid peroxidation. When mitochondria are damaged, oxidative stress generates reactive nitrite salts, producing highly reactive free radicals such as nitrogen dioxide, hydroxyl radicals, and carbonate radicals. These free radicals quickly induce lipid peroxidation in the phospholipid membrane of mitochondria, leading to respiratory dysfunction, disruption of calcium ion balance, mitochondrial permeability transition, and cell death[39; 40].

(7) Mitochondrial DNA (mtDNA)

Mitochondrial DNA, also known as mtDNA, is located on the inner membrane matrix side of the mitochondria, close to the site where reactive oxygen species are produced. Due to the lack of protective proteins and DNA repair mechanisms, oxidative damage and mutations in mtDNA can quickly occur during mitochondrial respiration[41; 42; 43]. After spinal cord injury (SCI), oxygen-free radicals accumulate significantly in the injured spinal cord cells, causing severe damage to the antioxidant defence system[18]. This dramatically

increases the likelihood of mtDNA mutations. Mutations in mtDNA within the injured segment of the spinal cord can impair essential functional regions of the genome, thereby affecting energy metabolism. Severe reduction in ATP production can lead to cell damage and tissue necrosis[41]。

IV. Treatment

Treatment of spinal cord injury Currently, there is no practical method for regenerating spinal cord neurons in the treatment of spinal cord injury. However, early treatment is crucial for prognosis. A study collected 171 cases from 139 centres worldwide. Most patients maintained an average arterial pressure between 80 and 90 mmHg during treatment. Arterial oxygen tension was maintained at 80-100 mmHg, and arterial carbon dioxide tension at 35-40 mmHg[44]. In patients requiring spinal surgery, slightly more than half believed that platelet count should be maintained above $100{,}000\times10^9$/L. Prothrombin time/activated partial thromboplastin time should be less than 1.5 times that of the regular control group to ensure safety. Corticosteroids were not used in most patients during treatment, and hypothermia treatment depended on specific circumstances. There are global variations in the treatment of spinal cord injury. More precise treatments require further experimental research.

The treatment of spinal cord injury requires a comprehensive approach to address different issues. In addition to surgical and pharmacological treatments, other treatment modalities can be applied to spinal cord regeneration, including stem cell technology, gene therapy, neuronal programming, cell transplantation, 3D printing technology, biomaterials, nanotechnology, and immunotherapy. These technologies have the potential to promote spinal cord regeneration. Although the clinical trial results of specific cell therapies have shown their safety, their efficacy has yet to be confirmed. Additionally, there is ongoing research on combining biomaterials with drugs or cells to treat spinal cord injury, but further experimental studies are still needed.

(a). Drug treatment

Drug treatments for spinal cord injury include medications that inhibit the immune system or inflammatory signalling pathways, such as nonsteroidal anti-inflammatory drugs (indomethacin), minocycline, cyclosporine and corticosteroids like methylprednisolone[45]. These medications have been subject to controversy in the treatment process, as different trials have shown varying effects and potential complications. Additionally, minocycline can bind to proteins in mitochondria and prevent the release of factors contributing to cell death. At the same time, atorvastatin, an effective cholesterol biosynthesis inhibitor, can reduce cell apoptosis, mitigate the effects of ischemia-reperfusion injury, and improve limb motor function prognosis[46].

(b) Cell Transplantation in Spinal Cord Injury

Stem cells have the potential to treat and repair damaged spinal cord tissues. They can differentiate into neurons or replace damaged cells, secrete neurotrophic factors, and inhibit inflammatory responses to exert therapeutic effects[47]. Various types of stem cells are used for transplantation, including mesenchymal stem cells, embryonic stem cells, neural stem cells, induced pluripotent stem cells, germinal stem cells, and adult endogenous stem cells.

Each type of stem cell has its advantages and disadvantages. For example, bone marrow mesenchymal stem cells possess intense proliferation and multi-lineage differentiation capabilities. After transplantation into the injured spinal cord area, they can survive long-term and support the differentiation of neurons and glial cells, promoting axonal growth[48]. Mesenchymal stem cells can improve the pathological microenvironment and promote self-repair, immune modulation, neuroprotection, and anti-apoptotic effects[49; 50]. Embryonic stem cells can differentiate into neurons and glial cells, supporting neural tissue regeneration[51; 52; 53; 54; 55; 56]. Neural stem cells can regulate glial scar formation, promote differentiation, and facilitate the survival and growth of injured neurons[48]. Germinal stem cells have the potential to differentiate into various neural cell types, while adult endogenous stem cells can generate astrocytes and oligodendrocytes[57; 58; 59].

Combining stem cells and bioengineering approaches has shown sound therapeutic effects in treating spinal cord injury and has become a promising research direction[60]. However, the

optimal dosage and timing of stem cell therapy for spinal cord injury still need further confirmation[61]. Relying solely on stem cell-based treatments may not ultimately improve the prognosis.

(c) Application of Exosomes in Spinal Cord Injury

In recent years, research on the therapeutic use of secretomes from mesenchymal stem cells (MSCs) in spinal cord injury has made significant progress, and utilizing MSC secretomes for cell-free therapy has become a promising direction[62; 63]. Within this field, exosomes derived from MSCs have gained considerable attention. They can potentially improve the integration of local progenitor cells during neural regeneration and are considered a novel therapeutic approach for central nervous system degenerative diseases. MSC-derived exosomes can secrete factors with anti-inflammatory properties, alleviate mitochondrial dysfunction, and maintain the integrity of alveolar structures, thereby reducing the expression of mitochondrial apoptotic proteins in acute lung injury [64]. These studies provide new insights and possibilities for the treatment of spinal cord injury and neurodegenerative diseases.

(d) Gene Therapy

Gene therapy is considered a novel approach that aims to elucidate the mechanisms underlying impaired neuronal regeneration after spinal cord injury and promote axonal regrowth[65]. This method involves manipulating the expression of growth factors in the injured area to improve the local microenvironment, facilitate axonal regeneration, and guide regenerating axons towards their target direction. Researchers have also used retrograde transduction of viral vectors to modify damaged neurons genetically, regulating their intrinsic growth capacity to achieve the goal of repairing spinal cord injury[66]. These approaches offer new avenues and potential for treating spinal cord injury.

Although a wide range of genes have been studied, there is no consensus on which gene or genes are most effective in promoting axonal regeneration. It will most likely be necessary to target multiple genes in different cell types, such as injured neurons in the central nervous system or primary sensory neurons and glia at the injury site, to achieve successful axonal regeneration[67].

(e) Neuronal Reprogramming

Cellular reprogramming is an innovative technology that has emerged in recent years[68], bringing revolutionary changes to regenerative medicine and the entire field of life sciences, offering hope for central nervous system neuronal regeneration and repair. Direct cellular reprogramming is a method that transforms non-neuronal cells in a terminally differentiated state into neurons under different conditions to compensate for missing neurons[69; 70; 71; 72]. Non-neuronal somatic cells can be reprogrammed into neurons by overexpressing neuron-specific transcription factors[73]. It has been found that the Notch1 signalling pathway is involved in reprogramming astrocytes into neurons[74]. These findings provide new avenues for neural regeneration and repair.

(f) 3D Printing Technology

With 3D printing technology, hydrogel composites of hydroxybutyric chitosan and nano short fibres with microchannel structures can be constructed to simulate the microenvironment and mechanical strength of articular cartilage[75; 76]. This allows for regulating the survival and differentiation of human mesenchymal stem cells, enabling the repair of cartilage tissue damage. Bio-3D printing technology combines biological materials with neural stem cells, precisely controlling cell density and distribution and constructing biologically active scaffolds that mimic the structure and function of the natural spinal cord, effectively repairing spinal cord injuries[77]. To rescue SCI injuries, a recent study used 3D bioprinting technology to construct a hydrogel with conductive properties similar to the natural spinal cord[78]. With the continuous development and in-depth research of 3D printing technology, utilizing different printing methods, bio-inks, and cells, neural tissue engineering has achieved specific results in spinal cord injury repair.

(g) Neural Scaffold Materials

In recent years, extensive research has made significant progress in the reconstruction of regenerative microenvironments after spinal cord injury, spinal cord injury regeneration and repair, and clinical translation research. Researchers have developed neural scaffold materials and established functional biomaterial preparation

techniques that enable the specific binding of scaffold materials with regenerative factors or stem cells[79]. By transplanting these scaffold materials, a favourable microenvironment for neural regeneration can be reconstructed, and a large segment-deficient complete transection spinal cord injury model has been established[80]. The research results indicate that neural bridging is the primary mechanism by which functional biomaterials promote motor recovery in animals with complete spinal cord injuries. Furthermore, Chinese researchers are committed to the clinical application of related technologies and have made much progress. These advancements have placed China at the forefront of clinical translation research in spinal cord injury regeneration and repair[81].

(h) Platelet Lysate

Platelet lysate is a liquid rich in regenerative and reparative components, including growth factors, proteins, cytokines, and chemokines[82]. It possesses neurotrophic support, antioxidant properties, and anti-inflammatory effects, making it potentially valuable for neurodegenerative and traumatic pathologies. Platelet lysate has been widely used in orthopaedics for treating bone injuries, sports-related injuries, non-healing wounds, ulcers, and diabetic foot, among others.

Current research primarily focuses on animal and in vitro models, and there is a lack of large-scale multicenter clinical trials to assess its long-term safety. Furthermore, recognized usage standards and treatment guidelines are lacking[83].

Some studies have indicated that platelet lysate improves motor function in mice, reducing cortical neuroinflammation and oxidative stress in the injured area. This effect is achieved by downregulating pro-inflammatory genes and reducing reactive oxygen species levels. These studies provide initial support for platelet lysate as a reliable and effective source of neurorecovery factors[84]. Although platelet lysate has been applied in various diseases, relevant research in spinal cord injury patients is still lacking. These studies preliminarily support platelet lysate as a reliable and effective source of neurorecovery factors.

V. Summary

Spinal cord injury is a disabling condition, and current drug treatments have limited effectiveness. Management strategies include assessment, pre-hospital care, treatment, rehabilitation, and complication management. Recent research has focused on cell transplantation, 3D printing, nerve scaffolds and platelet lysate. Cell transplantation using various types of cells has shown promise in improving prognosis. 3D printing can create structures for tissue repair. Nerve scaffold materials create an environment conducive to nerve regeneration. Platelet lysate, rich in regenerative components, has potential applications. Challenges include the need for more clinical trials and unified treatment guidelines. However, research in these areas provides hope for improving outcomes and quality of life for spinal cord injury patients. Future research and clinical practice will drive further advancements in treatment.

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