Review Article

Weijian Kong, Tingting Hao, Xiaoliang Xiong, Xue Shi, Haijing Zhang, and Yinlong Zhao*

Application of magnesium and its compounds in biomaterials for nerve injury repair

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Abstract: Neural injuries, including peripheral nerve injury and spinal cord injury, are prevalent clinical conditions that can lead to significant sensory and motor dysfunction. Due to the limited regenerative capacity of neural tissues, current treatment methods often yield unsatisfactory outcomes. In recent years, neural tissue engineering has emerged as a promising strategy for promoting nerve repair. Among various biomaterials, magnesium and its compounds have attracted significant interest for their biocompatibility, biodegradability, and biological activity. This review comprehensively summarizes the pathological mechanisms underlying neural injuries, particularly focusing on peripheral and spinal cord injuries. It explores the multifaceted roles of magnesium in nerve repair, including neuroprotection, anti-inflammatory effects, oxidative stress mitigation, and promotion of nerve regeneration. Furthermore, the review highlights current applications of magnesium and its derivatives in the design of biomaterials for neural tissue engineering, analyzing both their advantages and limitations. This review aims to provide valuable insights and guidance for future research and development of magnesium-based strategies in nerve injury repair.

Keywords: magnesium, peripheral nerve injury, spinal cord injury, nerve injury repair, nerve tissue engineering materials

1 Introduction

Neural injury, encompassing peripheral nerve injury (PNI) and spinal cord injury (SCI), represents a significant clinical challenge due to its profound impact on sensory and motor functions [1]. These injuries often result from trauma, surgery, or disease and can lead to long-term disability, severely compromising the patient's quality of life [1,2]. Despite ongoing advancements in clinical and surgical techniques, the treatment of neural injury remains largely unsatisfactory, especially for SCI, due to the extremely limited regenerative ability of neural tissue, where functional recovery is often limited or absent [3]. Therefore, how to effectively promote the repair and functional reconstruction of injured neural tissue has become the focus of neural regeneration research in recent years, and it is of great clinical significance and urgency to improve motor and sensory function recovery after injury [4,5].

One of the core difficulties in nerve injury repair lies in the intrinsic limitations of the nervous system's regenerative capacity. Unlike many other tissues, neural tissues exhibit poor self-repair abilities, particularly within the central nervous system. In PNI, although some regeneration is possible, outcomes are frequently hindered by delayed intervention, misdirection of regenerating axons, and limited availability of autologous grafts [6,7]. In the case of SCI, the mainstream treatment method in current clinical practice is still to relieve local compressive injury through surgical treatment, supplemented by hormone shock and neurotrophic drugs [8,9]. Complex pathophysiological changes, including glial scar formation, inflammation, and inhibitory extracellular environments, further obstruct neuronal regeneration and functional recovery [10]. In summary, due to the limited regenerative ability and complex tissue structure of neural tissue, it is difficult to achieve satisfactory treatment results with the body's repair. Given these challenges, the development of innovative therapies that can actively promote nerve repair is of urgent importance.

Neural tissue engineering materials have gradually become a research hotspot in neural injury repair in recent years [11,12]. Neural tissue engineering materials can be designed into various structures according to the location and form of the injury [13–15], and at the same time, neural tissue engineering materials have good carrying capacity and modification potential, allowing the introduction of

* **Corresponding author: Yinlong Zhao,** Department of Nuclear Medicine, The Second Hospital of Jilin University, Changchun, China, e-mail: yinlong@jlu.edu.cn
Weijian Kong, Tingting Hao, Xiaoliang Xiong, Xue Shi, Haijing Zhang: Department of Nuclear Medicine, The Second Hospital of Jilin University, Changchun, China

intervention factors with therapeutic effects on the basis of matrix materials, such as cells, drugs, and growth factors, thereby promoting the reconstruction of nerve fibers and the repair of nerve functions [16–18]. For example, for completely severed peripheral nerves, nerve conduits can be constructed using biomatrix materials, such as PLGA and PCL, to physically connect the severed ends and form a separation with the surrounding tissues to build a channel for nerve regeneration [19,20]. For spinal cord contusion, a fiber membrane can be designed to cover the bruised area to form protection and local treatment can be achieved through the loading of drugs and cytokines as well as other neural regeneration substances [21]. For completely severed spinal cord tissue, a local filling can be formed in the injured area using the good load-bearing capacity and suitable biological properties of hydrogels, and the reconstruction of the neural signal pathway can be promoted by the introduction of neural stem cells, drugs, and nutritional factors [22,23].

In the process of applying neural tissue engineering materials to neural injury repair, discovering new biomaterials or modifying existing materials to further enhance the comprehensive performance of materials has always been the core direction of research [24,25]. Magnesium, an essential element for the human body, participates in various enzyme-catalyzed reactions and various metabolic cycle processes in the body and plays an important role in cell energy metabolism, synthesis of life substances, regulation of various transport proteins, ion channels, *etc.* [8,26,27]. For neurons, magnesium is also indispensable. Magnesium participates in the synthesis of membrane phospholipids, affects the opening of cell membrane calcium ion channels, regulates the level of calcium ions inside and outside the cells, participates in the formation of myelin and synapses, affects the release of neurotransmitters, and has an important regulatory effect on neurons [28]. In the context of nerve injury, magnesium exerts neuroprotective effects by blocking excessive calcium influx through NMDA receptors, thereby reducing excitotoxicity. Moreover, it mitigates oxidative stress and inflammatory responses, two major contributors to secondary neuronal damage following trauma [29].

Magnesium is currently widely used in diseases related to the nervous system, such as magnesium cerebrovascular disease, epilepsy, migraine, and preeclampsia [30–32]. In recent years, magnesium-containing biomaterials, including pure magnesium, magnesium alloys (*e.g.*, Mg–Zn, Mg–Li), and magnesium-releasing compounds (such as magnesium oxide or magnesium salts), have been increasingly incorporated into nerve repair scaffolds. These materials can provide mechanical support, regulate local microenvironments, and promote cell survival and axonal growth. Importantly, their degradable nature allows them to be gradually absorbed by the body, reducing the need for secondary surgical removal. Furthermore, advances in surface modification and composite fabrication have enabled the tuning of degradation rates and the enhancement of therapeutic efficacy [33]. Magnesium-based materials can also enhance the electrical conductivity of scaffolds, a crucial factor for supporting neural signaling and functional recovery [34]. The ability to combine magnesium with other bioactive agents, such as growth factors, stem cells, and conductive polymers, has opened new avenues for developing multifunctional platforms for both PNI and SCI repair [19].

Therefore, in order for researchers to better understand the application status of magnesium and its compounds in neural injury tissue engineering materials, this review starts from the pathophysiological changes in neural injury, introduces the potential mechanism of magnesium in promoting neural injury repair, and details the application form, modification methods, and therapeutic effect of magnesium in the design of existing neural tissue engineering materials.

2 Overview of SCI and PNI

2.1 Pathological changes and regeneration process after PNI

PNI initiates a series of time-dependent pathological events that influence the repair outcome [35]. In the immediate phase, within hours of injury, axonal disruption and damage to local blood vessels lead to ischemia and edema at the injury site. Injured neurons undergo chromatolysis, characterized by swelling of the cell body, peripheral displacement of the nucleus, and dissolution of Nissl bodies [36–38]. Wallerian degeneration rapidly begins in the distal segment, where axons fragment and the myelin sheath disintegrates [39]. Over the next several days (acute phase), Schwann cells dedifferentiate, proliferate, and begin clearing debris alongside infiltrating macrophages, which are critical for removing damaged cellular components [40,41]. Schwann cells align longitudinally to form Bands of Büngner, structural pathways that guide axonal regrowth. In the subacute phase, spanning 1–4 weeks post-injury, axonal sprouts from the proximal stump begin to extend through these bands, aided by Schwann cell-derived neurotrophic factors such as NGF and BDNF [42,43]. Electrical activity at the injury site activates signaling cascades like cAMP-PKA and MAPK, which further promote axonal elongation and synaptic connectivity. In the chronic phase (beyond 4 weeks), successful axonal

reconnection may result in remyelination by Schwann cells and partial functional recovery. However, misdirected growth or prolonged denervation can result in incomplete reinnervation, muscle atrophy, and lasting functional deficits (Figure 1).

2.2 Pathological changes and regeneration process after SCI

The repair and reconstruction of SCI present greater challenges than those associated with PNIs [44,45]. SCI progresses through a complex sequence of pathophysiological events, beginning with an immediate phase marked by mechanical trauma to neural and vascular structures. Within minutes to hours, primary injury causes hemorrhage, ischemia, and disruption of ion homeostasis, including excessive calcium and sodium influx and glutamate-mediated excitotoxicity, which together trigger acute neuronal death [46,47]. In the subsequent acute phase (within the first 48–72 h), the blood–spinal cord barrier breaks down, allowing immune cell infiltration [48,49]. Activated microglia and macrophages release pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, which amplify the secondary injury cascade [50,51]. Simultaneously, astrocytes begin to proliferate, initiating glial scar formation [52,53]. While scar tissue can help contain local inflammation and necrosis, thereby protecting adjacent healthy tissue, it also impedes neuronal growth and axonal regeneration, ultimately obstructing the restoration of nerve function and reducing the efficiency of mental imagery [54–56]. During the subacute phase (3–14 days post-injury), inflammation continues, leading to further cell death and axonal degeneration. Although endogenous neural stem cells proliferate, they predominantly differentiate into astrocytes rather than neurons or oligodendrocytes, contributing to scar tissue rather than regeneration [57,58]. As the injury enters the intermediate and chronic phases (from 2 weeks onward), mature glial scars and cystic cavities form, posing both physical and chemical barriers to axonal regrowth. Myelin degradation persists, and although limited remyelination may occur, the inflammatory microenvironment and inhibitory extracellular matrix components hinder meaningful recovery [59–61]. In the long-term phase (months to years post-injury), structural and functional recovery is minimal, and chronic symptoms such as spasticity, sensory loss, or neuropathic pain often persist,

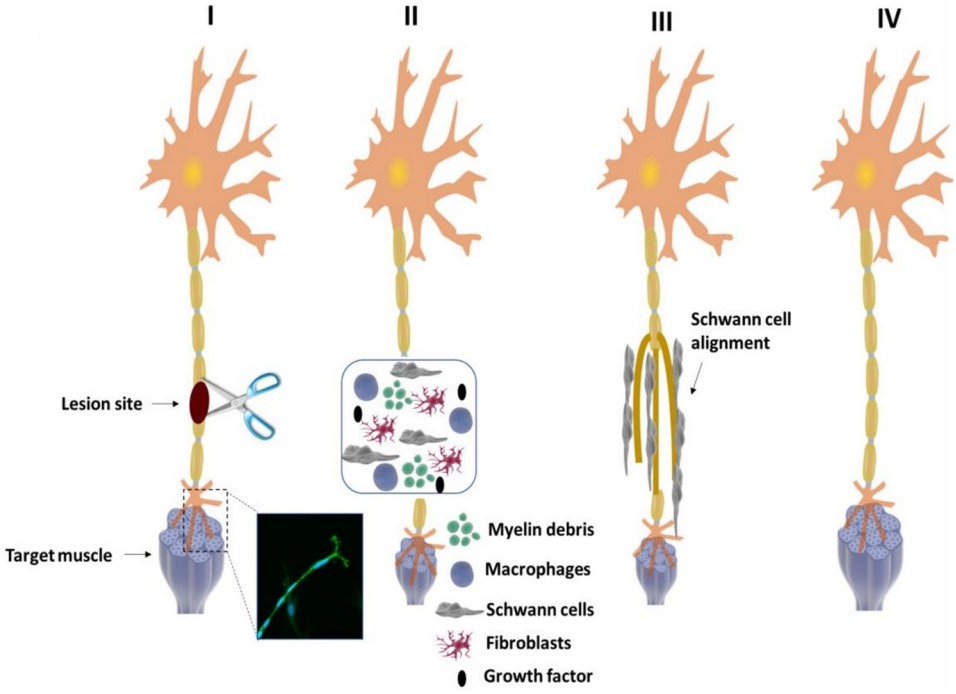

Figure 1: Progression of Wallerian degeneration [39]. (I) A single axon with enwrapping myelinating Schwann cells suffers a traumatic injury; (II) the axon breaks, and the distal stump undergoes cellular changes. Distal to the injury, there is a destruction of the remaining intact axon and disintegration of the myelin cover, leaving debris behind. Macrophages and Schwann cells, which turned to a pro-regenerative phenotype, accumulate at the lesion site and scavenge the debris; (III) Schwann cells align in the Bands of Bũngner. These tubes provide a permissive growth environment and guide extending axons toward distal targets; and (IV) if the axon is able to traverse the injury gap, the distal target becomes re-enervated, and the neuron becomes fully functional.

emphasizing the need for advanced therapeutic strategies to support regeneration (Figure 2).

The body's self-repair of SCI progresses through three stages: acute, subacute, and chronic. After SCI, thrombin activation in blood vessels leads to clot formation, preventing hematoma and edema expansion [62]. Cytokines and chemokines induce microglia and macrophages to clear debris and release pro-inflammatory cytokines, attracting more immune cells to the injury site [63]. In the subacute phase, neural stem cells migrate to the injury area, predominantly differentiating into astrocytes that produce glial fibrillary acidic protein, limiting injury [64,65]. A small part of stem cells differentiate into nerve cells and oligodendrocytes, protecting normal nerve tissue. In the chronic phase, astrocyte-produced collagen fibers form glial scars that encase the injury, while nerve fibers undergo degeneration and cyst formation, forming scar tissue [66,67]. Despite these repair efforts, SCI's self-repair capacity is limited, highlighting the need to enhance the SCI microenvironment through external interventions to promote nerve cell and fiber regeneration for effective SCI repair (Table 1).

3 Mechanism of magnesium in SCI and PNI recovery

Nerve injury can arise from various factors, including traumatic events such as mechanical injury, compression, and stretch injuries, often resulting from accidents or repetitive motions. Metabolic conditions like diabetes and nutritional deficiencies, particularly of B vitamins, can impair nerve function. Inflammatory processes from autoimmune diseases or infections also contribute to nerve damage. Toxic exposures to chemicals or radiation can directly harm nerve tissues, while genetic disorders may predispose individuals to neuropathies. Additionally, vascular issues leading to ischemia can compromise blood flow and contribute to nerve injury. Among these injury causes, trauma or exercise is the most common cause of nerve injury. Although magnesium is used in various physical and chemical forms in biomaterials, such as pure magnesium metal, magnesium alloys, magnesium oxide, or magnesium salts, its biological effects are ultimately mediated through its divalent ionic form (Mg^{2+}). In physiological environments, these different forms degrade or dissolve to release Mg^{2+} ions, which are the active species responsible for magnesium's role in nerve repair. Magnesium can affect the nerve repair process after nerve injury in the following ways.

3.1 Neuroprotective effects through regulation of calcium ion channels

Neural injuries often accompany the damage of nourishing blood vessels, leading to neural ischemia and hypoxia [68]. When neurons lose normal levels of oxygen supply,

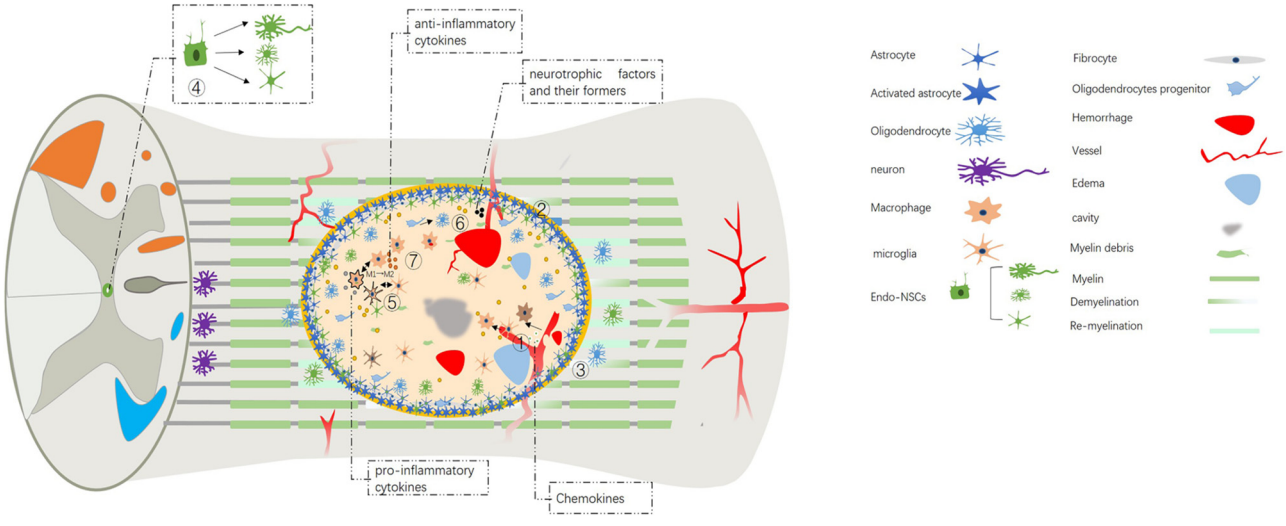

Figure 2: Microenvironment imbalance of SCI [61]. ① Hemorrhage and ischemia. ② Scar formation. ③ Demyelination and re-myelination. ④ Differentiation balance of endogenous neural stem cells. ⑤ Transformation of the phenotypes of microglia and macrophages. ⑥ Imbalance of neurotrophic factors and their pro-peptides. ⑦ Imbalance of the cytokines and chemokines.

Table 1: Differences between SCI and PNI recovery

	SCI repair	PNI repair
Regenerative capacity	Limited axonal regeneration due to glial scar formation and a non-permissive environment	Robust axonal regeneration aided by Schwann cell support and regeneration channels
Inflammatory response	Severe and prolonged inflammation, with high expression of IL-1β, TNF-α, and IL-6; extensive microglial and astrocyte activation	Moderate, self-limiting inflammation, with effective macrophage response and Schwann cell modulation
Repair mechanism	Limited axon regeneration and neuron replacement	Axon regeneration
Glial scar formation	Significant astrocyte proliferation, forming glial scars	Schwann cell proliferation, forming regeneration channels, less scarring
Repair time	Long and complex, slower functional recovery	Relatively quick, better functional recovery
Treatment methods	Stem cell transplantation, gene therapy, neuroprotective drugs, *etc.*	Nerve suturing, nerve grafting, nerve conduits, *etc.*
Functional recovery	Difficult functional recovery, typically severe functional impairment	Better functional recovery, the potential for full recovery

mitochondrial damage and energy metabolism disorders occur, causing a decrease in ATP production and enzyme activity [69]. This will activate the NMDA receptor on the cell membrane, which is a special type of calcium ion channel [70]. After the hypoxic injury, the opening of the NMDA calcium ion channel causes a large accumulation of calcium ions in the cell, forming calcium overload, which further exacerbates the disorder of cellular energy metabolism, leading to the generation of oxygen free radicals and oxidative phosphorylation, the formation of a large amount of excitatory amino acids glutamate and GABA, and ultimately leading to the death of ischemic neurons [71]. Magnesium ions are natural antagonists of calcium ions, and they can inhibit the inflow of calcium ions by competitively binding with NMDA receptors and at the same time inhibit Mg^{2+}/Ca^{2+} exchange by Mg^{2+}/Na^{+} exchange, causing excessive intracellular calcium ions to flow out, reducing the concentration of calcium ions within the cell, inhibiting the activation of calcium-calmodulin kinase II (CaMK-II), and alleviating neuronal damage [72]. Magnesium ions can also reduce the secondary neuronal damage caused by excitatory amino acids by antagonizing their neurotoxicity (Figure 3) [73].

3.2 Antioxidant effect

After SCI and PNI, various reactive oxygen species increase, including ROS and NOS. These reactive oxygen species cause overoxidation of proteins, lipids, and nucleic acids in cells, leading to abnormal cell function and degeneration and death of neurons [75]. Studies have found that magnesium ions can inhibit lipid peroxidation, free radical generation, and cell membrane hyperpolarization to prevent neuronal damage [76]. Magnesium ions can reduce the generation of endogenous NO by inhibiting the activation of INOS and reducing the generation of xanthine oxidase, superoxide dismutase, and oxygen free radicals [77]. Fujita, Keigo, and others found that the increase in intracellular magnesium ion levels can reduce the cell oxidative stress damage induced by hydrogen peroxide by maintaining mitochondrial membrane potential (MMP) [78]. In addition, in recent years, some researchers have incorporated magnesium into nanoparticles and loaded them into biomaterials [79]. Magnesium reacts with reactive oxygen in an acidic environment and neutralizes reactive oxygen; meanwhile, it generates magnesium ions, which further exert the effect of clearing reactive oxygen and reducing cell oxidative stress damage [80,81].

3.3 Inhibition of neuroinflammation response

In the early stage of nerve injury, macrophages migrate to the injury area and release inflammatory factors such as IL-1, IL-6, and TNFα [82]. These pro-inflammatory factors further activate microglia and astrocytes to infiltrate and proliferate, exacerbating the inflammation in the injury area and leading to secondary neuron death [83]. Magnesium ions can antagonize the above process, promoting the repair and regeneration of neurons by inhibiting inflammation. Pan *et al.* found that magnesium supplements can reduce sciatic nerve damage by promoting the expression of bcl-2 and bcl-x [84]. Hu *et al.* found that magnesium can inhibit the inflammatory response induced by activated macrophages, thereby promoting the differentiation of mesenchymal stem cells. When the level of magnesium ions decreases, the levels of pro-inflammatory factors such as IL-1, IL-6, and TNFα in the microenvironment

will increase accordingly, which exacerbates inflammation [85].

3.4 Nerve regeneration effect

Magnesium can directly regulate neural stem cells and promote the differentiation of neural stem cells into new neurons [86,87]. Liao *et al.* found that adding magnesium ions to neural progenitor cells can activate the ERK/CREB pathway, promote the differentiation of neural progenitor cells into neurons, and inhibit their differentiation into astrocytes [88]. Jia *et al.* found that the addition of magnesium to neural stem cells can promote cell proliferation, and its potential mechanism may be related to the effect of magnesium on cellular mitochondrial function [89]. In the case of low extracellular magnesium concentration, the intracellular magnesium ion level is reduced, and mitochondrial ROS is increased, causing DNA damage and activation of p53, NF-κB signaling pathways, and ultimately leading to cell death. Increasing magnesium concentration can effectively reverse this process (Figure 4) [90].

The nerve fibers of humans and most mammals are myelinated nerve fibers, which are wrapped in myelin formed by Schwann cells. After nerve injury, Schwann cells can secrete neurotrophic factors such as NGF to promote the survival and axon regeneration of damaged neurons [91]. Pan *et al.* found that by increasing the magnesium concentration in the nerve tissue of the injury area through a high-magnesium diet, the nerve behavior and electrophysiological function after sciatic nerve injury can be improved. In a high-magnesium environment, the deposition of inflammatory cells in the injury area is reduced, and the expression level of inflammatory factors decreases. *In vitro* experiment results show that the decrease in Schwann cell apoptosis is consistent with the significantly increased expression of bcl-2 and bcl-x and the downregulation of active caspase-3 and cytochrome C expression [84]. Li *et al.* constructed a sciatic nerve injury model and also proved the promoting effect of magnesium on myelin axon regeneration after nerve injury. By implanting magnesium wire into the injury area, the expression of nerve growth factor, p75 neurotrophic factor receptor, and tyrosine receptor kinase A mRNA in the injury area are all upregulated, and the number of cross-sectional nerve fibers and regenerated axons also increase [92]. The above research shows that in addition to directly protecting neurons, magnesium can also indirectly promote the regeneration of neurons by promoting Schwann cells and other neuro-supportive cells to secrete nerve growth factors.

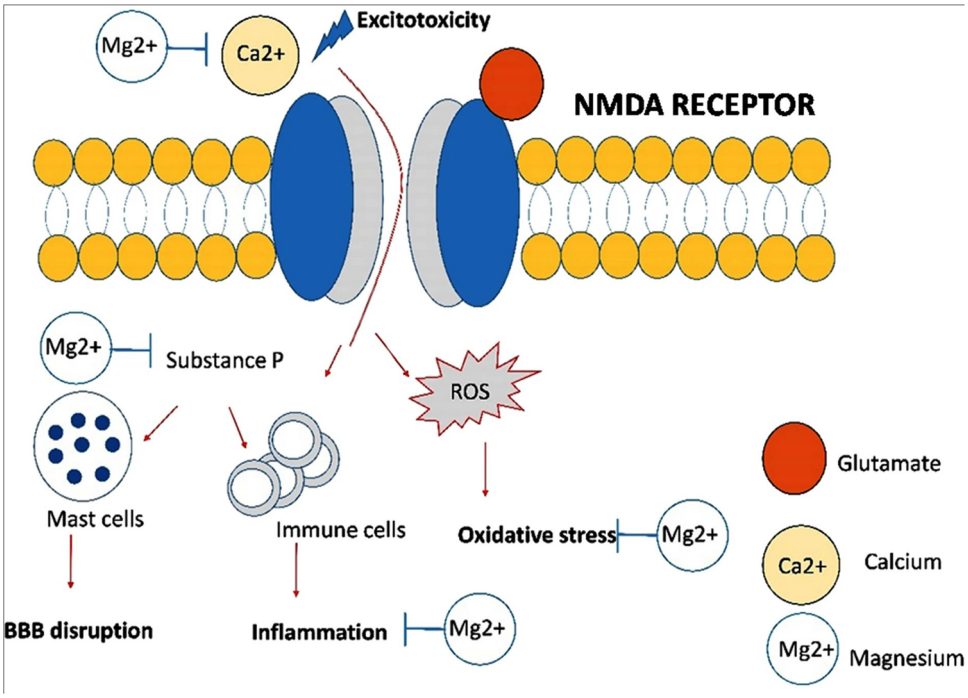

Figure 3: Magnesium ions are natural antagonists of calcium ions, and they can inhibit the inflow of calcium ions by competitively binding with NMDA receptors. Excessive calcium influx in the brain causes various complications in the brain such as excitotoxicity, BBB disruption, inflammation, and oxidative stress. Magnesium is found to be beneficial in neurological diseases by correcting the above-mentioned complications [74].

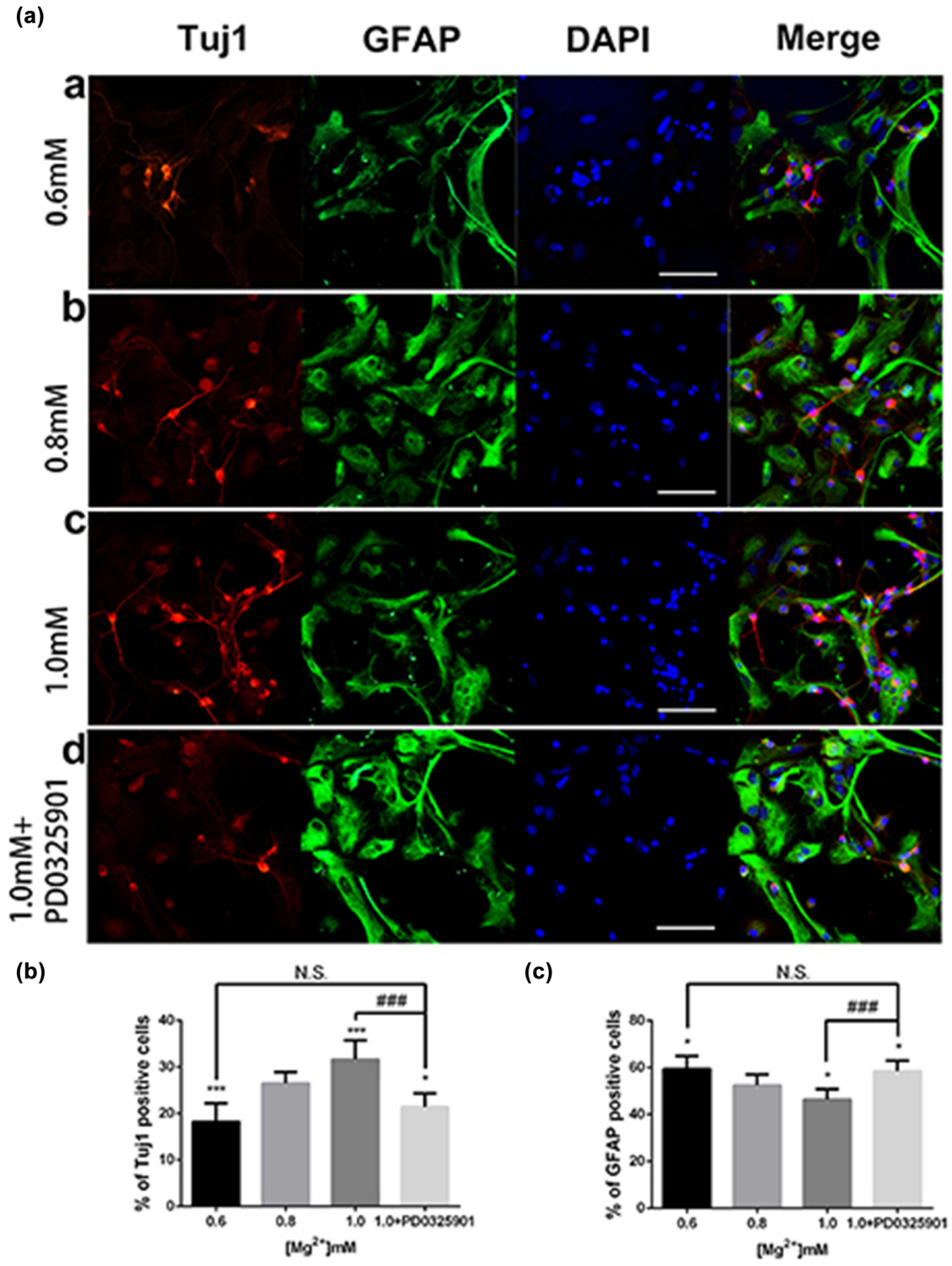

Figure 4: Magnesium promotes the differentiation of neural progenitor cells into neurons and inhibits their differentiation into astrocytes. Immunocytochemistry of adult NPCs differentiated at various magnesium concentrations and in the presence of an ERK inhibitor. (a) The percentage of Tuj1-positive cells increased (b), and the percentage of GFAP-positive cells decreased (c) after differentiation with an increase in magnesium concentration. Supplemented with ERK inhibitor PD0325901, the percentage of Tuj1-positive cells decreased while the percentage of GFAP-positive cells increased compared with the control group (0.8 mM) and the group with an elevated magnesium concentration (1.0 mM) [88].

3.5 Enhancing local electrical activity

The conduction of nerve impulses is transmitted in the form of electrical signals within neurons. When nerve injury occurs, the electrical signal cannot be transmitted to the distal effector or lower-level neurons, so it loses its normal function. A large number of studies have shown that adding conductive components to biomaterials to enhance the conductivity of materials can enhance the reconstruction of nerve functions [93,94]. When combined electrical stimulation is used to treat nerve injury, the use of biomaterials with proper conductive ability or good electrical activity can further improve the treatment effect [14,15]. As a metal, magnesium has good conductivity (22.6 $\times 10^6$ S/m). For peripheral nerves and spinal cord tissues, when performing normal nerve functions, their conductivity is about 0.01–10 S/m, so only a small amount of magnesium needs to be added to the material to enhance the overall conductivity of the biomaterial to reach the level compatible with normal tissues [95,96]. Gonçalves *et al.* constructed a PVA conduit with electrical activity by adding magnesium chloride to polyvinyl alcohol, and a directional conduit for PNI repair was prepared. The results showed that compared with pure PVA conduits, the conductivity of modified conduits with added magnesium chloride significantly increased from $1.5 \pm 0.5 \times 10^{-6}$ to $130.0 \pm 0.3 \times 10^{-6}$ S/m [34]. The above research shows the feasibility of enhancing the electrical activity of biomaterials by adding magnesium.

4 Application of magnesium and its compounds modified biomaterials in PNI and SCI recovery

Neural tissues such as peripheral nerves and spinal cord tissues have very limited self-repair effects under the influence of adverse external environments such as inflammatory reactions, ischemic hypoxia, and scar formation after injury. For peripheral nerves, sometimes autologous nerve transplantation can be used to achieve better nerve function repair, but their sources are limited and might cause nerve damage during transplantation [97]. Compared with peripheral nerves, the structure and the pathological changes after injury of the spinal cord tissue are more complex, which makes its repair more difficult, and there is currently no satisfactory repair method. The construction of biodegradable repair materials has a very good application prospect in the recovery of nerve injuries. The application of biomaterials provides exogenous healing factors such as neurotrophic factors and neural stem cells for nerve injury repair by protecting nerve tissue regeneration and promoting nerve regeneration and functional reconstruction after nerve injury [98,99]. For example, constructing a nerve conduit scaffold to connect the severed ends of the injured sciatic nerve protects nerve fibers from the influence of scar tissue and inflammatory cells while providing a growth channel for nerve fiber regeneration at the same time [100]. In view of the good properties of magnesium in nerve regeneration and nerve repair, in recent years, more and more researchers have considered using magnesium as a nerve repair material or a component of materials for application in peripheral nerves and SCIs. According to the difference in the type of magnesium added in the biomaterials, it can be roughly divided into three categories: pure magnesium, magnesium alloy, and magnesium ions.

4.1 Pure magnesium

Pure magnesium is the earliest form of magnesium used in neural tissue engineering materials. Peripheral nerves have a clearer tissue morphology; except for nerve fibers and Schwann cells, there are almost no other supporting cells or tissues. Therefore, for PNIs, the construction of nerve conduits to connect the two ends of the injury can achieve better repair effects. Vennemeyer *et al.* added magnesium wire to the polycaprolactone nerve conduit to treat rat sciatic nerve injury. The results showed that magnesium wire has good biocompatibility and promotes the functional recovery of injured nerves without causing additional inflammation [101]. The research of Hopkins *et al.* also proved that adding magnesium wire to the nerve conduit can promote axon extension (Figure 5) [102].

On the basis of the research using magnesium wire alone, Zhang *et al.* prepared a magnesium scaffold with silk protein (SF) as the core of magnesium wire, and the scaffold was impregnated in chitosan (CS) solution and freeze-dried to form S/Mg-SF/CS nerve conduit. The nerve conduit with added Mg has better mechanical strength and can effectively promote the repair of rat sciatic nerve injury [103]. Compared with the autograft group, the nerve conduit scaffold group has no significant difference in the diameter and thickness of the distal nerve myelin. Cai *et al.* constructed a GDNF-Gel/HA-Mg scaffold for PNI repair by coating hydroxyapatite on the surface of the magnesium conduit and GDNF-loaded GelMA hydrogel to extend the magnesium degradation time and achieve continuous

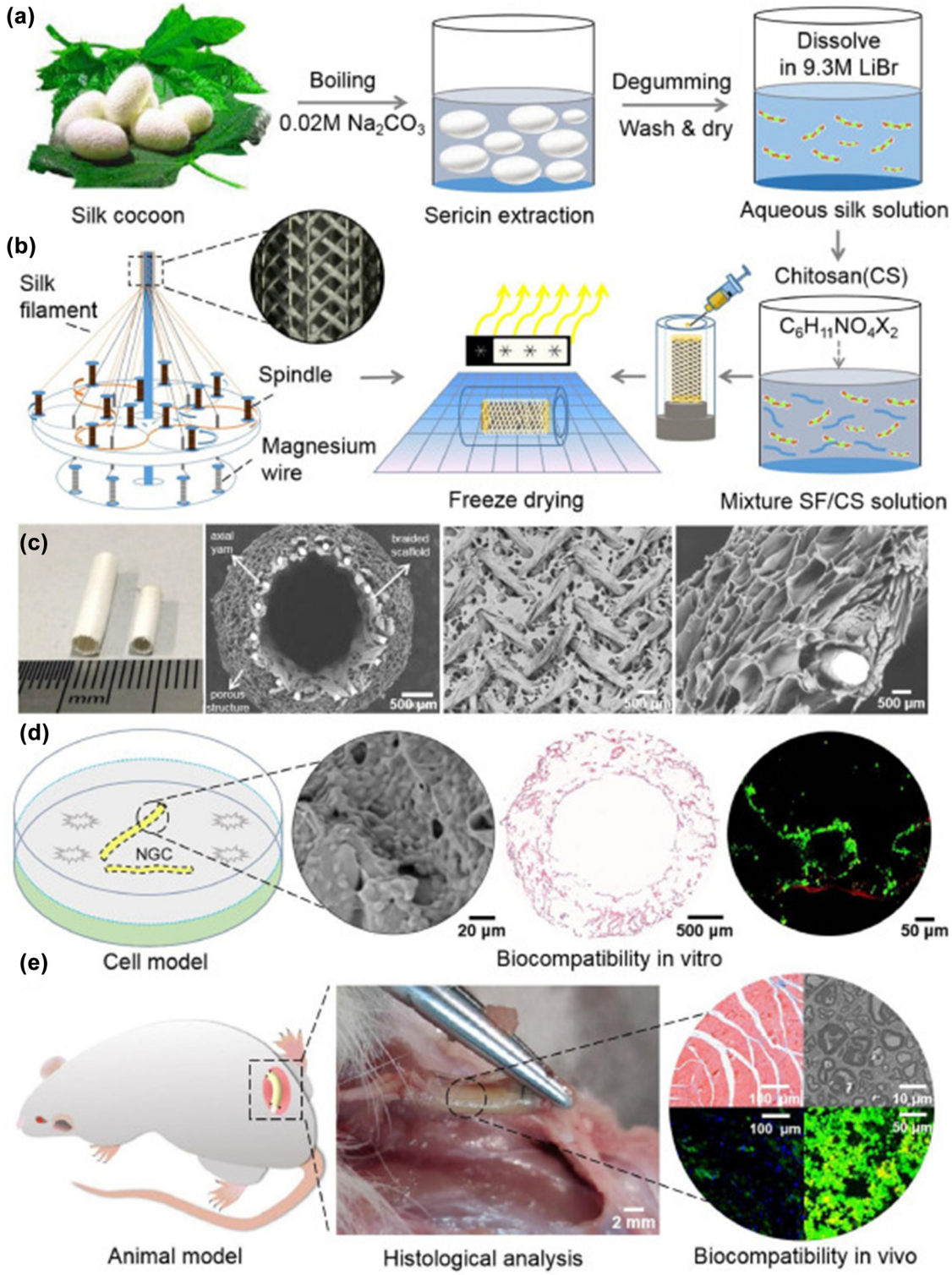

Figure 5: Schematic of the fabrication process for S/Mg-SF/CS NGCs. (a) Preparation of SF solution: Boiling silk cocoons and degumming sericin to obtain an aqueous SF solution; (b) fabrication process of NGCs using textile engineering and molding technologies: SF yarns and Mg filaments were braided as an inner layer, followed by freeze-drying with a mixture of SF/CS solution; (c) images and morphologies of composite and porous structures of prototype S/Mg-SF/CS NGC samples; and (d) *in vitro* and (e) *in vivo* assessment to evaluate efficiency of repair using rat Schwann cells and Sprague–Dawley rats [103].

delivery of growth factors [104]. The results show that the GDNF-Gel/HA-Mg scaffold can significantly increase the number of axon regeneration in the rat sciatic nerve injury model, and the thickness of the nerve fiber myelin is significantly higher than that of the control group. Wu *et al.* used the conductivity of magnesium to construct a degradable electric nanogenerator-based ultrasound-driven *in vivo* electric stimulation nerve conduit. This conduit uses PHBV and PLLA as matrix materials, potassium sodium niobate as a piezoelectric dopant, and magnesium and molybdenum as dual electrodes, which can achieve local electrical stimulation under ultrasound excitation [105]. This ultrasound electrical stimulation nerve conduit can effectively enhance the electrophysiological function of the sciatic nerve after injury and also increase the length and thickness of myelin regeneration.

However, although magnesium has good tissue compatibility, conductivity, antioxidant, and neuroprotective abilities, the use of magnesium to enhance the performance of biomaterials still has an issue that cannot be ignored. Magnesium, as an active metal, has a fast degradation rate. It will undergo electrochemical corrosion under acidic conditions and a liquid environment in the body [106]. The implanted pure magnesium often degrades completely in about 2 weeks [107]. However, the process of nerve repair and regeneration often requires a longer time. For peripheral nerves, it takes 2–4 weeks, and for the regeneration of spinal cord tissue, it takes even longer [108]. The mismatch between the degradation time and the regeneration and repair process makes it impossible to provide continuous protection during the repair process. At the same time, the rapid degradation of magnesium may also cause the accumulation of degradation products, affecting the nerve regeneration process and even producing adverse effects [109]. Therefore, this problem needs to be addressed by modifying magnesium to give it a longer degradation cycle and more stable biological properties.

Sebaa *et al.* covered a layer of conductive polymer PEDOT coating on the Mg surface by electrochemical deposition. After the coating is covered, magnesium has better corrosion resistance, and its corrosion rate (2.64 mm/year) is significantly lower than that of untreated magnesium (38.98 mm/year) [110]. Tatu *et al.* used another method to extend the degradation time of metallic magnesium [111]. They removed the oxide layer on the surface of the metallic magnesium by polishing it to expose the smooth metallic magnesium surface and then covered the oxide layer on the surface of the metallic magnesium by plasma electrolytic oxidation (PEO). The results showed that the degradation rate of the magnesium wire after oxidation treatment was significantly lower than that of the polished group without oxidation. This modified magnesium wire has good biocompatibility, can alleviate muscle denervation atrophy symptoms, and can promote rat sciatic nerve fiber regeneration to a certain extent.

4.2 Magnesium alloy

In addition to pure magnesium, magnesium alloys have also been extensively researched in neural tissue engineering scaffolds. Compared with pure magnesium, magnesium alloys can provide other metal ions, such as Zn, Li, and Ca, which can promote nerve repair in conjunction with Mg [112]. At the same time, its biological properties, such as corrosion performance, mechanical strength, and biocompatibility, can be easily adjusted by altering the proportion and type of other elements in the alloy. Li *et al.* used AZ31 magnesium alloy as the implant material to treat rat sciatic nerve injury. The results showed that compared with the control group, the treatment group implanted with AZ31 magnesium wire significantly increased the axon regeneration and myelin coverage rate of the sciatic nerve and improved nerve function [92]. Fei *et al.* explored the biological functions of three magnesium alloys, NZ20 (Mg-2Nd-Zn), ZN20 (Mg-2Zn-Nd), and Mg-10Li on nerve cells. The results showed that the cellular toxicity of the three alloys can be ignored in the short term (1 day), and ZN20 and Mg-10Li have lower neurotoxicity and better biological properties [113]. Sun *et al.* prepared a PCL nerve conduit scaffold containing Li–Mg–Si bioceramics; the nerve conduit scaffold can promote macrophages to differentiate into M2 phenotype for regeneration, promote the migration and differentiation of Schwann cells, up-regulate the expression of neurotrophic factors in a β-catenin-dependent manner, and promote myelin regeneration in rat sciatic nerve injury [114].

Similar to pure magnesium, surface modification of magnesium alloys can also extend their degradation time. Monfared *et al.* prepared a Mg–Zn–Ca metallic glass alloy by melt spinning and covered tannic acid/poly(N-vinylpyrrolidone) (TA/PVPON) on the alloy surface to extend the degradation time of the alloy. The results showed that the coating significantly improved the corrosion resistance of the Mg–Zn–Ca alloy. After 7 days, the magnesium ion release rate of the alloy modified by the coating was only one-third of that of pure magnesium. The cell experiment results showed that Schwann cells can normally adhere and grow on the material surface, promoting the extension of synapses and the growth of axons [115]. Liu *et al.* used AZ91D magnesium alloy as the matrix

material to prepare carbon nanotubes (CNTs) and calcium phosphate (CaP)/CS-modified CNT-CaP/CS-AZ91D composite material. The CNTs on the surface of the composite material enhance the corrosion resistance of the alloy. The results of *in vitro* cell experiments show that the ERK signal transduction of DRG neurons grown in the CNT-CaP/CS-AZ91D extraction solution is activated, which promotes the growth of neurons (Figure 6) [116].

4.3 Magnesium ions

Magnesium ions, as another form of magnesium element, can directly exert neuroprotective and nerve regeneration-promoting effects in biomaterials. In addition, magnesium in the form of ions can be more conveniently added to various matrix materials, enhancing the overall performance of nerve regeneration biomaterials. Huang and others constructed an anisotropic microsphere-freeze gel composite material loaded with L-sucrose magnesium (MgT). This composite material has an anisotropic porous structure and can achieve sustained release of magnesium ions in 4 weeks. This composite material containing MgT can significantly promote the osteogenic differentiation of bone marrow mesenchymal stem cells, the tubular formation of human umbilical vein endothelial cells, and the differentiation of neurons *in vitro* [117]. Gao *et al.* used SF and alginate (Alg) to construct a cell-adaptive Alg-Mg/SF hydrogel containing magnesium ions. This hydrogel can rebuild the local microenvironment after being implanted in the injured sciatic nerve area, recruit macrophages in a short time and induce them to transform into M2 phenotype, promote axon and myelin regeneration, and accelerate muscle atrophy recovery (Figure 7) [118].

Yao *et al.* developed an injectable hydrogel of diphosphonate salt containing magnesium ions for rat sciatic nerve injury. This hydrogel can achieve sustained delivery of magnesium ions and promote neurite growth in a concentration-dependent manner by activating the PI3K/Akt signaling pathway and Sema5b [119]. Compared with the control group, the PCL nerve conduit with diphosphonate salt hydrogel containing magnesium ions significantly enhanced the nerve axon and myelin regeneration after 12 weeks of surgery, and the reinnervation of the injured nerve was significantly improved. Ramburrun *et al.*

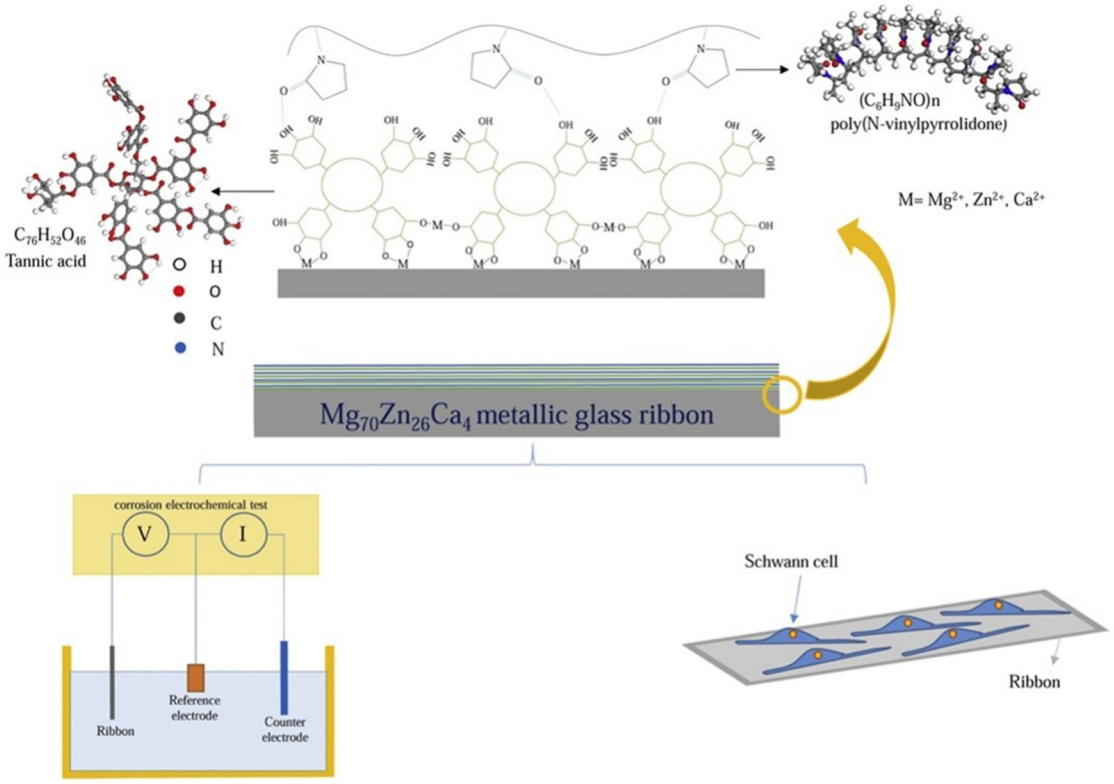

Figure 6: Schematic illustration of the magnesium-based metallic glass ribbon with a tannic acid/poly(N-vinylpyrrolidone bilayer coating for nerve tissue engineering purposes [115].

prepared a three-in-one electro-spun film based on (3-hydroxybutyric acid-co-3-hydroxypentanoic acid) PHBV, magnesium oleate (MgOl), and *N*-acetyl-L-cysteine (NAC) and made it into a nerve conduit for the treatment of nerve injury [120]. The magnesium ions in MgOl and NAC synergistically promote the proliferation of PC12 cells and promote neurite extension through nucleation and neurotrophic effects, accelerating the recovery of damaged nerve function.

4.4 Application of magnesium in biomaterial-based SCI repair

Given the successful application of magnesium and its modified materials in peripheral nerve repair biomaterials, some researchers have begun to try to use magnesium in the construction of SCI repair biomaterials. Compared with peripheral nerves such as the sciatic nerve and brachial plexus, the structure of the spinal cord tissue is more complex. Spinal cord tissue not only contains a large number of nerve fibers but also contains considerable amounts of neuro-supportive cells such as astrocytes, microglia, and nourishing components such as blood vessels [121]. Therefore, the construction of biomaterials for SCI repair needs to consider more related factors. Ischemia and hypoxia, direct death of neurons, axon rupture in the early stage of injury and oxidative stress, infiltration of inflammatory cells, and secondary apoptosis of neurons during the late stage are all problems that need to be solved. Therefore, when constructing biomaterials for SCI repair, a single matrix material or modified material often cannot meet all needs. At the same time, because the repair process of SCI is longer than the repair process of peripheral

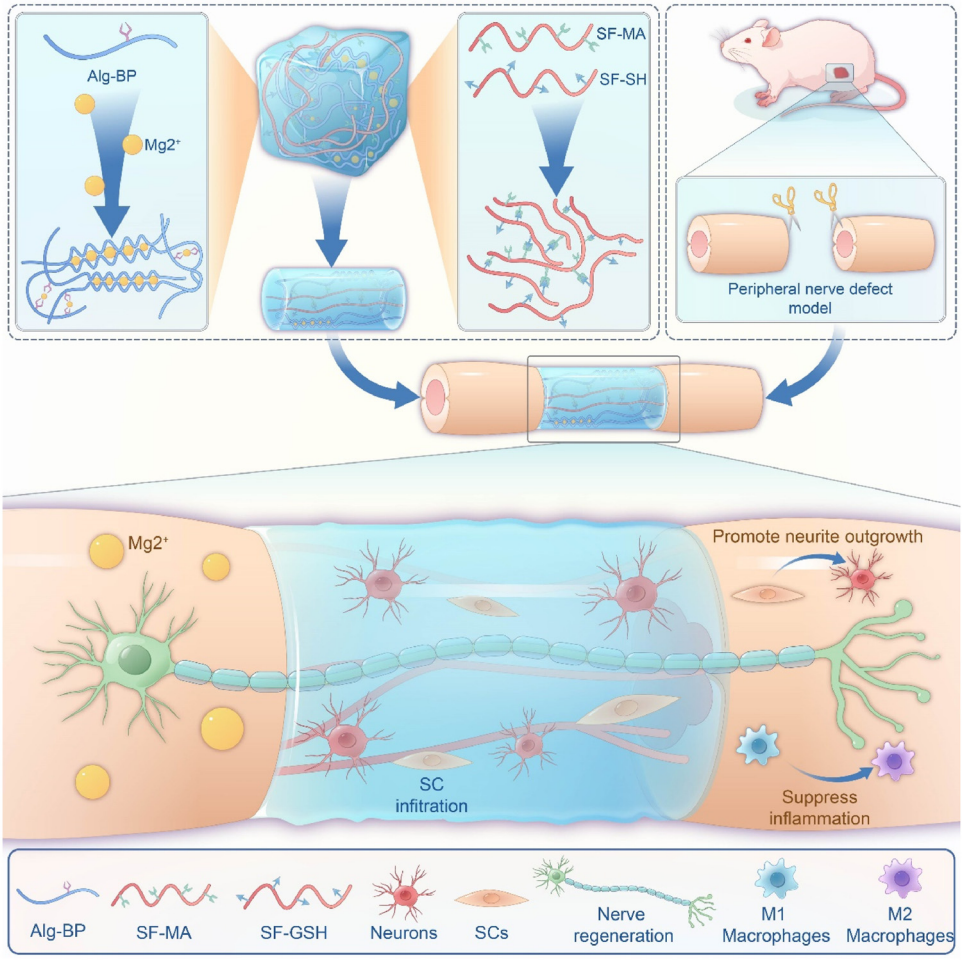

Figure 7: Schematic illustration of the production of the Alg-Mg/SF-adaptable hydrogel and its application in promoting peripheral nerve regeneration. The Alg-Mg/SF-adaptable hydrogel consists of interpenetrating polymeric networks with Alg-Mg and SF. The hydrogel conduits can promote *in situ* peripheral never regeneration by facilitating the outgrowth of axons, infiltration of SCs, and recruitment of macrophages [118].

nerves, it is necessary to achieve a long-term stable release of magnesium in biomaterials. Compared with pure magnesium, magnesium oxide or magnesium salt has more stable chemical properties, and its degradation time is longer under similar *in vivo* conditions, so it is more suitable for the construction of SCI repair biomaterials. Based on the above reasons, researchers currently choose to add magnesium compounds as modified materials to the matrix materials and construct multifunctional composite biomaterials together with other drugs or cells for SCI repair and have achieved certain therapeutic results.

Zhu *et al.* prepared Mg/Al layered double hydroxide nanoparticles (LDH) by co-precipitation and hydrothermal treatment techniques [122]. Cell experiment results show that these nanoparticles can accelerate the migration of NSCs, promote neural differentiation, regulate the activation of calcium ion channels, and generation of action potentials. Moreover, loading neurotrophic factor 3 (NT3) in nanoparticles can further enhance the directional differentiation and migration ability of NSCs. Implanting LDH-NT3 nanoparticles into the injury site of SCI mice can promote the formation of newborn neurons in the injury area and the expression of transforming growth factor β and reverse the transformation of macrophage M1/M2 phenotype. Electrophysiological test results show that in the LDH-NT3 treatment group, a larger electrical signal amplitude and a shorter latency were observed, and the co-localization immunofluorescence staining results also showed that the reconstruction of the nerve signal pathway at both ends of the injury in the treatment group achieved better results (Figure 8).

Xie *et al.* developed a MgO/poly(L-lactide-co-ε-caprolactone) (PLCL) scaffold containing the agonist PUR and retinoic acid (RA) [123]. MgO is prepared by the chelation calcination method. The obtained MgO nanoparticles have a porous structure and good adsorption capacity. The hydrophilicity and mechanical strength of the MgO-modified PLCL scaffold are significantly improved. By adding MgO nanoparticles to the matrix material, the release time of MgO in the system is also extended. After 4 weeks, it can still dissolve and release at a relatively uniform speed, extending the maintenance time for the magnesium ion in the system. The MgO in the scaffold can stably and continuously release magnesium ions to the local environment. The released magnesium ions can bind to NMDAR to block the inflow of calcium ions, reduce cell apoptosis caused by calcium overload, and PUR/RA can promote the recruitment of endogenous NSCs and neuron differentiation. The two jointly act on the local injury to reduce the death of nerve cells and the formation of neuroglial scars, promote axon regeneration, and promote the reconstruction of nerve function and the recovery of sensory-motor function in the mouse SCI model.

5 Conclusion and prospect

This review systematically introduces the pathophysiological changes that occur after nerve injury, elaborates on the potential mechanism of magnesium in nerve injury repair, and details the application of magnesium and its

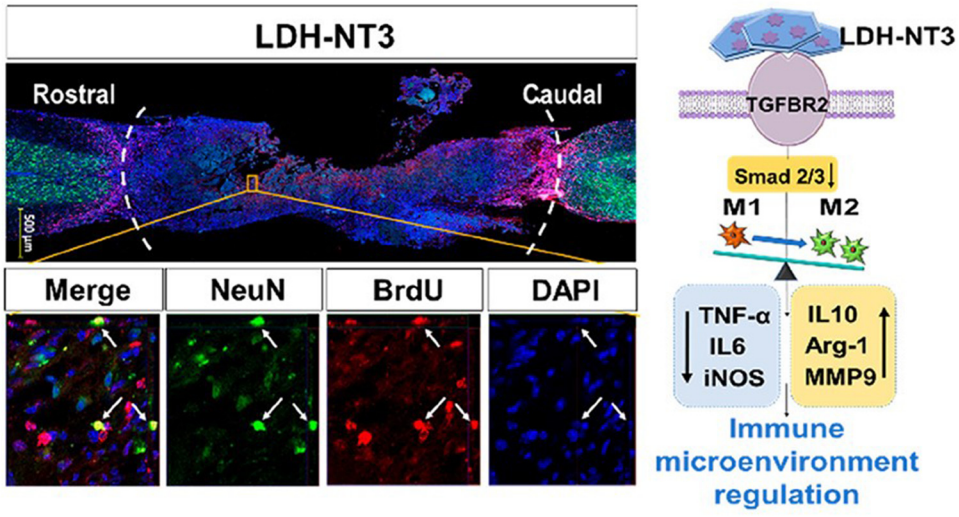

Figure 8: The neural regeneration and immunoregulation functions of Mg/Al layered double hydroxide (Mg/Al-LDH) nanoparticles in completely transected and excised mice and the immune-related mechanisms [122].

modified compounds in nerve injury repair. Magnesium can protect nerve cells from being damaged in various ways, such as regulating the opening of calcium ion channels, reducing calcium overload, clearing reactive oxygen species, reducing inflammatory response, and improving tissue electrical activity. At the same time, it can directly promote nerve fiber regeneration and the reconstruction of nerve signal pathways by promoting the proliferation of Schwann cells and axon regeneration, and promote neuron differentiation. The application of magnesium and its compounds in biomaterials can significantly improve the neuroprotective ability of the material, promote the recovery of nerve injury, and the reconstruction of nerve function. It has great application potential in the design and construction of neural tissue engineering scaffolds.

In addition to magnesium, the metals widely used in nerve injury repair materials also include gold, silver, copper, iron, and zinc. Magnesium has many advantages compared with these materials. First, magnesium, as a human microelement, exists in large quantities in the body, so it has a greater safety dose and better biocompatibility when applied to the body compared with heavy metals such as gold, silver, and copper. Table 2 shows the application form and dosage of magnesium and its compounds in biomaterials for nerve injury repair. Although the dosage of magnesium varies greatly among different studies, all studies show good biocompatibility and safety. In addition, after nerve injury, magnesium can directly regulate the repair of nerve injury from the level of injury occurrence mechanism by regulating ion channels, while metal ions such as gold, silver, and copper mainly regulate indirectly by regulating oxidative stress to reduce inflammation. Therefore, magnesium has a more direct intervention effect. Finally, compared with other materials commonly used for nerve damage repair, magnesium has better chemical activity, which gives magnesium a larger modification space and modification means, which is conducive to researchers in the subsequent development of composite materials with more functional and biological properties. However, we also need to pay attention to the challenges for the application of magnesium and its modified compounds in nerve injury repair biomaterials.

Although magnesium and its compounds have exhibited a good therapeutic effect on nerve injury repair *in vitro* experiments, there remains a considerable gap before these findings can be translated into clinical applications. At present, biomaterials containing magnesium used in clinical trials are mainly focused on bone regeneration and bone tumor applications. Magnesium can provide mechanical support, promote bone regeneration in bone repair, and can achieve better application results.

Table 2: Application form and dosage of magnesium and its compounds in biomaterials for nerve injury repair

Magnesium form	Other components of biological materials	Application parameters of magnesium in research	Ref.
Pure Mg	Acidic keratin hydrogel PCL	10 mm long with 0.25 mm diameter	[101]
Pure Mg		Maximum 20 mm long with 0.25 mm diameter	[102]
Pure Mg	Silk fibroin (SF) and CS	12 mm long with 0.1 mm diameter	[103]
Pure Mg	Gelatin methacryloyl (Gel), hydroxylapatite (HA), and GDNF	Length 12 mm, inner diameter 2 mm, and thickness 0.5 mm	[104]
Pure Mg	Potassium sodium niobate (KNN), PLLA, PHBV, and PCL	15 nm thick magnesium (Mg) electrode layers were coated on both sides of the PHBV/PLLA/KNN film (1.5 × 1.5 cm^2) *via* thermal evaporation	[105]
Pure Mg	—	5 × 5 × 0.25 mm	[110]
Pure Mg	—	20 mm long with 0.25 mm diameter	[111]
Mg alloy	Mg–3%Al–1%Zn	8 mm long with 3 mm diameter	[92]
Mg alloy	2 wt%Zn, 0.5 wt% Nd, Mg; 2 wt%Nd, 0.2 wt% Zn, Mg; and 10 wt% Li, Mg	Diameter of 10 mm and thickness of 4 mm	[113]
Mg alloy	Li–Mg–Si (LMS)	Maximum concentration of 15% LMS	[114]
Mg alloy	$Mg_{70}Zn_{26}Ca_4$	Maximum 4 mm thickness	[115]
Mg alloy	CNTs, CaP, and CS	1 cm × 1 cm × 0.5 cm	[116]
Mg ion	CS, sodium alginate (SA), and magnesium l-threonate (MgT)	Maximum concentration of 100 nM MgT	[117]
Mg ion	SF and Alg	Concentration of 200 nM $MgCl_2$	[118]
Mg ion	PCL and bisphosphonates (BPs)	Maximum concentration of 40 nM $MgCl_2$	[119]
Mg ion	Magnesium-oleate (MgOl), PHBV, and *N*-acetyl-L-cysteine (NAC)	Maximum concentration of 60% w/w MgOl	[120]
Mg ion	Mg–Al-LDH	Concentration of 3 mmol $Mg(NO_3)_2$ with 1 mmol $Al(NO_3)_3$	[122]
Mg ion	Purmorphamine (PUR), RA, and PLCL;	Maximum weight ratios 50:100 of MgO/PLCL	[123]

However, biomaterials containing magnesium have not yet been used in clinical studies of nerve injury regeneration, mainly because there are still some problems to be solved before this leapfrog goal can be achieved.

The regulation of the degradation process of magnesium in the body is the main problem that needs to be dealt with. The repair of nerve injury is a long-term process, and it often takes 4–8 weeks to achieve functional reconstruction, which greatly exceeds the degradation rate of magnesium itself. Therefore, it is necessary to modify magnesium or combine it with other substances to extend the release time of magnesium in the material so as to better match the needs of the nerve injury repair process. At the same time, the biocompatibility of the modified magnesium compound needs to be re-verified to avoid the adverse effects of new substances introduced during the modification process on nerve cells. To solve this problem, it is a promising way to build a slow-release system or a controlled-release system. Liposomes, protein microspheres, or hydrogels are used to separate magnesium from the external environment. The stable release of magnesium from the external environment can be achieved by adjusting the degradation conditions and degradation time of these embedded materials, and the existence time of magnesium in the system can be extended to meet the needs of the whole process of nerve injury repair. In addition, the specific mechanism of magnesium in the role of nerve injury repair in materials also needs to be further explored. Existing research mainly focuses on the verification of functional recovery elicited by magnesium after injury. Future research should focus on elucidating the role of magnesium and its compounds in nerve injury repair and provide a novel and promising treatment method for nerve injury recovery. We believe that, based on existing research results, new modification or synthesis methods can be developed to use magnesium and its compounds as core materials to construct composite neural tissue engineering materials with comprehensive adaptability. This will enable the regulation of various injury repair processes, such as microenvironment modulation, vascular regeneration, and pathway reconstruction after nerve injury, ultimately achieving effective functional recovery after nerve damage.

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Conflict of interest: The authors state no conflict of interest.

Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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