Review Article

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The drug delivery systems based on nanoparticles for spinal cord injury repair

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Abstract: Spinal cord injury (SCI) represents a devastating central nervous system trauma that results in the loss of sensory and motor function. Due to its complex pathological mechanisms and the unsatisfactory therapeutic effects of surgery, medication, and rehabilitation methods currently used in clinical practice, the treatment of this disease still faces enormous challenges. Over the past few decades, researchers have been committed to identify a reliable and potent therapeutic strategy for SCI, and the nano-delivery system has been proven to be more effective. The nanoparticles exhibit favorable controllable release characteristics and targeting ability toward spinal cord tissue, which may overcome the limitations of conventional drug delivery methods and confer exceptional therapeutic efficacy upon the nano-delivery system through sophisticated design, assembly, and surface modification. This review outlines a multimodal treatment strategy and the current application status based on nanoparticles for repairing SCI, with special emphasis on their application prospects, characteristics, and limitations. The discussion delves into the efforts and challenges involved in applying nanoparticle drug delivery technology for clinical SCI repair.

Keywords: spinal cord injury, drug delivery systems, nanoparticles, target therapy

1 Introduction

1.1 Epidemiology of spinal cord injury (SCI)

SCI is a condition characterized by debilitating spinal cord function resulting from trauma or disease. According to statistics, the annual incidence of SCI worldwide is estimated to range from 700,000 to 1.2 million cases, primarily caused by traffic accidents, falls, violence, sports, and surgical complications [1]. The American Spinal Injury Association classifies SCIs into five distinct categories: Category A represents a complete SCI, indicating no preservation of motor or sensory function below the level of injury; Categories B, C, and D denote incomplete SCI, signifying partial preservation of motor or sensory functions; and Category E indicates complete preservation of motor and sensory functions post-injury [2]. The incidence and etiology of SCI are influenced by various factors, including geographical location, age distribution, and gender demographics. In terms of region, SCI incidence is higher in low- and middle-income countries, and patients have a higher mortality rate [3]. In developed countries, road traffic accidents are the main

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cause of injury, while falls are the main cause in developing countries [4]. In terms of age and gender, older people and males are more likely to develop SCI than younger people and females. The high incidence of SCI in the elderly is attributed to the decline in physical function and potential health issues such as osteoporosis and spinal stenosis. The incidence of SCI in males is almost twice that in females, due to differences in occupational choices and participation in high-intensity sports [1]. In children with SCI, up to 80% of spinal injuries occur in the cervical spine, while in adults, this proportion is 30% [5]. The high incidence of cervical SCI in children is mainly due to the larger head-to-body ratio and underdeveloped paraspinal muscle tissue. Among all injury sites, cervical SCI has the highest incidence, accounting for more than 50% of traumatic SCI, and its incidence is much higher than that of thoracolumbar injuries, leading to more disability [6]. Traumatic cervical SCI often leads to multi-organ dysfunction, with cardiovascular and respiratory system failure being common, resulting in post-SCI mortality. In recent years, the rapid evolution of drug delivery systems has led to significant advancements in the therapy for SCI. Despite these strides, SCI patients continue to face a high risk of mortality, with nearly half requiring hospitalization during the first year post-injury [7]. This highlights the critical need for further research and development to improve treatment outcomes and reduce the associated health risks for individuals affected by SCI. Early diagnosis and treatment are crucial for improving patient survival and quality of life.

1.2 Pathological mechanisms of SCI

The pathological progression of SCI is typically categorized into two distinct stages: primary injury and secondary injury (Figure 1). Primary injury encompasses the initial trauma and local tissue damage resulting from fractures, as well as spinal cord stretching, bending, twisting, tearing, compression, or displacement [8]. Primary injury in SCI predominantly damages the gray matter of the spinal cord, causing damage to cell membranes and disrupting blood vessels, which results in spinal shock, accumulation of neurotransmitters, ischemia, and vasospasm [9]. Primary injury occurs immediately upon the application of external forces to the spinal cord, leading to direct structural damage or functional impairment of the spinal cord, which is typically irreversible. The treatment and prognosis of primary injury mainly depend on the severity of the injury, and the most effective treatment currently available is surgical decompression of the injured spinal cord within 24 h post-injury. Secondary injury refers to the events that occur following neural tissue damage, with the injury spreading from the original site to adjacent tissues, as well as the infiltration of the damaged tissue by cells of the immune inflammatory system [10]. The extent of secondary injury is directly proportional to that of primary injury, and the secondary injury can be delayed. In contrast to the majority of irreversible primary injuries, secondary mechanisms of injuries are considered promising therapeutic opportunities for patients with SCI. Secondary injury encompasses a variety of mechanisms, such as

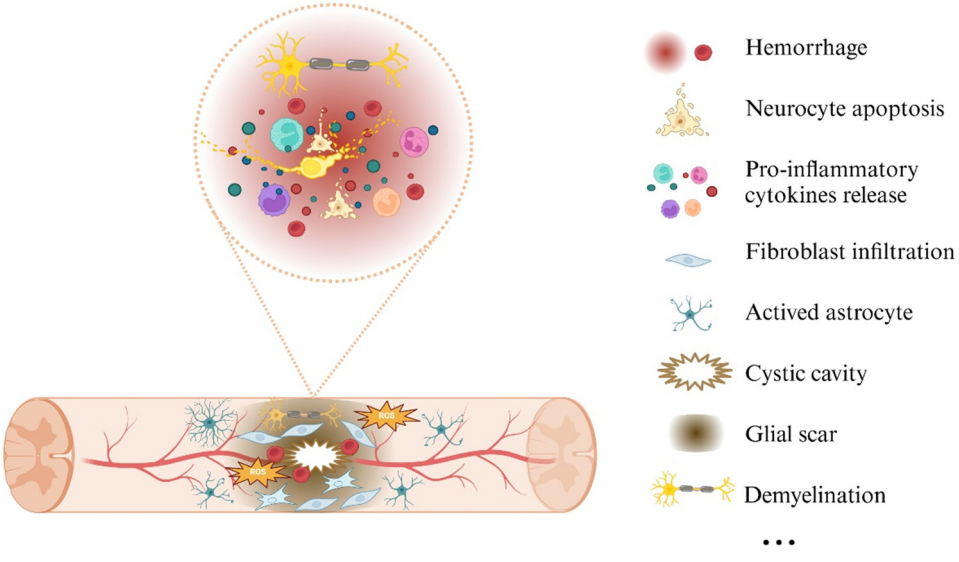

Figure 1: Pathophysiology of SCI. A series of pathological and physiological changes after SCI: hemorrhage, neurocyte apoptosis, demyelination, pro-inflammatory cytokines release, fibroblast infiltration, astrocyte activated, cystic cavity and glial scar formation, *etc*.

vascular injury and ischemia, exacerbated cell death, oxidative stress, immune infiltration and local inflammation, and neuroglial disturbances [2].

Here, we categorize the pathological characteristics of secondary injury into three pivotal pathophysiological events. First, the small blood vessels at the injury site suffer extensive damage, resulting in ischemia, hypoxia, and thrombosis. Vascular damage impairs the blood–spinal cord barrier (BSCB), leading to the extravasation of blood molecules or red blood cells. The ischemia-related event is the depletion of ATP, which, when exhausted, fails to maintain the concentration gradients of Na^+/K^+ and Ca^{2+}, ultimately leading to the formation of cytotoxic edema [11]. Vascularization and remodeling of blood vessels play a crucial role in neuronal repair and functional recovery after SCI. Secondly, reactive oxygen species (ROS) are generated during ischemia, and an excess of ROS overwhelms cellular antioxidant defenses, leading to oxidative stress. Oxidative stress is considered a hallmark of SCI injury, and previous studies have demonstrated that SCI is associated with a reduction in cellular glutathione and an increase in ROS [12]. Oxidative stress-induced cell membrane disruption and depolarization result in the opening of voltage-dependent channels, leading to an excessive influx of calcium ions. Calcium overload impairs crucial protein structures in the central nervous system (CNS) by hindering cellular respiration and activating calcium-dependent lipases and proteases, ultimately leading to damage. This series of events ultimately results in immune cell recruitment, cell apoptosis, synaptic connection disruption, axonal degeneration, shrinking, and demyelination [13]. Finally, primary injury to the spinal cord triggers an inflammatory response mediated by the immune system, which plays a dual role in protecting and promoting secondary damage after SCI. Persistent inflammation contributes to the death of tissue cells, damaged tissue is cleared by microglia and macrophages, leaving behind fluid-filled cavities and glial scars filled with star-shaped glial cells [14]. The expression of axon growth-inhibiting molecules, along with the formation of neural glial scars and cysts, becomes a physical barrier to prevent nerve fibers from reconnecting.

1.3 Approaches for SCI treatment

The treatment of SCI poses a significant challenge for healthcare professionals. Despite advances in medicine, most interventions for SCI are palliative, and functional recovery is rare. Current acute-phase treatment measures for SCI include pre-hospital emergency care, medication therapy, surgical intervention, and rehabilitation training [15]. Surgery is one of the preferred treatments for SCI, aimed at stabilizing the spinal column and performing intramedullary and extradural decompression if needed. Regarding medication therapy, neuroprotection is one of the most critical strategies for neurological recovery in the acute and subacute phases of SCI [16] The goal is to minimize and prevent the spread of secondary spinal cord lesions, thereby reducing cell apoptosis or necrosis and promoting neuronal and axonal survival. Another strategy for SCI repair is improving neural cell regeneration and restoring neural cell connections [17].

One approach involves administering high-dose methylprednisolone (30 mg/kg bolus followed by a continuous infusion of 4.24 mg/kg/h over 5 h) after diagnosis and initial stabilization. Early administration of methylprednisolone within the first 8 h after SCI can help reduce acute inflammatory responses. However, the current method of administering methylprednisolone is inefficient, and the use of high-dose methylprednisolone is associated with severe side effects such as sepsis, gastrointestinal bleeding, and pneumonia. Furthermore, studies suggest that it is detrimental to neurological recovery. Therefore, there is a need to seek more effective and safer alternative methods to overcome the limitations of existing SCI treatment methods.

A novel strategy for SCI treatment is to reduce acrolein concentrations in neural tissues. Oxidative stress, acrolein accumulation, and inflammation are hallmarks of secondary injury in SCI [18]. The accumulation of acrolein was the result from lipid peroxidation, and the acrolein can rapidly react with proteins, DNA, and phospholipids, leading to membrane damage, mitochondria dysfunction, and myelin disruption, ultimately exacerbating secondary injury in SCI. Liu *et al.* designed a polyethylene glycol-conjugated polypeptide (PPAH) with hydrazide groups on its side chains to ameliorate secondary injury following SCI [19]. The results of this study demonstrate that PPAH is capable of scavenging toxic aldehydes produced after traumatic SCI, and administration of PPAH to an SCI model rat exhibited anti-inflammatory effects, neuroprotection, and inhibition of demyelination.

2 Nanoparticle delivery targeting strategies for SCI treatment

In the treatment of SCI, the targeting capability of nanoparticles is as crucial as their efficacy. Nanoparticles can be

specifically designed to target the unique pathological processes and tissue structures associated with SCI. Targeted nanoparticles are capable of navigating within the body to the damaged spinal cord tissue, allowing therapeutic agents to be delivered more precisely to the SCI site, thereby reducing the impact on non-target tissues and lowering the risk of side effects. This is particularly important for SCI treatment, as the neural tissues surrounding the spinal cord are highly sensitive to drugs, and improper drug distribution may lead to additional damage. We summarized some important targeting strategies for SCI treatment in Figure 2.

2.1 Responsive targeting strategy

The responsive targeting strategies of nanoparticles in SCI treatment mainly include pH-responsive targeting and matrix metalloproteinases (MMPs)-responsive targeting. In SCI, the environment is typically acidic due to cellular hypoxia, death, and inflammatory responses, which can be exploited for the design of drug release triggers. For instance, in a study by Zhu *et al.*, nano-scale layered double hydroxides (LDHs) were utilized to achieve targeted drug release in the acidic microenvironment of SCI [20]. These layers can intercalate different anions, forming nanocomposites that release the entrapped drugs under low pH conditions. The study of Yang *et al.* designed a pH-responsive mesoporous polydopamine nano-delivery platform that targets and aggregates in the acidic microenvironment altered in the SCI site for drug release [21]. Liu and his colleagues developed an *in situ* reaction-generated aldehyde-scavenging polypeptides (PAH)-curcumin conjugate nanoassemblies for SCI treatment [22]. In response to oxidative and acidic microenvironment of SCI, these nanoassemblies can release PAH and curcumin, then produce a neuroprotective effect by scavenging toxic aldehydes and oxygen species in SCI rat model.

MMPs are a group of proteases that are highly active at the site of SCI. Nanoparticles responsive to MMPs can undergo structural changes or localized degradation under the action of MMPs, allowing for the selective release of drugs in the damaged area and achieving localized therapy. In the study by Zhang *et al.*, gelatin-coated mesoporous silica nanoparticles (MSNPs) were used to carry drugs, and the degradation of gelatin by MMPs facilitated the release of drugs to the target area [23]. Similarly, in a study by Rao *et al.*, peptides recognized and cleaved by MMPs were used to modify nanoparticles, a responsive release method that synchronizes the release of anti-inflammatory factors with the inflammatory response, providing a new approach for the treatment of SCI [24].

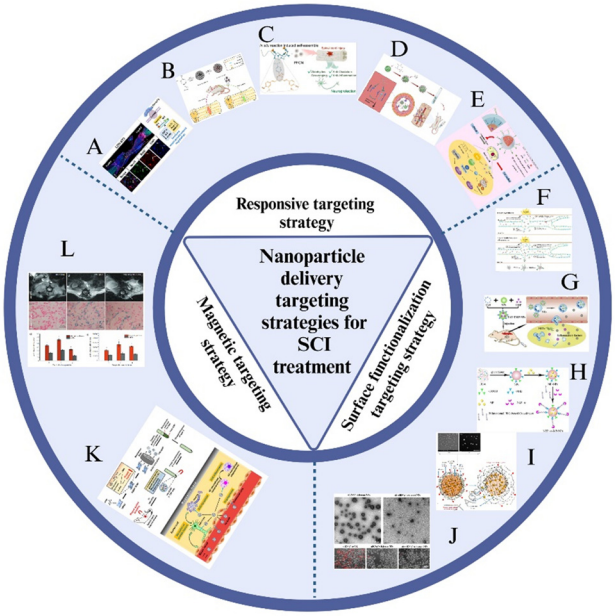

Figure 2: Nanoparticle delivery targeting strategies for SCI treatment. (a)–(e) Responsive targeting strategy [20–24]. Copyright 2021, ACS Nano, copyright 2023, J Nanobiotechnology, copyright 2024, ACS Nano, copyright 2021, Nanomedicine, and copyright 2019, J Mater Chem B. (f)–(j) Surface functionalization targeting strategy [25–29]. Copyright 2022, Free Radic Biol Med, copyright 2021, J Control Release, copyright 2019, J Nanobiotechnology, copyright 2017, Drug Dev Ind Pharm, and copyright 2017, J Nanobiotechnology. (k), (l) Magnetic targeting strategy [30,31]. Copyright 2018, Nano Lett, and copyright 2015, Neural Regen Res.

2.2 Surface functionalization targeting strategy

The surface of nanoparticles can be chemically modified to introduce specific ligands, such as peptides, antibodies, and proteins, to confer specific targeting capabilities. The team of Herr developed a novel approach for SCI treatment by injecting a hydralazine conjugated to folate (F-HDZ) medication in a model rat of SCI [25]. Since the folate can specially binding with folate receptors 1 and 2 located on the membrane of activated macrophages, the hydralazine can target deliver to the immune cells in injury regions of SCI. This system can dramatically reduce acrolein concentration in the site of injury and effectively eliminate the side effect of hypotension. Li *et al.* conjugated the cell-penetrating HIV trans-activator of transcription peptide to human serum albumin nanoparticles, leveraging the

phagocytic action of intravascular neutrophils to rapidly recruit the nanoparticles to the site of SCI inflammation response [26]. Lin *et al.* targeted the nanoparticles to CNS by binding NEP1-40 peptides to inhibitory protein receptors on the surface of oligodendrocytes [27]. Wu *et al.* utilized albumin modification to target albumin receptors, thereby enabling the precise release of drugs at the site of inflammation [28]. Gao and Li conjugated nanoparticles with mouse IgG antibodies to promote Fc receptor-mediated phagocytosis of M1-polarized macrophages *in vitro*, targeting M1 macrophages to reduce the expression of inducible nitric oxide (NO) synthase after SCI [29].

2.3 Magnetic targeting strategy

By incorporating magnetic materials into nanoparticles, it is possible to use external magnetic fields to guide the nanoparticles to specific areas. Iron oxide nanoparticles (IONPs) are one of the most common types of magnetic nanoparticles, known for their good biocompatibility and stability, and can be used as carriers to deliver therapeutic agents to the site of SCI. Kim *et al.* prepared simulated exosome (EXO) nanovesicles containing IONPs to carry therapeutic growth factors, precisely delivering them to target cells [30]. In another study, mesenchymal stem cells loaded with superparamagnetic IONPs were targeted to the SCI site [31]. Superparamagnetic IONPs exhibit stronger magnetization properties, meaning they can achieve saturation magnetization under lower external magnetic fields.

3 Nanoparticle delivery systems for SCI treatment

The majority of drugs used to treat SCI suffer from poor stability in the vascular system, off-target organ accumulation, or inability to cross the BSCB to reach the site of injury, limiting their effectiveness [13]. This has resulted in promising preclinical drugs for SCI treatment failing to accumulate in the patient's tissues and play a role in treating the disease [32]. Therefore, there is an urgent need to develop new non-invasive treatment approaches to address the delivery issue of SCI-related drugs. Nano-delivery systems offer a potential non-invasive and multi-modal therapeutic strategy with the following advantages. First, nano-carriers may improve drug bioavailability through targeted delivery and prolonged circulation time. Second, nano-carriers can pass through barriers such as the BSCB and cell membrane walls. In addition, the larger surface area allows compounds (such as targeting moieties or drugs) to bind to the surface. Moreover, the nano-carriers themselves, in the absence of drugs, can modulate the immune response toward an anti-inflammatory and pro-regeneration phenotype through multi-modal mechanisms that affect various inflammatory responses [33]. Therefore, the delivery of nano-systems represents an attractive strategy for SCI treatment, with many nano-materials being studied and showing promising results. The following sections will discuss the latest SCI nano-delivery strategies based on different types of nanoparticles, as described and shown in Figure 3.

3.1 Polymer nanoparticles for SCI treatment

Due to their excellent biocompatibility, polymer nanoparticles are the most commonly used nanocarriers for drug delivery to the spinal cord [34]. Among them, polylactic acid-hydroxy acid copolymer (PLGA) is an advantageous drug delivery system in SCI because of its strong controllable drug release, resistance to external factors, and biodegradable properties. It hydrolyzes into lactic acid and glycolic acid, and is further metabolized into water and carbon dioxide, and eventually excreted by the lungs. Its safety has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency and it is now officially listed as a pharmaceutical excipient [35]. Additionally, its material characteristics can be adjusted, such as lactide ratio, molecular weight, and pore size, to control the degradation rate and drug release rate of the nanoparticles, thus meeting different therapeutic needs. In recent years, PLGA hydrogels, microspheres, and nanoparticles have been used in spinal cord regeneration and functional recovery [36]. It has been demonstrated that PLGA–cell interactions are an effective strategy for improving therapeutic benefits in animal models. For example, Azizi *et al.* prepared ChABC enzyme-loaded PLGA nanoparticles (PLGANPs) for SCI treatment [37]. After treatment, these nanoparticles promoted myelin formation and degradation of glial scars in model animals. Similarly, PLGA-based biodegradable nanoparticles were used to deliver antioxidant enzymes, protecting mitochondrial function from oxidative stress and preventing cytochrome c release, inhibiting caspase-3 activation, and protecting the spinal cord from apoptosis and further degeneration [38]. This suggests that it can be a useful nanomedicine in the early stages of SCI to reduce the impact of primary injury

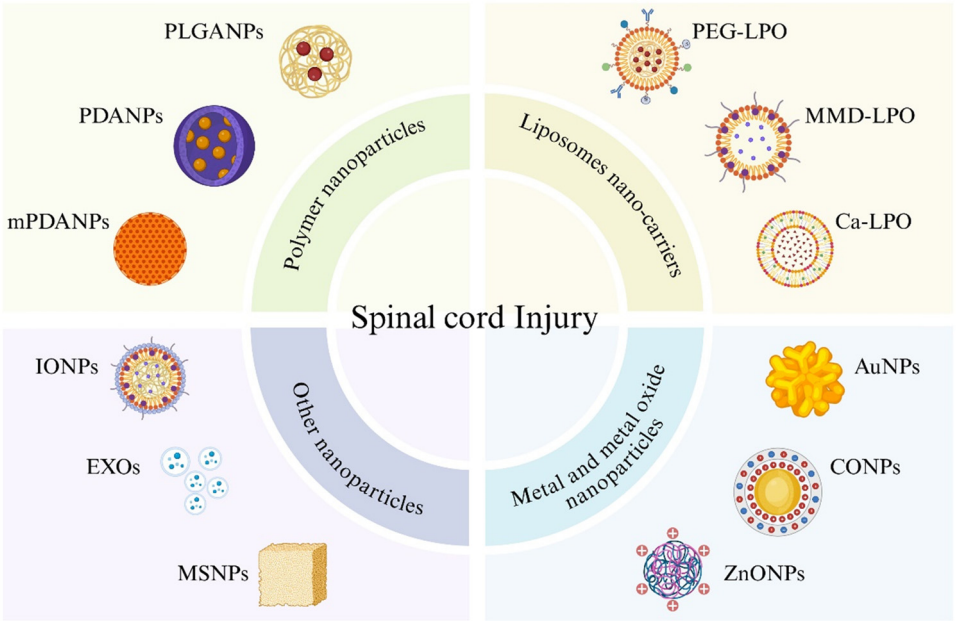

Figure 3: Schematic of the classification of nanoparticles for SCI repair. Note: polylactic acid-hydroxy acid copolymer nanoparticles, PLGANPs; polydopamine nanoparticles, PDANPs; mesoporous polydopamine nanoparticles, mPDANPs; poly ethylene glycol coated liposomes, PEG-LPO; macrophage membrane-disguised liposomes, MMD-LPO; cationic liposomes, Ca-LPO; Au nanoparticles, AuNPs; cerium oxide nanoparticles, CONPs; zinc oxide nanoparticles, ZnONPs; mesoporous silica nanoparticles, MSNPs; iron-oxide nanoparticles, IONPs; exosomes, EXOs.

responses and promote neural functional recovery. Additionally, studies have shown that MP-encapsulated PLGA nanoparticles are more effective than systemic delivery of free MP in continuous delivery for SCI [39]. These nanocarriers are suitable candidates for neuroprotection and axonal regeneration. However, the limitation of PLGANPs is their low drug loading capacity, which requires multiple preparations and precise designs to achieve high drug loading, indicating that PLGA preparation is relatively complex and requires high technical and equipment conditions. Additionally, as PLGA is negatively charged, it may limit its binding and delivery of some cationic drugs.

Chitosan nanoparticles (CSNPs) primarily interact with other negatively charged biomaterials, such as natural polysaccharides and growth factors, through their cationic properties, allowing them to form composite materials that retain biological activity [40]. This property also enables it to interact with negatively charged membranes in the blood–brain barrier, allowing it to cross the physiological barriers [41]. Utilizing these properties, Li *et al.* designed chitosan-modified hollow manganese dioxide nanoparticles for delivering resveratrol to help it cross the blood–brain barrier and exhibit slow-release drug delivery to mitigate oxidative stress and reduce inflammation to exert neuroprotective effects [42]. Sabourian and her colleagues reported a pH-responsive lipopolysaccharide-bonded chitosan-quantum dots/poly acrylic acid nanoparticles applied for SCI therapy in rats [43]. Due to the ligand of lipopolysaccharide, which can physically interact with the receptor of toll-like receptor 4 located on the membrane of reactive astrocytes, the smart nanoparticles can target reactive astrocytes to prevent of glial scar formation and inhibition of axon outgrowth. Upon uptake by reactive astrocytes, the nanoparticles encounter the acidic pH within early to late-endosomes, triggering nanoparticle swelling and facilitating endosomal escape, thereby enabling the safe delivery of bioactive therapeutics to the cell nucleus. Fang and Song's research team used chitosan as a nanoshell for delivering CeO_2 nanoparticles [44]. The nanosystem was observed to increase its own regeneration and neuroprotective activity in SCI repair, making it a promising biocompatible material for SCI repair.

Polydopamine nanoparticles (PDANPs) are considered as an ideal biomaterial for biomedical applications due to their excellent biocompatibility and inherent antioxidant properties [45]. Their monomer, dopamine, is a natural neurotransmitter in the brain. The antioxidant or anti-inflammatory mechanism of PDANPs is to eliminate the generated ROS. Compared to other drug delivery systems, PDANPs have several advantages. First, the preparation of PDANPs is simple and does not require organic solvents, providing great convenience for their research and application. Additionally, due to the excellent adhesion of PDANPs, they can also coat various types of organic and

inorganic nanoparticles. Surface chemical functional groups can perform secondary modifications on the surface of polydopamine under alkaline conditions, which gives polydopamine great potential and advantages in nanoparticle preparation and functionalization. In one study, by using the broad-spectrum cytokine adhesion properties of PDANPs (TNFα, IL-6, and IL-10), neuronal survival and motor recovery were promoted in an injured rat model [46]. Although PDANPs have the aforementioned advantages, their preparation methods and quality control still need to be further optimized and standardized. In addition, because PDANPs have strong self-oxidation, their long-term stability also requires further research and improvement [47].

Mesoporous polydopamine nanoparticles (mPDANPs) comprise a plentiful mesoporous size cavity structure in the surface which offers a large surface area for drugs and results in a greatly increase in the drug loading capacity of the mPDANPs delivery system. Shi and his colleagues developed mPDANPs loaded with rapamycin for SCI therapy in model rats [48]. Rapamycin can decrease ROS production by inhibiting the mammalian target of the rapamycin protein, which further attenuates the secondary inflammation, reduces neural tissue damage, and accelerates locomotor recovery after SCI. The solubility of rapamycin is extremely low in the water, and that greatly hinders its applications. The mPDANPs delivery system can not only improve the solubility of rapamycin but also increase the drug loading capacity. This study demonstrates that mPDANPs nanoparticles can sustain release of rapamycin, remove excess ROS, and finally promote tissue regeneration, neurogenesis, and motor function recovery.

3.2 Liposomes (LPOs) nano-carriers for SCI treatment

LPOs can load different types of drugs in their hydrophobic bilayer and hydrophilic cavity, protecting the payload from degradation, ensuring its accumulation at the site of the lesion, and enhancing the therapeutic effect [49]. As an effective nanodrug carrier, LPOs has been applied in clinical practice. When using high-dose drugs for treating SCI, the nanocarriers such as LPOs can significantly reduce systemic side effects by enabling site-specific drug precise delivery to the injured spinal cord. Currently, some liposomal drugs have been clinically approved, including anticancer drugs (*e.g.*, doxorubicin liposome injection), antifungal drugs (such as liposomal amphotericin B injection), and drugs for high cholesterol (such as LipoPtyl). The use of these drugs shows that LPOs has good biocompatibility and safety in clinical treatment, and can achieve targeted delivery and prolong the half-life of drugs. In SCI treatment, some studies have explored the possibility of using LPOs as carriers to deliver drugs such as inhibitors of macrophage migration inhibitory factor (MIF), nerve growth factors, and anti-inflammatory agents, and have made some progress. The team of Saxena developed a poly ethylene glycol 2000-coated LPOs (PEG-LPOs) encapsulating a small molecular inhibitor of MIF (Chicago sky blue, CSB) to investigate the therapeutic window and the effects of liposomal CSB after SCI [50]. By administering the LPOs intravenously 48 h post-injury in SCI model rats, they found that this liposomal CSB can improve BSCB integrity and protect axons from demyelination. Another example of a LPO preparation for spinal cord regeneration is the vitamin E succinate-grafted ε-polylysine nanoparticles prepared by Zhang *et al.*, which were precompressed with pOXR1 and loaded into cationic liposomes [51]. These nanostructures protect DNA from DNaseI degradation, maintain its activity, and successfully transport it into cells. Therefore, the nanosystem reduces neuronal apoptosis, attenuates oxidative stress, inhibits inflammation, and promotes functional recovery after acute traumatic SCI. Tang *et al.* proposed a different approach by manufacturing macrophage membrane-disguised LPOs encapsulating minocycline [52]. Note that the nanocarrier can prolong drug circulation time, accumulate at the site of SCI, enhance therapeutic effects, and exhibit anti-apoptotic activity. The drug release from LPOs is usually achieved through LPO dissolution, rupture, or permeation. However, this release mechanism may not provide sustained and controllable drug release. To achieve more precise drug release control, responsive elements (such as temperature, pH, and enzymes) need to be introduced on LPOs or auxiliary techniques (such as magnetic or light stimulation) need to be used for adjustable drug release. Although, LPOs have the advantage of low immunogenicity, nontoxic, highly engineerable, biodegradable, and FDA approval, they were still limited to clinical application by the high uptake of liver and spleen.

3.3 Metal and metal oxide nanoparticle delivery systems for SCI treatment

Au nanoparticles (AuNPs) can be used for drug delivery, biological imaging, and photothermal therapy [53]. In SCI, AuNPs can be used for both local and systemic drug delivery and treatment. AuNPs have the properties of inertness and non-immunogenicity, good biocompatibility and biodistribution, and ease of preparation and modification. They can be easily synthesized and functionalized with different biomolecules without changing their

biological activity. AuNPs can achieve the effects of reducing drug toxicity and improving low bioavailability by combining drug delivery [54]. AuNPs have been shown to enhance neuronal differentiation of embryonic spinal cord-derived neural stem cells (NSCs), promote nerve axon regeneration, and reduce astrocyte differentiation thereby inhibiting glial fibrillary acidic protein barrier formation. In addition, AuNPs also contribute to the polarization regulation of monocyte-derived macrophages [55].

Magnesium–aluminum nanoparticles have good biocompatibility, vegetative-neurological and anti-inflammatory properties. LDH is a type of clay with anionic and anion exchange properties, and LDH has achieved remarkable performance in accelerating neural differentiation and NSC migration. Zhu *et al.* developed Mg/Al-LDH nanoparticles carrying NT3 for SCI repair in completely transected and excised mice [20]. This study demonstrates that LDH-NT3 targeted transforming growth factor (TGF)-β receptor 2 to promote the expression of TGF-β2, and further accelerates axonal growth and neural regeneration, and the data show that the Mg/Al-LDH nanoparticles loaded with NT3 achieved better recovery effects than LDH itself.

Cerium oxide nanoparticles (CONPs) have good antioxidant properties and biocompatibility, and can be used to promote cell proliferation and treat many diseases, including Alzheimer's disease, Parkinson's disease, and SCI [56]. In SCI treatment, the self-catalytic ability of CONPs is of great significance. The self-catalytic effect of CONPs in SCI treatment refers to their ability to catalytically decompose hydrogen peroxide (H_2O_2) in the presence of H_2O_2, producing oxygen free radicals and hydroxyl free radicals, thereby achieving self-repair [57]. This self-catalytic reaction can degrade H_2O_2 into water and oxygen, and eliminate excessive H_2O_2, thereby protecting the cells in the SCI site from oxidative stress damage. In addition, CONPs can also act as antioxidants, further protecting cells at the SCI site by clearing free radicals and other harmful substances produced within cells [58]. This antioxidant effect can reduce cell damage and inflammatory reactions caused by oxidative stress, thereby promoting the repair and regeneration of SCI. Therefore, the self-catalytic ability of CONPs is of great significance in SCI treatment, as it can help maintain cell homeostasis and promote self-repair.

Zinc oxide nanoparticles (ZnONPs), as a type of semiconductor nanomaterial, possess unique photocatalytic and electrocatalytic properties, making them promising photocatalysts for promoting neural regeneration and repair after SCI by generating electrons and holes after absorbing light energy and activating intracellular signaling pathways. Some studies suggested that the PI3K/Akt signaling pathway may play a crucial role in the protective effects of ZnONPs after SCI [59]. Additionally, ZnONPs can act as an electrocatalyst to release NO at the injury site, which is an important neurotransmitter for promoting neuronal growth and regeneration in the spinal cord. Moreover, ZnONPs also exhibit anti-inflammatory, antioxidant, and pro-angiogenic capabilities, indicating their potential as a novel therapeutic approach for SCI. As a drug delivery system, ZnONPs can be easily prepared for low-cost and large-scale production, and drug molecules can be adsorbed and embedded into their surface and inner pores for efficient drug delivery. However, the control of drug release from ZnONPs is relatively difficult and depends on various factors, such as pore size, surfactants, and drug molecule structures.

3.4 Other nanoparticle delivery systems for SCI treatment

MSNPs can be used for drug delivery and treatment by loading various drugs due to their high porosity [60]. However, their application is greatly restricted due to their non-biodegradability. Moreover, research has shown that MSNPs can worsen the disruption of the BSCB, increasing the expression of heat shock proteins and ubiquitin after SCI, which is detrimental to spinal cord recovery.

EXOs are a type of extracellular vesicle secreted by multiple kinds of cells and function as intercellular messengers through bioactive substances (such as proteins, lipids, and nucleic acids) enclosed within them. Due to their ability to inducing axon regeneration, supporting neuronal survival, and modulating neuroinflammation, cells including stem cells, Schwann cells, and olfactory ensheathing cells (OECs) have been investigated as potential therapies for SCI. Guo *et al.* reported that mesenchymal stem cell-derived exosomes (MSC-Exo) could pass through the blood–brain barrier and migrate to the area of SCI [61]. When given intranasally, the MSC-Exo loaded with phosphatase and tensin homolog small interfering RNA dramatically enhanced axonal growth and neovascularization, leading to functional recovery in SCI rats. In addition, Hong Fan isolated EXOs from purified OECs supernatant by PEG-based method and nanoparticle tracking analysis, and they transplanted these OEC-derived EXOs and the conditioned medium of OECs to rats to explore a new therapeutic strategy for SCI based on EXO-immunomodulation [62]. This research manifests that the OECs-derived EXOs can efficiently inhibit the pro-inflammatory polarization of macrophage/microglia, promote the neuronal survival, increase preservation of axons, and facilitate functional recovery after SCI.

In summary, these nanoparticle delivery systems have demonstrated a variety of advantages in SCI treatment, but they also face some challenges. We have summarized the advantages and disadvantages of various nanoparticle delivery systems in SCI treatment in Table 1. Future research needs to further optimize the preparation methods and quality control of these nanoparticles to enhance their application prospects in SCI treatment.

4 Problems and deficiencies in nanoparticle delivery systems

Over the past decade, remarkable advancements have been achieved in the development of nanomaterial for SCI repair. Scientists have designed various nanoscale drug delivery systems for SCI treatment by selecting suitable nanomaterials, and fine-tuning their particle size and surface properties. For example, drug loading and release can be efficiently achieved through the use of polymer nanoparticles, lipid nanoparticles, or metal nanoparticles. These nanoparticles enhance drug solubility and stability, facilitating the passage of drugs across the blood–brain barrier, augment drug accumulation in the injury area, and improve drug distribution in the central nervous system. The delivery of growth factors, cytokines, or gene therapy drugs *via* nanoparticles can stimulate neural cells survival and regeneration. Additionally, nanoparticle drug delivery systems can modulate immune responses, mitigate inflammation, and provide analgesic effects, thereby minimizing secondary damage and inflammation after SCI. Preclinical studies with nanomaterials have demonstrated promising potential to change SCI treatment. However, upon scrutinizing recent research on nanoscale drug delivery for SCI, certain challenges and limitations have come to light.

Table 1: Comparative analysis of various nanoparticle delivery systems for SCI treatment

Type of nanoparticle delivery system	Advantages	Disadvantages
PLGA	1. Excellent biocompatibility 2. Controllable degradation rate and drug release 3. Ability to combine with various drugs or targeting molecules	1. Limited drug loading capacity 2. Complex preparation requiring advanced technology and equipment 3. Negatively charged, limiting binding to cationic drugs
CSNPs	1. Cationic properties enable binding with negatively charged biomaterials 2. Ability to cross the blood–brain barrier 3. Targeting capability to inhibit glial scar formation	1. pH responsiveness may be affected by the *in vivo* environment 2. Long-term stability needs further investigation
PDANPs	1. Good biocompatibility and antioxidant properties 2. Simple preparation without organic solvents 3. Ability to bind multiple cytokines to promote nerve regeneration	1. Strong auto-oxidation, affecting long-term stability 2. Preparation methods and quality control need optimization
mPDANPs	1. High drug loading capacity 2. Improved drug solubility 3. Sustained drug release	1. Potential toxicity issues need investigation 2. Complex preparation process
LPO **nanocarriers**	1. Protect drugs from degradation 2. Targeted delivery, reducing systemic side effects 3. Widely used in clinical applications	1. Difficult to achieve controlled drug release 2. High uptake by liver and spleen 3. Stability issues
AuNPs	1. Excellent biocompatibility 2. Easily modifiable 3. Promote neuronal differentiation and axon regeneration	1. High cost 2. Unclear *in vivo* metabolism and excretion
CONPs	1. Catalytic antioxidant ability 2. Decompose H_2O_2 to protect cells	1. Long-term stability needs investigation 2. Potential for metal ion accumulation
MSNPs	1. High porosity for loading multiple drugs 2. Surface modifiability for targeted delivery	1. Non-biodegradable 2. Potential to disrupt the BSCB
EXOs	1. Natural biocompatibility 2. Ability to cross the blood–brain barrier 3. Immunomodulation and promotion of nerve regeneration	1. Low extraction efficiency, difficult to produce at scale 2. Complex mechanisms need further investigation

Currently, there is a dearth of comprehensive and systematic research on nanoparticle drug delivery for SCI, which constrains our understanding of the optimal design of nanoparticle drug delivery systems, the selection of most efficacious drugs, and the development of superior delivery strategies. Moreover, most studies focus on short-term efficacy evaluation, neglecting to assess long-term outcomes. Gaining the long-term efficacy of nanoparticle drug delivery systems is crucial for determining their actual application in the treatment of SCI. In addition, the safety and toxicity of nanoparticles as drug delivery vehicles require further research. Although many studies have reported the biocompatibility of nanoparticles, more comprehensive toxicity evaluations is still needed to ensure their safety in clinical applications. Moreover, the therapeutic strategies for SCI that have shown promise in animal models require further extensive research before nanoparticles can be effectively translated into clinical therapies for SCI.

5 Prospects

To tackle these challenges, the following directions and strategies can be considered. First, strengthen interdisciplinary collaboration: research on nanoparticle drug delivery systems for SCI requires collaboration across multiple disciplines such as materials science, biology, and pharmacy. Strengthening collaboration and communication between disciplines can promote new ideas and innovations and help solve current challenges. Second, systematic research design: in order to better understand the efficacy and mechanisms of nanoparticle drug delivery systems, we need to design more systematic and comprehensive research. This includes comparative evaluations of different nanoparticle materials and drugs, studies on various delivery strategies, and evaluations of long-term effects. For instance, polyethyleneimine (PEI) and poly-lactide-co-glycolide (PLGA) are polymeric nanoparticles normally used in gene delivery. PEI-based nanoparticles have the advantage of high delivery efficiency, but induce high cytotoxicity duo to its high positive surface charge. PLGANPs have been clinically approved by the FDA for the good characteristics of biodegradability and biocompatibility, despite their inefficiency in gene delivery. When combined with arginine-modified PEI polymers with PLGANPs, co-transfecting the two polymeric nanoparticles system, in primary human astrocytes, the nuclear localization of plasmid DNA and the gene expression was greatly improved without inducing toxicity to astrocytes or neurons [63]. Third, long-term effect evaluation: to assess the long-term effects of nanoparticle drug delivery systems, we need to conduct more long-term follow-up studies. This will provide a more comprehensive assessment of treatment efficacy and help determine the best treatment options for patients with different types and degrees of SCI. Additionally, further research should focus on the safety and toxicity assessment of nanoparticle drug delivery systems. This can include *in vitro* and *in vivo* experiments to evaluate the biocompatibility, cell toxicity, immune reactions, and long-term systemic toxicity of nanoparticles. Employing a range of methodologies, such as cell experiments, small animal models, and histological analysis, can comprehensively evaluate the safety of nanoparticle drug delivery systems and provide strong support for their further clinical translation. Lastly, develop multifunctional nanoparticle drug delivery systems: when designing nanoparticle drug delivery systems, multifunctionality can be considered to further improve treatment efficacy. For example, combining drug delivery with imaging functions can achieve real-time monitoring and evaluation of treatment efficacy; combining the delivery of bioactive molecules, such as growth factors or gene therapy, can promote nerve regeneration and repair; and combining other drug delivery systems, such as hydrogels and nanoparticles, can enhance the sustained release of drugs. In summary, while research on nanoparticle drug delivery systems for SCI has made significant strides, certain challenges remain. Through interdisciplinary collaboration, systematic research design, long-term effect evaluation, and safety and toxicity assessment, we can overcome these challenges and gradually implement the nanoparticle drug delivery systems in SCI treatment. Such advancements will provide more effective therapeutic options for SCI patients, thereby enhancing their quality of life and facilitating functional recovery.

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