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Numerous nanoparticles as drug delivery system to control secondary immune response and promote spinal cord injury regeneration

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ABSTRACT

Spinal cord is the major communicating system between the brain and the body, injury to the spinal cord will completely cut or damage the information and signal exchanges between brain and different parts of the body. Spinal cord injury (SCI) regulates the physical, cellular, and molecular function of the body. SCI could cause impairment in blood flow, breathing, temperature, body pressure and sensory appendages. Thus, serious steps must be taken to prevent and heal SCI in human body by severe damages and shocks. Nanoparticles are emerging in the field of biomedicine and gained attention as drug carriers, imaging, mediator for supportive chemical and accelerating the immunes cells. In recent time, nanoparticles are gaining interest towards improving or modifying the immune system for the treatment of SCI. The drug delivery efficacy of nanoparticles makes them easy to incorporate and load with molecules used for the treatment of SCI, also it enhances the recovery time by targeting localization, altering the signalling pathways and cellular uptake. Researchers are using nanoparticles with different synthesis methods, morphology, incorporating materials, stability and site of target. But exploring the ability of nanoparticles towards improving the healing mechanism, regeneration of SCI and accelerating the treatment time is the major necessity. Thus considering the lesser exposure of nanoparticles in the area of spinal cord injury and regeneration of cells, the present review give a brief knowledge about the different types of nanoparticles and its role in SCI therapy.

1. Introduction

Globally, around 40 to 80 new cases per million population are reported with spinal cord injuries (SCI) every year. The aetiology of SCI is complicated as it interrupts bodily, cellular and molecular functions, the intensity of which varies on the severity and type of injury [1,2]. The cause of SCI may either traumatic, which include occupational injuries, road accidents, sports injuries, injuries from fall and violence, or non-traumatic which include pathological cause by tumour, communicable diseases, musculo-skeletal diseases, and hereditary diseases. Spinal cord lesion affects sensory and motor control of appendages, and also involuntary regulation, the effect of which extended to impair respiration, blood circulation, pressure and temperature control, digestion and excretion as well as sexual function of the body [3]. Currently, two different tactics; regenerative medicine and rehabilitation are followed by the medical professionals to recover from motor and sensory dysfunction after SCI. However, rehabilitation methods such as motor training and electrical stimulation, and regeneration of cells using stem cells have not resulted in efficient recovery from SCI [4]. This implies the necessity to search new treatment methodologies with help of advent scientific technology, even though there has been immense volume of SCI research.

The nanotechnology discipline deals with extremely small particles with size ranging from 0.1 to 100 nm. Nanoparticle possesses wide variety of functions and studied in different area of research including chemistry, physics, engineering, material science and biology [5,6]. Nanoparticles (NPs) can be synthesized using different types of organic and inorganic materials namely, polymers, liposomes, metals, metal

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oxides, silica, biological molecules, etc [7–12]. Nanotechnology in medical field covers prevention, diagnosis, and treatment of diseases and traumatic injury, thereby preserve, and improve the human health [12]. Using nanoparticles for cell therapy and tissue engineering for the treatment of SCI will increase the success rate. Incorporating nanoparticles with cell components, manipulation of cell growth, differentiation, and construction of extracellular matrix will improve SCI treatment strategies [13]. In the present scenario, prudently designed nanoparticles in particular dendrimers, carbon fullerenes, nano shells, composites, nanotubes, nanowires, scaffolds and micelles are used to target injured area (Fig. 1).

In SCI treatment, nanoparticles are majorly used for targeting specific cell and tissues for drug delivery along with imaging [5]. Therapeutic applications based on NPs offer numerous distinct strategies aimed for non-invasive recovery from SCI and associated health issues. In the present review, brief knowledge is given on the type of NPs and its forms in association with functional recovery from SCI, that have been focused by research studies.

2. Limitation of SCI treatment methods

The spinal cord connects the central nerves system to peripheral nerves system and peripheral tissues. Cells reside in spinal cord are neurons and non-neuronal glial cells including microglia, oligodendrocytes, and astrocytes. Besides, ependymal cells and endogenous stem cells also existed [5]. Complications in repairing SCI injuries are majorly due to intrinsic and extrinsic factors. In former, neurons have less regenerative ability owing to deficient growth promoting signals, and insufficient availability of subcellular machinery to enable cone formation and axonal elongation [14].

Immediately after SCI, cells of the immune system actively cross the blood brain barrier (BBB) or blood-spinal cord barrier (BSCB) to eliminate the dead cells and debris. But this process activates the local proinflammatory responses, which further potentiate oligodendrocyte and cause neuron death, demyelination of axon and oxidative stress [15]. After SCI, the astrocytes switches to reactive state and accumulates densely around the site of injury in the glial scar and transforms into barrier like structure [14], to attempt wound repair, but in turn act as a physical barrier. In addition, increased fibroblast response due to SCI tend to form matrix components which further obstruct neural regeneration [14]. Chodroitin sulfate proteoglycans secreted by meningeal cells or scar-like formation by fibrous natured connective tissues also act as barrier [16]. Recent studies evidences that axon regeneration may not be occurred even after preventing the astrocytes and glial scar which are thought to have debated role in preventing axon regeneration [2]. However, overall defence mechanism in human body blocks the regenerative process at the injury site.

Typically, after SCI, patients undergo surgical treatment but less opt for therapeutic options for regeneration, because of limitations in the later [17]. Rather, neuroprotective drugs such as indomethacin and ibuprofen (progress motor recovery), methylprednisolone (supress inflammatory cytokines), granulocyte colony-stimulating factor (enhance migration and production of endothelial cells), riluzole (hinderance of glutamate transporter activity), minocycline (protect nerve function), tetramethylpyrazine (inhibit inflammation, reduce apoptosis, blood vessel dilation) and monoclonal antibodies to inhibit neurite growth are used in SCI treatment [18,19]. Apart from this, myelin-associated inhibitor and fibroblast growth factor are broadly in used in clinical therapy [19]. Usually, high doses of these drugs are requiring ensuring local accumulation and satisfactory efficacy, in turn cause hazardous off-target toxicity. High doses of methylprednisolone were reported to root for immunosuppression and increased diseases susceptibility [20].

Uncertainty of drugs target, off-target drug accumulation and inability to cross BSCB are the major challenges, because of which the existing treatment methodologies to remove regenerative barriers or promote the axon myelination and elongation often failed to reach the site of injury [17]. Adopting such ineffective methodologies to treat serious pathophysiology of SCI is a major challenge over years. Consequently, the necessity to develop new therapeutic strategies, to address proinflammatory reactions and complicated immune response, are being increasing [18].

3. Nanoparticle drug delivery system: A better option for SCI treatment

Nanoparticles drug delivery system, a novel approach in SCI treatment to reduce degradation, improve absorption, reduce side effects, enhance distribution, expand the bioavailability of drugs [19,21]. The physiochemical properties of nanoparticles such as size, configuration, and surface chemistry can be personalised to achieve successful treatment outcomes. Diverse nanocarriers include polymer NPs, solid lipid NPs, peptide polymer-based NPs, metallic NPs, silica NPs, chitosan NPs and dendrimers are studied for varying drug delivery applications (Table 1). Such non-invasive methods lower the risk of off-target

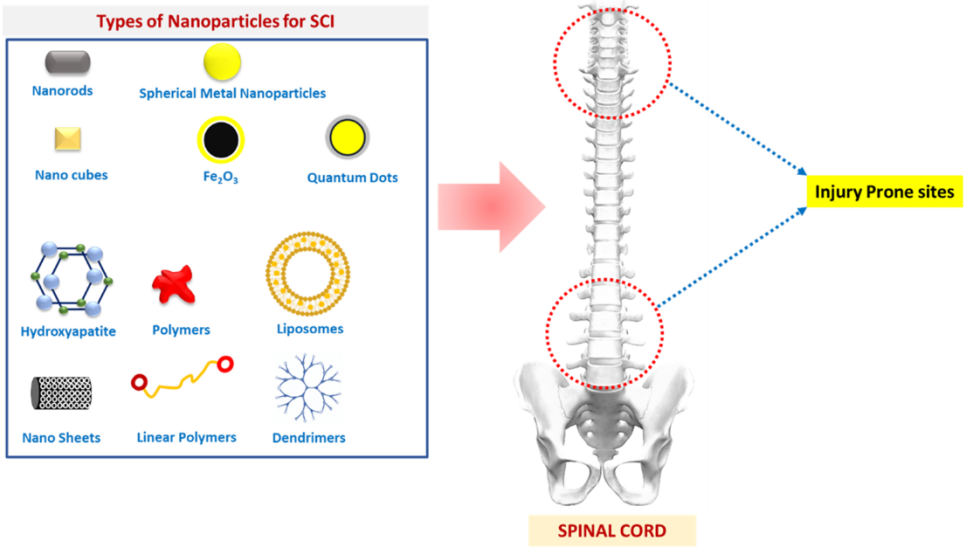

Fig. 1. Schematic representation of different types of nanoparticles suggested for Spinal Cord Injury Treatment and Diagnosis.

Table 1
Various types of nanoparticles and their role in curing spinal cord injury. Table was prepared based on the review article [4]. NPs – nanoparticles

Major types of nanoparticles	Scientific observations	Reference
Inorganic nanoparticles		
	Iron oxide NPs in directed the neurite outgrowth towards the applied external magnetic field	[63,64]
	Iron oxide NPs enhanced the movement of Schwann cells by crossing Astrocyte-Schwann cell boundary	[65]
	Magnetic chitosan nanocombosite scaffold effect on the viability of schwann cells to enhance the regeneration of sciatic nerve	[66]
	Superparamagnetic iron oxide NPs used to image the neuron stem cells	[67]
	Superparamagnetic iron oxide NPs along with electronspun fibres encourages the neurite out growth in ganglia	[67]
	Iron oxide NPs accumulated in the cytoplasm of neuronal progenitor cells, used for localization	[67]
	Alginate-magnetic short nanofibers 3D composite hydrogels enhanced the neuronal differentiation using the encapsulation by olfactory mucosa stem cells	[68]
Magnetic NPs	Combination of Superparamagnetic iron oxide NPs and gold NPs enhanced neuron cellular differentiation	[69]
	Gold (Au) NPs improves the solubility and stability of Zonisamide, a drug for Sci treatment.	[45]
	PEG-AuNPs attenuated inflammatory responses and improved motor neuron survival and myelination of axons	[70]
	Moderate quantity of gold NPs irrespective of size do not affect neuron differentiation	[71]
	Graphene oxide-AuNPs accelerated neuron cell functions by enhancing neurite growth and elongation	[46]
	Combined activity of electrical stimulation and gold NPs enhanced neurite growth.	[46]
	Gold NPs with 6-mercaptopurine and neuron-penetrating peptide significantly enhances the neurite growth	[48]
	Chitosan-zinc oxide nanocomposite improved the function and morphometry of sciatic nerve	[37]
	Macrophage-mediated gelatin coated mesoporous silica NPs enhanced the therapeutic effect of pirfenidone.	[72]
Silica NPs	Hollow silica NPs can penetrate the nerve cell in size dependant manner	[73]
Organic NPs		
	Chitosan NPs encapsulated by nerve growth factor can transdifferentiate mesenchymal cells into neurons	[74]
	Scaffold of Calcium titanate hybridized chitosan NPs promoted the proliferation and functions of Schwann cells	[75]
Polymeric NPs	Thiolated trimethyl chitosan mediated the expression of brain derived neurotrophic factor enhances the expression of neurofilament and growth associated protein in damaged nerves	[41]
	Hydroxyapatite NPs with containing collagen type I hydrogel improved the sciatic functional index	[41]
	Poly (amidoamine) (PAMAM) dendrimers with peptides enhanced neurite differentiation and proliferation of pheochromocytoma cells	[41]
Dendrimers	Dendrimer linked cyanine-5 fluorescent dye accumulated in astrocytes and macrophages	[41,76]
	PAMAM dendrimers localize in glial cells at the injury site	[77]
Biologically derived NPs		
Exosomes	Mesenchymal stem cells derived exosomes caused the loss of Purkinje cells, cerebellar myelin loss and neuroinflammation	[78]
	Exosomes derived from mesenchymal stem cells enhanced the growth of cortical neurites	[79]
	Exosomes containing Micro RNAs with activated TRPV1 receptors promotes pro-inflammatory phenotype. Also, the process of macrophage recruitment for inflammation was extended	[80]

delivery, encourage the cellular communications and improve the drug uptake by non-phagocytic cells [18]. Moreover, nanoparticles offer safe, non-toxic and biocompatible drug delivery, with reduced immunogenicity (reduced tracing by immune cells), increased drug solubility and additional circulation time in blood [19]. Nanoparticles can cross the BSCB after SCI as the integrity of BSCB get disturbed due to injury in nerves and/or vessels in spinal cord and tight junction become relaxed. Added permeability in BSCB occurs for weeks, permits the entry of endothelial cells, astrocytes and other larger molecules to injured tissue area. At this time, it is possible to deliver nanoparticles at injured site, more efficient nanoparticle accumulation can be observed [22].

The requirement of nanoparticle delivery after BSCB repairing can be achieved by several possible ways include manipulation of size and surface charge of nanoparticles [23], and decoration with Triphenyl phosphonium (TPP)-functionalized poly(lactide-co-glycoside)-poly (ethylene glycol) (PLGA-PEG) [24]. Coating nanoparticles with a hydrophilic layer of poly ethylene glycol (PEG) can help to outflow from clearance mechanism driven by immune system [25]. Nanoparticles with improved half-life can be a better selection that will not be removed by clearance mechanism of heterogenous population of phagocytic cells in tissues [18]. Moreover, nanoparticles are designed to reach the appropriate target by conjugating with corresponding peptides [26]. Nanoparticles used for various therapeutic agents should be studied thoroughly (Fig.2) and extra modifications can be made to achieve additional features such as size alteration, easy imaging, easy uptake, etc. The composition and features of cells in nervous system is unique, require advanced drug delivery strategies to guarantee successful outcome. Numerous strategies used in nanotechnology to improve its therapeutic effect are briefly discussed in this review.

4. Polymer-based nanoparticles for SCI treatment

4.1. PEGylation of nanoparticles

Proteins and peptides arrive into the blood stream from exterior are easily degraded and cleared, a responsive mechanism exerted by mononuclear phagocyte system (MPS) of immune system to impart protection. Similar responsive character is also presented to nanoparticles which are foremost focus in SCI treatment [27]. Coating the surface of nanoparticle with immunologically inert component resists nanoparticle interaction with immune cells in the blood stream [26]. Polyethylene glycol (PEG), a polymer, possesses long history of safety as it was proved that PEG covalently attached to bovine serum albumin and liver catalase proteins by Davis and Abuchowski in 1977 [28]. PEG has been classified as Generally regarded as safe (GRAS) by the food and drug administration (FDA) [25]. PEG can extend the circulation time of nanoparticles in the blood stream without affecting its activity. PEGylation protects the nanoparticles aggregation by forming a hydrated cloud to prevent its collaboration with other nanoparticles. Also, PEGylated nanoparticles escape from phagocytosis, and opsonization. Coating the nanoparticles with PEG reduces the systemic toxicity that is generated by nanoparticles on erythrocyte bring about aggregation [25]. Nanogels prepared with the combination of PEG, polyethyleneimine (PEI) and rhodamine dye demonstrated enhanced microglia internalization and other different cellular uptake. PEG used

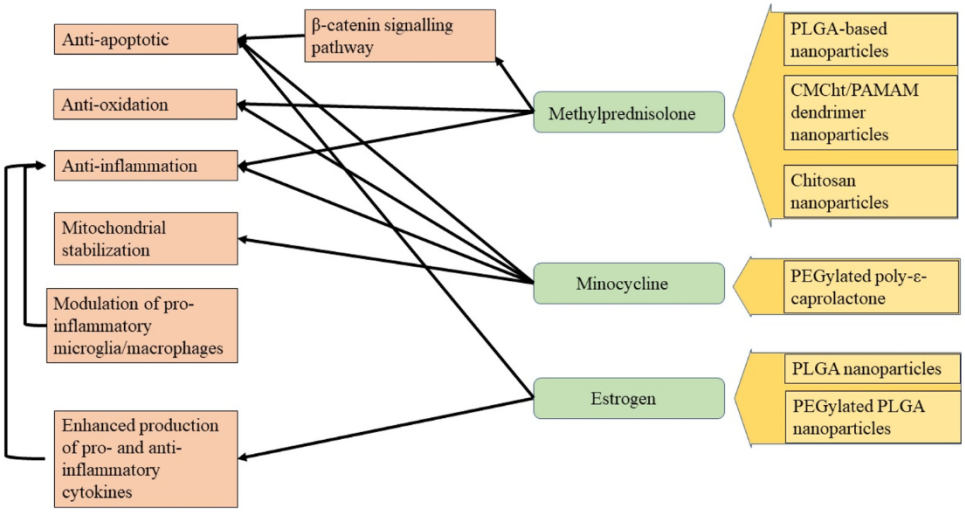

Fig. 2. Most common nanoparticle drug delivery system for accepted drugs, mitigate the cellular functions after spinal cord injury. PLGA - Poly D,L-lactic-co-glycolic acid; CMCht/PAMAM - Carboxymethylchitosan/polyamidoamine; PEG - polyethylene glycol [9].

in this study was undergone surface modification by altering the hydroxyl groups with various linkers, which maximize microglia internalization [29].

Use of silica-PEG nanoparticles incorporated with hydralazine drug in lessening secondary injury by scavenging acrolein, a neurotoxic. Nanoparticle synthesized from silica forms porous network which accommodate therapeutic drug and transport throughout the body. PEG attached with the injured tissue membrane, serving to find the target, scavenge the acrolein and thereby reduces oxidative stress [7]. Composite constructed with mesoporous silica, arctigenin and CAQK act as a potential drug delivery system to avoid side effects of high dose drugs [30]. Mesoporous silica nanoparticles with and without PEG coating have obtained more attraction as drug delivery system in the field of nanomedicine [31].

However, there are certain factors which affect the circulation of PEG coated nanoparticles include high PEG molecular weight, which further increases the size of the nanoparticles and affect PEG surface density. Large sized nanoparticles may get attracted by MPS efficiently [25].

4.2. poly(lactide-coglycolide) (PLG/PLGA)-based nanoparticles

Poly (lactide-coglycolide) based nanoparticles (PLGNPs) with size of 500 nm diameter were used to reprogramme innate immune cells such as monocytes and neutrophils. Negatively charged PLGNPs were internalized by marrow derived macrophages (MARCO) and majority driven to accumulated in spleen, only lower proportion is directed to spinal cord. Thus, rapid influx of monocytes and neutrophils are restricted to the injury site, where they contribute to promote secondary injury. Steering the innate immune cells to spleen avoid deleterious effect of inflammatory response caused by cell trafficking, and create an appropriate microenvironment for tissue regeneration with the help of modest amount of NP-mediated regenerative innate immune cells in spinal cord. Moreover, PLGNPs defeated both fibrotic and glial scar formation. A regenerative microenvironment created by PLGNPs contribute to the enhancement in axon myelination and SCI recovery [32].

Administration of PLG marked NPs even at fourth week of post injury localized the NPs at lesion site. Near-infrared (NIR) dye loaded with NPs aided to image the retention period of NP, which showed significant retention of PLGNPs after one week of post administration. Biodegradation of PLG polymer creates a state of release of loaded NPs [33]. Panyam et al. described different kinetics for drug release and degradation of NPs, where drug release would rely on its own physical characteristic feature, loading method and releasing mechanism, rather biodegradation of NPs would majorly rely on the polymer composition (lactide: glycoside) and its molecular weight [34].

5. Polysaccharide based NPs

Biocompatible nanomaterials synthesised from natural polymers include starch, chitosan, silk fibrins, albumin, gelatine, and collagen are trusted for less toxicity. Carbohydrate nanocarriers possesses the general characteristic features of any other polymer-based NPs, and also mostly available in nature [27]. Carbohydrate polymers can be isolated from cell wall of plants and bacteria, extracellular materials in animals, and exoskeletons of arthropods. Various kinds of carbohydrate derivatives are made with biochemical modifications, capable to incorporate with animal tissues such as mucous and epithelial membranes [27]. Chitosan (Ch) is a natural linear polysaccharide obtained from chitin. Ch-based nanoparticles (Ch-NPs) are known for antimicrobial ability, carrier for drug delivery, membrane separators, and sensing agent in tissue engineering [35,36]. Chitosan function as conduit in endorsing regeneration of damaged neurons [37]. A nanocomposite conduit structured by chitosan and zinc oxide, the later showed severe cytotoxicity when it used alone, progressed the sciatic nerve function in rat model by enhancing the production of proteins responsible for myelin sheath formation and axon regeneration [37]. Less cytotoxicity of zinc oxide was observed in the cells detected with chitosan nanocomposite. Chitosan scaffolds are extensively used for nerve regeneration in CNS as well as PNS [38]. Therapeutic applications of Ch-NPs can be enhanced by developing scaffold and polymers combinations, respective studies with different forms chitosan conduits are given in table (Table 2).

6. Protein-based nanoparticles for SCI treatment

Protein polymers isolated from plant or animals include collagen, elastin, gelatine, albumin, silk, and soy are used to coat the NPs during drug delivery [39]. Human serum albumin (HAS) NPs can be efficiently engulfed by neutrophils which are the quickly recruited leucocytes to the inflammatory site. HAS-NPs conjugated with cell penetrating peptide of trans-activator of transcription (TAT) for efficient uptake and delivery [19]. In the inflammatory cells of mouse model, tetramethyl pyrazine loaded TAT-NPs showed significantly efficient uptake and also inhibition of inflammatory cells by reducing the availability of cytokines IL-6 and TNF-α. Conjugation of HSA and non-toxic TAT improves the success rate of drug tetramethyl pyrazine, which is known for dilating

Table 2
Different forms of chitosan-based nanoparticles and their mechanism of action in controlling severity of spinal cord injury in in vitro and in vivo models

Chitosan based conduit	Cells/Animal model	Observations	Reference
Chitosan grafts with vitamin E and pyrroloquinoline	Sciatic nerves were exposed to nanoparticle conduit using surgical operation in male Wistar rats	Increase in the size of nerve fiber, axon diameter and myelin sheath	[38]
Chitosan NPs scaffold constructed with the hybridization of alginate and chitosan hydrogel, further loaded berberine	Scaffold with endometrial stem cells and without stem cells are transplanted into SCI rats	Progression in immunoreactivity, sensory and motor function recovery, regeneration of spinal cord, restricted secondary damage	[81]
Chitosan Nps encapsulated with curcumin and filled into the conduit which was prepared with poly-L-lactic acid (PLLA) and surface modified multi-wall carbon nanotubes (mMWCNT)	Conduit was sutured to bridge both sides of injured sciatic nerve adjoins the proximal and distal nerve stumps	Regeneration of sciatic nerve with no other side effect or impacts	[82]
Chitosan NPs packed with cerium oxide NPs	Characterization techniques	Nano-compatible, possesses catalytic oxidative recovery properties, expected to enhance neuroprotection and regeneration in spinal cord.	[83]
Magnetic peptide imprinted chitosan NPs composite, further loaded with nucleoproteins (dCas9-VPR and guide RNA) by immobilization method	To study the activation of OSKM genes (code for reprogramming transcription factors) in human embryonic kidney (HEK) 293 T cells	High expression of OSKM genes, empower cell differentiation	[84]
Chitosan-laminin scaffold	Co-transplanted with bone-marrow-derived mesenchymal stem cells	Enhance recovery from spinal cord injury and associated defects	[85]
Chitosan-Calcium titanate (Ch/$CaTiO_3$) hybrid scaffold	Schwann cells	Enhance attachment, growth and functions of Schwann cells, further peripheral nerve regeneration	[75]
Chitosan-zinc oxide nanocomposite	Conduit was placed in left sciatic nerve using surgically fixed stumps	Diameter and count of myelinated fibers increased, results in functional recovery and improved morphometric indices	[37]
Thiolated trimethyl chitosan (TMCSH) NPs to deliver brain-derived neurotrophic factor (BDNF) gene	Delivery to peripheral neurons by peripheral and intramuscular administration in nerve crushed mice	Expression of BDNF enhanced in neural tissues, resulted functional recovery. Expression of neurofilament and protein GAP-43 (growth promoter). More axon density and myelination achieved.	[86] [87]
Nanomicelles made with stearic acid-chitosan and sesamol	Cell culture study using NSC-34 cells as neurons	Stability of micelles, Enhancement in the activity of enzymatic and non-enzymatic systems, impact NF-κB signaling pathway which control inflammatory proteins	
Chitosan based hydrogel	Mesenchymal cells isolated from EGFP-positive mice (mice express enhanced green fluorescent protein), in vivo study in C57BL/6 J mice	Non-toxic over mesenchymal cells, so as to show its anti-oxidant properties, biocompatible for in vivo studies.	[88]
Chitosan-g-glycidyl methacrylate-xanthan hydrogel	Implanted in the left sciatic nerve	Cell proliferation and spinal cord recovery	[89]

blood vessels, inhibiting apoptosis, improving the recovery as well as inhibiting inflammatory response. On the other hand, antioxidant and anti-inflammatory activities exerted by tetramethyl pyrazine prevents secondary injury and endorse the recovery of locomotory functions [19].

Chondroitin sulphate proteoglycans (CSPGs) are reported as the chief inhibitory molecules of neurite elongation, and neuronal growth in mammalian CNS [40]. The enzyme, Chondroitinase ABC (ChABC) can inhibit the side chains of CSPGs and enhance regeneration, sprouting and recovery of axons. ChABC loaded PLGA NPs enhanced myelination and cleavage in CSPGs of olfactory ensheathing cells (OESs), the result of which encourage neuronal regeneration injury site [41]. Polyethylene glycol-polycaprolactone (PEG-PCL) polymer conjugated with cysteine-isoleucine-lysine-arginine-glycine (CIKRG) peptides using thiolene reaction (also known as alkene hydrothiolation). Conjugated PEG-PCL were loaded into NPs and efficiently internalized into dorsal root ganglion specifically neurons. Progression in pAKT expression (pTEN inhibitor) (which plays a major role in neuroprotection and axonal outgrowth) and progression in neurite density observed in neurons indicated the successful drug delivery by PEG-PCL NPs [42].

Collagen is the most abundant protein present in the human body, plays vital role in formation of axon sheath and nerve fascicles. Collagen type 1 is widely present in nervous system but undergo degradation due to SCI. Administration of collagen type I hydrogel containing hydroxyapatite NPs to showed higher proliferation of Schwann cells *in vitro* and improved sciatic functions in vivo, suggesting an effective therapy for SCI [43]. Adopting a suitable fabrication method helps to reduce the drawbacks during the synthesis of protein-based nanoparticles [44].

7. Metal nanoparticles

Metal NPs possesses variety of application as conductive composites, majorly synthesized from gold, platinum, and silver have been experimented for their biomedical applications. Yet, limited studies have been performed to investigate the regenerative effect implemented by metal NPs [4]. Among metal NPs, gold NPs (Au NPs) are attractive and widely investigated for its therapeutic applications, as it can be easily modelled into numerous shapes such as nanorods, hexagons, nanoribbons, nanotubes, nanoplates, nano cubes, nanowires, etc [45] (Table 3). Biocompatibility and non-immunogenic features make gold NPs as appropriate option to be used as a nano-carrier in neurological treatments [4]. Cytotoxicity studies on gold NPs biosynthesized from *Juglans regia* bark extract, further loaded with zonisamide, showed higher toxicity towards CTX TNA2 cells (astrocytes), reduces astrocyte lush to injury site after SCI, therefore considered as good therapeutic agent for SCI recovery

Table 3
Possible therapeutic applications of gold nanoparticles and the results of various studies conducted in the same field

Gold nanoparticle drug delivery system	Cells/Animal model	Observations	Reference
Electrospun composite scaffolds [Plasmonic AuNPs covered with nano-sized graphene oxide, later integrated with polycaprolactone]	Schwann cells (S42) and pheochromocytoma (PC12) (neuronal cells model) rat cell	Nanoparticles provided large surface area, increase in neuronal cell function, neurite length, and nerve repairing	[46]
AuNPs with citrate capping	Dorsal root ganglions excised form rats	Better internalization by neurons and ganglia, direct exposure on AuNPs did not harm neuronal growth	[71]
Au coated superparamagnetic iron oxide (SPIO) core NPs	PC-12 cells of rat pheochromocytoma	Improved cellular uptake, served as a nerve growth factor, enhanced cell differentiation and neurite length	[69]
Electrospun nanofiber scaffolds decorated with AuNPs	Neurons of medical leech	Neurite elongation with formation of complex branches	[90]
Plasmonic excitation of AuNPs using near-IR light (NIR)	Cultured hippocampal neurons dissected from rats	Suitable method to control neuronal activity and cell signalling using NP assisted localized optical stimulation (NALOS)	[91]
AuNPs fabricated with polyrthyleneimine	PC-12 cell lines from pheochromocytoma of rats	Uniform distribution of AuNPs on PC12 cells with the help of electrical stimulation showed enhanced neurite growth	[47]
Silk-gold nanocomposite conduit	Neurotmesis grade sciatic nerve injury model in rats	Structural and functional recovery of sciatic nerves, improved potential of motor units and muscle action	[92]
Modified AuNPs using 6-mercapto-purine and neuron penetrating peptide	Human neuroblastoma (SH-SY5Y) cells	Higher metabolic activity and improved neurite growth	[48]
AuNPs/ Polyvinylidene fluoride (PVDF) composite electrospun mat	PC-12 cell line of adrenal medulla from rat	Nanofibers possesses piezoelectricity, suitable for use as scaffolds in nerve tissue engineering	[93]

[45].

Nanoparticle scaffolds are the form of carrier which are developed by electrospinning, bioprinting and chemical modification of compatible metals. Scaffolds improves the proliferation, adhesion and metabolic activities. Gold NPs enfolded with reduced graphene oxide (RGO) engineered polycaprolactone based composite scaffolds enhanced neurite growth and neuronal cell functions [46]. Rat pheochromocytoma derived PC-12 cell lines grown in the presence of gold NPs deposition onto PEI coated glass surface demonstrated improved neurite growth using electrical stimulation [47]. Conjugation of gold NPs with neuron-targeting peptides enhances the uptake by endocytosis mediated by peptide association with γ-aminobutyric acid (GABA) receptor or nicotinic acetylcholine receptor in human neuroblastoma cells. An anti-inflammatory drug, 6-Mercaptopurine, loaded in gold NPs encouraged cell differentiation, neurite growth, and synaptogenesis, which are the accepted roles of 6-Mercaptopurine [48].

Unlike Silver NPs, gold NPs are generally non-toxic even if the particle size is larger (30 to 100 nm) [4]. While gold NPs have been used in SCI treatment as conductive composites, iron-oxide NPs have been used for their magnetic properties. Moreover, iron-oxide nanoparticles are suitable for magnetic resonance imaging [4].

8. Immuno-modulatory nanoparticles (iNPs)

They are distinct from the conventional nanoparticles as the iNPs can modulate the immune cells independently. Without the incorporation of other therapeutic agents including drugs, iNPs alter immune functions to related to the spinal cord recovery [18]. iNPs are tuned for diverse nanomedical applications by altering its own physiochemical properties, encoded iNPs for a specific immunomodulatory feature can contribute to unique or collaborative functional role [49].

Disruption of BSCB lead to rapid monocyte invasion to the injury site, differentiated into macrophages which act as a boon or ban after SCI. Several studies demonstrated the advantageous role of macrophages in clearing debris and encouraging axon regeneration by secreting anti-inflammatory cytokines and neurotrophic factors [50]. However, such rapid invasion of immune cells twitched to secondary injury progressions like axon demyelination, fibrosis, glial scar formation, and cell death. Few studies suggested that rapid influx of hematogenously-derived macrophages is the root of axonal degeneration rather not microglia-derived macrophages [21]. Carboxylate poly (lactide-*co*-glycoside) (PLGA) iNPs specifically binds to hematogenously-derived macrophages and drive to spleen where they killed by apoptosis [51]. PLGA iNPs reduces the number of inflammatory macrophages and thereby lowers the cytokine level and fibrotic scar formation without affecting resident microglia and glial scar formation [52]. Park et al., demonstrated therapeutic effect of PLG based NPs by reprogramming neutrophils and monocytes without using any conventional drugs. Negatively charged NPs with zeta potential can divert inflammatory monocytes and neutrophils towards spleen, thus attenuate inflammation in injury site [32]. PLG-iNPs induced macrophage polarization and reduced both gliotic and fibrotic scar formation 3-fold. Additionally, improvement in axon regeneration, myelination and locomotor function observed [32]. In mice models, intravenous administration of PLG-iNPs were not found to disturb resident microglia count. Rather, activated microglia reduced inflammatory cytokines and thereby inhibited fibrotic scar formation but not glial scar [52]. In SCI treatment, application of iNPs helps to alleviate pro-inflammatory responses that occur after injury, works on immunomodulation and neuroprotection, which improve the conviction over nanomedicine in SCI treatment.

9. Applications of other nanoparticles

Recent researches focus on the use of anti-oxidants, to attenuate of oxidative damage in the course of secondary injury, to treat the SCI. Reports showed that high levels of reactive oxygen species (ROS) produced during SCI induce the severity of damage and show a chief role in the progression of secondary injury [53]. Oxidative resistance 1 plasmids (pOXR1) were constructed and conjugated with vitamin E succinate-grafted ε-polylysine cationic NPs. Cationic liposomal encapsulation provided enhanced transfection efficiency and lower toxicity. pOXR1-liposomal NPs encouraged the SCI recovery by reducing oxidative stress, suppressing apoptosis, and reducing inflammation in acute traumatic SCI [54]. Lipid polymer nanoparticles with reactive oxide

species (ROS) scavenging showed a promising therapeutic effect in contusive spinal cord injury rats. ROS scavenging NPs were prepared by encapsulation of poly [propargyl (methylthio) acetate- *co* -ethylene glycol di (β- mercaptopropionate) (poly (PMT- *co* -EGDM)) polymer by lecithin and 1,2-distearoyl-snglycero- 3-phosphoethanolamine- *N* -carboxy (polyethylene glycol) (PEG-DSPE). The prepared NPs attenuated secondary injury by lowering the ROS levels and down regulating the inflammatory response responsible for oxidative stress in SCI rats [55].

ROS induced secondary injury was well explained in the previous studies, as insufficient supply of glucose and oxygen to injury site led to ischemic condition after SCI [56]. This condition creates sequential biochemical changes in mitochondria, including loss of adenosine triphosphate (ATP) production and several others [57]. Insufficient availability of ATP causes calcium accumulation and oxidative stress [58]. Therefore, exogenous delivery of antioxidant enzymes such as catalase and superoxide dismutase with the help of NP drug delivery system (nano-SOD/CAT) would alleviate oxidative stress at injury site [58]. This study revealed the protective ability of nano-SOD/CAT on mitochondria and attenuation of further progression to secondary injury at affected area.

Local administration of nanofiber, incorporated with lipid polymer poly(e-caprolactone) (PCL) and methyl cobalamin using electrospinning method, to the nerve injury site demonstrated a positive therapeutic approach for sciatic nerve damage. PCL nanofiber has been approved by FDA and served as a biocompatible and biodegradable artificial durometer, with no contrary effect. PCL linked Methyl cobalamin, a form of vitamin B12, promotes neurite growth and neuronal survival, improved the functions of sciatic nerve in rat model [59]. There are numerous emerging studies, proved the potential ability of nanoparticles as drug delivery system as well as immunomodulators. All of them aiming to find out nanoparticles with non-toxicity, bio-compatibility, and at the same time excellent in its own potency.

10. A look into the negative face of nanomedicine

There are few studies which suggested possible disadvantages of nanoparticles, knowledge of that is essential to avoid drawbacks in nanomedicine technology. Among the metal nanoparticles, silver NPs were reported to exert negative effects such as disruption of neural cytoskeleton, and reduction in neurite length and suppression of differentiation. Silver NPs crosses BBB and stimulate the production of pro-inflammatory cytokines, reactive oxygen species, and nitric oxide, all these ends in neuroinflammation [60]. Silver NPs shed throughout the day while using consumer products which are manufactured with the same. Even though such less quantity of silver NPs do not sufficient to influence DNA fragmentation in the neural cells of adults, it can accumulate in developing neurons of children. Silver NPs exposure to neural stem cells tend to produce f-actin inclusions which inhibit β-catenin signalling pathway. Alternations in β-catenin signalling pathway causes changes in neurite length. Thus, regular exposure to silver NPs from consumer products may alter the brain functions of children [61]. An earlier study by Minorava et al., [62] suggested that AuNPs also employ detrimental effects on cell function which can be withdrawn by removing AuNPs.

11. Conclusion

Nanomedicine, a division of nanotechnology, is one of most promising and growing therapeutic strategy for spinal cord injury. Nanoparticles can enable treatment technology in health sector by improving the delivery of drug, modulating inflammatory responses and restore functional response for SCI. Though there have been bulk research studies on demonstrating potential ability of nanoparticles in the treatment of SCI, concern needed for sufficient number of clinical trials. But still, the complexity associated with SCI patients is a major challenge to overcome. Using nanoparticles to initiate or accelerate the immune modulatory responses will help in performing efficient treatment of patients with severe SCI. In addition, further improving the type of material used for the synthesis of nanoparticle will also give additional benefits in diagnosis and treatment of SCI. Detailed study analysis of the positive and negative effects exerted by nanoparticles is to be performed for diminishing the drawbacks of this system. Implementing multifactorial approaches to solve complex immune dysfunctions and proinflammatory condition using site specific or cell targeting nanoparticle will help in improving the delivery or modulate the immune functions. This will lead to a outbreaking incident and support the SCI patient to recover from long term pain and disabilities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

References

[1] H.S. Chhabra, K. Sarda, Clinical translation of stem cell based interventions for spinal cord injury — Are we there yet? Adv. Drug Deliv. Rev. 120 (2017) 41–49, https://doi.org/10.1016/j.addr.2017.09.021.
[2] E.J. Bradbury, E.R. Burnside, Moving beyond the glial scar for spinal cord repair, Nat. Commun. 10 (2019) 1–15, https://doi.org/10.1038/s41467-019-11707-7.
[3] P.C. Bucy, Spinal cord injury, Neurobiologia 36 (1973) 67–76.
[4] E.A. Kiyotake, M.D. Martin, M.S. Detamore, Regenerative rehabilitation with conductive biomaterials for spinal cord injury, Acta Biomater. (2020), https://doi.org/10.1016/j.actbio.2020.12.021.
[5] J.M. Zuidema, R.J. Gilbert, D.J. Osterhout, Nanoparticle Technologies in the Spinal Cord, Cells Tissues Organs. 202 (2016) 102–115, https://doi.org/10.1159/000446647.
[6] S.K. Rai, S. Ganeshan, R. Mariappan, A.P. Rajendran, A. Balasubramaniem, A. Pugazhendhi, P. Varalakshmi, Mesoporous nanoparticles for the delivery of (9S, E)-8-ethyl-9-methylnonadec-6-en-3-one (EME): A study of anti-inflammatory and tumor suppressing potential in RAW 264.7, He La and HepG2 cell lines, Process Biochem. 111 (2021) 1–11, https://doi.org/10.1016/j.procbio.2021.10.004.
[7] D. White-Schenk, R. Shi, J.F. Leary, Mesoporous silica nanoparticles for treating spinal cord injury. Imaging, Manip. Anal. Biomol. Cells, Tissues XI, SPIE, 2013, p. p. 858716, https://doi.org/10.1117/12.2004916.
[8] Q. Hu, Y. Lu, Y. Luo, Recent advances in dextran-based drug delivery systems: From fabrication strategies to applications, Carbohydr. Polym. 264 (2021) 117999, https://doi.org/10.1016/j.carbpol.2021.117999.
[9] Y.H. Song, N.K. Agrawal, J.M. Griffin, C.E. Schmidt, Recent advances in nanotherapeutic strategies for spinal cord injury repair, Adv. Drug Deliv. Rev. 148 (2019) 38–59, https://doi.org/10.1016/j.addr.2018.12.011.
[10] R. Shanmuganathan, T.N.J.I. Edison, F. LewisOscar, P. Kumar, S. Shanmugam, A. Pugazhendhi, Chitosan nanopolymers: An overview of drug delivery against cancer, Int. J. Biol. Macromol. 130 (2019) 727–736, https://doi.org/10.1016/j.ijbiomac.2019.02.060.
[11] S. Sathiyavimal, S. Vasantharaj, F. LewisOscar, R. Selvaraj, K. Brindhadevi, A. Pugazhendhi, Natural organic and inorganic–hydroxyapatite biopolymer composite for biomedical applications, Prog. Org. Coatings 147 (2020) 105858, https://doi.org/10.1016/j.porgcoat.2020.105858.
[12] F. LewisOscar, C. Nithya, S. Vismaya, M. Arunkumar, A. Pugazhendhi, P. Nguyen-Tri, S.A. Alharbi, N.S. Alharbi, N. Thajuddin, In vitro analysis of green fabricated silver nanoparticles (AgNPs) against Pseudomonas aeruginosa PA14 biofilm formation, their application on urinary catheter, Prog. Org. Coatings. 151 (2021) 106058, https://doi.org/10.1016/j.porgcoat.2020.106058.
[13] A. Hasan, M. Morshed, A. Memic, S. Hassan, T.J. Webster, H.E.S. Marei, Nanoparticles in tissue engineering: Applications, challenges and prospects, Int. J. Nanomedicine. 13 (2018) 5637–5655, https://doi.org/10.2147/IJN.S153758.
[14] P.G. Nagappan, H. Chen, D.Y. Wang, Neuroregeneration and plasticity: A review of the physiological mechanisms for achieving functional recovery postinjury, Mil. Med. Res. 7 (2020) 1–16, https://doi.org/10.1186/s40779-020-00259-3.
[15] C.M. Dumont, L.D. Shea Margul, Tissue engineering approaches to modulate the inflammatory milieu following spinal cord injury, Cells Tissue Organs. 202 (2016), https://doi.org/10.1159/000446646. Tissue.
[16] Mohsen Gomes, Bachmann, Harnessing nanoparticles for immunomodulation and vaccines, Vaccines. 5 (2017) 1–15.
[17] C. Saraiva, C. Praca, R. Ferreira, T. Santos, L. Ferreira, L. Bernardino, Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenrative diseases, J. Control. Release. 235 (2016) 34–47.

[18] A. Chakraborty, A.J. Ciciriello, C.M. Dumont, R.M. Pearson, Nanoparticle-Based Delivery to Treat Spinal Cord Injury—a Mini-review, AAPS PharmSciTech. 22 (2021) 1–9, https://doi.org/10.1208/s12249-021-01975-2.
[19] J. Li, J. Wei, Y. Wan, X. Du, X. Bai, C. Li, Y. Lin, Z. Liu, M. Zhou, Z. Zhong, TAT-modified tetramethylpyrazine-loaded nanoparticles for targeted treatment of spinal cord injury, J. Control. Release. 335 (2021) 103–116, https://doi.org/10.1016/j.jconrel.2021.05.016.
[20] B. Suberviola, A. González-Castro, J. Llorca, F. Ortiz-Melón, E. Miñambres, Early complications of high-dose methylprednisolone in acute spinal cord injury patients, Injury 39 (2008) 748–752, https://doi.org/10.1016/j.injury.2007.12.005.
[21] J.C. Gensel, B. Zhang, Macrophage activation and its role in repair and pathology after spinal cord injury, Brain Res 1619 (2015) 1–11, https://doi.org/10.1016/j.brainres.2014.12.045.
[22] J. Park, T.J. Decker, S.R. Dominique, B.J. Cummings, A.J. Anderson, L.D. Shea, Reducing inflammation through delivery of lentivirus encoding for anti-inflammatory cytokines attenuates neuropathic pain after spinal cord injury Jonghyuck, J. Control. Release. 290 (2018) 88–101, https://doi.org/10.1016/j.jconrel.2018.10.003.Reducing.
[23] J.A. Brown, S.L. Faley, S.L. Faley, Y. Shi, K.M. Hillgren, G.A. Sawada, T.K. Baker, J. P. Wikswo, J.P. Wikswo, J.P. Wikswo, J.P. Wikswo, E.S. Lippmann, E.S. Lippmann, E.S. Lippmann, Advances in blood-brain barrier modeling in microphysiological systems highlight critical differences in opioid transport due to cortisol exposure, Fluids Barriers CNS. 17 (2020) 1–12, https://doi.org/10.1186/s12987-020-00200-9.
[24] B. Surnar, U. Basu, B. Banik, A. Ahmad, B. Marples, N. Kolishetti, S. Dhar, Nanotechnology-mediated crossing of two impermeable membranes to modulate the stars of the neurovascular unit for neuroprotection, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E12333–E12342, https://doi.org/10.1073/pnas.1816429115.
[25] S. suk Jung, Q. Xu, N. Kim, J. Hanes, E.M. Laura, PEGylation as a strategy for improving nanoparticle-based drug and gene delivery, Physiol. Behav. 99 (2016) 28–51, https://doi.org/10.1016/j.addr.2015.09.012.PEGylation.
[26] K.K. Takashi, R. Maldonado, Nanoparticles for the induction of Antigen-Specific Immunological tolerance, Front. Immunol. 9 (2018).
[27] R. Ansari, S.M. Sadati, N. Mozafari, H. Ashrafi, A. Azadi, Carbohydrate polymer-based nanoparticle application in drug delivery for CNS-related disorders, Eur. Polym. J. 128 (2020), https://doi.org/10.1016/j.eurpolymj.2020.109607.
[28] A. Abuchowski, J.R. McCoy, N.C. Palczuk, T. van Es, F.F. Davis, Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase, J. Biol. Chem. 252 (1977) 3582–3586, https://doi.org/10.1016/s0021-9258(17)40292-4.
[29] E. Mauri, P. Veglianese, S. Papa, A. Mariani, M. De Paola, R. Rigamonti, G.M. F. Chincarini, S. Rimondo, A. Sacchetti, F. Rossi, Chemoselective functionalization of nanogels for microglia treatment, Eur. Polym. J. 94 (2017) 143–151, https://doi.org/10.1016/j.eurpolymj.2017.07.003.
[30] G. Sun, S. Zeng, X. Liu, H. Shi, R. Zhang, B. Wang, C. Zhou, T. Yu, Synthesis and Characterization of a Silica-Based Drug Delivery System for Spinal Cord Injury Therapy, Nano-Micro Lett. 11 (2019) 1–20, https://doi.org/10.1007/s40820-019-0252-6.
[31] V. Daund, S. Chalke, A.P. Sherje, P.P. Kale, ROS responsive mesoporous silica nanoparticles for smart drug delivery: A review, J. Drug Deliv, Sci. Technol. 64 (2021) 102599, https://doi.org/10.1016/j.jddst.2021.102599.
[32] J. Park, Y. Zhang, E. Saito, S.J. Gurczynski, B.B. Moore, B.J. Cummings, A. J. Anderson, L.D. Shea, Intravascular innate immune cells reprogrammed via intravenous nanoparticles to promote functional recovery after spinal cord injury, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 14947–14954, https://doi.org/10.1073/PNAS.1820276116.
[33] Y. Gao, S. Vijayaraghavalu, M. Stees, B.K. Kwon, V. Labhasetwar, Evaluating accessibility of intravenously administered nanoparticles at the lesion site in rat and pig contusion models of spinal cord injury, J. Control. Release. 302 (2019) 160–168, https://doi.org/10.1016/j.jconrel.2019.03.026.
[34] J. Panyam, M.M. Dali, S.K. Sahoo, W. Ma, S.S. Chakravarthi, G.L. Amidon, R. J. Levy, V. Labhasetwar, Polymer degradation and in vitro release of a model protein from poly(D,L-lactide-co-glycolide) nano- and microparticles, J. Control. Release. 92 (2003) 173–187.
[35] S. Mohebbi, M.N. Nezhad, P. Zarrintaj, S.H. Jafari, S.S. Gholizadeh, M.R. Saeb, M. Mozafari, Chitosan in Biomedical Engineering: A Critical Review, Curr. Stem Cell Res. Ther. 14 (2018) 93–116, https://doi.org/10.2174/1574888x13666180912142028.
[36] B.R. Rizeq, N.N. Younes, K. Rasool, G.K. Nasrallah, Synthesis, bioapplications, and toxicity evaluation of chitosan-based nanoparticles, Int. J. Mol. Sci. 20 (2019), https://doi.org/10.3390/ijms20225776.
[37] M. Iman, M. Araghi, Y. Panahi, R. Mohammadi, Effects of Chitosan-Zinc Oxide Nanocomposite Conduit on Transected Sciatic Nerve: An Animal Model Study, Bull. Emerg. Trauma. 5 (2017) 240–248, https://doi.org/10.18869/acadpub.beat.5.4.521.
[38] A. Azizi, S. Azizi, B. Heshmatian, K. Amini, Improvement of functional recovery of transected peripheral nerve by means of chitosan grafts filled with vitamin E, pyrroloquinoline quinone and their combination, Int. J. Surg 12 (2014).
[39] A.A. Yetisgin, S. Cetinel, M. Zuvin, A. Kosar, O. Kutlu, Therapeutic nanoparticles and their targeted delivery applications, Molecules. 25 (2020), https://doi.org/10.3390/molecules25092193.
[40] J.W. Fawcett, R.A. Asher, The glial scar and central nervous system repair, Brain Res. Bull. 49 (1999) 377–391, https://doi.org/10.1016/S0361-9230(99)00072-6.
[41] M. Azizi, F. Farahmandghavi, M.T. Joghataei, M. Zandi, M. Imani, M. Bakhtiari, H. Omidian, ChABC-loaded PLGA nanoparticles: A comprehensive study on biocompatibility, functional recovery, and axonal regeneration in animal model of spinal cord injury, Int. J. Pharm. 577 (2020) 119037, https://doi.org/10.1016/j.ijpharm.2020.119037.
[42] J. Xu, Y. Chau, Polymeric nanoparticles decorated with BDNF-derived peptide for neuron-targeted delivery of PTEN inhibitor, Eur. J. Pharm. Sci. 124 (2018) 37–45, https://doi.org/10.1016/j.ejps.2018.08.020.
[43] M. Salehi, M. Naseri-Nosar, S.E. Barough, M. Nourani, A. Vaez, S. Farzamfar, J. Ai, Regeneration of sciatic nerve crush injury by a hydroxyapatite nanoparticle-containing collagen type I hydrogel, J. Physiol. Sci. 68 (2018) 579–587.
[44] E. Kianfar, Protein nanoparticles in drug delivery: animal protein, plant proteins and protein cages, albumin nanoparticles, J. Nanobiotechnology 19 (2021) 1–32, https://doi.org/10.1186/s12951-021-00896-3.
[45] C. Fang, Z. Ma, L. Chen, H. Li, C. Jiang, W. Zhang, Biosynthesis of gold nanoparticles, characterization and their loading with zonisamide as a novel drug delivery system for the treatment of acute spinal cord injury, J. Photochem. Photobiol. B Biol. 190 (2019) 72–75, https://doi.org/10.1016/j.jphotobiol.2018.11.011.
[46] R. Jaswal, S. Shrestha, B.K. Shrestha, D. Kumar, C.H. Park, C.S. Kim, Nanographene enfolded AuNPs sophisticatedly synchronized polycaprolactone based electrospun nanofibre scaffold for peripheral nerve regeneration, Mater. Sci. Eng. C. 116 (2020) 111213, https://doi.org/10.1016/j.msec.2020.111213.
[47] M. Adel, M. Zahmatkeshan, B. Johari, S. Kharrazi, M. Mehdizadeh, B. Bolouri, S. M. Rezayat, Investigating the effects of electrical stimulation via gold nanoparticles on in vitro neurite outgrowth: Perspective to nerve regeneration, Microelectron. Eng. 173 (2017) 1–5, https://doi.org/10.1016/j.mee.2017.03.006.
[48] Y. Xiao, E. Zhang, A. Fu, Promotion of SH-SY5Y cell growth by gold nanoparticles modified with 6-Mercaptopurine and a neuron-penetrating peptide, Nanoscale Res. Lett. 12 (2017).
[49] I. Ifergan, S.D. Miller, Potential for Targeting Myeloid Cells in Controlling CNS Inflammation, Front. Immunol. 11 (2020) 1–17, https://doi.org/10.3389/fimmu.2020.571897.
[50] R. Shechter, O. Miller, G. Yovel, N. Rosenzweig, A. London, J. Ruckh, K.W. Kim, E. Klein, V. Kalchenko, P. Bendel, S.A. Lira, S. Jung, M. Schwartz, Recruitment of Beneficial M2 Macrophages to Injured Spinal Cord Is Orchestrated by Remote Brain Choroid Plexus, Immunity. 38 (2013) 555–569, https://doi.org/10.1016/j.immuni.2013.02.012.
[51] D. Wagner, S. Johnson J, D.Z. Yan, J.-H. Lim, T. Mudalige, S. Linder, Polyethylene glycol-functionalized poly (Lactic acid-co-glycolic acid) and graphene oxide nanoparticles induce pro-inflammatory and apoptotic responses in Candida albicans-infected vaginal epithelial cells, PLoS One. 12 (2017).
[52] S.J. Jeong, J.G. Cooper, I. Ifergan, T.L. McGuire, D. Xu, Z. Hunter, S. Sharma, D. McCarthy, S.D. Miller, J.A. Kessler, Intravenous immune-modifying nanoparticles as a therapy for spinal cord injury in mice, Neurobiol. Dis. 108 (2017) 73–82, https://doi.org/10.1016/J.NBD.2017.08.006.
[53] S.C. Ahuja, W.R. Jefferson, S. Nori, K.R.N. Mark, C. Druschel, C. Armin, G. M. Fehlings, Traumatic spinal cord injury, Dis. Prim. (2017).
[54] J. Zhang, Y. Li, J. Xiong, H. Xu, G. Xiang, M. Fan, K. Zhou, Y. Lin, X. Chen, L. Xie, H. Zhang, J. Wang, J. Xiao, Delivery of pOXR1 through an injectable liposomal nanoparticle enhances spinal cord injury regeneration by alleviating oxidative stress, Bioact. Mater. 6 (2021) 3177–3191, https://doi.org/10.1016/j.bioactmat.2021.03.001.
[55] T. Zhang, F. Lin, W. Liu, Y. Liu, Z. Guo, C. Xiao, X. Zhuang, X. Chen, Reactive oxide species-scavenging lipid-polymer nanoparticles for neuroprotection after spinal cord injury, Appl. Mater. Today. 24 (2021) 101109, https://doi.org/10.1016/j.apmt.2021.101109.
[56] L.C. O'Brien, A.S. Gorgey, Skeletal muscle mitochondrial health and spinal cord injury, World J. Orthop. 7 (2016) 628–637, https://doi.org/10.5312/wjo.v7.i10.628.
[57] N.E. Scholpa, R.G. Schnellmann, Mitochondrial-based therapeutics for the treatment of spinal cord injury: Mitochondrial biogenesis as a potential pharmacological target, J. Pharmacol. Exp. Ther. 363 (2017) 303–313, https://doi.org/10.1124/jpet.117.244806.
[58] S.S. Andrabi, J. Yang, Y. Gao, Y. Kuang, V. Labhasetwar, Nanoparticles with antioxidant enzymes protect injured spinal cord from neuronal cell apoptosis by attenuating mitochondrial dysfunction, J. Control. Release 317 (2020) 300–311, https://doi.org/10.1016/j.jconrel.2019.12.001.
[59] K. Suzuki, H. Tanaka, M. Ebara, K. Uto, H. Matsuoka, S. Nishimoto, K. Okada, T. Murase, H. Yoshikawa, Electrospun nanofiber sheets incorporating methylcobalamin promote nerve regeneration and functional recovery in a rat sciatic nerve crush injury model, Acta Biomater. 53 (2017) 250–259, https://doi.org/10.1016/j.actbio.2017.02.004.
[60] T. Wu, M. Tang, The inflammatory response to silver and titanium dioxide nanoparticles in the central nervous system, Nanomedicine 13 (2018), https://doi.org/10.2217/nnm-2017-0270.
[61] R.J. Cooper, M.N. Menking-Colby, K.A. Humphrey, J.H. Victory, D.W. Kipps, N. Spitzer, Involvement of β-catenin in cytoskeleton disruption following adult neural stem cell exposure to low-level silver nanoparticles, Neurotoxicology 71 (2019) 102–112, https://doi.org/10.1016/j.neuro.2018.12.010.
[62] T. Mironava, M. Hadjiargyrou, M. Simon, V. Jurukovski, M.H. Rafailovich, Gold nanoparticles cellular toxicity and recovery: Effect of size, concentration and exposure time, Nanotoxicology 4 (2010) 120–137, https://doi.org/10.3109/17435390903471463.
[63] C. Riggio, M.P. Calatayud, M. Giannaccini, B. Sanz, T.E. Torres, R. Fernández-Pacheco, A. Ripoli, M.R. Ibarra, L. Dente, A. Cuschieri, G.F. Goya, V. Raffa, The orientation of the neuronal growth process can be directed via magnetic

nanoparticles under an applied magnetic field, Nanomedicine Nanotechnology, Biol. Med. 10 (2014) 1549–1558, https://doi.org/10.1016/j.nano.2013.12.008.
[64] M. Marcus, M. Karni, K. Baranes, I. Levy, N. Alon, S. Margel, O. Shefi, Iron oxide nanoparticles for neuronal cell applications: Uptake study and magnetic manipulations, J. Nanobiotechnology 14 (2016) 1–12, https://doi.org/10.1186/s12951-016-0190-0.
[65] L. Huang, B. Xia, Z. Liu, Q. Cao, J. Huang, Z. Luo, Superparamagnetic iron oxide nanoparticle-mediated forces enhance the migration of Schwann cells across the Astrocyte-Schwann cell boundary in vitro, Front. Cell. Neurosci. 11 (2017) 1–14, https://doi.org/10.3389/fncel.2017.00083.
[66] Z. Liu, S. Zhu, L. Liu, J. Ge, L. Huang, Z. Sun, W. Zeng, J. Huang, Z. Luo, A magnetically responsive nanocomposite scaffold combined with schwann cells promotes sciatic nerve regeneration upon exposure to magnetic field, Int. J. Nanomedicine. 12 (2017) 7815–7832, https://doi.org/10.2147/IJN.S144715.
[67] R.L. Azevedo-Pereira, B. Rangel, F. Tovar-Moll, E.L. Gasparetto, M. Attias, C. Zaverucha-do-Valle, R. Jasmin, Mendez-Otero, Superparamagnetic iron oxide nanoparticles as a tool to track mouse neural stem cells in vivo, Mol. Biol. Rep. 46 (2019) 191–198, https://doi.org/10.1007/s11033-018-4460-9.
[68] S. Karimi, Z. Bagher, N. Najmoddin, S. Simorgh, M. Pezeshki-Modaress, Alginate-magnetic short nanofibers 3D composite hydrogel enhances the encapsulated human olfactory mucosa stem cells bioactivity for potential nerve regeneration application, Int. J. Biol. Macromol. 167 (2021) 796–806, https://doi.org/10.1016/j.ijbiomac.2020.11.199.
[69] M. Yuan, Y. Wang, Y.X. Qin, Promoting neuroregeneration by applying dynamic magnetic fields to a novel nanomedicine: Superparamagnetic iron oxide (SPIO)-gold nanoparticles bounded with nerve growth factor (NGF), Nanomedicine Nanotechnology, Biol. Med. 14 (2018) 1337–1347, https://doi.org/10.1016/j.nano.2018.03.004.
[70] F. Papastefanaki, I. Jakovcevski, N. Poulia, N. Djogo, F. Schulz, T. Martinovic, D. Ciric, G. Loers, T. Vossmeyer, H. Weller, M. Schachner, R. Matsas, Intraspinal delivery of polyethylene glycol-coated gold nanoparticles promotes functional recovery after spinal cord injury, Mol. Ther. 23 (2015) 993–1002, https://doi.org/10.1038/mt.2015.50.
[71] P. Madhusudanan, C. Jerard, N. Katiyar, G. Raju, S.A. Shankarappa, Effect of gold nanoparticle treated dorsal root ganglion cells on peripheral neurite differentiation, Toxicol. Vitr. 74 (2021) 105175, https://doi.org/10.1016/j.tiv.2021.105175.
[72] B. Zhang, Z. Ding, J. Dong, F. Lin, Z. Xue, J. Xu, Macrophage-mediated degradable gelatin-coated mesoporous silica nanoparticles carrying pirfenidone for the treatment of rat spinal cord injury, Nanomedicine Nanotechnology, Biol. Med. 37 (2021) 102420, https://doi.org/10.1016/j.nano.2021.102420.
[73] Q. Liu, C.M. Santamaria, T. Wei, C. Zhao, T. Ji, T. Yang, A. Shomorony, B.Y. Wang, D.S. Kohane, Hollow Silica Nanoparticles Penetrate the Peripheral Nerve and Enhance the Nerve Blockade from Tetrodotoxin, Nano Lett. 18 (2018) 32–37, https://doi.org/10.1021/acs.nanolett.7b02461.
[74] B. Mili, K. Das, A. Kumar, A.C. Saxena, P. Singh, S. Ghosh, S. Bag, Preparation of NGF encapsulated chitosan nanoparticles and its evaluation on neuronal differentiation potentiality of canine mesenchymal stem cells, J. Mater. Sci. Mater. Med. 29 (2018) 1–13, https://doi.org/10.1007/s10856-017-6008-2.
[75] G. Li, Q. Xiao, R. McNaughton, L. Han, L. Zhang, Y. Wang, Y. Yang, Nanoengineered porous chitosan/CaTiO3 hybrid scaffolds for accelerating Schwann cells growth in peripheral nerve regeneration, Colloids Surfaces B Biointerfaces. 158 (2017) 57–67, https://doi.org/10.1016/j.colsurfb.2017.06.026.
[76] Y. Guo, A.M. Johnson, M. Zara, M.K. Mishra, R.M. Kannan, N.R. Miller, S. L. Bernstein, Dendrimers target the Ischemic lesion in rodent and primate models of nonarteritic anterior ischemic optic neuropathy, PLoS One. 11 (2016).
[77] E. Nance, F. Zhang, M.K. Mishra, Z. Zhang, S.P. Kambhampati, R.M. Kannan, S. Kannan, Nanoscale effects in dendrimer-mediated targeting of neuroinflammation, Biomaterials 101 (2016) 96–107, https://doi.org/10.1016/j.biomaterials.2016.05.044.
[78] H.J. You, S. Bin Fang, T.T. Wu, H. Zhang, Y.K. Feng, X.J. Li, H.H. Yang, G. Li, X. H. Li, C. Wu, Q.L. Fu, Z. Pei, Mesenchymal stem cell-derived exosomes improve motor function and attenuate neuropathology in a mouse model of Machado-Joseph disease, Stem Cell Res. Ther. 11 (2020) 1–11, https://doi.org/10.1186/s13287-020-01727-2.
[79] M.A. Lopez-Verrilli, A. Caviedes, A. Cabrera, S. Sandoval, U. Wyneken, M. Khoury, Mesenchymal stem cell-derived exosomes from different sources selectively promote neuritic outgrowth, Neuroscience 320 (2016) 129–139, https://doi.org/10.1016/j.neuroscience.2016.01.061.
[80] R. Simeoli, K. Montague, H.R. Jones, L. Castaldi, D. Chambers, J.H. Kelleher, V. Vacca, T. Pitcher, J. Grist, H. Al-Ahdal, L.F. Wong, M. Perretti, J. Lai, P. Mouritzen, P. Heppenstall, M. Malcangio, Exosomal cargo including microRNA regulates sensory neuron to macrophage communication after nerve trauma, Nat. Commun. 8 (2017), https://doi.org/10.1038/s41467-017-01841-5.
[81] S. Mahya, J. Ai, S. Shojae, H.A. Khonakdar, G. Darbemamieh, S. Shirian, Berberine loaded chitosan nanoparticles encapsulated in polysaccharide-based hydrogel for the repair of spinal cord, Int. J. Biol. Macromol. 182 (2021) 82–90, https://doi.org/10.1016/j.ijbiomac.2021.03.106.
[82] H.K. Jahromi, A. Farzin, E. Hasanzadeh, S.E. Barough, N. Mahmoodi, M.R. H. Najafabadi, M.S. Farahani, K. Mansoori, S. Shirian, J. Ai, Enhanced sciatic nerve regeneration by poly-L-lactic acid/multi-wall carbon nanotube neural guidance conduit containing Schwann cells and curcumin encapsulated chitosan nanoparticles in rat, Mater. Sci. Eng. C. 109 (2020) 110564, https://doi.org/10.1016/j.msec.2019.110564.
[83] X. Fang, H. Song, Synthesis of cerium oxide nanoparticles loaded on chitosan for enhanced auto-catalytic regenerative ability and biocompatibility for the spinal cord injury repair, J. Photochem. Photobiol. B Biol. 191 (2019) 83–87, https://doi.org/10.1016/j.jphotobiol.2018.11.016.
[84] M.H. Lee, C.C. Lin, J.L. Thomas, J.A. Li, H.Y. Lin, Cellular reprogramming with multigene activation by the delivery of CRISPR/dCas9 ribonucleoproteins via magnetic peptide-imprinted chitosan nanoparticles, Mater. Today Bio. 9 (2021) 100091, https://doi.org/10.1016/j.mtbio.2020.100091.
[85] S.M. Amr, A. Gouda, W.T. Koptan, A.A. Galal, D.S. Abdel-Fattah, L.A. Rashed, H. M. Atta, M.T. Abdel-Aziz, Bridging defects in chronic spinal cord injury using peripheral nerve grafts combined with a chitosan-laminin scaffold and enhancing regeneration through them by co-transplantation with bone-marrow-derived mesenchymal stem cells: Case series of 14 patient, J. Spinal Cord Med. 37 (2014) 54–71, https://doi.org/10.1179/2045772312Y.0000000069.
[86] C.D.F. Lopes, N.P. Gonçalves, C.P. Gomes, M.J. Saraiva, A.P. Pêgo, BDNF gene delivery mediated by neuron-targeted nanoparticles is neuroprotective in peripheral nerve injury, Biomaterials. 121 (2017) 83–96, https://doi.org/10.1016/j.biomaterials.2016.12.025.
[87] N. Wang, H. Yu, Q. Song, P. Mao, K. Li, G. Bao, Sesamol-loaded stearic acid-chitosan nanomicelles mitigate the oxidative stress-stimulated apoptosis and induction of pro-inflammatory cytokines in motor neuronal of the spinal cord through NF-κB signaling pathway, Int. J. Biol. Macromol. 186 (2021) 23–32, https://doi.org/10.1016/j.ijbiomac.2021.06.171.
[88] B. M, G. M, G. P, F. E, F. R, T.-T. C, Chitosan-based hydrogel to support the paracrine activity of mesenchymal stem cells in spinal cord injury treatment, Sci. Rep. 9 (2019) 6402.
[89] E.A. Elizalde-Peña, I.A. Quintero-Ortega, D.G. Zárate-Triviño, A. Nuño-Licona, J. Gough, I.C. Sanchez, D.I. Medina, G. Luna-Barcenas, (Chitosan-g-glycidyl methacrylate)-xanthan hydrogel implant in Wistar rats for spinal cord regeneration, Mater. Sci. Eng. C 78 (2017) 892–900, https://doi.org/10.1016/j.msec.2017.03.005.
[90] K. Baranes, M. Shevach, O. Shefi, T. Dvir, Gold Nanoparticle-Decorated Scaffolds Promote Neuronal Differentiation and Maturation, Nano Lett. 16 (2016) 2916–2920, https://doi.org/10.1021/acs.nanolett.5b04033.
[91] F. Lavoie-Cardinal, C. Salesse, M. Meunier, P. Koninck De, Gold nanoparticles-assisted all optical localized stimulation and monitoring of Ca 2 signalling in neurons, Sci. Rep. 6 (2016) 20619.
[92] S. Das, M. Sharma, D. Saharia, K.K. Sarma, M.G. Sarma, B.B. Borthakur, U. Bora, In vivo studies of silk based gold nano-composite conduits for functional peripheral nerve regeneration, Biomaterials 62 (2015) 66–75, https://doi.org/10.1016/j.biomaterials.2015.04.047.
[93] A.S. Motamedi, H. Mirzadeh, F. Hajiesmaeilbaigi, S. Bagheri-Khoulenjani, M. A. Shokrgozar, Piezoelectric electrospun nanocomposite comprising Au NPs/PVDF for nerve tissue engineering, J. Biomed. Mater. Res. - Part A 105 (2017) 1984–1993, https://doi.org/10.1002/jbm.a.36050.