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Review Article

Investigating nanoparticle's utilization in stem cell therapy for neurological disorders

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Abstract: Stem cell therapy is a promising area of regenerative medicine, offering potential treatments for various life-threatening disorders. Stem cells are classified based on their differentiation potential into totipotent, pluripotent, and multipotent stem cells. Among them, mesenchymal stem cells (MSCs) are widely used in regenerative medicine due to their tissue regeneration capabilities and ability to differentiate into multiple cell types. Stem cells are being explored for treating neurodegenerative disorders like Parkinson's, Alzheimer's, Huntington's, and amyotrophic lateral sclerosis (ALS). These conditions result from progressive neuronal degeneration, leading to irreversible damage. Challenges such as cell survival, immune rejection, tumor formation, and ethical concerns related to embryonic stem cells need to be addressed. Nanotechnology is emerging as a tool for enhancing stem cell therapy, improving targeted delivery and effectiveness. Nanoparticles possess the ability to create microenvironments as substrates, facilitate targeted administration, and enable real-time, precise imaging of stem cells. This review explores the integration of stem cells and nanotechnology as regenerative medicine tool for neurodegenerative disease treatment, analyzing current strategies and therapeutic approaches. Integrating nanotechnology with stem cell therapy may significantly improve targeted delivery and enhance regenerative outcomes for neurodegenerative disorders.

Keywords: Stem cells, nanoparticles, neurological disorders

Introduction

Stem cell therapy represents a promising domain of regenerative medicine in contemporary healthcare. This advanced sector provides prospects for curing life-threatening disorders. The primary emphasis of healthcare research is on stem cell-based regenerative medicine, which replaces sick tissue with healthy tissue and repairs damaged tissues.

Stem cells are categorized into distinct categories according to their differentiation potential: totipotent stem cells, pluripotent stem cells, and multipotent stem cells [1]. Totipotent cells possess the capability to develop into whole organisms and are generated following the initial divisions post-fertilization. Pluripotent stem cells possess the capacity to develop into the three germ layers found in the embryo. Embryonic stem cells serve as a source for the extraction of pluripotent stem cells. Multipotent stem cells develop into a restricted variety of cell types specific to their tissue of origin. They originate from adult tissues and are utilized in regenerative medicine [2]. Adult stem cells are being considered as gold standard in stem cells therapies [3]. In vitro, mesenchymal stem cells are classified as multipotent stem cells that possess tissue regeneration properties and have the potential to differentiate into a variety of cell types, including osteoblasts, myocytes, adipocytes, and chondroblasts. They manifest the cluster of differentiation (CD) surface markers, which include CD90, CD73, and CD105 through gene expression and are derived from

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bone marrow. Stem cells possess two primary characteristics: their capacity for self-renewal through division to generate new cells and their ability to differentiate into specialized cell types, both of which are essential for the regular functioning of the nervous system [4].

In 2006, researchers made significant progress in stem cell research by generating cells that have comparable physical, chemical, and transcriptional characteristics to embryonic stem cells. They scrutinized that the overexpression of four transcription factors - OCT4, KLF4, SOX2, and MYC - facilitated the generation of pluripotent stem cells from completely differentiated fibroblasts. The discovery of these cells, known as induced pluripotent stem cells, sparked a revolutionary shift in stem cell research, which has continued to this day [5].

The utilization of stem cell therapy in neurodegenerative disorders, ophthalmic conditions, diabetes, dental applications, and dermatological problems is on the rise. Several academic institutions have set up tissue and stem cell banks to aid with stem cell therapy. The California Institute for Regenerative Medicine has established a collection of induced pluripotent cells that provide researchers with cell lines for investigating genetic alterations and disease models [6]. Moreover, the umbilical cord is also utilized in stem cell banking [7]. Stem cells are being utilized in drug delivery as Trojan horses for the treatment of cancer and amyotrophic lateral sclerosis [8, 9]. They possess features such as angiogenic, neurotropic, and anti-inflammatory effects to expedite the repair of wounded tissue. Stem cells are being engineered through gene therapy to enhance functionality with increased selectivity [10].

Neurodegenerative disorders, for instance, Parkinson disease, Alzheimer disease, Huntington disease, and amyotrophic lateral sclerosis pose significant challenges to contemporary medicine globally. These disorders are linked to the progressive degeneration and death of neurons in the brain or spinal cord resulting from damage, stroke, or trauma. Neurons are the fundamental units of the nervous system responsible for transmitting and receiving impulses throughout the body. Neurons possess a restricted ability to repair, leading to cumulative damage from diseases that renders the impairment irreversible. The global impact of these diseases is profound, impacting numerous persons and imposing economic and social burdens. Over 55 million individuals globally are afflicted with Alzheimer's disease [11], and approximately 8.5 million individuals are afflicted with Parkinson's disease [12]. They put a burden on society due to the absence of effective medicines in spite of decades of research. To mitigate the burden of neurodegenerative illnesses, novel therapy techniques are being investigated for their treatment. This resulted in unique ways for stem cell research aimed at regenerating damaged nerve cells and restoring function. The growing research on stem cell therapy has made it a compelling choice, and the use of nanotechnology for the delivery of stem cells in neurodegenerative illnesses is swiftly advancing.

Stem cell research has numerous problems, including cell survival, integrity maintenance, tumor formation, immunological rejection by the host, cell delivery, site-specific targeting, long-term impacts, and monitoring by healthcare experts. Numerous ethical questions pertain to the utilization of embryonic stem cells, including the participation of embryos, permission and ownership of genetic material, ethical ramifications of gene editing, access and equity in stem cell therapies, as well as regulatory and safety concerns. All of these obstacles and ethical considerations must be resolved prior to treatment. This review aims to elucidate the potential of stem cells in conjunction with nanotechnology for neurodegenerative diseases. The goal is to review current stem cell strategies, analyze therapeutic approaches, and explore study stem cells and nanotechnology for neurodegenerative disorders.

Nanotechnology in stem cells

Nanotechnology is the manipulation of materials at the nanoscale to create new structures with enhanced functionality. Nanoparticles may be classified as organic, inorganic, metallic or carbon-based. Organic nanoparticles are composed of organic molecules such as lipids, glycosides, and peptides. Organic nanoparticles are dynamic, biodegradable, exhibit reduced toxicity, and possess the ability to traverse biological barriers. Liposomes, micelles, vesicles, dendrimers, and polymeric nanoparticles constitute organic nanoparticles. Inorganic nanoparticles, composed of inorganic materi-

als, possess distinct physicochemical qualities such as high stability, inertness, and facile functionalization, facilitating cellular entrance and minimizing the risk of immunogenic reactions. Metallic nanoparticles are composed of metals including gold, silicon, silver, magnesium, iron. Magnetic nanoparticles possess an iron oxide with substantial magnetic energy, enabling detection by MRI. Carbon-based nanomaterials exhibit mechanical strength, thermal conductivity, electrical conductivity, and flexibility including carbon nanotubes, nanodiamonds, and graphene.

In field of stem cell therapy, nanotechnology can assist in stem cell isolation, purification, differentiation, imaging, tracking, regenerative medicine, and tissue engineering. Nanomaterials have been used for imaging and tracing, gene or drug delivery, scaffolds for tissue engineering, designed nanostructures have been used to regulate the proliferation and differentiation of stem cells, which will speed up the understanding and controlling the microenvironmental signals, helping to improve stem cells-based therapy. Nanoparticles can assist in stem cell delivery to the dopaminergic regions of the brain, helping to restore the lost neurons. In combination with neuroprotective agents encapsulated in nanoparticles, this therapy could halt or slow down disease progression.

Collagen nanofiber, carbon nanofiber, graphene oxide nanoparticles, and assembling peptides are examples of nanoparticles that are safe, biocompatible, and biodegradable. Magnetic nanoparticles have diverse application for instance, they are utilized for labeling of stem cells and the separation of labeled cells by magnetic force or flow cytometry. The imaging and tracing of stem cells can be performed by different nanoparticles i.e. quantum dots, gold nanorods, and magnetic nanoparticles (MNPs) [13]. In tissue engineering, the designing of nanoscale scaffolds is employed to stimulate stem cells to differentiate into specific cell types that replicate the body's native tissues. In 2006, a study was conducted in which they developed a scaffold to design peptide nanofibers to promote the survival and differentiation of mouse adult neural stem cells in a cell culture system [14]. Nanopatterning is employed to facilitate direct attachment, self-renewal, proliferation, and differentiation of stem cells [15].

Stem cell therapy is frequently linked to a low likelihood of graft survival, challenges in cell integration, immunological rejection, and delayed therapeutic outcomes, which restrict its clinical application. The nanoparticles possess features that stimulate the emission of many bioactive factors for anti-inflammation, anti-apoptosis, immunoregulation, cellular metabolism, protection of dopaminergic neurons, and alleviation of motor dysfunction, rendering them suitable agents for stem cell regulation. Nanoparticles influence the microenvironment of stem cells through nanoscale scaffolds. Nanoparticles are employed to monitor stem cells by labeling.

Neural stem cells

Neural stem cells are usually isolated from embryonic or adult brain tissue. These cells possess the capability to differentiate into different cell types such as neurons, oligodendrocytes, and astrocytes. However, their behavior in vivo is unpredictable due to different factors. Firstly, there is inadequate correlation between the behavior of neural stem cells *in vitro* and *in vivo*. The solution to this issue involves nanostructured scaffolds composed of appropriate nanoscale materials and architectures for the development of neural stem cells, which possess the capacity to replicate in vivo extracellular environments. Secondly, different drugs are employed to stimulate neural stem cells but their physicochemical profile and inadequate bioavailability present challenges. This issue can be addressed by discharging molecules from diverse nanoparticle systems and adjusting the structure and composition of these systems [16].

Various researchers have employed nanotechnology to address the aforementioned issues. Raspa *et al*. have synthesized self-assembling peptides (Ac-FAQ) in conjunction with poly(ε-caprolactone)-poly(d,l-lactide-co-glycolide) (PCL-PLGA), resulting in electrospun fibers for a nanostructured scaffold that exhibited favorable in vivo and in vitro responses for neural stem cell development. In addition, a cellular MRI technique was developed utilizing gold nanoparticle linked with improved deoxythymidine oligonucleotides containing Gd(III) che-

lates and a red fluorescent Cy3 moiety to visualize *in vivo* transplanted human brain stem cells [17]. A study also scrutinized tracking of neural stem cells in rats by labeling them with ultrasmall superparamagnetic iron oxide conjugated to Molday ION Rhodamine B which was detected by dual magnetic resonance and optical imaging [18]. A curcumin-encapsulated PLGA nanoparticles were prepared that effectively differentiated neural stem cells in the hippocampus and subventricular zone of adult rats [19].

Embryonic stem cells

Embryonic stem cells are a type of pluripotent stem cells derived from the inner cell mass of a blastocyst in an embryo. They possess significant differentiation and self-renewal capabilities to develop into many cell types. The risks associated with embryonic stem cells include tumorigenesis and immunological rejection.

Various researchers have employed nanotechnology for targeting stem cells, facilitating delivery of drugs, and enhancing differentiation. A research study prepared superparamagnetic iron oxide nanoparticles for embryonic stem cells (ESCs) labeling which effectively tracked embryonic stem cells in rats with a cortical or spinal cord lesion in animal models of stroke and spinal cord injury. Magnetic nanoparticles have ability to direct stem cells to specific brain regions, making possible for treatment of diseases such as Parkinson's disease and cerebral trauma [20]. Scientists have monitored stem cell development by quantitative real-time PCR and the analysis of immune cell chemistry in mice, where an embryonic stem cell line was expressing green fluorescent protein under the promoter for the MN-specific gene Hb9 [21]. Magnetic nanoparticles were investigated to regulate the size of human embryoid bodies that enhanced neural development efficiency of human embryonic stem cells [22]. In addition layered double hydroxide (LDH) nanoparticles were studied to serve as carriers for the development of motor neurons from mouse embryonic stem cells [23].

Induced pluripotent stem cells

Induced pluripotent stem cells are derived from adult somatic cells through genetic reprogramming, which restores the cells to a pluripotent state by the expression of specific genes and transcription factors that sustain the state stem cell.

Different researchers are exploring ways to efficiently transplant these stem cells in to patients via nanotechnology. The CRISPR/Cas9 [24] and TALENs (transcription activator-like effector nucleases) are being used by researchers to modify the genomes of induced pluripotent stem cells [25]. In order to quickly and accurately produce specific cell lines from induced pluripotent stem cells, a non-viral gene delivery system was created using mesoporous silica nanoparticles [26, 27] formulated heparinized cationic solid lipid nanoparticles encapsulating nerve growth factor, which modulatedthe membrane charge of induced pluripotent stem cells throughout neuronal differentiation.

Mesenchymal stem cells

Mesenchymal stem cells are a type of multipotent adult stem cells capable of differentiating into many lineages and are found in the interstitium of various tissues and organs, for instance, bone marrow, adipose tissue, umbilical cord, menstrual blood, endometrial polyps, and molar cells. Transplanted mesenchymal stem cells provide regenerative potential as they move to damaged cell populations to deliver nutrients to indigenous cells for tissue homeostasis. They participate in promoting angiogenesis, modulating the immune system, facilitating mitosis, and aiding tissue healing and restoration. Different researchers have used nanotechnology for improving efficiency of mesenchymal stem cells. A study utilized engineered poly (lactic-co-glycolic acid) scaffold to facilitate the proliferation of mesenchymal stem cells, positively impacting their division and neural development [28]. A research developed dextran-coated iron oxide nanoparticles that enhance the efficiency of human mesenchymal stem cells in a mouse model of Parkinson disease rendering them as a possible clinical tool [29].

Nano-based stem cell therapy for neurodegenerative disorders

Degeneration of the nervous system owing to the death of neurons is a hallmark of neurodegenerative diseases. Conditions that cause degeneration of nervous system include

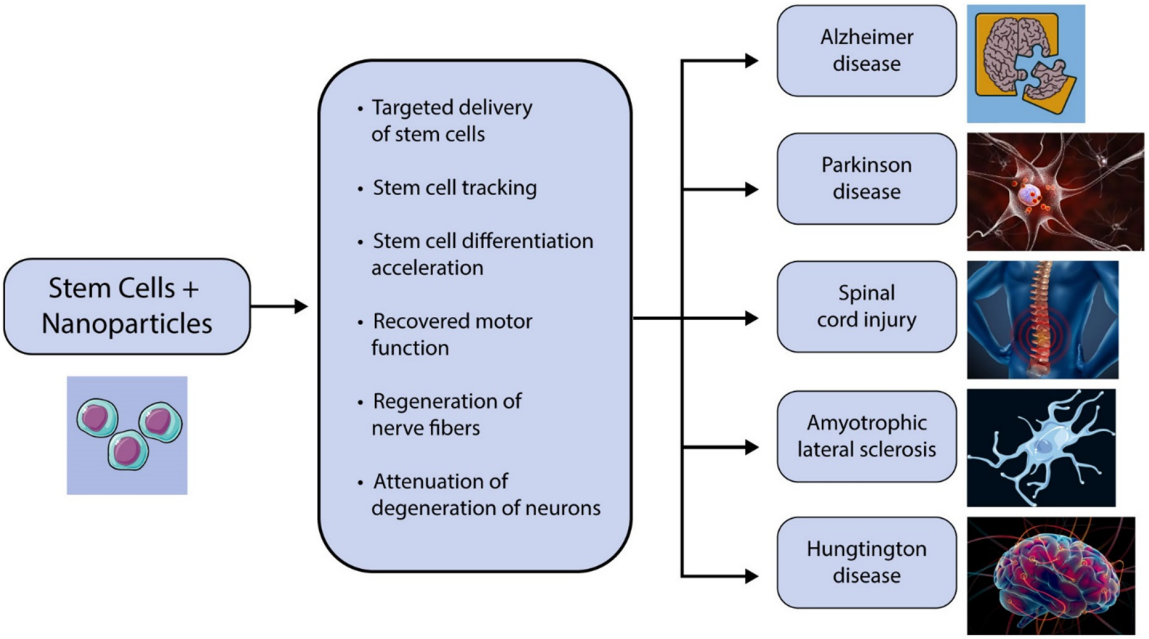

Figure 1. Stem cell nanotechnology for neurodegenerative disorders.

Parkinson's disease, Alzheimer's disease, and spinal cord injuries. There is the possibility of managing disorders in order to minimize symptoms. Although, it is difficult to transport drugs to the brain because of the blood-brain barrier, a membrane that prevents outside substances from entering the central nervous system. Alternatively, promising approach that shows promise in addressing the drug delivery issue is the integration of stem cells with nanotechnology (**Figure 1**).

Alzheimer disease

Alzheimer's disease is a form of dementia resulting from the progressive degeneration of basal forebrain cholinergic neurons. It is characterized by loss of memory and cognitive abilities. The presence of β-amyloid plaques and tau neurofibrillary tangles is indicative of Alzheimer disease (AD) [30]. The lesions contain abundant amyloid plaques and neurofibrillary tangles [31]. Stem cell therapy coupled with nanotechnology is a promising avenue for disease treatment. Neural stem cell therapy has been documented to enhance memory and cognitive function in rat models of Alzheimer's disease [32], developed nerve growth factor-poly (ethylene glycol)-poly (lactic-co-glycolic acid) nanoparticles that enhanced the development of neural stem cells *in vitro*. In another study galantamine hydrobromide-loaded solid lipid nanoparticles were formulated in conjugation with bone marrow-derived mesenchymal stem cells, providing protection against Alzheimer's disease in rat model [33]. In addition chiral nanoparticles were developed having high chirality to hasten the differentiation of neural stem cells (NSCs) in mouse into neurons which have potential for biomedicine [34].

A group of researchers developed human Wharton's jelly-derived mesenchymal stem cells branded with dextran coated superparamagnetic iron oxide nanoparticles to magnetically deliver them to the hippocampus area which caused improvement of cells in hippocampus [35]. Shahidi *et al.* engineered mesenchymal stem cells labeled with polyvinyl alcohol-coated selenium nanoparticles for the co-treatment of rats having Alzheimer's disease, resulting in enhanced memory reacquisition and significant neuroprotection effect [36]. Yu *et al*. devised a novel methodology for cell differentiation and oxidative stress alleviation by integrating antioxidative nanozymes inside a matric of metal and organic compounds infused with small interfering RNA (siSOX9) and retinoic acid, that ultimately resulted in nerve regeneration [37]. Gholamigerav and his coworkers formulated a therapy that combines mesenchymal stem cells with selenium nanoparticles,

yielding superior neuroprotection compared to individual treatments [38]. Similarly, human Wharton's jelly-derived mesenchymal stem cells tagged with iron oxide nanoparticles, exhibiting enhanced cerebral retention efficacy under magnetic guiding [39]. Wang *et al*. engineered human umbilical cord mesenchymal stem cells tagged with superparamagnetic nanoparticles consisting of Fe_3O_4 and polydopamine shells, enhancing targeted delivery, memory enhancement, cognitive function, and neuroprotective factor production in mice [40]. Neural stem cells were labeled with ferritin nanoparticles, resulting in a neurosphere that enhanced the self-renewal capability and differentiation of neural stem cells [41]. In another research human neural stem cells were engineered embedded with gold nanoparticles, which demonstrated a protective effect against Aβ-induced cellular damage and mitochondrial dysfunction in human neural stem cells [42].

Parkinson disease

Parkinson's disease is a neurological disorder characterized by the progressive deterioration of the central nervous system, resulting from a reduction in dopaminergic neurons in the substantia nigra. Dyskinesia, rigidity of the limbs, imbalance, and rest tremors are motor issues that may appear as signs of Parkinson disease. The progressive nature of Parkinson's disease over time makes it prone to drugs resistance. The potential for improved neuroprotection and tissue repair abilities in Parkinson's disease is being explored by stem cell regeneration therapy. Nanomaterials increase specific surface area, reactive sites, surface reactivity, and biocompatibility. Nanomaterials, in conjunction with stem cell therapy, function as drugs carriers and facilitate the tracking of stem cells [43]. Magnetic nanoparticles based human adipose stem cells, leads to the improved stem cell-based therapy [44]. Biocompatible and traceable polymeric nanoparticles (NPs) containing perfluoro-1, 5-crown ether (PFCE) and complex microRNA-124 were found to regulate neuronal gene expression. These nanoparticles effectively enhanced the intrinsic brain repair mechanism by internalization of miR-124 NPs by neural stem cells, promoting neuronal differentiation [45]. Another study developed super paramagnetic iron oxide nanoparticles for labeling of adipose-derived stem cells in a rat model of PD, where they used external magnets to deliver and track transplanted stem cells in the target tissue [46].

An injectable bioactive hydrogel utilizing tannic acid and gold nano-crosslinker was found to enhance the proliferation and development of neural stem cells for the treatment of rats. This study leads to the observation that it has anti-inflammatory and antioxidative capabilities [47]. Human mesenchymal stem cells were engineered with dextran-coated iron oxide nanoparticles, that improved differentiation of stem cells to dopaminergic neurons and augmenting neuroprotection [29]. Perfluoro-1,5-crown ether, a coat of protamine sulphate, and complex microRNA-124 were used to create biocompatible and traceable polymeric nanoparticles that efficiently entered neural stem/progenitors cells and neuroblasts and promoted their neuronal commitment and maturation [45]. In rat models of Parkinson's disease, a magnetically focused cell delivery method was created for olfactory ectomesenchyme stem cells via the internasal pathway, which demonstrated improved therapeutic results [48]. In another research nanoparticles were developed coated with neural stem cell membranes loaded with antisense oligonucleotides, facilitating the distribution of these oligonucleotides and enhancing dopaminergic neuron regeneration for the treatment of Parkinson's disease [49].

Spinal cord injury

Spinal cord injury (SCI) results from damage to the spinal cord. It is a debilitating condition characterised by deficits in motor, sensory, and autonomic functions resulting from trauma or injury. Numerous spinal cord injuries result from bullet penetration, vehicular collisions, athletic incidents, or falls.

Spinal cord damage results in two fundamental pathophysiological events: primary injury and secondary injury. The primary injury results from initial trauma, pressure or mechanical forces that cause the rupture of blood vessels and damage to neurons. The secondary injury is induced by chemical reactions and biological processes subsequent to the primary injury, leading to oxidative damage, calcium-mediated injury, immune responses, necrosis, cerebral hemorrhage, inflammatory reactions, oedema,

and additional tissue damage, culminating in axonal damage, demyelination, and cavitation at the injury site. This results in the formation of a glial scar, marked by increased neuronal and oligodendrocyte mortality, as well as an elevation of axonal growth inhibitory factors. The quality of life is diminished when a spinal cord injury occurs. For the therapy of this condition, appropriate therapeutic measures are required. In rat models, stem cell therapy has demonstrated positive effects, making it a potentially useful therapeutic alternative [50]. A hybrid alginate-chitosan hydrogel loaded with valproic acid chitosan nanoparticles was synthesized that activated human endometrial stem cells for the purpose of spinal cord injury regeneration [51]. Rahimi et al. (2023) developed a scaffold using cerium oxide nanoparticles to enhance the proliferation and regeneration of nerve cells in a rat model of spinal cord injury, resulting in motor improvement and pain reduction [52]. Biocompatible polymeric nanoparticles containing lipopolysaccharide-bonded chitosan and quantum dots were also found to stimulate reactive astrocytes in spinal cord injury [53].

Magnetic nanoparticles in transplantation of mesenchymal stem cells, facilitate functional restoration in spinal cord injury patients by promoting axonal regeneration and sprouting [54]. A hybrid gelatin/alginate hydrogel scaffold infused with curcumin and poly (lactic-co-glycolic acid), subsequently implanted with endometrial stem cells, resulted in nerve fiber regeneration [55]. Liu *et al*. (2022) synthesized selenium nanoparticles that induced differentiation and proliferation of neural stem cells, hence facilitating nerve regeneration [56]. Soto *et al*. (2021) synthesized citric acid-coated superparamagnetic iron oxide nanoparticles that were conjugatged to adipose-derived mesenchymal stem cells, facilitating systemic transplantation [57].

Curcumin-loaded noisome nanoparticles positively influenced human neural stem cells in a rat model, presenting a possible therapeutic method for traumatic brain injury [58]. Neural stem cells embedded in a dual-degradable hydrogel containing siRNA-Sema3A-loaded poly-l-lysine-coated gold nanoparticles, demonstrated functional recovery in rat models of spinal cord injury [59]. Another study investigated the impact of a pulsed electromagnetic field on magnetic nanoparticle (MNP)-infused human bone marrow-derived mesenchymal stem cells in the damaged spinal cord of rats to facilitate lesion repair [60]. Electrospun thiolate (SH)/aligned (A) poly(lactic-co-glycolic acid) (PLGA) nanofibrous mats conjugated with gold nanoparticles, demonstrated favorable outcomes in spinal cord injury [61].

Mahya *et al*. (2021) formulated an alginate/chitosan hybrid hydrogel infused with berberine/chitosan nanoparticles, subsequently including endometrial stem cells, demonstrating beneficial results [62]. In a study gold nanospheres were utilized to label stem cells for their transfer into the spinal cord, enabling real-time visualization for enhanced precision and non-toxic transport of stem cells [63]. While umbilical cord mesenchymal stem cells labeled with aggregation-induced emission (AIE)-Tat nanoparticles were found useful in tracing, repair and treatment of spinal cord injury [64]. Lee *et al*. (2020) developed macrophage membrane-fused exosome-mimetic nanovesicles (MF-NVs) by combining macrophage membranes with MSCs (mesenchymal stem cells) derived from umbilical cord blood, demonstrating therapeutic promise in mouse SCI (spinal cord injury) model [65]. Zeraatpisheh *et al*. developed fingolimod-loaded poly lactic-co-glycolic acid nanoparticles injected by neural stem/progenitor cells in a murine model, resulting in tissue regeneration and enhanced neurological capabilities [66]. Mouse embryonic stem cells tagged with superparamagnetic iron oxide nanoparticles were monitored via MRI indicating potential use of magnetic nanoparticles in medical imaging [67]. Similarly Sykova and Jendelova utilized iron oxide nanoparticles to label bone marrow mesenchymal and embryonic stem cells for the assessment of cellular migration to a lesion site via magnetic resonance imaging [68]. Li *et al*. engineered MnO2 nanoparticle-dotted hydrogel to facilitate the growth of mesenchymal stem cells (MSCs) through adhesive and nerve tissue bridging [69] (**Table 1**).

Huntington disease

Huntington's disease is a rare, inherited condition that progressively degenerates nerve cells in the brain. Huntington's disease impairs an

Table 1. Application of stem cells and nanoparticles therapy for treatment of neurodegenerative disorders

Uses of stem cells	Nanoparticles	Stem cells	Neurodegenerative disorders	References
Learning and memory improvement Replenishment of basal forebrain cholinergic neurons	Galantamine nanoparticles	Mesenchymal stem cells	Alzheimer disease	31
Differentiation of neural stem cells into functional neurons was accelerated	Chiral nanoparticles	Neural stem cells	Alzheimer disease	32
Attenuation of degeneration of neurons Boosting of cholinergic functions in the hippocampus	Superparamagnetic Iron Oxide Nanoparticles	Mesenchymal stem cells derived from human Wharton's jelly	Alzheimer disease	33
Reducing the deposition of Aβ Increasing the concentration of brain-derived neurotrophic factor Neuroprotection	Selenium nanoparticles	Adipose-derived mesenchymal stem cells	Alzheimer disease	34
Recovered motor function	Magnetic nanoparticles	Adipose derived stem cells	Parkinson disease	42
Promoted their neuronal commitment and maturation of neural stem cells	Nanoparticles (NPs) containing perfluoro-1,5-crown ether (PFCE) and coated with protamine sulfate to complex microRNA-124	Neural stem cells	Parkinson disease	43
Targeted delivery and homing of stem cells	Super paramagnetic iron oxide nanoparticles	Adipose-derived stem cells	Parkinson disease	44
Exhibition of self-healing property Long-term proliferation and differentiation of stem cells toward neurons.	Hydrogel prepared by cross-linking chitosan and tannic acid modified gold nano-crosslinker	Neural stem cells	Parkinson disease	45
Regeneration of the damaged nerve fibers	Alginate -chitosan hydrogel with valproic acid containing chitosan nanoparticle	Human endometrium stem cells	Spinal cord injury	49
Nerve regeneration Motor improvement Pain reduction	Scaffold containing cerium oxide nanoparticles	Neural stem cells	Spinal cord injury	50
Regeneration and sprouting of axons Reducing formation of post-traumatic syrinx	Magnetic nanoparticles	Mesenchymal stem cells	Spinal cord injury	52
Stem cells tacking and treatment of motor dysfunction	Superparamagnetic iron oxide nanoparticles	Human embryonic stem cells	Huntington disease	69
Increased the differentiation rate and myelinogenic potential of Schwann-like cells	Nerve growth factor- chitosan nanoparticles	Human adipose-derived stem cells	Huntington disease	70
Tracking of stem cells	Labelling with fluorescence nanoparticles and Hoechst-33258	Umbilical cord mesenchymal stromal cells	Amyotrphic lateral sclerosis	74

individual's functional abilities. It typically leads to physical, mental, and psychological disorders. In a rat model of Huntington's disease superparamagnetic iron oxide nanoparticles tagged mesenchymal stem cells, which were found to lessen cell tracking and brain damage [70]. Islam *et al*. used human embryonic stem cells tagged with superparamagnetic iron oxide nanoparticles to alleviate motor impairment in a Huntington rat model [71]. Razavi *et al*. synthesized nerve growth factor and gold-chitosan nanoparticles and assessed the differentiation potential of human adipose-derived stem cells (h-ADSCs) into Schwann-like cells [72]. In another study ferritin nanoparticles were engineered to enhance the self-renewal and differentiation of neural stem cells and neural progenitor cells [41]. Semeano et al. developed magnetic nanoparticles (MNPs) within polymeric coatings that triggered neural differentiation of murine embryonic stem cells and human induced pluripotent stem cells through an external magnetic field, promoting migration and neuronal maturation [73].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is an idiopathic, fatal condition that leads to the degeneration of the human motor system. Amyotrophic lateral sclerosis is categorized as motor neuron disease. The damage to both upper or lower motor neurons can cause muscle weakness and eventual paralysis. It is primarily classified within the neuromuscular domain and non-motor neuroaxis in disease pathology.

Bigni et al. utilized superparamagnetic iron oxide nanoparticles to identify human amniotic fluid cells for cellular tracking in a murine model [74]. A group of scientists utilized growth factors encapsulated in mesoporous nanoparticles on a mouse embryonic stem cell line expressing green fluorescent protein (GFP) controlled by promoter for the MN-specific gene Hb9, resulting in neural development [21]. Violatto *et al*. evaluated the behavior of umbilical cord mesenchymal stromal cells labeled with fluorescent nanoparticles in healthy or early symptomatic transgenic mice, suggesting it as a potential tracking method [75].

A study investigated the effect of FM19G11-loaded gold nanoparticles on self-renewal and proliferation processes in ependymal stem progenitor cells [76]. An in vivo study scrutinized human iPSC-derived from neural cells labeled with silica-coated cobalt zinc ferrite nanoparticles and poly-l-lysine-coated iron oxide superparamagnetic nanoparticles to examine their effects on proliferation and neuronal differentiation, indicating their potential as a candidate for in vivo therapy [77]. Park *et al*. (2020) studied the effects of ultrasmall iron oxide nanoparticle surface coatings on proliferation, cellular uptake, and multipotency of neuronic stem cells [78]. Kou *et al*. (2021) developed amphiphilic solid lipid nanoparticles encapsulating nerve growth factor and retinoic acid to facilitate the differentiation of induced pluripotent stem cells into neurons [79]. It is established that engineered nanomaterial-based scaffolds by mimicking the stem cell microenvironment, improve their survival and differentiation into neurons [80, 81]. However, improving the capacity of regulating the microenvironment is essential factor for controlling tissue regeneration and manipulating stem cell behavior [82].

Conclusion

The integration of nanoparticles and stem cell therapy offers numerous advantages in the treatment of neurological diseases. Treatment of neurological diseases requires the understanding of molecular mechanisms behind major conditions. Nanoparticles provide the microenvironment for the investigation of these molecular mechanisms. Optimization of the nanoparticles is essential for efficient targeted delivery and differentiation of stem cells. The use of nanotechnology in stem cell therapy has transformed the impact of stem cell viability, heterogeneity, uniformity, regulated differentiation, and tumor formation rates on transplantation. As research on novel nanomaterials expands, enhanced nanomaterials that will advance stem cell therapy are being identified. The primary focus of the research is the toxicity of nanoparticles, with the development of biocompatible nanotherapeutics.

Disclosure of conflict of interest

None.

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