REVIEW

Nanotherapeutic and Stem Cell Therapeutic Strategies in Neurodegenerative Diseases: A Promising Therapeutic Approach

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Abstract: Neurodegeneration is characterized by progressive, disabling, and incurable neurological disorders with the massive loss of specific neurons. As one of the most promising potential therapeutic strategies for neurodegenerative diseases, stem cell therapy exerts beneficial effects through different mechanisms, such as direct replacement of damaged or lost cells, secretion of neurotrophic and growth factors, decreased neuroinflammation, and activation of endogenous stem cells. However, poor survival and differentiation rates of transplanted stem cells, insufficient homing ability, and difficulty tracking after transplantation limit their further clinical use. The rapid development of nanotechnology provides many promising nanomaterials for biomedical applications, which already have many applications in neurodegenerative disease treatment and seem to be able to compensate for some of the deficiencies in stem cell therapy, such as transport of stem cells/genes/drugs, regulating stem cell differentiation, and real-time tracking in stem cell therapy. Therefore, nanotherapeutic strategies combined with stem cell therapy is a promising therapeutic approach to treating neurodegenerative diseases. The present review systematically summarizes recent advances in stem cell therapeutics and nanotherapeutic strategies and highlights how they can be combined to improve therapeutic efficacy for the treatment of neurodegenerative diseases.

Keywords: nanotherapeutic, nanomaterials, stem cell therapy, neurodegenerative diseases

Introduction

Neurodegenerative diseases are characterized by the formation of disease-specific misfolded proteins, progressive neuronal degeneration and loss, and, ultimately, they lead to cognitive and/or sensorimotor dysfunction. They include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple system atrophy (MSA).[1–3] In these diseases, some specific neuronal subsets, such as dopaminergic neurons, motor neurons, or cholinergic neurons, gradually lose their structure, function, or number, leading to specific types of nervous system dysfunctions.[4,5] Therapeutic progress in neurodegenerative diseases remains slow due to insufficient understanding of disease pathogenesis and the difficulty of drugs crossing the blood–brain barrier (BBB).[6–8] Currently available treatments for neurodegenerative diseases can only alleviate symptoms and are not sufficient to prevent neurodegenerative processes. Therefore, effective treatments are urgently needed.

Among various therapeutic approaches, stem cell therapy is considered as one of the most promising approaches for the treatment of neurodegenerative diseases.[5,9,10] Stem cell-based therapeutic strategies mainly include directly replacing damaged cells in interested tissues by transplanting exogenous stem cells or indirectly promoting the renewal of damaged nerve tissues by activating endogenous neural progenitor cells, as well as autocrine/paracrine effects.[11,12] However, stem cell therapy is hampered by critical issues such as poor differentiation and survival after cell transplantation, insufficient homing of stem cells to the injured site, and the inability to track and monitor the injected/transplanted stem cells in vivo.[13–15]

With the development of nanotechnology, nanomaterials hold great promise in the treatment of neurodegenerative diseases due to their unique properties, such as high surface area-to-volume ratios, tunable surface chemistry, enhanced electrical conductivity, high mechanical strength, unique fluorescence and superparamagnetic properties.[16–18] These unique properties enable some nanomaterials to combat oxidative stress and scavenge abnormally aggregated proteins.[19–21] Meanwhile, since nanomaterials can cross the BBB, they are ideal stem cell/drug/gene carriers to achieve targeted delivery to the brain and even allow noninvasive tracking by imaging techniques.[6,22–24] Furthermore, engineered nanomaterial-based scaffolds can mimic the stem cell microenvironment to improve stem cell survival and promote their differentiation into neurons.[13,25] Therefore, the cooperation of nanotherapeutic and stem cell therapeutic strategies can improve the therapeutic effect of neurodegenerative diseases and obtain better clinical benefits. Accordingly, this review focuses on recent advances and systematically summarizes the applications and challenges of nanotherapeutics combined with stem cell therapy for the treatment of neurodegenerative diseases.

Stem Cell Therapeutic Strategies

Stem cells are a class of cells that can proliferate, self-renew, and differentiate into various mature cell lines. Stem cell therapy has been used to treat neurodegenerative diseases for decades, especially for the treatment of PD, with considerable success in various cell transplantation studies.[26–28] Stem cell therapeutic strategies for neurodegenerative diseases mainly include direct replacement of damaged or lost cells, secretion of neurotrophic and growth factors by autocrine/paracrine effects, or activation of endogenous neural precursor cells.[11,29,30] Endogenous neural precursor cells are usually poorly differentiated; exogenous stem cells promote their proliferation and differentiation and restore cell survival microenvironments, enabling activation of endogenous neural precursor cells.[29] The transplanted cells provide a variety of bioactive exosomes, neurotrophic factors, and cytokines that play important therapeutic roles for the injured nerve tissue by self-secretion as well as promoting the secretion of peripheral nerve cells, such as nerve growth factor (NGF), neurotrophin-3 (NT3), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and insulin growth factor (IGF).[31–33] These secreted bioactive products can promote endogenous neuronal growth, stimulate neurogenesis, decrease apoptosis, regulate inflammation, and encourage synaptic connection from damaged neurons.[11,34] Furthermore, stem cells have a homing effect: they can recognize and migrate to the injury or lesion site and then generate new neural cells to repair the injury.[35,36]

At present, embryonic stem cells (ESCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) are the main stem cell types used in the treatment of neurodegenerative diseases.[11,29,37] As shown in Figure 1, the benefits and limitations of these stem cells in basic research and preclinical trials are summarized. Each type of stem cell has its particular advantages and disadvantages, which require understanding the characteristics of the various stem cell types and their rational design based on the desired application and outcome.[5,38]

Nanotherapeutic Strategies

Nanotherapeutic strategies increasingly play an important role in the diagnosis and treatment of neurodegenerative diseases in recent years.[39,40] Various novel nanomaterials are fabricated for the treatment of neurodegenerative diseases (Figure 2). Drug treatment of neurodegenerative diseases often fails due to the poor permeability of compounds to the BBB, which functions as a defense system and prevents the penetration of most drugs, while nanomaterials can pass through.[8,15] Therefore, nanomaterials are often fabricated as carriers for drugs/genes/cells. In order to obtain "intelligence" nano-drug delivery systems, functionalized targeting ligands (eg, RGD Peptides, transferrin, insulin) can confer targeting specificity to nanocarriers.[41] In addition, the controlled release of loaded drugs can be achieved by self-degradation of the carrier, or by internal or external stimuli (eg, redox, pH, temperature, magnetic field, light, etc.), thereby minimizing the dosage of drugs.[42,43] Nanocarriers can provide protection for their loaded "cargo" and effectively transport them to inaccessible areas, such as the brain.[8]

Protein misfolding and aggregation is a common pathogenic hallmark in various neurodegenerative disorders, including AD, PD and HD.[2] Studies have shown that nanomaterials can act as bioactive nanomedicines to eliminate reactive oxygen species (ROS) and even suppress toxic protein aggregation.[21,44] More importantly, some nanomaterials possess enzymatic properties that can effectively catalyze enzyme substrates under mild conditions.[45] They can serve as an alternative to natural enzymes and are expected to provide new ideas and approaches for the treatment of neurodegenerative diseases.[20,46]
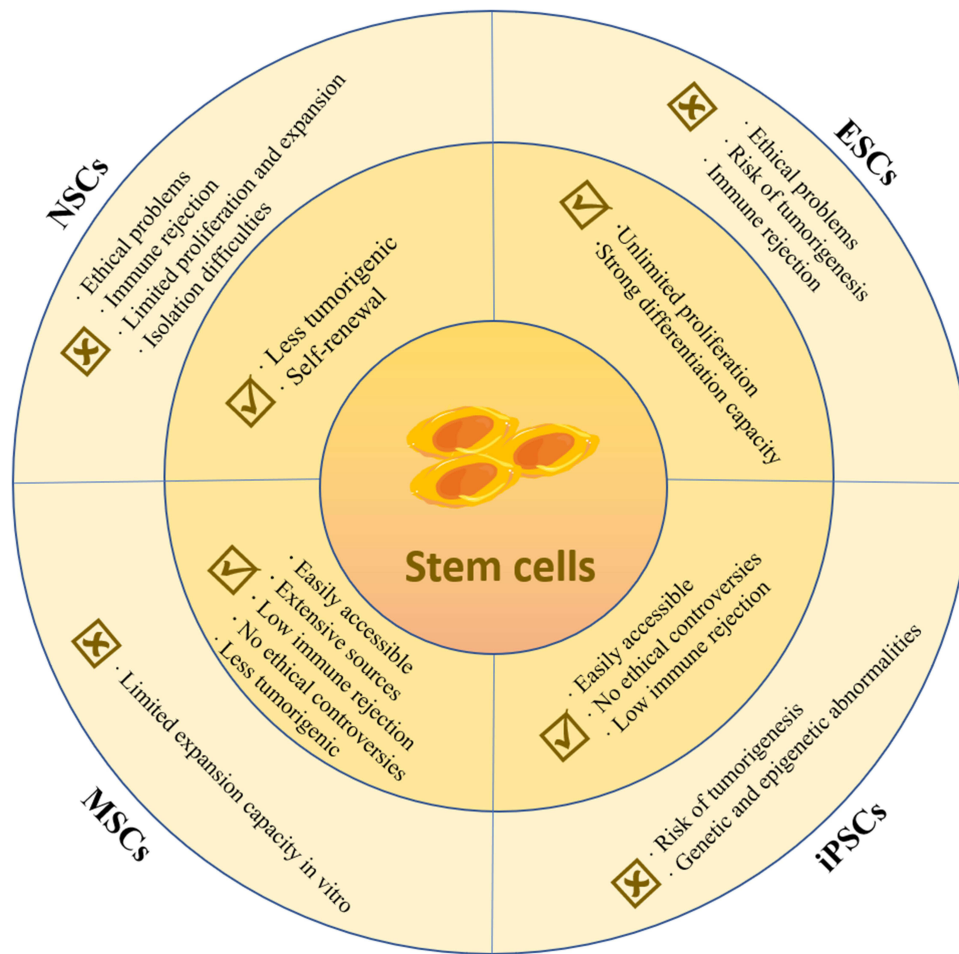
Figure 1 Advantages and limitations of various types of stem cells in the treatment of neurodegenerative diseases.
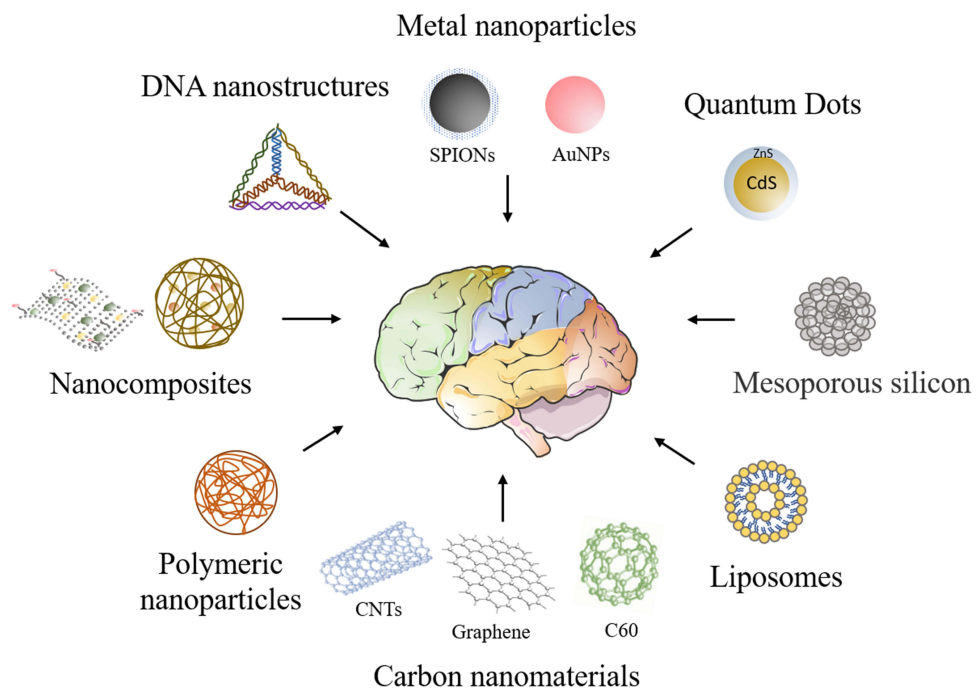

Figure 2 Various novel nanomaterials for the treatment of neurodegenerative diseases.

Additionally, nanoparticles can also act as bioactive nanomedicines to clear abnormally aggregated proteins by modulating the autophagy-lysosomal pathway (ALP) and the ubiquitin proteasome system (UPS) pathways.[47,48]

In addition, nanomaterials can also be used for imaging/contrast/tracing in neurodegenerative disease treatment. Nanomaterials including rare-earth fluorescent materials, metal nanoclusters as well as quantum dots (QDs) can be exploited as fluorescent agents for bioimaging.[49,50] Also of note, due to the excellent magnetic properties and optical properties, gold nanoparticles (AuNPs) as well as superparamagnetic iron oxide nanoparticles (SPIONs) can also serve as contrast agents for medical real-time imaging.[51,52]

Combined Nanotherapeutic and Stem Cell Therapeutic Strategies for the Treatment of Neurodegenerative Diseases

The dimensionality of nanomaterials plays an important role in the formation of their physical, chemical, and biological properties. Nanomaterials can be classified into zero-dimensional (0D, three dimensions are in the range of nanoscale), eg, nanoparticles; one-dimensional (1D, one dimension is not in the nanoscale range), eg, nanotubes, nanowires, and nanofibers; and two-dimensional (2D, two dimensions are not in the nanoscale range), eg, graphene and polymer membranes.[53] 0D nanomaterials are more suitable as bioactivate supplements, nanocarriers or cell labels for stem cell therapy; 1D or 2D nanomaterials and their composites are more worthy of investigation and exploration as 2D/three-dimensional (3D) nanoscaffolds for stem cell differentiation.

Currently, nanotherapeutic strategies as well as stem cell therapy have shown some advantages and certainly some inadequacies in the treatment of neurodegenerative diseases, respectively. The combination of the two methods could have advantages complementary to each other and improve the therapeutic efficacy. Therefore, stem cell therapy in collaboration with nanotherapeutic strategies will show great potential for the treatment of neurodegenerative diseases (Figure 3).
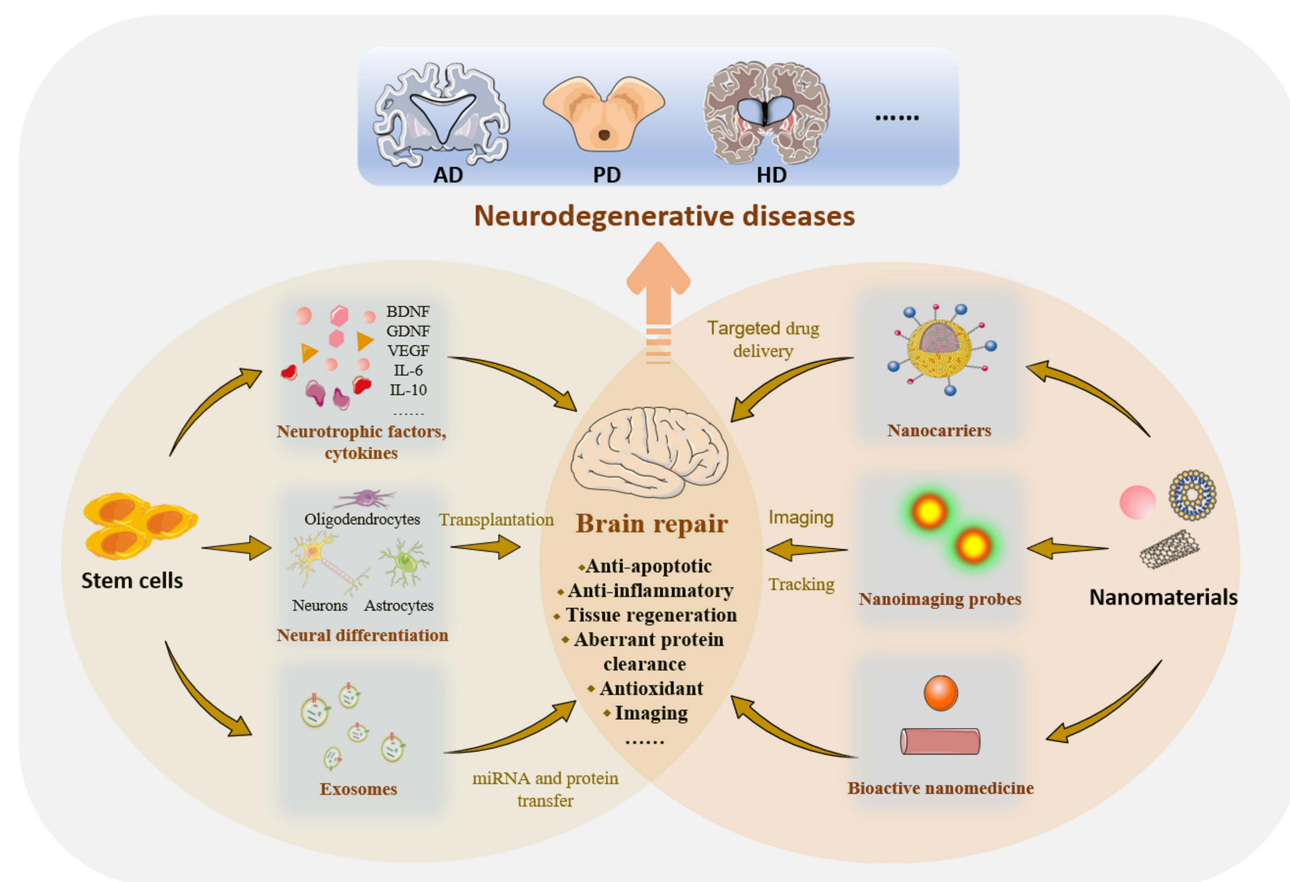

Figure 3 Schematic illustration of the cooperation of nanomaterials and stem cell therapies for brain repair in neurodegenerative diseases.
Abbreviations: BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; VEGF, vascular endothelial growth factor; IL-6, Interleukin-6; IL-10, Interleukin-10.

Nanoparticles as Bioactivate Supplements for Stem Cell Neural Differentiation

In addition to chemical stimuli, physical stimuli can also influence the fate of stem cell differentiation. The size, shape, charge, and surface modification of nanoparticles may all have an impact on the differentiation fate of stem cells.[16,54,55] Nanoparticles can act as mechanical stimuli to activate certain signaling pathways in stem cells, thereby inducing differentiation.[56] Thus far, nanoparticles including carbon nanoparticles, metal nanoparticles, semiconductor nanoparticles, and DNA nanostructures have been demonstrated to promote stem cells toward neural differentiation through their physicochemical properties.[57–61]

Carbon nanoparticles, including carbon nanotubes (CNTs), graphene, and carbon 60 (C60), have been studied for neural differentiation of stem cells.[55] For example, Ren et al synthesized a water-soluble fullerene C60 derivative by modifying amino acid (alanine) residues on its surface (Ala-C60).[62] The results show that Ala-C60 not only promoted the proliferation and differentiation of NSCs into neurons but also could resist oxidative stress.[62] In addition, co-transplantation of CNTs/human olfactory bulb-derived NSCs mixture restored cognitive deficits and neurodegenerative changes in a trimethyltin-induced neurodegenerative rat model.[63] Here, CNTs appeared to provide support while increasing the tendency of transplanted NSCs to differentiate into neurons rather than glia and thus may serve as promising candidates in stem cell therapy for different neurodegenerative diseases.[63]

In addition to the general properties that nanomaterials possess, metal nanomaterials have unique optical, electrical, and magnetic properties that can regulate stem cell fate through the introduction of external electromagnetic fields (EMF).[64–66] As representative metal nanoparticles, AuNPs are known for their optoelectronic properties, biosafety, and high flexibility in particle size, shape, and functional structures.[23,67] AuNPs become transiently magnetized when exposed to a specific EMF frequency, thus enabling more direct transmission of EMF energy to the target cells, which in turn regulates the stem cell fate.[65,68] Chang et al injected arginine-glycine-aspartic acid (RGD)-conjugated AuNPs into the mouse hippocampal dentate gyrus simultaneously with EMF stimulation and showed that they could effectively activate adult brain NSCs in the mouse brain and increase hippocampal neurogenesis in the brains of an aged and progeria mouse model, thus alleviating aging symptoms.[65] Similarly, electromagnetic AuNPs facilitate efficient direct lineage reprogramming to induce dopamine neurons under specific EMF conditions, effectively and non-invasively alleviating symptoms in a mouse PD model.[68]

Selenium nanoparticles (SeNPs), as a kind of semiconductor nanomaterial, can scavenge free radicals and are an effective antioxidant with neuroprotective effects.[69] In AD rat models, SeNPs not only improve cognitive impairment but also increase the level of BDNF and reduce oxidative stress in the brain.[70,71] Co-administration of SeNPs and MSCs may provide a suitable environment for the proliferation and differentiation of transplanted cells, as well as improve cell survival, which is better than that of SeNPs or MSCs treatment alone.[70,71]

Nanomaterials as Carriers to Deliver Drugs and Stem Cells for Neurodegenerative Disease Treatment

As mentioned above, with the advantages of good biocompatibility and easy functionalization, nanoparticles are ideal carriers for nucleic acid and drug delivery in vitro and in vivo and have great potential for biomedicine applications. These carriers can load and transport cargos by adsorption, embedding, or covalent binding. Various nanomaterials, such as inorganic nanoparticles, polymer nanoparticles, DNA nanostructures, and lipid nanoparticles, have shown great potential in stem cell therapy of neurodegenerative diseases.[72–79] Among them, composite nanocarriers, which have multiple functions and can act coordinately and synergistically with each other, have attracted increasing attention. Zhang et al constructed a traceable PCB-based poly (2-hydroxyethyl methacrylate)-RA-poly (carboxybetaine) cell-penetrating peptide (PHEMA-RA-PCB-CPP)/SPIONs/siSOX9 delivery system with temporally controlled release of siSOX9 and RA, which can effectively control the differentiation of NSCs into neurons and significantly improve the cognition and memory of AD mice.[80] Meanwhile, due to the presence of SPIONs in this delivery system, it can also be tracked by magnetic resonance imaging (MRI) in vivo. Notably, during stem cell therapy, pathologically high levels of oxidative stress at the injury site can damage transplanted/newborn neurons, thereby affecting the efficacy of stem cell therapy, and nanomaterials with nanozyme activity appear to address this problem well.[19,20,81] Ceria-decorated metal-organic framework nanoparticles with nanozyme activity can be used to co-deliver siSOX9 and RA to promote neurogenesis.[82] On the one hand, the cooperation of siSOX9 and RA can well promote neuronal directional differentiation. On the other hand, ceria possesses superoxide dismutase (SOD)-like and catalase (CAT)-like activities, which can eliminate ROS

and avoid its oxidative damage to newborn neurons, thereby prolonging survival.[82] Altogether, these promising results imply that the novel multifunctional nanocomposites are promising drug carriers for the treatment of neurodegenerative diseases.

In addition to being nucleic acid and drug delivery vehicles, nanomaterials also have the ability to promote stem cell migration and even deliver stem cells across the BBB. Studies have shown that, in the 6-Hydroxydopamine hydro-bromide (6-OHDA)-induced PD mouse model, after intracerebral injection of dextran-coated iron oxide nanoparticles (Dex-IONPs)-labeled human MSCs (hMSCs) in a 6-OHDA-induced PD mouse model, Dex-IONPs could promote hMSCs migration to the site of DA neuron injury and induce their differentiation into DA-like neurons.[83] Moreover, the homing nature of stem cells, especially MSCs, makes it possible to treat neurodegenerative diseases by noninvasive stem cell transplantation. However, in the absence of exogenous carriers, only a few stem cells can enter the brain after transplantation by noninvasive routes. With magnetic targeted cell delivery technology, magnetic labeling of MSCs with SPIONs, accompanied by the application of an external magnet on the region of interest, greatly improves the delivery and homing of stem cells through the BBB into the target tissue in a rat model of PD.[84] All in all, while providing protection to their loaded stem cells and homing to the lesion site for the repair of damaged neurons, nanocarriers can also take advantage of their own biological activity or nourish neurons via loaded relevant drugs, eliminate oxidative stress, or even scavenge aberrant aggregated proteins.

Nanomaterials as Scaffolds for Stem Cell Neural Differentiation

2D Extracellular Matrix

2D cell culture in Petri dishes is a traditional cell culture method in vitro. Some physical and biological factors, such as growth factors, hormones, and other chemical or biological molecules, as well as the extracellular matrix, can determine the differentiation fate of stem cells.[85,86] Among them, the surface chemistry, stiffness, alignment, topography, and several other parameters of the cell culture matrix (substrate) are important factors in stem cell differentiation.[87–89] Combining the unique characteristics of nanomaterials with advanced cell culture methods can effectively promote the differentiation of stem cells to produce specific cell types of the central nervous system, such as functional neurons.[88,90,91]

The special topography of nanomaterials has been studied as an extracellular matrix (ECM) to control stem cell growth and differentiation into neural cells.[92,93] For example, aligned Gly-Tyr-Ile-Gly-Ser-Arg peptide-functionalized PCL nanofibers exhibited accelerated neural differentiation of MSCs.[94] Furthermore, biodegradable nanostructured poly (l-lactide-co ε-Caprolactone) (PLCL) elastomeric scaffolds that combine ordered nanopatterned topography with graphene oxide (GO) functionalization can accelerate neural differentiation of mNSCs into mature neurons and glial cells.[25] These results illustrate that the ordered nanotopography may better mimic the natural ECM in promoting neural differentiation of stem cells. In addition, biocompatible silica nanozigzags sculpted by a glancing angle deposition were shown to promote the differentiation of neural stem cells into electrophysiologically active neurons in the absence of traditional chemical growth factors.[95] Silica nanozigzags exhibit a unique groove-like topography, and their inherent physical characteristics, such as topographical features and stiffness, may play an important role in promoting specific neuronal phenotypic differentiation.[95]

The unique photothermal and electrical conductivity of nanomaterials can also serve as an extracellular matrix for stem cell differentiation. AuNPs possess good biocompatibility, chemical and physical stability, effective thermal transduction, optical properties, and easy surface functionalization and can be used for photothermal therapy.[96] An artificial extracellular matrix made of gold nanocage-coated glass coverslips can promote the differentiation of rat NSCs into neurons, which can be further enhanced by laser-induced thermal stimulation.[97] In addition, graphene film, as a 2D nanomaterial, has good conductivity and can be used as a conductive substrate for stem cell differentiation. Guo et al differentiated AMSCs (cultured on graphene film) into functional neurons within 15 days by placing a rotary magnet on top of a culture system without any inducer.[17] In this system, the graphene film acts as a wireless electrical signal generator driven by the electromagnetic induction.[17]

More importantly, nucleic acids and drugs can also be loaded or assembled onto the surface of scaffolds for further modulation of neural differentiation of stem cells. microRNA-222-containing chitosan nanoparticles combined with silk fibroin nanofibrous scaffolds showed enhanced neuronal differentiation of NSCs.[98] Moreover, the release of methylene blue (MB) from GO-coated electrospun nanofibrous scaffolds can modulate the function of neural progenitor cells.[99] This MB-loaded nanofibrous scaffold could reduce tau phosphorylation and protect NPCs from apoptosis, which may be a versatile treatment for AD and other neurodegenerative diseases.[99]

3D Nanoscaffolds

Although the classic 2D cell culture can manipulate the fate of stem cells, cells exist in a 3D form in their natural physiological environment within living organisms. 3D cultures can better replicate this state. Compared with the traditional 2D method, the 3D culture model is closer to the natural microenvironment of cells in tissues and organs and represents cell-cell/cell-matrix interactions and cell migration as they are in vivo.[100] 3D hybrid nanomaterial scaffolds have been demonstrated to be able to mimic the natural microenvironment to promote stem cell proliferation and differentiation for stem cell-based tissue engineering.[101,102] Moreover, 3D nanostructured scaffolds can be transplanted into animals and provide support and protection for the stem cells they carry.[22]

Inorganic and carbon nanomaterials are ideal materials for 3D nanoscaffolds due to their unique biological and physico-chemical properties and nanotopography. 3D nanoscaffolds are usually composites composed of some natural polymers (eg, chitosan, collagen, hyaluronic acid (HA), or fibrin) and synthetic nanomaterials (eg, PLGA, PCL, CNTs, or GO).[103] Natural source nanomaterials can guarantee biocompatibility for stem cell differentiation due to their good biodegradability and low antigenicity,[103,104] while synthetic nanomaterials can be modified in terms of surface topography, mechanical properties, and electrical properties, which make them favorable for the differentiation of stem cells into neural cells.[105,106] Although 3D nanoscaffolds have shown great application prospects in nerve regeneration for degenerative diseases, nanocomposites are often restricted due to their nonbiodegradability, poorly controlled release of drugs, and limited biocompatibility, thus delaying their clinical application. To solve these problems, a bioactive 3D reduced graphene oxide (rGO)-collagen hybrid scaffold composed of type I collagen as a basic material and assembled on the surface of a layer of rGO nanosheets was developed.[107] This 3D rGO-collagen hybrid scaffold can not only maintain the porous 3D structure and good biocompatibility but also delay the biodegradation rate and endow the scaffold with good conductivity, ultimately promoting MSC proliferation and differentiation into neural cells.[107] In addition, Yang et al developed a neurogenic drug DAPT(N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester)-loaded 3D-MnO_2-laminin hybrid biodegradable nanoscaffold.[13] With degradable and controllable drug release, this hybrid nanoscaffold is a useful tool to improve the survival of stem cells and induce neuronal differentiation in vivo; thus, it may be a new means to treat neurodegenerative diseases.[13] Furthermore, DNA/histone proteins/K6-polyethylene glycol (PEG)-RGD supramolecular fibers have been fabricated as new 3D scaffolds that provide a biocompatible microenvironment for NSC encapsulation and in situ differentiation into oligodendrocytes, showing great potential in neural differentiation.[100] Supramolecular fibers provide new options for novel natural non-toxic scaffolds. They are biomacromolecules formed by the interfacial polyelectrolyte complexation (IPC) process of DNA and histones that can be naturally metabolized into small molecules; various bioactive molecules such as growth factors and chemokines can also be incorporated to further regulate stem cell fate.[100] In conclusion, 3D nanoscaffolds are promising candidates for improving cell survival and differentiation in patients with neurodegenerative diseases undergoing stem cell transplantation. Notably, this approach still needs to overcome several major obstacles, including the sudden release of drugs, insufficient cell adhesion support, and slow degradation rate of scaffolds. Researchers are actively developing new nanomaterials, using biocompatible, degradable nanomaterials, and functionalizing their surfaces to address these issues.

Nanoparticle-Based Stem Cell Labeling and Tracking

Stem cell therapy is a promising technique for neurodegenerative disease treatment, but how to monitor the transplanted cells remains a challenge. Monitoring the injected/transplanted cells is required to determine their function and fate, as well as the optimal cell type, route, dose, and timing of administration.[108–110] In the past, the success of transplantation was usually assessed by evaluating the improvement of symptoms. Although a few patients have significant improvement in clinical studies, others usually have limited or even no improvement in symptoms. Additionally, limited information is known about the distribution, migration, differentiation, and survival of transplanted stem cells in the brain, which represents a major obstacle to the clinical application of stem cells. Therefore, simple and effective noninvasive cell tracking and imaging technology is urgently needed to evaluate the fate of transplanted stem cells in real time.

Noninvasive monitoring methods can determine the safety and efficacy of cell therapy by tracking the location of transplanted cells in real time, and optimal doses and routes of administration can be selected based on cell distribution; thus, monitoring methods provide critical information for the progress of cell replacement therapy.[111,112] The main brain

imaging techniques that can be used to track cells in vivo are MRI, X-ray computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT).[113–115] However, these techniques usually require appropriate contrast agents to label transplanted cells to enhance contrast. Nanomaterials are promising candidates for contrast agents because of their unique optical properties, cellular uptake, surface functionalization, and good biocompatibility. Utilizing nanoparticles for cell tracking and imaging typically consists of two steps: (I) labeling cells in vitro using appropriate nanoparticles as contrast agents; and (II) transplantation/injection of labeled cells to the target area, followed by the selection of suitable imaging techniques for noninvasive imaging.

MRI allows long-term tracking of transplanted/injected cells in a noninvasive manner to see if transplantation is successful, with the only requirement being the use of appropriate contrast agents for labeling transplanted cells. Magnetic nanoparticles, especially gadolinium (III) chelates and SPIONs, are the most commonly used contrast agents in MRI detection.[52,116] In recent years, SPION-labeled stem cell tracking for MRI has been used in studies on several neurodegenerative diseases, including AD, PD, and HD.[84,117–120]

To reduce the accumulation and cytotoxicity of SPIONs in tissues and maximize biocompatibility, biopolymers are usually coated on their surface.[83] Hour et al labeled Wharton's jelly-derived MSCs with dextran-coated SPIONs and delivered them magnetically to the hippocampal region of AD rat brains.[118] Studies have shown that dextran-coated SPIONs can deliver MSCs to reach the hippocampus and improve AD cognitive impairment by attenuating neuronal degeneration and enhancing cholinergic function in the hippocampus.[118] At present, most methods for stem cell labeling are nonspecific and rely on electrostatic interactions between cells and nanoparticles. To solve this problem, Egawa et al constructed a DNA hybridization system for labeling NSCs with SPIONs for MRI monitoring post-transplantation.[51] In this hybridization system, oligo[dT]20 ssDNA and lipid molecule DPPE (1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine) were conjugated by using PEG as a linker (oligo[dT]20-PEG-DPPE, which can be anchored to cell membranes via its hydrophobic DPPE tail), while the complementary ssDNA (oligo[dA]20) was conjugated to maleic acid-coated SPIONs (oligo[dA]20-SPIONs). NSC labeling could then be performed simply by DNA hybridization, which improved the specificity of NSC labeling.[51] In the rat striatum, labeled cells can be detected by MRI imaging for up to one month after transplantation.[51] In addition, magnetic nanomaterials can also be fabricated into composites with other nanomaterials to improve their biocompatibility, cellular uptake, or thermal stability for better in vivo MR imaging. For example, in vivo tracking of a PD mouse model after stem cell transplantation by MRI revealed that adipose-derived MSC transplantation using magnetic silica core–shell nanoparticles as a contrast agent increased the distribution to the brain, particularly the substantia nigra, which may be a potential therapeutic strategy for PD.[116] Meanwhile, DNA-gadolinium-AuNPs exhibited improved T1 contrast and excellent cellular uptake that can be visualized by MRI imaging to better understand the survival and location of implanted cells.[52]

Several studies have also explored the use of AuNPs for cell labeling and tracking the movement and behavior of cells after transplantation in vivo by CT imaging.[23,52] CT imaging is one of the more widely used medical imaging techniques due to its convenience, rapidity, and high spatial resolution.[121] Gold provides better contrast with its higher atomic number and X-ray absorption coefficient compared with the clinical contrast agent iodine.[122] Therefore, it's in vivo labeling situation can be more clearly monitored in real time by combining CT imaging techniques. Kim et al developed nanocomplexes for stem cell tracking by coating PLL and rhodamine isothiocyanate B (RITC) on the surface of 40 nm citrate-stabilized AuNPs.[121] After transplantation into the rat brain, labeled hMSCs could be clearly visualized using a micro-CT scanner, whereas cell viability, proliferation, and differentiation were not affected.[121] Similarly, using this technique, Perets et al traced the migration and homing patterns of exosomes derived from MSCs (MSC-exo) administered intranasally in different brain pathologies (including AD and PD).[123] The imaging technique enables noninvasive, longitudinal neuroimaging and whole-brain tracking, which can be used to diagnose brain deficiencies and further facilitate targeted drug delivery.

It is worth noting that there is an inherent question with any form of nanoparticle labeling, that is, whether the observed signal represents live cells during long-term imaging, which seems to be addressed only by the addition of a reporter gene, as it is only expressed by live cells.[121] However, the incorporation of reporter genes brings risks of unstable transfection, cell biological changes, immunogenicity, and low sensitivity in vivo.[23] To summarize, although there are still some problems to be solved in long-term noninvasive imaging, the greatest value of nanomaterial-based cell imaging is that it can immediately image cell distribution and verify the accuracy of cell delivery.
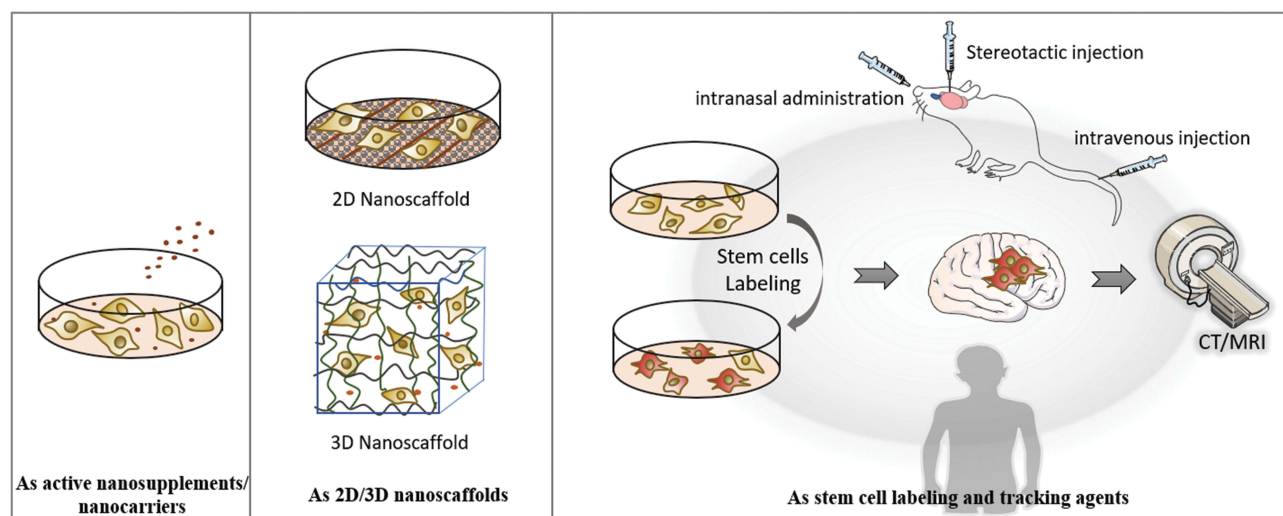
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Figure 4 Schematic representation of the application of nanomaterials in stem cell therapy of neurodegenerative diseases.

Conclusions and Future Perspectives

Both stem cell therapy and nanotherapeutic strategies have shown great advantages in the treatment of neurodegenerative diseases. However, each treatment has limitations, and there is currently no therapy that can cure neurodegenerative diseases. Therefore, combining stem cell therapy with nanotherapeutic strategies would greatly enhance the therapeutic effects on neurodegenerative diseases, providing new insights into the treatment of neurodegenerative diseases. The schematic representation of the application of nanomaterials in stem cell therapy of neurodegenerative diseases is shown in Figure 4. The application of various nanomaterials in stem cell therapy for neurodegeneration is mentioned above, and a summary is listed in Table 1.

Table 1 A Summary of the Application of Nanomaterials and Stem Cells in Cooperation for the Treatment of Neurodegenerative Diseases

	Nanomaterials	Chemical Modifications/ Loading Components/ Additional Stimulation	Cell sources	In vitro/ In vivo	Application	Ref.
Nanosupplements and nanocarrier	AuNPs	Electromagnetic stimulation	NSCs	In vivo	Increased hippocampal neurogenesis	[65]
	ssDNA-AuNPs	Circularly polarized light	NSCs	In vivo	Neuronal differentiation	[67]
	AuNPs GSH-cleavable nanocomplex	siRNA against SOX9	NSCs	In vitro	Stimulate and track NSC differentiation	[78]
	Dextran-coated iron oxide nanoparticles		hMSCs	In Vitro	DA-like neurons	[83]
	Magnetic Fe$_3$O$_4$ nanoparticles	Collagen	ESCs/ iPSCs	In vivo	Promote migration and neuronal maturation	[64]
	Polymeric nanoparticles	RA	NSCs	In vitro	Neuronal differentiation	[77]
	PPFLMLLKGSTR peptide-amphiphilic solid lipid nanoparticles	NGF and RA	iPSCs	In Vitro	Neuronal differentiation	[73]

(*Continued*)

Table 1 (Continued).

	Nanomaterials	Chemical Modifications/ Loading Components/ Additional Stimulation	Cell sources	In vitro/ In vivo	Application	Ref.
	Bioreducible Lipidoid Nanoparticles	Cas9 mRNA and sgRNA	hMSCs	In vitro	Neural-like differentiation	[72]
	Hydroxyapatite (HAp) nanorods		NSCs	In vitro/vivo	Neuronal differentiation	[54]
	RGD/TAT-functionalized Chitosan-graft-PEI-PEG nanovector	pCMV-EGFP-Ntf3	NSCs	In vitro	Neuronal differentiation	[74]
	TDNs	miR132-ASO	mESCs	In vitro	Enhance DAergic neurons differentiation	[79]
	Fullerene C60	Alanine	NSCs	In vitro	Proliferation and Neuronal Differentiation	[62]
	CNTs		NSCs	In vivo	Neuronal differentiation	[63]
	SeNPs		MSCs	In vivo	Neuroprotection	[70]
	Chitosan-coated SeNPs		MSCs	In vivo	Neuroprotection	[71]
	Chitosan-Gold Nanocomposites		MSCs	In vivo	Neuronal differentiation	[61]
	Metal-organic frameworks encapsulated nanozyme	siSOX9 and RA	mNSCs		Neuronal differentiation	[82]
2D and 3D nano-scaffolds	Graphene film	Electrical stimulation	MSCs	In vitro	Neuronal differentiation	[17]
	Gold nanocage-coated extracellular matrix surfaces	Laser irradiation	rNSCs	In vitro	Neuronal differentiation	[97]
	Graphene-coated homogeneous plasmonic metal (Au) nanoarrays	Dual-enhanced Raman scattering	hNSCs	In vitro	Neuronal differentiation	[87]
	Poly L-Lactic Acid Nanofibrous	Wireless electric stimulation	NSCs	In vitro	Neuronal differentiation	[89]
	Biocompatible silica nanozigzags	Sculptured by glancing angle deposition	NSCs	In vitro	Neuronal differentiation	[95]
	2D PCL nanofibrous scaffolds		NSCs	In Vitro	Neuronal cells and glial cells	[88]
	GO-coated electrospun nanofibrous scaffolds	Methylene blue (MB)	NPCs	In vitro	Neuroprotection	[99]
	Silk fibroin nanofibrous scaffolds	MicroRNA-222- chitosan nanoparticles	NSCs	In vitro	Neuronal differentiation	[98]
	Ordered nanopatterned topography PLCL scaffolds	GO functionalization	NSCs	In vitro	Neurons and glial cells	[25]
	AuNPs-contained PCL and chitosan scaffolds		MSCs	In vitro	Neuronal differentiation	[91]
	Electrospun PCL and graphene nanocomposite		MSCs	In Vitro	Functional dopaminergic neurons	[90]

(Continued)

Table 1 (Continued).

	Nanomaterials	Chemical Modifications/ Loading Components/ Additional Stimulation	Cell sources	In vitro/ In vivo	Application	Ref.
	3D PLGA microfiber scaffolds		iPSC	In vitro	Neuronal differentiation	[102]
	3D alginate hydrogel	MMP and RGD peptides	NSCs	In vivo	Dopamine neurons	[22]
	3D rGO-collagen hybrid scaffold		MSCs	In vitro	Neuronal differentiation	[107]
	3D hydroxyethyl cellulose/glycine/RuO_2 composite scaffolds		MSCs	In vitro	Neuronal differentiation	[101]
	3D-MnO_2-laminin hybrid nanoscaffolds	DAPT drugs	hiPSC-NSCs	In vivo	Neuronal differentiation	[13]
	Chromatin-inspired supramolecular nanofibers	K6-PEG-RGD peptide	NSCs	In situ	Oligodendrocytes	[100]
Nanotechnology-based stem cell labeling and tracking	Magnetic silica core-shell nanoparticle	MRI	MSCs	In vivo	Labeling and delivery of transplanted MSCs	[116]
	AuNP-PLL-RITC Nanocomplexes	Micro-CT.	MSCs	In vivo	Labeling and tracking	[121]
	AuNPs as labeling agents	X-ray CT	MSCs	In vivo	Tracking migration and homing of MSCs-derived exosomes	[123]
	SPIONs	MRI	hESCs	In vivo	Ameliorate motor function and cell tracking	[117]
	PLL hydrobromide -SPIONs	MRI	MSCs	In vivo	Labeling and delivery of MSCs	[84]
	SPIONs	MRI	MSCs	In vivo	Labeling and delivery of MSCs	[118]
	Magnetic Fe_3O_4 and polydopamine shells	MRI	MSCs	In vivo	Labeling and delivery of MSCs	[119]
	Hydrophobic SPIONs-negative let-7b ASO	MRI	NSCs	In vivo	Tracing transplanted cells/ secretion of BDNF	[120]
	TPETPAFN dots		hESCs	In vivo	Labeling of transplanted ESCs	[126]
	PBAE-PLGA-Ag_2S-RA-siSOX9 nanoformulation		NSCs	In vivo	Aβ clearance and Neural differentiation	[127]

Despite many advantages, the clinical application of nanocarriers and nano contrast agents still faces several challenges, such as potential cytotoxicity, batch-to-batch variation of polymeric nanoparticles, and nonbiodegradability of inorganic nanoparticles.[124,125] Therefore, it is necessary to improve the synthesis method and develop multifunctional, biocompatible, and degradable composite nanocarriers. In addition, to improve the controlled release and targeting of drugs of nanocarriers, novel nanomaterials with appropriate surface modification and specific physical and biochemical characteristics should be further developed.

Nanotherapeutic strategies combined with stem cell therapy, from laboratory experiments to clinical application, are still in the process of continuous improvement and development. The safety profile of nanotherapeutic strategies, as well

as how they improve the efficacy of stem cells in treating neurodegenerative diseases, is also a research hotspot, and biocompatible degradable materials would be the first choice.

In conclusion, although various obstacles and challenges remain, nanotherapeutic strategies combined with stem cell therapy remain a promising approach for the future treatment of neurodegenerative diseases. It is believed that, as research continues to deepen and a variety of new nanomaterials are discovered, people will surely benefit from this technology.

Author Contributions

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