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Nanoparticle technology and stem cell therapy team up against neurodegenerative disorders

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ABSTRACT

The convergence of nanoparticles and stem cell therapy holds great promise for the study, diagnosis, and treatment of neurodegenerative disorders. Researchers aim to harness the power of nanoparticles to regulate cellular microenvironment, improve the efficiency of cell and drug delivery to the brain, and enhance the survival of stem cell transplants. Understanding the various properties of different nanoparticles is key to applying them to clinical therapies; the many distinct types of nanoparticles offer unique capacities for medical imaging, diagnosis, and treatment of neurodegeneration disorders. In this review we introduce the biology of Alzheimer's, Parkinson's Disease, and amyotrophic lateral sclerosis, and discuss the potentials and shortcomings of metal, silica, lipid-based, polymeric, and hydrogel nanoparticles for diagnosis and treatment of neurodegenerative disorders. We then provide an overview of current strategies in stem cell therapies and how they can be combined with nanotechnology to improve clinical outcomes.

1. Introduction

Neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are devastating diseases that have become increasingly common as life expectancy increases and the global population ages. In the United States, Alzheimer's alone is the 6th leading cause of death, with an annual economic cost over $236 billion [1]. Treatment of neurodegenerative disease has been slow to progress due to contradicting hypotheses of the physiological causes of disease, alongside extreme difficulty in shuttling drugs across the blood-brain barrier (BBB) [2,3]. Additionally, widespread neuronal cell death is particularly difficult to target, and lack of robust regenerative capacity in the central nervous system (CNS) renders most treatments ineffective [4,5]. Two major avenues of research to address these problems are stem cell transplantation, often directly into the brain, and nanoparticles that can cross the BBB [2,5,6]. The joining of these two fields is especially useful for the combination of diagnostics and treatment, commonly termed theranostics [7]. Here we review the current status of using nanomedicine in concert with stem cell therapy to diagnose, track progression, and treat neurodegenerative diseases.

1.1. Biology of the BBB

The brain is incredibly sensitive to toxins in the bloodstream, and requires a specialized microenvironment for optimal function [8]. The BBB creates a selective barrier composed of cerebral capillary endothelial cells linked by tight junctions that prevent movement of molecules between cells. Additionally, the P-glycoprotein (P-gp) pump on endothelial cells actively effluxes cytotoxic molecules unidirectionally across the apical membrane and into the luminal space, thereby removing foreign molecules that bypass the BBB [2,9]. The barrier is further reinforced by microglia, pericytes, and astrocytes that sheath the endothelial tube [10,11]. Small, lipophilic molecules and gases can diffuse across the BBB down a concentration gradient, while large and hydrophilic molecules require the use of transporters. Three mechanisms of transport exist in the BBB: carrier-mediated transport (CMT), receptor-mediated transcytosis (RMT), and adsorptive-mediated transcytosis (AMT) (Fig. 1). CMT principally transports relatively small molecules and nutrients like glucose, amino acids, and ascorbic acid using protein carriers. RMT and AMT, on the other hand, use vesicles to endocytose and shuttle larger proteins and molecules across the BBB. While RMT is highly selective due to the requirement of

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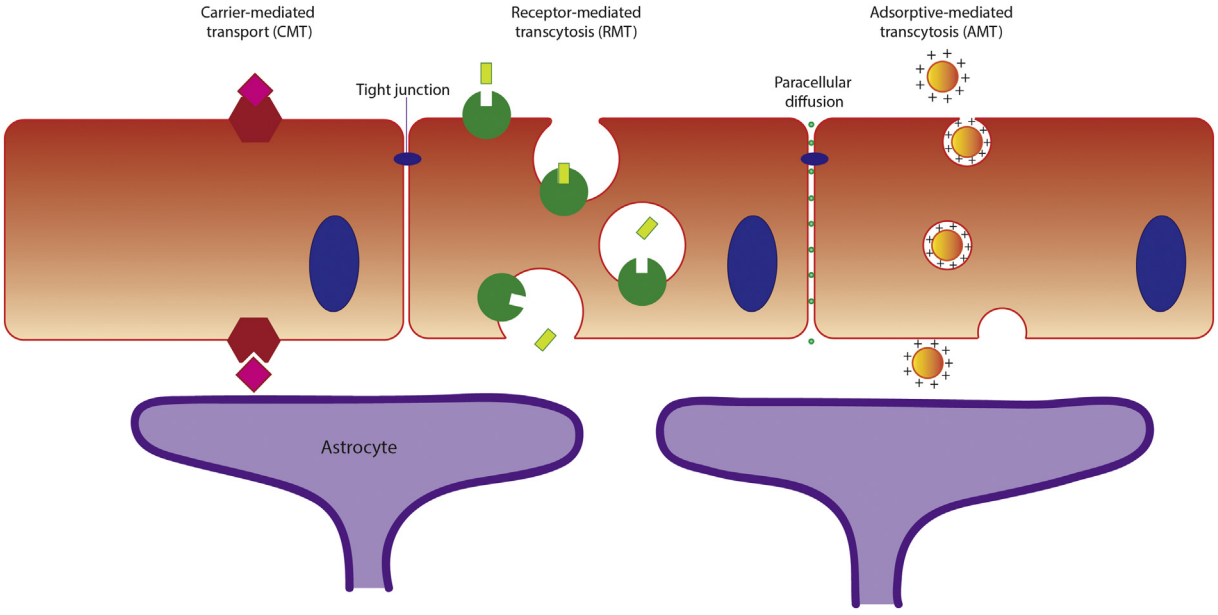

Fig. 1. The biology of the blood-brain barrier is crucial for understanding how drugs can reach the brain. Three major transport mechanisms exist: carrier-mediated transport (left), receptor-mediated transcytosis (center), and adsorptive-mediated transcytosis (right). Paracellular diffusion can also occur between epithelial cells.

receptor-ligand recognition, AMT depends on less specific interactions between cationic compounds and the negatively charged sulfated proteoglycans on the endothelial plasma membrane [12,13]. Nanoparticle delivery has taken advantage of both the specificity of RMT and the pliability of AMT, which allow for preferential drug targeting to the brain and independence from membrane receptors, respectively [11]. Delivery of nanomedicine that can cross the BBB is considered non-invasive, and is one of the most promising strategies of treating neurodegenerative disease.

1.2. Drug clearance

Many drugs, including nanomedicine, are quickly degraded when exposed to the circulatory system. The reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS), consists of immune cells that recognize and clear drugs within a few hours of administration. Macrophages are the primary actors of the MPS, and clear nanoparticles in the liver or spleen as blood flows through these organs [14,15]. Encapsulation in nanoparticles is not sufficient for drugs to evade clearance, but a number of surface modifications on top of nanoparticles are highly effective in increasing stability and circulation time. These surface modifications can be applied to almost every type of nanotechnology described below. The most successful modification is polyethylene glycol (PEG), which improves both the stability and biological performance of many nanoparticles [14,16]. PEG has unlimited water solubility, a high degree of conformational entropy, and a large excluded volume, which is the volume created by the physical presence of PEG alongside steric hindrance that cannot be penetrated by other molecules. This effectively provides a shield for the nanoparticle core, thereby reducing breakdown and improving circulation time [14,16]. These properties have led to multiple hypotheses on how PEG helps nanoparticles evade engulfment by macrophages, including a steric barrier, reduction of protein adsorption, and binding to specific proteins that help mask the nanoparticle (Fig. 2) [17–19]. While PEG is incredibly useful in almost every form of nanomedicine, some studies have shown that mice develop an immune response to multiple doses of PEG, causing worsened circulation time of PEGylated nanoparticles [20].

1.3. Pathobiology of neurodegenerative diseases

1.3.1. Alzheimer's disease (AD)

As the most common neurodegenerative disorder in people over 65, Alzheimer's has garnered incredible scientific and financial investment. Symptoms include progressive decline in memory, judgment, language skills, and other cognitive functions [21]. The molecular causes are still poorly understood, though two hypotheses have become central: amyloid beta (Aß) deposition and neurofibrillary tangle (NFT) formation (Fig. 3a). NFTs are made of hyper-phosphorylated tau protein that form tangles after dissociating from destabilized microtubules, while Aß plaques form from fragments of amyloid precursor protein (APP) that accumulate in Alzheimer's patients. Aß plaques are deposited outside of neurons, while NFTs occur within the cell, and both cause decreases in synaptic signaling and eventually promote neuronal death. Massive neuronal death causes a significant decrease in brain volume,

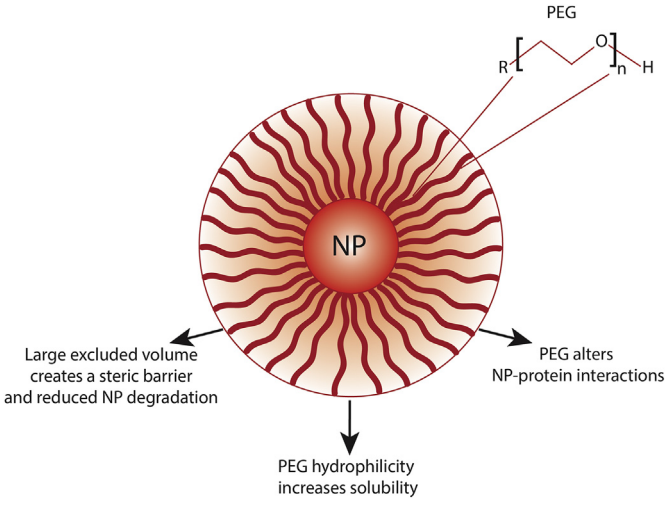

Fig. 2. Surface coating of nanoparticles (NP) with polyethylene glycol (PEG) is a commonly used technique that enhances NP stability, solubility, and mediates NP interaction with the physiological environment.

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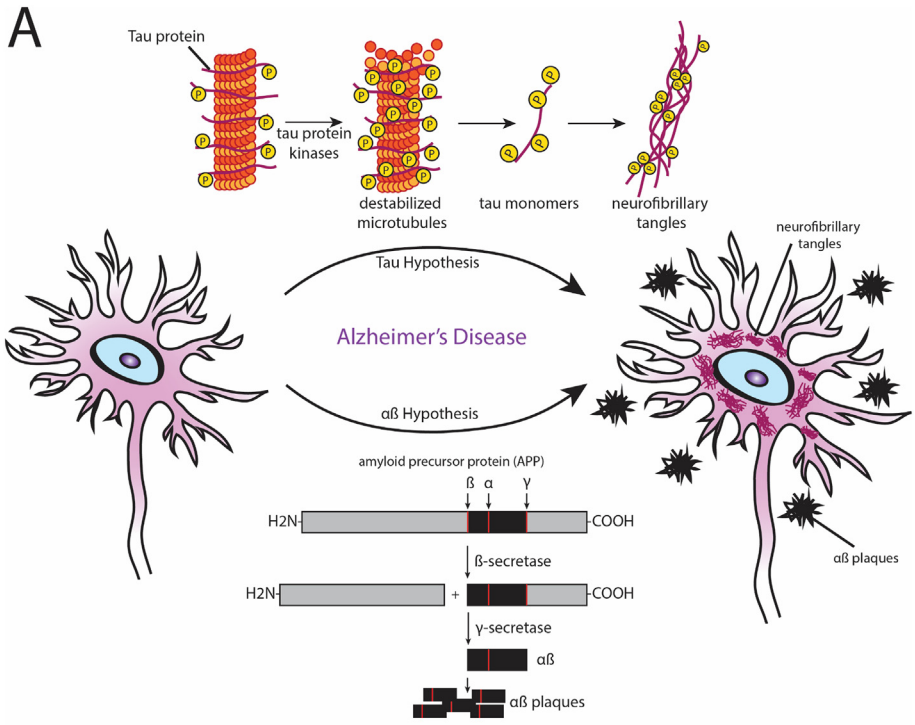

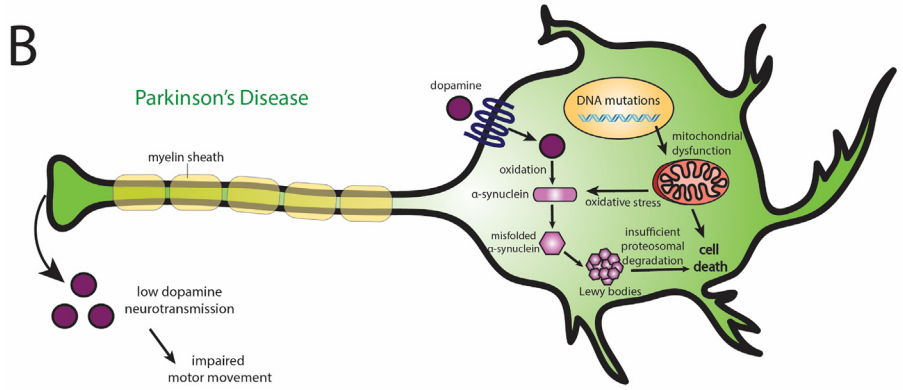

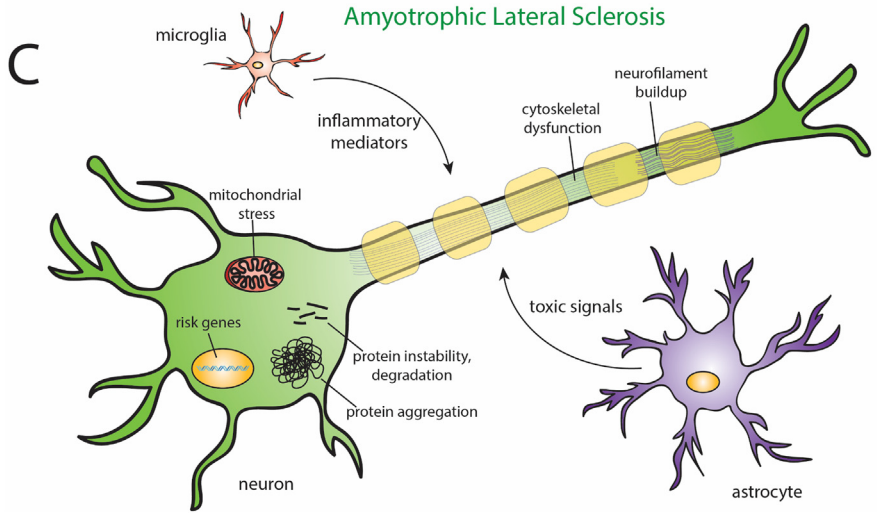

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particularly in the telencephalon, which contributes to the severe decline in cognitive abilities [22]. In addition to synaptic dysfunction, mitochondrial activity becomes imbalanced, leading to oxidative stress, accumulation of reactive oxygen species (ROS), decreased mitochondrial adenosine triphosphate concentration, and increased intracellular calcium levels [23,24]. Current therapeutic strategies target Aß plaques and NFTs for breakdown, and try to reduce ROS in the brain. Despite 6 currently FDA-approved treatments for Alzheimer's, none are curative and efficacy varies greatly across individuals [23].

1.3.2. Parkinson's disease (PD)

Neurodegeneration in PD is a result of formation of Lewy bodies coupled with dopaminergic neuron death in the substantia nigra. Lewy bodies are aggregates of α-synuclein protein that occur in the cell body and processes of neurons (Fig. 3b). PD causes progressive onset of tremors, body rigidity, slowing of voluntary movement, instable posture, and other motor dysfunctions. Current medications attempt to treat the symptoms, but cannot reverse the significant loss of dopaminergic neurons. Several genes have been discovered to contribute to PD and have led to the model that protein folding and dysfunction of the ubiquitin-proteasome pathway could also contribute to disease progression. Additionally, mitochondrial dysfunction and oxidative stress are commonly found in neurons of patients with PD. The heterogeneity in pathology and underlying causes of PD makes treatment especially difficult. Specific molecular pathologies, like α-synuclein aggregation and mitochondrial dysfunction, are potential targets for pharmacological intervention. Surgical treatments that have been investigated include deep brain stimulation of the subthalamic nuclei and cell transplantation [25–27].

1.3.3. Amyotrophic lateral sclerosis (ALS)

Degeneration of motor neurons in the motor cortex, brainstem, and spinal cord of ALS patients causes severe symptoms of paralysis, difficulty swallowing, difficulty speaking, and respiratory failure. With no cure, the average progression from onset to death is 20 to 48 months [28]. The cause of ALS remains largely unknown, though over 40 genes have been identified as risk factors. Continued research suggests that protein instability, aggregation, and degradation, especially of RNA- and DNA-binding proteins, could play a role in the molecular pathology of ALS. Additionally, impairment of neuronal cytoskeletal function and roles of non-neuronal cells contribute to disease pathology (Fig. 3c). Specifically, astrocytes derived from ALS patients can be toxic to motor neurons in co-culture, indicating that intercellular signaling plays a major role in motor neuron degeneration [29]. This also muddies attempts to regenerate motor neurons, as the *in vivo* environment is largely toxic. Nonetheless, the lack of effective drug treatments has led to the exploration of stem cell transplantation to replace motor neurons alongside pharmacological attempts to reduce the severity of the microenvironment [30]. This dual approach is especially amenable to combined nanotechnology and stem cell therapy, since it addresses both cell replacement and modulation of the microenvironment of transplanted cells.

2. Current nanotechnologies

A wide variety of nanoparticles exist with varying sizes, properties, and functions (Fig. 4). Here, we describe the major categories of nanoparticles that have been well-studied for application to neurodegenerative disease.

2.1. Metal nanoparticles

Metal nanoparticles have garnered significant interest for their capacity to cross the BBB and enhance imaging of the brain. They can also be coated with various ligands, like antibodies or proteins, for drug delivery into the CNS. Additional properties that can be modulated to alter nanoparticle function are shape, size, surface coverage, and stability through synthesis method [31].

2.1.1. Gold nanoparticles (AuNPs)

Gold nanoparticles are one of the best documented tools for CNS imaging and treatment [11]. The gold core has several defining optical properties, termed plasmonic properties, which make it ideal for imaging applications. Specifically, gold has a surface plasmon resonance (SPR), which is the resonation of surface conduction electrons induced by the oscillating electromagnetic wave created by light striking the particle. This resonance leads to the formation of an ionic core as an oscillatory dipole is generated along the axis of light radiation [31]. The oscillation of electron charge is particularly localized in nanoparticles, and quickly decays with distance from the dielectric surface, with a spatial resolution correlated to nanoparticle size [32]. SPR also depends on the composition, shape, structure, and environment of the nanoparticle [33,34]. Using SPR, nanoparticles absorb light, which is then either scattered, emitted, used to quench nearby fluorescence, or released as heat [31,35]. These optic properties can be utilized for *in vivo* imaging through X-rays or micro-CT scanning. AuNPs absorb and reduce X-rays better than traditional CT contrast agents like iodine, allowing for superior contrast and increased precision in visualization of nanoparticle location [36–38]. In the context of stem cell therapy, researchers aim to track transplanted cells loaded with AuNPs. A recent study successfully complexed 40 nm AuNPs with two ligands, poly-L-lysine (PLL) and rhodamine B isothiocyanate (RITC), to increase nanoparticle uptake by human mesenchymal stem cells (hMSC). AuNP uptake did not inhibit cell proliferation or differentiation, and labeled hMSCs showed strong attenuation, or visibility, during *in vitro* micro-CT imaging. This study further found that injecting a minimum of 2×10^5 gold-labeled hMSC directly into rat brains allowed for visualization with micro CT 30 min post-injection. In the future this could allow for CT-guided stem cell injection into the brain or immediate confirmation of successful injection in humans [39]. In addition to cell tracking, AuNPs have been modified to target and degrade β-amyloid aggregates *in vitro*. Specifically, a gold core was conjugated to apolipoprotein E3 (ApoE3), which promotes interaction with amyloid aggregates and increases BBB crossing, and Curcumin, a fluorescent hydrophobic probe used to track the gold particles. Once the ApoE3-conjugated gold binds to β-amyloid aggregates, the SPR of gold is then used to treat with light, which is absorbed and then released as heat to promote aggregate dissociation [40].

2.1.2. Silver nanoparticles (AgNPs)

Silver nanoparticles have been investigated for their ability to cross the BBB and induce an immune response in the brain. When injected intraperitoneally, the AgNPs can reach the hippocampus, an important region for neurodegenerative disorders [41]. AgNPs naturally have antibacterial characteristics that make them promising in some cases, but they induce inflammatory and neurodegenerative gene expression responses at 5 μg/mL dose in mouse neural cells [42]. However, this immune response was also recently shown to improve the ability of microglia, the immune cells of the brain, to express enzymes that

Fig. 3. (A) Alzheimer's Disease is thought to have two central molecular phenomena: (1) the formation of neurofibrillary tangles from tau proteins (top), and (2) the formation of amyloid-beta plaques from amyloid precursor protein cleavage (bottom). These lead to intracellular neurofibrillary tangle formation and extracellular aß plaque formation, respectively. (B) Parkinson's disease is characterized by several molecular pathways, particularly the formation of Lewy bodies from α-synuclein protein and oxidative stress caused by mitochondrial dysfunction. This can cause reduced dopamine neurotransmission, which leads to the common symptoms of impaired motor movement and tremors. (C) Molecular causes of ALS are still largely unknown, though multiple cell types in the brain, like microglia and astrocytes, are thought to contribute to neuronal dysfunction. Additionally, improper protein processing leads to aggregation or precocious degradation.

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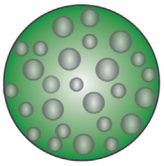
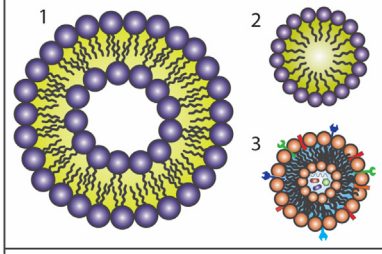
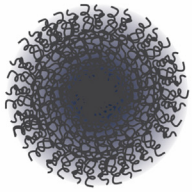
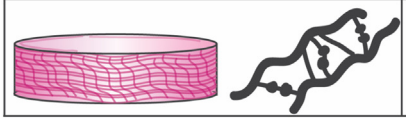
General Appearance	Name	Size	Advantages	Disadvantages
	metal nanoparticles: gold silver metal-oxide	1-50 nm (gold) 3-200 nm (silver) 50-150 nm (SPIO) 10-50 nm (USPIO)	readily cross BBB, good optical properties, can be easily coated, can reduce oxidative stress	cytotoxicity, difficult to target, do not degrade
	quantum dots	2-10 nm	long photo-stability, good optical properties, good for cell tracking, biocompatible	can induce inflammatory response small size limits drug delivery
	mesoporous silica	25-100 nm	efficient drug carriers, cross BBB (size-dependent), highly pliable	few studies in vivo
	lipid nanoparticles: liposomes (1) micelles (2) exosomes (3)	20 nm - 2.5 μm (1) 5-100 nm (2) 30-100 nm (3)	can carry both hydro- phylic and phobic drugs, pliable drug release kinetics, some already FDA- approved	exosome contents need further charachterization, targeting is limited
	polymeric nanoparticles: PLA PLGA	1-300 nm	highly pliable, well-studied, long-term circulation of encapsulated drugs, biocompatible, many synthesis strategies	can be too large, difficult to use for imaging
	hydrogels	10-300 nm	gel and liquid stages, highly biocompatible, good for encapsulating cells	can be difficult to target, expensive

Fig. 4. An overview of nanoparticles commonly used to treat or study neurodegenerative disorders.

produced an overall anti-inflammatory effect and reduced reactive oxygen species (ROS). This was dependent on AgNPs being absorbed specifically by microglia, in which the AgNPs are partly dissolved to form non-reactive silver sulphide (Ag_2S) on the silver core surface. This in turn changes the expression profiles of microglia to reduce their toxicity toward dopaminergic neurons [43]. Unfortunately, AgNPs delivered nonspecifically to the brain often cause cytotoxicity, especially to neurons, and the inert silver can accumulate over time [44,45]. In order for AgNPs to be effective in treating neurodegenerative diseases, they must be specifically targeted to individual neural cell types, or coated with ligands that reduce their cytotoxicity. Nonetheless, AgNPs should not be dismissed, as their enhanced ability to cross the BBB could lead to exciting options for drug delivery or immunotherapy.

2.1.3. Metal-oxide nanoparticles

Iron oxide (Fe_3O_4), cerium oxide (CeO), and zinc oxide (ZnO) nanoparticles have all been developed as tools for imaging and as therapies to reduce oxidative stress in the brain [11]. The magnetic properties of these metals make them useful for magnetic resonance imaging (MRI). Also, passage of the BBB in mice can be significantly enhanced by applying an external magnetic field prior to systemic injection of Fe_3O_4 NPs, allowing the NPs to reach the brain parenchyma [46]. To further increase delivery specificity, magnetic fields can be used to guide NP delivery to a particular region of the brain, thereby reducing the dose necessary for treatment [11]. Fe_3O_4 NPs can be divided into two categories based on size: 50–150 nm diameter superparamagnetic iron oxide (SPIO) and 10–50 nm diameter ultrasmall superparamagnetic iron oxide (USPIO) [47]. USPIOs are used primarily as MRI contrast agents, while SPIOs can be further modified for neuroregenerative functions. SPIO gold NPs coated with nerve growth factor (NGF) were recently shown to promote neuron growth and differentiation using dynamic external magnetic fields *in vitro* [48]. Other macromolecules, like short hairpin RNA (shRNA), have also been immobilized onto Fe_3O_4 NPs to reduce neuronal apoptosis in a model of Parkinson's Disease [49]. A variety of modified SPIOs have been added to human neural stem cells (hNSC) without impairing cell viability or proliferation, and allowed tracking of transplanted NSCs by MRI for up to 3 months post-transplantation in mice [47,50].

Cerium and zinc oxide nanoparticles are more commonly used to reduce reactive oxygen species (ROS) and nitrosative stress, which have been implicated in neurodegenerative disease and neuronal death. Cerium oxide nanoparticles, also called nanoceria, can reduce superoxide anions, hydrogen peroxide, and peroxynitrite by converting between Ce^{4+} and Ce^{3+} [51]. Similarly, zinc oxide nanoparticles can be used to reduce ROS, and can be engineered for diagnosis and treatment of Alzheimer's Disease [52,53]. Iron, cerium, and zinc all still pose risks for neurotoxic metal buildup, meaning dosage needs to be very carefully controlled in any treatment for neurodegenerative disease [54,55].

2.2. Quantum dots (QDs)

Quantum dots are fluorescent semiconductor nanocrystals that are chemically stable in physiological conditions, have long-term photostability, and emit fluorescent wavelengths correlated to their

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size [56,57]. The metalloid crystalline core is most commonly made of cadmium selenium (CdSe), and is surrounded by a zinc sulfide (ZnS) shell that enhances solubility in water [58]. QDs usually range from 2 to 10 nm in diameter, and are often coated with a ligand to increase their physiologic function [5,59]. For example, QDs have been coated with Aβ peptide such that they will form aggregates with Aβ plaques *in vivo* and allow for image quantification of Alzheimer's Disease diagnosis and progression [60]. Similarly, another study functionalized QDs with dopamine, which changed the fluorescent properties of the QDs in a manner dependent on the interaction of dopamine with cysteine, a process implicated in some neurodegenerative diseases. This dynamic technique provides unique insight into the molecular reactions occurring inside cells, and allows for careful monitoring of dopaminergic neurotoxicity [61]. QDs are also extremely useful for tracking transplanted cells. QDs have been added to mesenchymal stem cells (MSCs) prior to transplantation into the sciatic nerve, and allowed *in vivo* tracking for at least 35 days [62]. Additionally, QDs coated with a zwitterion and a lipopeptide that increased uptake by NSCs were used to track NSC migration after injection into embryonic chick brains. When injected into the brain of embryonic day 4 (E4) chicks, the QDs became widely distributed through the brain and remained detectable through embryonic day 15, by which time cells were able to clear the QDs from the brain. Importantly, the chicks hatched and grew normally, indicating that these QDs were fully biocompatible [63]. Another critical finding in QD technology is that they can be aerosolized and reach the brain through short-term inhalation, leading to rapid olfactory uptake and axonal transport to the olfactory bulb. However, this method also induced a pro-inflammatory response by activating microglia, indicating a potential damaging effect that needs to be carefully considered when applying QDs to stem cell therapy [64].

2.3. Silica nanoparticles

Silica nanoparticles are transparent and inert, and can be conjugated to a variety of fluorescent probes. They are also porous, making them potential drug carriers, and can be surface modified for added functionality [65,66]. Silica NPs can penetrate neurons *in vivo* without cytotoxicity in *Drosophila*, making them an exciting target for neurodegeneration treatment [67]. They can also cross the BBB in mice, with transport efficiency being dependent on size [68]. This permeation is maintained when drugs or contrast agents are loaded onto the NPs, which is crucial for clinical function [69]. For example, silica NPs loaded with small interfering RNA (siRNA) against SOX9 can mediate the fate of NSCs *in vitro* [70]. In addition to shuttling drugs to the brain, silica NPs can be modified such that they release ligand over long periods of time. Silica NPs surface-modified with amino groups and containing brain-derived neurotrophic factor (BDNF) were able to persist in ganglion neurons and release BDNF over a period of 80 days [71]. Overall, silica NPs are highly pliable with good biocompatibility, though more studies need to be carried out *in vivo* prior to clinical use in humans.

2.4. Lipid-based nanoparticles

Lipids and other organic molecules that naturally occur in cells are useful tools in nanomedicine due to their enhanced biocompatibility relative to inorganic molecules. Lipid nanocarriers also evade efflux once in the brain, making them ideal drug carriers both for nanoparticle treatment and co-treatment with stem cell therapy [72].

2.4.1. Liposomes

Liposomes are made of at least one lipid bilayer surrounding an aqueous space that can be filled with a large variety of compounds, with diameters ranging from 20 nm to 2.5 μm [16]. Importantly, liposomes can encapsulate both hydrophilic (in the aqueous core) and lipophilic (in the lipid layer) compounds, making them one of the most popular nanocarriers used for drug delivery [2,5]. A large variety of lipids can be used to make liposomes, with the most common choices including cholesterol, sphingomyelin, phosphatidylcholine, 1,2-Dimyristoyl-sn-glycreo-3-phosphocholine (DMPC), 1,2-Dimyristoyl-sn-glycreo-3-phosphoglycerol (DMPG), 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), and other variations of phospholipids [73,74]. Phospholipids containing choline, namely phosphatidylcholine or lecithin, are the most popular building blocks for liposomes because they are dipolar at physiological pH, with a positive charge on the quaternary ammonium and a negative charge in the phosphate headgroup [75,76]. The lipid shell can be stabilized for a longer half-life by adding cholesterol, or other sterols, during synthesis. This in turn regulates the rate of drug release [77]. Numerous liposome therapies with cholesterol incorporated into the membrane have already been approved by the Food and Drug Administration (FDA) [78]. Furthermore, liposomes can be surface-coated with ligands that enhance their stability or delivery to the brain. PEGylation increases efficiency of liposomes crossing the BBB, and targeting ligands facilitate receptor-mediateds crossing of the BBB or cellular endocytosis. Proteins, antibodies, nucleic acids, carbohydrates, and more can be bound to the outer headgroup of a liposome with varying degrees of surface coverage. It is vital that the targeting ligand be bound to the liposome in a way that does not mask the epitope necessary for biological function [79]. Hydrophobic ligands that cannot be directly incorporated into the lipid shell can be conjugated with a chemical linker [80]. Ligands can even be conjugated to the outer end of PEG, allowing for two layers of liposome coating [16].

Some liposomes have been specifically developed to treat neurodegenerative disease. One study developed liposomes conjugated with apolipoprotein E (ApoE) to enhance delivery of siRNA or plasmid DNA to the brain. This helped target the liposomes to neural stem and progenitor cells, making it a promising candidate for coordinated treatment with stem cell therapies [81]. Similarly, liposomes can be loaded with peptides like H102 that break β-sheets to help treat Alzheimer's Disease. Such liposomes can be administered intranasally and successfully penetrate the brain parenchyma. In rat models of Alzheimer's Disease, these H102 liposomes ameliorated spatial memory impairment, inhibited plaque formation, and increased enzymatic activity that supported cell survival [82]. A recent study also found that intranasal delivery of liposomes containing celecoxib (CB), a cyclooxygenase-2 inhibitor, cleared β-amyloid aggregates in neurons, thereby alleviating cognitive decline in a mouse model of Alzheimer's Disease. These liposomes were made using erythrocyte membranes (EM) instead of traditional phospholipids, which improved bioavailability and are promising materials for clinical trials. The CB-EM liposomes simultaneously induced neurogenesis and reduced apoptosis, addressing two of the major clinical concerns in Alzheimer's Disease [83]. In addition to treating symptomatic neurodegeneration, liposome research has addressed the issue that many clinical trials fail once patients have already experienced neurodegeneration, but that treatment is not applicable prior to the onset of symptoms. To this end, liposome treatment of a pre-symptomatic stage mouse model of Alzheimer's Disease effectively delayed deposition of Aβ plaques and prevented memory impairment [84].

2.4.2. Micelles

While liposomes are made of lipid bilayers with an aqueous internal compartment, micelles are lipid monolayers that self-assemble in polar medium to form a hydrophobic fatty acid core and hydrophilic polar surface. DSPE and phosphatidylethanolamine (PE) are commonly used phospholipids to make micelles, though amphiphilic polymers are also a common substrate for micelle synthesis [74]. Micelles range from 5 to 100 nm in size, making them much smaller than liposomes [85]. Their hydrophobic core can be loaded with drugs that would otherwise be insoluble *in vivo*, and the small micelles can efficiently pass the BBB. Loading curcumin into micelles significantly increases its bioavailability and plasma concentration relative to free curcumin, which could greatly improve curcumin as a therapy for Alzheimer's disease [85,86].

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2.4.3. Exosomes

Though not traditionally seen as a synthesized nanoparticle, exosomes generated from *in vitro* cell culture can be used to treat neurodegeneration. Exosomes are membranous vesicles excreted by a cell that can contain almost any cellular molecule, including proteins, lipids, DNA, RNA, and siRNA [5,87]. They are generally 30 to 100 nm in diameter and have a very high efficiency of crossing the BBB, though they can also be produced by all cell types in the brain and are naturally found in the cerebrospinal fluid (CSF) [87,88]. Interestingly, the molecular contents of exosomes stray from the norm in patients with Alzheimer's, schizophrenia, or bipolar disorder. Exosomal miRNAs in particular are mis-regulated, and Alzheimer's patient exosomes showed high levels of full-length and c-terminal fragments of Aβ precursor protein, which could contribute to the spread of symptoms to other brain cells [89,90]. The apparent power of exosomes in the pathology of neurodegenerative disorders led researchers to engineer the system for stem cell therapies. MSC therapy promotes angiogenesis and neurogenesis by stimulating signaling pathways that regulate brain plasticity and repair, pointing toward a paracrine mode of action as opposed to cell replacement [87,91]. In concordance, MSCs secrete a high number of exosomes, which modulate the microenvironment of nearby degenerating cells [92,93]. Injecting MSC-derived exosomes into the bloodstream of rats exposed to focal cerebral ischemia and stroke supported neurovascular remodeling and thereby significantly improved neurological function [94]. Exosomes can be engineered to contain specific miRNAs that help treat neurodegeneration, like miR-133b for stroke. Specifically, when MSCs are cultured with extracts from ischemic brain tissue, they secrete exosomes with vast numbers of miRNAs that upregulate both neurogenesis and angiogenesis [87,95]. Exosomes produced by hematopoietic stem cells (HSCs) can also cross the BBB and deliver functional cargo, like siRNA, plasmid DNA, and proteins to brain cells [87]. More work is needed to better characterize the molecular profiles of exosomal cargo and to understand exactly how this cargo is inducing neural recovery. Additionally, exosomes should be further engineered to enhance stability *in vivo* and improve specificity in targeting to individual cell types in the brain.

2.5. Polymeric nanoparticles

Polymeric nanoparticles have pliable physical properties, synthesis techniques, and degradation rates *in vivo* that make them useful drug carriers. They can reduce immunogenicity of the cargo and improve pharmacokinetic properties of encapsulated proteins [96]. The most commonly used polymeric materials include poly(lactic acid) (PLA), poly($_{D,L}$-lactic-*co*-glycolic acid) (PLGA), poly(aspartic acid), poly (glycolic acid) (PGA), and poly(butylcyanoacrylate) (PBCA). These polymers have also been broadly applied to other regenerative fields, and are therefore promising materials for treating neurodegeneration [2,97].

The shared characteristics of polymer NPs that make them useful drug carriers include multiple synthesis strategies, high stability and bioavailability, long-term circulation of encapsulated drugs, low immunoreactivity, and pliable physical characteristics [98]. Physical properties to be considered in the selection and synthesis of polymeric nanoparticles include particle size, shape, zeta potential, degradation rate, and encapsulation efficiency [99]. An incredible number of studies have been done using each of these polymers, so in this review we will provide only a few examples that demonstrate the potential of NPs for treating neurodegenerative disorders.

2.5.1. PLA nanoparticles

PLA is a standard biomaterial with low immunogenicity and long drug release kinetics. Though PLA itself is hydrophobic, it is often coated with hydrophilic PEG molecules to increase solubility and crossing of the BBB [100]. Additional ligands can be conjugated to PLA alongside PEG, like targeting peptides that bind specifically to Aβ plaques for diagnosis and treatment of Alzheimer's [100]. PLA can also be used to coat other nanoparticles, such as silica nanoparticles. The PLA coating not only improves biocompatibility and drug release kinetics, it can also be used as a sensor to release the cargo drugs only in specific microenvironments. For example, reactive oxygen species (ROS), which are often high in the brains of Alzheimer's patients, accelerate the degradation of PLA. This allows PLA to coat and protect encapsulated drugs until the NP reaches a microenvironment with high ROS, at which point the coating is degraded and the drugs are released to the site of neurodegeneration [101]. PLA NPs have successfully been loaded into MSCs for transplantation and treatment of malignant glioma, though use in stem cell therapies for neurodegeneration has yet to be shown [102].

2.5.2. PLGA nanoparticles

PLGA is a synthetic polymer that has been approved by the FDA for various biomedical applications [103]. PLGA is hydrolyzed into glycolic acid and lactic acid *in vivo*, making it highly biocompatible. It is particularly useful for sustained drug release and brain-specific targeting through conjugation with various surface ligands [96]. One recent study enhanced the delivery of the hydrophilic drug, nattokinase, across the BBB through encapsulation in PLGA followed by coating of the NP with Tet1 peptide, which has a high affinity for neurons and promotes retrograde transport. These PLGA NPs successfully downregulated amyloid aggregation and improved the stability of the nattokinase protein as a treatment for Alzheimer's [96].

2.5.3. Polymer nanoparticles in cell therapy

Synthetic polymer NPs have recently been combined with stem cell treatment to enhance NSC differentiation and allow for transplanted cell tracking [5]. PLGA NPs coated with SOX9 plasmid DNA and anti-Cbfa-1 siRNA were added to human mesenchymal stem cells (hMSC) before transplantation into nude mice. This successfully enhanced the expression of genes that promote differentiation, and promoted chondrogenesis in an attempt to treat Huntington's disease [104,105]. Similarly, another study loaded dopamine onto PLGA NPs and injected these into a rat model of Parkinson's disease. The PLGA NPs improved drug trafficking across the BBB and successfully led to sustained release of dopamine into brain lesions and improvements in neurobehavioral function [106]. In addition to modulating cell behavior, NPs can be loaded with fluorescent dyes to allow for tracking of transplanted cells [107].

2.6. Hydrogels

Macroscopic hydrogels are polymer networks that contain a large volume of water in their structures, and often incorporate some form of extracellular matrix (ECM) components. ECM can be mixed with additional neurotrophic factors, like glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) to enhance the environment for neural cell transplantation [108,109]. Hydrogels are dynamic–the physical properties change dependent on the environment, allowing the gel to be liquid until it reaches a particular temperature or pH, such as physiological pH of the brain after injection [110]. Additionally, hydrogels can use self-assembling peptides (SAPs) that create a nanofibrous structure that mimics ECM [111]. These SAPs allow for additional functional motifs to be incorporated into the gel and there by enhance therapeutic potential. More conventional components of hydrogels used for neural cell culture include alginate polymer, Matrigel ®, collagen, or synthetic chemicals like HyStem™ (Advanced Biomatrix) made with hyaluronic acid and PuraMatrix™ (Corning) made of repeating arginine-alanin-aspartate-alanine sequences. Hydrogels can also be modified from liquid to gel through photopolymerisation or chemical polymerization using mild conditions that do not significantly harm encapsulated cell viability, and the mechanical properties, like stiffness, of the final gel form can significantly influence cell behavior [112].

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Macroscopic hydrogels have been extensively investigated for their use in neuroregeneration, since they can provide a highly tunable environment for transplanted cells and release therapeutic molecules for many weeks after transplantation. Moreover, hydrogels allow for culture of neural cells in 3D, which better recapitulates *in vivo* conditions and has led to the creation of a strong model of Alzheimer's disease [113]. However, bulk hydrogels are too large for efficient drug delivery across the BBB, and are limited to applications of cell transplantation [114–117].

A potential alterative to macroscopic hydrogels are the emerging field of nanogels, which are smaller in size (2–250 nm) and can be used to encapsulate drugs for delivery across the BBB [114]. Nanogels are mostly synthesized using photo (UV) or chemical crosslinking, especially click chemistry, to induce formation of covalent bonds across polymers to create a highly stable network [118,119]. Though the field of nanogels is still relatively new, applications to the treatment of neurodegenerative disease have already been shown. One study synthesized 20–30 nm nanoparticles with a polysaccharide pullulan backbone and cholesterol sidechains (CHP-nanogels) and showed that these nanogels can inhibit the formation of Aβ-fibrils by promoting a conformation change of Aβ-molecules from random coils to β-sheets or α-helices. Uptake of CHP-nanogels reduced cytotoxicity caused by Aβ-fibrils in PC12 cells by 60% *in vitro*. Additionally, amino-group modification of CHP-nanogels further increased inhibition of Aβ-fibrils formation due to enhanced electrostatic interactions between the nanogels and Aβ molecules [120]. Another study synthesized chitosan nanogels loaded with 25 mg/kg of the anti-cancer drug methotrexate. The gels were then coated with polysorbate 80 for targeting to the brain *via* low-density lipoprotein (LDL) receptor-mediated endocytosis by brain endothelial cells. These gels averaged 118.54 nm in diameter, and upon intravenous injection in rats produced significantly higher concentrations of methotrexate in the brain parenchyma compared to administration of free drug. However, polysorbate 80 coating did not further enhance targeting to the brain relative to uncoated gels [121]. Nonetheless, the major benefits of nanogel drug encapsulation are controlled release kinetics and enhanced passage through the BBB [121,122].

3. Stem cell therapies for neurodegenerative disease

The use of stem cell therapy to treat neurodegeneration posits the interesting idea that neurodegeneration and regeneration exist in some equilibrium in adult humans [123]. Though the existence of human adult neurogenesis has recently been called into question, there is significant evidence that treatment with stem cells can enhance neurogenesis in models of degenerative diseases [124–127]. Despite the varying pathophysiology of different neurodegenerative disorders, the loss of synaptic function is broadly related to cognitive impairment. Therefore, regenerative or replacement therapy with stem cell transplants could reduce cognitive decline in various degenerative disorders [128]. To date, the most promising avenues for stem cell therapy include neural stem cells, embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells (Fig. 5). Each is described in more detail below.

3.1. Neural stem cells

Neural stem cells (NSCs) can be derived from embryonic brain tissue or induced from patient somatic cells [129,130]. They are defined by their ability to differentiate into astrocytes, oligodendrocytes, and neurons [131]. Extensive studies on the signaling pathways that mediate NSC differentiation allow for careful control over NSC cell fate both *in vitro* and *in situ* [130]. Current clinical trials are focused on exogenous transplantation of NSCs, which have shown some promise in slowing progression of ALS in Phase I trials (clinical trial NCT01640067) upon injection of fetal NSCs into the spinal cord of patients [132]. Additionally, mouse studies with human neural stem cells have shown promise for NSC treatment of Alzheimer's disease. The HuCNS-SC human neural stem cell line improved cognition of AD mouse models by enhancing endogenous synaptogenesis. Transplanted cells successfully migrated and differentiated into immature neurons and glia, leading to significant increases in synaptic markers, including synaptophysin, synapsin, and growth-associated protein-43 (GAP-43). This improved cognitive function of two independent AD mouse models, but did not reduce Aß or tau pathology, indicating that the regenerative capacity of NSCs could help balance the degeneration occurring in the AD brain, but does not treat the underlying pathology [128].

Nanomedicine could shift the direction of NSC therapy from exogenous cell transplantation to activation of endogenous populations [133]. The replacement of functional neurons in neurodegeneration or after brain injury is incredibly low, with only 0.2% of injured neurons being functionally replaced after stroke [134]. The adult brain may lack the necessary developmental signals for axon regeneration and projection, and the distance NSCs must migrate to replace dying cells is often prohibitive of proper regeneration [130,135]. To address the shortcomings of NSC migration and integration into functional networks, nanoparticles have been studied as a method to improve the microenvironment of transplanted or *in vivo* NSCs to enhance their therapeutic action. For example, lipid nanocapsules coated with NFL-TBS.40–63, a synthetic peptide that mimics the tubulin-binding site of neurofilaments, selectively target NSCs in the sub-ventricular zone (SVZ) when injected into the adult rat brain or spinal cord [136]. By loading these nanocapsules with active biomolecules, endogenous NSCs could be activated to increase their recruitment for regeneration.

Nanoparticles have also been investigated as mediators of the fate of transplanted NSCs. In the context of Parkinson's disease, the replacement of dopamine neurons (DAN) is limited due to difficulties in guiding dopaminergic axons (DAx) or transplanted neurons to make them functionally connected to the *in vivo* network. One strategy to improve this involves using hydrogels loaded with chemo-attractive compounds like Sema3C protein, which successfully guided axon growth of rat and human dopaminergic neurons *in vitro* [110]. The goal of this work is to eventually use such hydrogels to guide axon growth into specific regions of the brain, like the striatum in PD patients. Hydrogels can also be used to fully encapsulate transplanted NSCs, which enhances survival of transplanted NSCs, attracts endogenous NSCs, and reduces differentiation into glial astrocytes in rats [111].

3.2. Embryonic stem cells

Embryonic stem cells (ESCs) are well known for their almost totipotent differentiation capacity and potent self-renewal abilities. However, both ethical and medical concerns have limited the use of ESCs for treating neurodegenerative diseases. The power of ESCs to divide and migrate rapidly creates a significant risk of tumor formation and cancer [137,138]. Furthermore, allogenic sources of ESCs can cause severe immune rejection in the host patient [23]. Nonetheless, ESCs have shown great potential in mouse models due to their ability to form dopaminergic neurons, which has not been accomplished using adult neural stem cells. These dopaminergic neurons are critical for treating Parkinson's disease, though it has yet to be shown that transplanted cells can functionally integrate into the neural network [127]. Additionally, ESC treatment of rats with spinal cord injury showed migration into the parenchyma and spinal cord and led to partial motor recovery, which gives hope to the ultimate goal of reversing motor degeneration in PD [139].

ESCs have incorporated NP technology largely for tracking the migration and differentiation of transplanted cells. Superparamagnetic iron oxide (SPIO) nanoparticles in conjunction with MRI allows for long-term imaging of transplanted cells [140]. Similarly, SPIO nanoparticles have been used alongside fluorescent cell fate markers to monitor both migration and differentiation *in vivo* [140]. Additionally, *in vitro*

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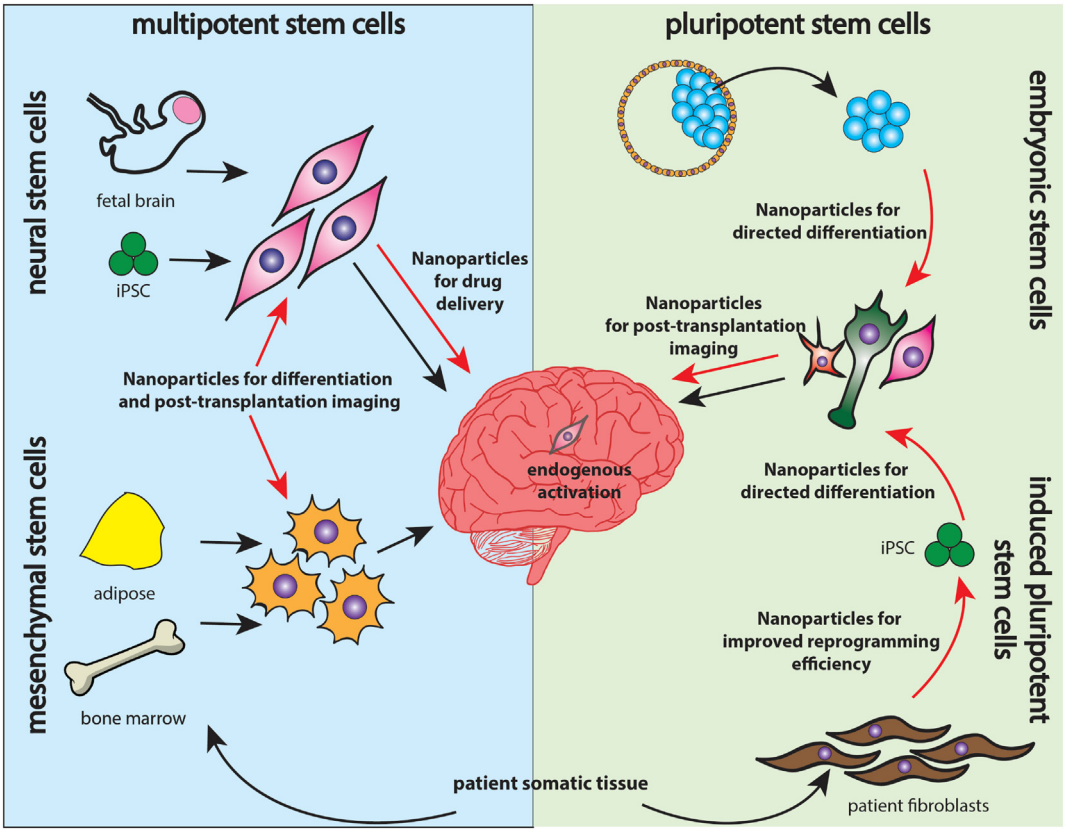

Fig. 5. Four categories of stem cells have been studied as potential therapies for neurodegenerative disorders. Neural stem cells (top left) and mesenchymal stem cells (bottom left) are multipotent populations that can be combined with nanoparticle medicine and transplanted into the brain. Embryonic stem cells (top right) and induced pluripotent stem cells (bottom right) are pluripotent populations that utilize nanoparticles both for reprogramming and differentiation as well as for drug delivery into the brain.

experiments have shown the function of NPs in directing differentiation of ESCs into motor neuron precursors; the use of mesoporous silica NPs eliminates the need for daily supplementation of soluble factors into the culture media, which is a significant strain on ESC culture [141].

3.3. Induced pluripotent stem cells (iPSCs)

Incredible progress has been made in the field of induced pluripotency since the 2006 discovery that terminally differentiated somatic cells can be reprogrammed into embryonic-like pluripotent stem cells [142]. This technology allows for major expansion and autologous transplantation of a patient's own reprogrammed cells, thereby eliminating immune rejection concerns. Use of iPSCs for cell therapy also bypasses the ethical concerns of harvesting ESCs [143]. Like ESCs, human iPSCs can be differentiated dopaminergic neurons, making them especially relevant to the treatment of PD. In contrast to ESCs, however, iPSCs do not spontaneously form DA neurons after transplantation, and must therefore be cultured to a sufficient progenitor stage prior to transplantation. If transplanted in a fully undifferentiated state, iPSCs often form teratomas (tumors), which remains a major concern in clinical applications and obtaining FDA approval for iPSC therapy [143]. The method of reprogramming is also critical for clinical safety, as traditional retroviral or lentiviral vectors can lead to unwanted viral integration in the iPSCs, causing chromosomal disruptions and mutations. Developments in using non-viral vectors like plasmid DNA, RNA, miRNAs, proteins, or small molecules have improved reprogramming efficiency and safety [144]. Calcium phosphate nanoparticles have been used as vehicles for delivery of plasmids for the four core pluripotency factors, Oct4, Sox2, c-Myc, and Klf4 to generate iPSCs with high efficiency [145].

The use of nanoparticles in iPSCs for treatment of neurodegenerative disorders is largely unexplored. One study showed that mesoporous silica nanoparticles can be internalized by iPSCs, indicating that they could be used to deliver drugs, gene therapy, or differentiation factors [146]. In the context of iPSC therapy for non-neurologic disorders, iPSCs have been grafted onto gelatin-PLGA NP scaffolds for assisted differentiation to generate insulin-producing pancreatic cells [147]. Similarly, lipid nanoparticles modified with heparin and nerve growth factor (NGF) can direct differentiation of iPSCs into neurons, though this has not been applied to neurodegenerative disorders [148]. Broadly, NPs have been shown to be compatible both for uptake by iPSCs and as scaffolds for iPSC transplantation.

3.4. Mesenchymal stem cells (MSCs)

MSCs are adult, self-renewing, multipotent stem cells that can differentiate to make bone, cartilage, fat, and epithelial cells *in vivo*, though they can be guided into differentiating down neuronal and glial fates *in vitro* [149,150]. MSCs can be harvested from bone marrow, umbilical cord, adipose tissue, or the spleen, making them relatively easy to collect from human patients. Once isolated, MSCs are expandable *in vitro* and can then be transplanted into the CNS. Their main function in neuro-regeneration is the production of neurotrophic factors, like BDNF and GDNF, which stimulate endogenous neurogenesis and activate microglia, which then increase clearance of Aß plaques [23]. MSCs can also secrete stromal-derived factor 1 (SDF1), angiopoietin-1, angiogenic cytokines, and ECM components, which improve angiogenesis and recruit neural progenitor cells [151].

The combination of MSC therapy and nanoparticles has been used to treat brain tumors and to study rodent models of neurodegenerative diseases. In targeting malignant gliomas, MSCs were loaded with polylactic acid (PLA) NPs and lipid nanocapsules containing coumarin-6, which allowed for fluorescent tracking of the NPs. The MSCs successfully carried the NPs toward a human glioma model with no loss in cell viability, indicating that MSCs may be a highly efficient delivery

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system for NPs [102]. In addition to delivering NPs to sites of lesion, MSCs have been loaded with SPION NPs to track cell migration and survival post transplantation in a rat model of Huntington's disease. SPION-labeled MSCs injected into the rat striatum significantly reduced the number of degenerating neurons 7 days after lesion by increasing FGF-2 expression in striatal cells and reducing dilation of the lateral ventricles. The SPIONs within the MSCs were detectable for over 60 days after transplantation using magnetic resonance imaging (MRI) [152].

4. Future perspectives

Nanoparticles and stem cell therapy encompass multiple prospects for improving our understanding and treatment of neurodegenerative disorders. One of the largest battles in treating neurodegeneration is the minimal understanding of the molecular mechanisms behind major disorders. The use of nanoparticles to grow stem cells in carefully controlled micro-environments *in vitro* is therefore valuable for addressing the need for better model systems of human neurodegenerative disorders. A strong push toward better models will reduce failure of clinical trials and improve cost efficiency of potential therapies; nanoparticles in concert with stem cell biology hold great potential for such models.

Beyond *in vitro* applications, nanoparticles should be further explored for diagnostic imaging, as this is a field that is rapidly growing and can already apply the known optical properties of nanoparticles to well-established imaging techniques. Metal nanoparticles in particular hold great promise, and their potential to both diagnose and treat neurodegenerative disorders should be a focus of upcoming studies. In particular, combining metal nanoparticles with stem cell transplantation creates exciting opportunities to track the state of the disorder and the success of treatment.

The greatest shortcoming of both nanoparticle and stem cell therapy studies is the lack of *in vivo* work. Currently, there are no clinical trials that use both nanoparticles and stem cell therapy to treat neurodegenerative disease. The BBB creates a major hurdle, and the danger of uncontrolled differentiation of transplanted stem cells poses a significant risk for human application. Pre-loading nanoparticles into stem cells and direct injection into the brain would provide a more robust treatment than either intravenous nanoparticle injection or injection of stem cells into the brain alone. Therefore, more extensive studies are needed to understand uptake and release dynamics of nanoparticles in stem cells used for transplantation. Ideally, nanoparticles will allow for careful control over stem cell transplantation, the subsequent microenvironment, stem cell differentiation, and treatment of damaged neighboring cells. Highly personalized therapies with careful monitoring will greatly improve the success of treatments for neurodegenerative disorders.

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