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MINIREVIEWS

Neural stem cells could serve as a therapeutic material for age-related neurodegenerative diseases

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Abstract

Progressively loss of neural and glial cells is the key event that leads to nervous system dysfunctions and diseases. Several neurodegenerative diseases, for instance Alzheimer's disease, Parkinson's disease, and Huntington's disease, are associated to aging and suggested to be a consequence of deficiency of neural stem cell pool in the affected brain regions. Endogenous neural stem cells exist throughout life and are found in specific niches of human brain. These neural stem cells are responsible for the regeneration of new neurons to restore, in the normal circumstance, the functions of the brain. Endogenous neural stem cells can be isolated, propagated, and, notably, differentiated to most cell types of the brain. On the other hand, other types of stem cells, such as mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells can also serve as a source for neural stem cell production, that hold a great promise for regeneration of the brain. The replacement of neural stem cells, either endogenous or stem cell-derived neural stem cells, into impaired brain is highly expected as a possible therapeutic mean for neurodegenerative diseases. In this review, clinical features and current routinely treatments of age-related neurodegenerative diseases are documented. Noteworthy, we presented the promising evidence of neural stem cells and their derivatives in curing such diseases, together with the remaining challenges to achieve the best outcome for patients.

Key words: Alzheimer's disease; Huntington's disease; Neural stem cells; Parkinson's disease; Cell therapy; Neurodegenerative diseases

Core tip: Neural stem cells present throughout life of human. The cells can be distinguished from differentiated progeny by acknowledging a few key features, including proliferation, self-renewal, multipotency and molecular markers. These features make neural stem cells as an essential component in the development of nervous system and in maintaining cell number of adult nervous tissues following injury and diseases. Besides conventional treatments, neural stem cells have been proposed as a promising approach to cure patients with neurodegenerative diseases. Several animal studies showed the efficiency of neural stem cells in treating age-related neurodegenerative diseases, in particular

Alzheimer's, Parkinson's and Huntington's diseases.

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INTRODUCTION

Neurodegenerative diseases are a global burden and often affect elderly population worldwide. The central and shared characteristics of neurodegenerative diseases are the loss of neuronal cells in either the central or peripheral nervous systems. Aging can cause chronic neurodegeneration, which results in the loss of particular neuronal subtypes over time. Parkinson's, Alzheimer's and Huntington's diseases are the three most dominant neurodegenerative diseases, found worldwide. In the brain, Alzheimer's and Huntington's diseases result in widespread loss of neurons, while Parkinson's disease involves the specific loss of midbrain dopaminergic neurons. In spite of an extensive effort to develop treatment against these neurodegenerative diseases, effective treatments still do not exist. Recently, cell therapy has been proposed as an attractive option, and the application of stem cell technology to regenerative medicine is rapidly progressed. Stem cell-based approaches are applicable for therapeutic purposes, for instance it might be possible to replace lost neurons or glia by transplantation of stem cell-derived nervous cells. Cell replacement might also be succeeded by activating endogenous neural stem cells in patients own brain to form new neurons and glia. In this review, we summarized clinical manifestations of the major age-related neurodegenerative diseases, in particular Parkinson's, Alzheimer's, and Huntington's diseases, together with their currently available treatments. The properties and characteristics of neural stem cells were presented, highlighting key features that enable neural stem cells to be a promising therapeutic material. Lastly, we documented evidence of neural stem cells and other stem cells to cure neurodegenerative diseases, especially Parkinson's, Alzheimer's, and Huntington's diseases.

CLINICAL MANIFESTATIONS OF AGE-RELATED NEURODEGENERATIVE DISEASES: ALZHEIMER'S, PARKINSON'S, AND HUNTINGTON'S DISEASES

Parkinson's disease (PD) is one of the most common movement malfunctions and affects nearly 1% in elderly population age over 60. The average age of onset at 55 years, and the frequency increases markedly with age[1,2]. There are several lines of studies proposing that genetic mutations or polymorphisms are correlated and can contribute to an increased risk of PD in senior population[3]. Although genetics are only influenced a minor group of PD, the studies of genetic factors improve an understand of the pathophysiology of PD. An increasing number of genetic risks appear to be connected with PD, and many of them followed Mendelian inheritance rules, including alpha-synuclein gene (*SNCA*, PARK1/4), parkin gene (*Parkin*, PARK2), P-TEN-induced putative kinase 1 gene (*PINK1*, PARK6), Daisuke-Junko 1 gene (*DJ-1*, PARK7), and leucine-rich repeat kinase 2 gene (*LRRK2*, PARK8). These genes have been conclusively proven as a monogenic etiology for familial parkinsonism[4]. To characterize PD, patients can be diagnosed by several key manifestations, including bradykinesia (slowness of establishing the voluntary movement and declination in speed of repetitive manners), resting tremor (4-6 Hz), and rigidity[5]. A group of clinical outcome usually presents in an asymmetrical manner. The presences of a change in handwriting with micrographia, reduced sense of smell and facial expression, and loss of arm swing on one side of the body are often noted as early clinical features[6,7]. When the disease progressively developed, gait instability, drooling of saliva, and impairment of postural reflexes will appear. Non-motor symptoms, such as neurobehavioral dysfunctions, insomnia, cognitive and sexual impairment may present in early or late stages of the disease progression. Depression and dementia are also common symptoms in non-motor presentation of PD's patients. A good response to levodopa treatment can differentiate PD from Parkinsonism due to other causes. The standard diagnosis for PD still relies on the neuropathological examination. All the cardinal signs of PD involve to motor disability in asymmetrical onset, without other causes of Parkinsonian syndrome and non-motor manifestations, including psychiatric symptoms[8]. The UK Parkinson's Disease Society Brain Bank criteria is commonly used as a reference.

Alzheimer's disease (AD) is a progressively degeneration of the brain cortex, manifested by memory and intellectual decline, and progressive deficiency of daily-living activities[9]. AD affects about 6% of the population aged over 65 years old worldwide. Age is considered the single utmost vital risk factor for AD ontogeny. Amyloid-β, oxidative stress, inflammation, and vascular injury appear to play an essential function in the neurodegeneration of AD[10]. Multiple genetic defects have been associated to the development of AD. Initially, the molecular genetics of AD can be obtained from early-onset AD families with autosomal dominant patterns of inheritance. Highly penetrant mutations were identified in three genes: *APP, PSEN1,* and *PSEN2*[11-13]. Interestingly, these genes are functionally participated in the processing of amyloid precursor protein. This suggests a central role of amyloid

precursor protein in AD pathology. Clinically, AD patients gradually evolve from the mildest to the most severe clinical manifestations of illness. Primarily, AD's patients present as an inability to restore newly acquired information, which can be examined by repetitively questioning. This short term memory impairment results from the atrophy of the hippocampus, especially the temporal horn[14]. The clinical features are an amnestic type of memory dysfunction, deterioration of visuospatial, and language deficits[15]. When the disease advances, devastation of other brain domains of cognition, including abstract thinking, language, judgment, calculation, and executive function, will develop. This impairment usually coincide with the aberration of art and social interpretations. AD patients evolve their symptoms from the loss of basic activities (*e.g.,* dressing, eating, and bathing) to higher functions of activities in daily living (*e.g*., shopping, business management). Psychiatric and behavioural instabilities also progress over the course of AD. Emotional disorders (*e.g.,* depression 25%-30%, anxiety 15%-25%, delusions in 20% of cases) and loss of initiation or apathy (up to 40%) commonly develop at early stage of AD and continue during disease progression. Motor and sensory dysfunctions, gait disorders, and other abnormal movements will appear at the late stage of the disease. The diagnosis of AD is frequently referred to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and the National Institutes of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[16]. The gold standard of AD diagnosis is based on neuropathological findings of neuritic plaques (extra-neuronal β amyloid-containing plaques) and intra-neuronal neurofibrillary tangles in patient's brain tissues.

Huntington's disease (HD) is a rare inherited neurological disease, manifested by unwanted choreiform movements, psychiatric instabilities and cognitive deficiency[17]. Disease onset is commonly between 30 and 50 years old and the patients with HD can present disease conditions at any time points during the disease progression. HD is a disease triggered by a repeated trinucleotide, CAG (more than 36 repeats), of Huntingtin gene located on the short arm of chromosome 4[18]. Large duplication of CAG repeats are susceptible to replication error of the chromosome during meiosis, leading to extension or reduction of the CAG repeats[19]. Choreiform movement is an early symptom, which causes limb incoordination and impaired function. This movement disorder is as a consequence of a selective neural cell death and atrophy in the putamen and caudate of the brain. Another significant feature in HD patients is an incapability to sustain a voluntary muscle contraction. The pattern of this symptom tends to change over time with other abnormal movements, such as rigidity, dystonia, and bradykinesia. HD patients might confront non-motor symptoms that could be more disturbing than motor symptoms, such as personality changes, impulsivity, abnormal perceptions, lack of insight, and disability to learn new information or knowledge[20]. Depression is also found and appears as a part of disease. Metabolic signs, for example weight loss and sleep problems, may contribute to depression of HD patients. A diagnosis of HD is relied principally on questionares, physical examination, family medical history, and neurological and psychiatric investigations. Brain imaging technology, in particular magnetic resonance imaging, can show structural alterations at specific locations in the brain affected by mutant Huntingtin protein. In spite of identification of the Huntingtin gene and other causative proteins, the mechanisms contributed to the pathogenesis and symptoms of HD remain largely elusive and this greatly hampers efficient development of clinical treatment.

CURRENT THERAPEUTIC APPROACH OF AGE-RELATED NEURODEGENERATIVE DISEASE

The early success in developing treatment strategies relied on the early understanding that PD is a DA deficiency disorder. Dopamine therapy is effective for improving both motor and non-motor symptoms in initial PD stage. Levodopa (LD) is considered as the most efficient and best accepted antiparkinsonian compound[21]. Initiating levodopa as first-line therapy may achieve optimal outcomes in terms of patient function in the early years of the disease. Catechol-O-methyltransferase (COMT) inhibition increases the peripheral bioavailability of LD and reduces 3-O-methyldopa formation. The administration of COMT inhibitors with LD ensures a more stable plasma LD level and, consequently, it improves motor fluctuations. The use of COMT inhibitors improve the half-life of LD, and the triple combination carbidopa (CD)-LD-entacapone provide the most sustained LD plasma level[22]. However, in long-term, this combination treatment is accompanied with the fluctuations of motor functions, dyskinesias and neuropsychiatric manifestations[23]. Switching to alternative LD formulations, or supplementation of therapy with additional agents are general strategies for managing motor complications associated with LD. In addition, severe staged patients continually developed features that do not respond well to LD treatment, such as motor fluctuations, freezing episodes, autonomic dysfunctions, gait instability, dementia, and symptoms related to side effects of other medications[24]. Surgical treatment is considered as an option for these patients who have motor fluctuations and dyskinesias, because these symptoms cannot be adequately managed by medications. The principal surgical option is deep brain stimulation, which has largely replaced neuroablative lesion surgeries for improving motor control[25]. Next, the principal risk factor for AD is age. Several routinely-used drugs

can alleviate diseased conditions, but do not prove significant disease-improving effects[26]. A number of therapeutic approaches intended at inhibiting disease progression are now developed into clinical trials. With disease advancement, brain degeneration in areas of memory, cognition, psychiatry, and movement, occurs to varying degrees. In clinical practice, non-medical interventions should be firstly tried, especially when symptoms are not causing distress to impact patients in daily living activity. Medical treatment for improving cognition, for instance acetylcholinesterase inhibitor, offers cognitive improvement (*e.g.,* memory deterioration, language dysfunctions, and executive dysfunction,) and psychiatric repairment (*e.g.*, depression, hallucination, agitation and delusion) in all stages of disease progression. The treatment with N-methyl-d-aspartate antagonist presents similar result, and this molecule can be applied in combination with acetylcholinesterase inhibitors in severe stage of AD patients[27]. Many clinical trials aim to target at the generation and eradication of amyloid-β (Aβ) peptide, a dominant element of AD pathogenesis. Currently, the anti-Aβ strategies are advancing with the increasing number of potential drugs. Direct interaction with Aβ of small molecules could diminish Aβ aggregation and deposition within the brain, thus reducing Aβ-mediated synaptic dysfunction and neuronal cell death. The primarily anti-Aβ drug to accomplish a clinical study was tramiprosate. Tramiprosate is a glycosaminoglycan derivative that binds to a single molecule of Aβ. The interaction of tramiprosate and Aβ reduces the aggregation and toxicity of Aβ, while promote the clearance of Aβ from the patient's brain. Although the treatment with tramiprosate was well tolerated, it fell short of an advantageous effect on the primary outcomes, which are the improvement on cognitive functions and clinical stages of AD patients. Another strategy to reduce Aβ level within the brain is to minimize its production. Gamma secretase, a transmembrane enzyme, is reportedly required for Aβ generation in several tissues, including brain. It cleaves at one end of the amyloid precursor protein, in which Aβ is generated. Tarenflurbil, a non-steroidal anti-inflammatory drug, was found to lower the activity of gamma secretase enzyme, and, consequently reduce Aβ production[28]. In a Phase Ⅱ of clinical trial in AD patients with mild-to-moderate symptoms, tarenflurbil was considerably safe and well tolerated; however, the beneficial effect of tarenflurbil on cognitive repairment was not observed[29]. One possible explanation for the disappointing outcome of tarenflurbil is that oral administration cannot elevate the concentration of tarenflurbil inside the brain to be at sufficient level to reduce Aβ production. An alternative approach focuses at modulating the abnormal aggregation of neurofibrillary tau protein, which is also another key feature of AD[30]. Tau protein is a microtubule-associated protein, and found predominantly in neurons. Tau protein functions in promoting and stabilizing the assembly of tubulin protein into microtubule filaments. In AD patients, hyperphosphorylation of tau protein is found in the cortex and hippocampus of the brain, and this could disrupt the original function of Tau protein. The hyperphosphorylated Tau results in self-assembly into paired helical filament structures that accumulate and form intraneuronal tangles, a neurotoxic agent. There are several compounds that can inhibit Tau-self aggregation. For instance, methylene blue, an extensively used histology dye, has been tested for its interference effect on Tau-self aggregation[31]. This compound is currently experimented as a potential effective molecule for AD treatment, since a Phase Ⅱ clinical study of methylene blue has been completed, and some outcomes suggested a drug benefit in a group of AD participants[32]. Nevertheless, it is noted that there are no effective treatments available for AD at the present. Thus, the current strategy of AD management is to decrease symptoms and improve patient's quality of life. It is sensible to expect that, in the coming years, an optimal synergistic combination of these therapeutic compounds will be formulated, which will be able to modify neurodegenerative cascade and, therefore, reduce the global impact on the brain of this dreadful disease.

Lastly, the treatment of HD has been focusing on relieving motor dysfunctions (chorea), cognitive decline and psychiatric manifestations[33]. Pharmacological treatment of Huntington's disease might not be necessary if symptoms are mild or not troublesome. Clinically, there are various potential drugs that show the capacity to correct the conditions of HD patients. Treating chorea is an important part of HD management, because it interferes to the quality of life of HD patients. Tetrabenazine was approved in 2008 by the United States Food and Drug Agency to control the involuntary periodic movements of the limbs and face, associated with chorea[34]. Tetrabenazine is a central monoamine extinguisher that reversibly binds to the type-2 vesicular monoamine transporter[35]. Dopamine and glutamate transmission and interaction are one of the affected pathway in the HD brain. The aberrations of this can result in striatal and cortical connection dysfunctions[36]. Therefore, most treatments, investigated at chorea, have targeted to these neurotransmitters and their receptors. Antipsychotic drugs, for instance clozapine, haloperidol, olanzapine, and, chlorpromazine, which act by reducing dopamine levels, are occasionally prescribed to lower chorea symptom[37]. A side benefit of these antipsychotic drugs is that they also help controlling the HD-associated psychotic behaviors. Besides pharmacological treatment, physical and occupational therapy at the initial stages of the disease can correct motor dysfunction and locomotion, which is due to the fact that exercises can reinforce muscle strength and improve balance and posture of HD patients[38]. Psychiatric therapy can help reducing stress, anxiety

Table 1 Characteristics and conventional treatment for Alzheimer's, Parkinson's and Huntington's diseases

Disease	Characteristics	Treatment	Ref.
Alzheimer's	Memory impairment Impaired reasoning and handling of complex tasks, poor judgment Changes in personality, behavior, or comportment	Medications: Cholinesterase inhibitors NMDA antagonist Non-medicals Psychological supports	[9,15,16,26,27,30]
Parkinson's	Motor symptoms (1) Rest tremor (2) Bradykinesia (3) Rigidity (4) Loss of postural reflexes Non-motor symptoms (1) Autonomic dysfunction (2) Cognitive/neurobehavioral abnormalities (3) Sleep disorders (4) Sensory abnormalities such as anosmia, paresthesias and pain	1 Medications Dopaminergics: (1) Levodopa (2) Ergot dopamine agonists (3) Non-ergot dopamine agonists Non-dopaminergic: (1) COMT inhibitors (2) MAO-B inhibitors 2 Non-medicals Ablative lesions Deep brain stimulation	[1,6-8,23-25]
Huntington's	Choreiform movement Cognitive impairment Behavior and psychological disorders	Medications Symptomatic agents	[17,18,20,33,36]

NMDA: N-methyl-D-aspartate receptor; COMT: Catechol-O-methyltransferase; MAO: Monoamine oxidase.

and depression, as well as help managing with the emotional changes associated with the disease. Table 1 summarized characteristics and conventional treatment for Alzheimer's, Parkinson's and Huntington's diseases.

NEURAL STEM CELLS: PROPERTIES AND CHARACTERISTICS

Several lines of studies suggest that stem cells exist in the central nervous system (CNS)[39]. Neural stem cells exist not only in the embryonic brain, but also in the adult nervous system of all mammals, including human. Neural stem cells can be distinguished from differentiated neurons by acknowledging a few key features, including proliferation, self-renewal, multipotency and molecular markers[40]. These features make neural stem cells as an important element in CNS development and in maintenance cell number following injury and diseases or natural cell turnover.

Proliferation and self-renewal

To reach the correct number of differentiated cells in the CNS, neural stem cells have to be precisely controlled a balance between cell proliferation and differentiation during the embryonic CNS development. This balance is regulated by both stimulatory and inhibitory signals to converge the requirements of the tissues in which neural stem cells provide newly differentiated progenies. Proliferation potential is one of the most essential characteristics of neural stem cells and it was shown that neural stem cells in adult brain can be propagated *in vitro* for years[41]. In order to generating a satisfactory number of neural stem cells, it is assumed that cell proliferation should be prevalent in the early developmental timing, and that more cells differentiate into a specific cell type during the latter phases. This indicates that there is a high possibility for producing two undifferentiated daughter cells at early stages of development (symmetric division), and later cell division prefers the production of differentiated neurons and glial cells (asymmetric division). Neural stem cells residing in the developing neocortex undertake both symmetrical and asymmetrical divisions throughout their life span[42]. Several pathways that interconnect to control cell proliferation have been well documented. Perhaps the best comprehensive studies are those cell signalling pathways that are triggered by growth factors. All types of neural stem cells are generally responsive to multiple family of growth factors; however, the exact set of growth factors should be exclusively required for neural stem cells at specific stages and could distinguish stage-specific neural stem cells. Early neural stem cells entirely respond to fibroblast growth factor2 (FGF2 or bFGF), and the loss of FGF ligands or FGF receptors results in a significant diminution of neural stem cell proliferation[43]. On the other hand, the late emerging neural stem cells demand either FGF2 or epidermal growth factor for their proliferation[44]. It is noted that cell self-renewal is tightly connected to this growth factor responsive potential. Self-renewal is considered as a pivotal identity of neural stem cells because it is indispensable for the cells to preserve themselves, therefore at least one of the progeny retains similar molecular characteristics to the mother stem cells. It is important to note that while a process of self-renewal occurs, neural stem cells may undergo changes in their abilities to produce different progeny during development[45].

Multipotency

To be characterised as a neural stem cell in the CNS, a cell must contain a differentiation potential to give rise to neurons, astrocytes and oligodendrocytes[41,46]. It is noted that neural stem cell plasticity is progressively restricted as development advances, for example early neural stem cells appear to be specified a wide range of phenotypes, from anterior to posterior parts of the brain, while late neural stem cells is only restricted to its origin[47]. It was presented that adult neural stem cells exist mainly in two areas of the brain, subventricular zone (SVZ) and sub granular zone (SGZ), can be propagated *in vitro* for years[41]. Neural stem cells in the SVZ can differentiate into olfactory neurons, while neural stem cells of SGZ differentiate into granular neurons of the dentate gyrus. However, when transplanting SVZ neural stem cells into dentate gyrus, they differentiate into calbindin-positive granular cells, while transplanting SGZ neural stem cells into the olfactory bulb, tyrosine- and calretinin hydroxylase-positive cells were observed. Furthermore, when transplanted into the developing eyes, hippocampal neural stem cells exhibited several morphological and immunological properties of retinal cells, including photoreceptors[48]. This implies that the fate of adult neural stem cells could be influenced by environmental cues[49]. In addition to the effects from environment, cell intrinsic programs also influence cell differentiation capacity. The robust intrinsic differences, with respect to distinct differentiation potential, has been shown to exist between neural stem cells isolated from different brain regions[50,51].

Molecular markers

Many efforts have attempted to define neural stem cells according to their biological properties and molecular markers. In addition to those biological parameters, a series of immunoreactive antigens could also distinguish neural stem cells from others. Markers that define this population are now being developed; thus, they are commonly characterised retrospectively on the foundation of their behaviours. The evaluation of self-renewal of neural stem cells can be initially accomplished by the expression of specific molecular markers that can distinguish them from postmitotically differentiated cells. The successive expression of various intermediate filament genes has offered a useful system to classify distinct cell types during the early embryonic neural stem cells. The intermediate filament Nestin and Vimentin are exclusively expressed in the mitotically active cells during neural tube formation[52]. Embryonic neural stem cells express several astrocytic markers, for instance brain lipid-binding protein, glutamate transporter, S100β, RC2 and 3CB2[53]. Together with their differentiation potential, these astrocytic features distinguish embryonic neural stem cells from other types of astrocytes and differentiated cells. On the other hand, adult SVZ neural stem cells appear to be slowly proliferating and long-term BrdU-retaining cells, which express GFAP and the glycoprotein CD133 (Prominin-1)[54]. Anatomical structures and comprehensive set of immunohistochemical markers help to ensure adult SVZ neural stem cell identity. A subset of these cells is identified by the expression of the intermediate filament Nestin, GFAP, transcription factor SOX2, and the RNA binding protein Musashi1, while absence of expression of the differentiated markers CD24, NeuN, and O4[55]. In the SGZ of the dentate gyrus, a comparable subset of neural stem cells expressing GFAP, SOX2 and Nestin resembles to dormant or quiescent adult neural stem cells which can give rise to mature astrocytes and neuroblasts[56].

An evolving regulatory networks governing neural stem cell identity is delineated by an integration of cell internal transcription factors with the cell extrinsic stimuli from an environment or culture conditions. Unrevealing how these regulatory network functions to control neural stem cells is essential to better understand of neural stem cell biology. Ultimately, it will also accelerate the progression of a novel targeted therapy by using neural stem cells for curing neurological disorders, for instance brain tumours, brain injuries, and also neurodegenerative diseases, for example HD, AD and PD.

POTENTIAL OF NEURAL STEM CELLS FOR TREATING AGE-RELATED NEURODEGENERATIVE DISEASES

Cell replacement by neural stem cell transplantation in the brain could alleviate pathological or functional deficits associated with diseases in the CNS. In addition to conventional clinical treatments, cell replacement therapy has offered the novel basis for the development of effective therapeutic strategies for human neurodegenerative diseases (Figure 1). It is hypothesised that the release of neurotransmitters and the production of neurotrophic factors from transplanted cells are possible mechanisms that promote neuronal regeneration in the damaged brain areas. PD is characterized by a vastly loss of midbrain dopaminergic neurons in the substantia nigra pars compacta and the striatum. It was reported that human fetal ventral mesencephalic tissues was successfully transplanted into the striatum of PD patients with advanced disease; however, this human tissue transplantation contains some limitation[57]. For example, a sufficient amount of fetal tissues was challenging to obtain and the survival and integration of transplanted cells in patient's brains was found to be minimal[58]. Besides, the development of abnormal movements was noticed in PD patients who have received embryonic nigral transplants. The potential propagation of Lewy body from host-to-graft tissues is also a serious concern[59]. The generation

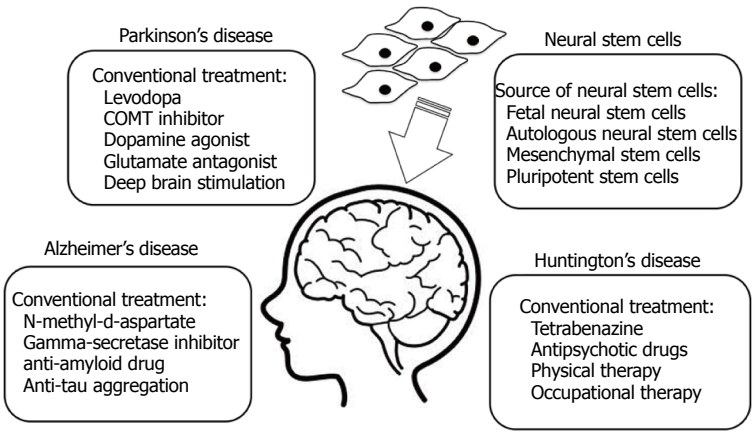

Figure 1 Neural stem cells as a therapeutic material for neurodegenerative diseases. Schematic image presents conventional treatments for Alzheimer's, Parkinson's, and Huntington's diseases. Neural stem cells serve as a potential therapeutic material, which can be obtained from several sources.

of dopaminergic neurons from stem cells could is considered as a practical and effective alternative for PD treatment. Previous studies demonstrated that dopaminergic neurons derived from human pluripotent stem cells contained comparable molecular profiling, biochemical and electrophysiological properties to human midbrain dopaminergic neurons[60]. Importantly, the transplantation of dopaminergic neurons derived from human pluripotent stem cells can restore pathological conditions of the diseased animals, which are mice, rats and monkeys, without overgrowth of the neurons[61]. Histological analysis of the brain indicated that the transplanted cells were well survived and integrated within the experimented animals. In addition to the derivation from human pluripotent stem cells, dopaminergic neurons can be generated by the direct conversion of human fibroblasts by overexpression of five key transcription factors, including *Mash1*, *Ngn2*, *Sox2*, *Nurr1*, and *Pitx1*[62]. The direct reprogrammed dopaminergic neurons were positively stained for several markers for dopaminergic neurons, and showed characteristics of dopamine uptake and production. Moreover, dopaminergic neurons generated from fibroblasts provided symptomatic improvement when transplanted into a rat PD models[62].

AD is classified by the degeneration and death of neurons throughout the brain, in particular in the basal forebrain, amygdale, hippocampus, and cortical areas. To date, AD therapy has been relied on small molecules designed to increase acetylcholine (Ach) concentration by inhibiting acetyl cholinesterase[63]. Since these drugs are only supportive without potential protection or regeneration against progressive brain destruction, there is a need for an effective treatment and stem cell-based therapeutic approach should satisfy this requirement. Rodent AD models that received neural stem cells grafts exhibited an increased hippocampal synaptic density and improved cognitive function[64]. Intraventricular transplantation of human neural stem cells overexpressing choline acetyltransferase (ChAT) sufficiently restored learning and memory ability of kainic-induced AD rats[65]. In addition, a recent study demonstrated that human mesenchymal stem cells can enhance autophagy in amyloid β-treated neurons and mice, thus promoting amyloid β clearance and increasing neuronal survival against amyloid β toxicity[66]. Transplantation of human adipose tissue-derived mesenchymal stem cells into the brains of aged mice enhance the levels of Ach, and consequently improve the cognitive and locomotor functions of the mice[67]. Interestingly, it was studied that ChAT-positive neurons could be directly generated from mesenchymal stem cells. These cells after transplantation could significantly improve learning and memory capacity of AD animal models[68]. Nevertheless, there is still an argument raising whether mesenchymal stem cells can cross lineage boundaries and transdifferentiate into neuronal cells.

HD is an autosomal dominant neurodegenerative disorder, identified by uncontrolled choreic movement, cognitive disruption, and emotional instability. Initial cell-based therapy was examined by using human fetal striatal grafts and showed some clinical positive outcome in HD patients[69]. However, the latter study found unpleasant results; grafted striatal tissues contributed to neural overgrowth and then tumour in an HD patient, who survived 5 years post-transplantation[70]. The transplantation of neural stem cells and striatal grafts into rodent HD models demonstrated that the medium spiny neurons of transplanted cells could integrate and form neuron circuitry in the host brain[71]. Transplantation of neural stem cells has been used not only to replace degenerated neurons, but also to protect striatal neurons against excitotoxic insults. Striatal injections of human neural stem cells into HD rodents showed incorporation into host tissues as well as migration to secondary sites associated with the disease pathology[72]. In addition to primary cells, human neural stem cells derived from human embryonic stem cells could provide a viable source for cell therapy in HD. Previous works showed that neurons expressing striatal markers could be induced from human embryonic stem cells and brain transplantation of these human embryonic stem cell-derived neurons leads to behavioural recovery in the diseased animals[73].

FUTURE PERSPECTIVE OF NEURAL STEM CELL-BASED THERAPY

Neurodegenerative diseases affect human well-being worldwide due to their devastating nature, cost, and lack of effective therapies. Although neural stem cells offer a great promise of treating these ailments, there are still several issues needed to be solved prior to the translation of neural stem cells into clinical setting. Several research groups around the world presented supportive data of the effectiveness of neural stem cells in correcting pathological conditions of neurodegenerative diseases; nevertheless, the exact mechanisms of how transplanted cells recover host brain function is not yet elucidated. Another important concern of neural stem cells after transplantation is the ability to migrate to the correct niche and the proper differentiation and maturation into desired neuronal cell types. And, importantly, if their growth cannot be appropriately controlled, neural stem cells may form tumor, which is more devastating condition than the original disease. Recent advance in cellular reprogramming can convert skin fibroblasts toward neural progenitor cells by chemical cocktail and hypoxia condition[74]. These induced neural progenitor cells express multiple neuron-specific proteins, generate action potentials, and give rise to several neuronal subtypes. Generation of induced neural progenitor cells from non-neural lineages could have important implications for several purposes, including neurodevelopmental study, neurological disease modeling, and regenerative medicine application. In the near future, we might have a better understanding of pathogenesis of neurodegenerative diseases through patient-specific induced neural stem cells. The combination gene therapy with induced neural stem cell transplantation could formulate a new paradigm of therapeutic strategy to cure mutation-caused diseases[75]. Altogether, while number of questions for neural stem cell application remain unanswered, the concerted efforts on neural stem cell research have already made a great progress toward cell replacement therapy in order to assure the best safety for patients.

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