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Review

Application of mesenchymal stem cells for neurodegenerative diseases therapy discovery

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ABSTRACT

Neurodegenerative diseases are central or peripheral nervous system disorders associated with progressive brain cell degeneration. Common neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis have been widely studied. However, current therapeutics only reduce the symptoms and do not ameliorate the pathogenesis of these diseases. Recent studies suggested the roles of neuroinflammation, apoptosis, and oxidative stress in neurodegenerative diseases. Mesenchymal stem cells (MSCs) exert anti-apoptotic, anti-inflammatory, and antioxidative effects. Therefore, investigating the effects of MSCs and their applications may lead to the discovery of more effective therapies for neurodegenerative diseases. In this study, we review different approaches used to identify therapies for neurodegenerative diseases using MSCs.

Contents

1. Introduction

Neurodegenerative diseases, characterized by substantial loss of neuronal cell populations or impairment of neuronal function, have become major health concerns worldwide. Common neurodegenerative diseases include Alzheimer's diseases (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [1].

The clinical symptoms of these diseases overlap [2]. For example, patients with PD, HD, or ALS share motor system deficits that make it difficult to control their movements [3,4]. Brain regions affected by neuronal loss vary and are specific to each disease. However, the mechanisms underlying neuronal loss are similar [2].

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Accumulating evidence suggests that neurodegeneration is related to oxidative stress damage and neuroinflammation, which is characterized by the activation of microglial and astrocytic cells [5–8]. Mitochondria are a major source of oxidative stress and cause of neuronal apoptosis [9]. Mitochondrial dysfunction has been reported in animal model of neurodegeneration diseases [10–12]. Disturbances in the redox balance due to neuroinflammation or mitochondrial dysfunction are implicated in the pathogenesis of several neurodegenerative diseases [13,14]. Therapeutic approaches targeting reactive oxygen species formation and neuroinflammation have yielded positive results [13].

Despite increases in the understanding of the pathogenesis of neurodegenerative diseases, development of treatments has lagged because of several factors, including a lack of methods to precisely deliver drugs into the lesion brain tissue [15,16], inhibition of specific inflammatory microglial/astrocytic phenotypes [17,18], and manipulation of specific messenger proteins that restore neuronal signaling pathways [19]. Recently, stem cell-based therapy has gained attention because of its ability to self-repair and regenerate the brain. The mechanisms underlying the effects of stem cells on the nervous system may surpass those of traditional medications for treating neurodegenerative diseases.

Neurodegeneration disturbs the circadian rhythm regulation in the brain [20–23]. Disruption of the sleep-wake cycle and circadian homeostasis plays pivotal roles in the biological mechanisms underlying neurodegeneration [24]. Recent studies reported the importance of circadian rhythm regulation on stem cell homeostasis and function [25,26]. Controlling circadian rhythms is a promising strategy for neurodegenerative diseases using stem cell-based therapeutics.

This review summarizes the current understanding of stem-cell based therapies for the treatment of neurodegenerative diseases and highlights the involvement of circadian rhythm sleep-wake disorders and role of mesenchymal stem cells (MSCs) in the era of antibody drugs.

2. Stem cell-based therapy and neurodegenerative diseases

Stem cells can be categorized as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells (ASCs). Blastocysts are the most common sources of ESCs. ESCs derived from blastocysts are pluripotent and can differentiate into all three germ layers [27,28]. iPSCs are derived from somatic cells that have been reprogrammed into a pluripotent state [29]. ASCs are obtained from a wide range of adult tissues such as the bone marrow, peripheral blood, and umbilical cord blood. ASCs are multipotent, which limits their differentiation potential compared with that of ESCs [30]. Use of ESCs in stem cell-based therapy is limited because of ethical issues, a lack of knowledge on their differentiation regulation, and the risk of tumorigenicity [27,31,32]. Unlike ESCs, iPSCs are not associated with ethical issues. However, the direct use of iPSCs in patients with neurodegenerative diseases poses a high risk of tumorigenicity, limiting their clinical application [33]. The development of genome editing techniques has expanded the application of iPSCs in neurodegenerative modelling. These models provide tools for studying the etiology of neurological diseases [34–36]. Thus, the roles of iPSCs in neurodegenerative diseases have mainly been determined through their application in creating platforms to study *ex vivo* pathology, particularly neurodegenerative disorders [37]. The most common ASCs used for therapeutic application in neurodegenerative diseases are MSCs because of their simple collection and diverse strategies for therapeutic use. After transplantation, MSCs can directly migrate to brain lesions and differentiate into neurons and glial cells, replacing and reconstructing damaged neurons [38]. After reaching the target areas, MSCs secrete a variety of regulatory chemicals, such as growth factors, cytokines, chemokines, and various enzymes that strongly modulate immune reactions, angiogenesis, and apoptotic processes [39–42].

The ability of MSCs to spontaneously migrate to inflamed tissues, also known as homing ability, has been widely studied. Recent studies suggested that MSC homing can be classified into non-systemic and systemic homing according to the administration route [43]. In non-systemic homing, MSCs are administered locally near the injured area and then translocated according to the chemokine gradient. In systemic homing, MSCs are administered into the bloodstream and undergo five additional steps—tethering and rolling, activation, arrest, transmigration, and migration—to reach the targeted site [44]. Since the primary advantage of MSC therapies is mainly their homing efficiency, intensive investigation is necessary to understand this process. Each neurodegenerative disease affects a specific brain region. Moreover, MSCs must cross the blood-brain barrier (BBB), which has distinct characteristics that prevent most cell types from entering the brain. Targeted administration via intracerebral injection is the most facile method for increasing the ability of MSCs to cross the BBB and reach the damaged brain regions. Numerous studies reported the development of medical technologies for intracerebral injections. Additionally, techniques focusing on optimizing systemic homing efficiency such as genetic modification, cell surface engineering, target tissue modification have been developed [44]. However, the appropriate route of MSC administration remains controversial [45–47].

Neuroinflammation is observed in the pathogenesis of almost all neurodegenerative diseases [48]. Inflammatory mediators such as cytokines and chemokines either increase or decrease the progression of neurodegeneration [49]. Elevated cytokine levels were reported to parallel the progression of neuroinflammation [50]; for example, IL-1 and TNFα significantly increase before neuronal cell death. *In vitro* and *in vivo* studies indicated that intracerebral administration of IL-1, TNFα, and IFNγ induces neuronal apoptosis [51–54]. In contrast, TGFβ, IL-10 are considered to be neuroprotective [50]. Cytokines mainly interact with glial cells. TNFα and IL-1 activate microglia and astrocytes, after which reactive microglia and astrocytes release additional cytokines that exacerbate or suppress neuroinflammation. Microglia and astrocytes polarize into different phenotypes. The M1 and A1 phenotypes are implicated in more severe neuroinflammation, whereas the M2 and A2 phenotypes are thought to have neuroprotective effects [8,55]. Interestingly, MSCs exert immunosuppressive effects via paracrine functions [56]. MSCs response to high levels of cytokines such as IL-1, TNFα, and IFNγ as activating factors to initiate their immunosuppressive effects [57]. After activation, MSCs produce exosomes (MSC-exos) containing bioactive molecules. These exosomes can penetrate the BBB, enter brain cells via membrane fusion, and subsequently modulate their physiological functions [58]. MSC-exos can also be isolated *in vitro* and systemically administered to patients to deliver bioactive molecules to brain lesions. Thus, administration of MSC-exos can prevent immune rejection and reduce the risk of infection [59]. MSC-exos can release bioactive substrates not only extracellularly to interact with receptors, but also intracellularly in the case of microRNAs to alter gene expression at the transcriptional level. Wen et al. reported that exosomes derived from MSCs ameliorated neuroinflammation and neuronal apoptosis via inducing transformation of the M1 phenotype towards the M2 phenotype. Their results suggested that microglial transformation is related to the microRNA-181b mediated IL-10/STAT3 pathway [60]. Zhao et al. also reported that MSC-exos significantly inhibited M1 microglial polarization and increased M2 microglial cells by reversing CysLT2R-ERK1/2-mediated microglia M1 polarization [61]. MSC-based therapy inhibits the polarization of A1 astrocytes and

promotes astrocytic polarization toward the A2 phenotype [62]. In addition to their roles in microglial and astrocyte polarization, MSCs show potential as cell-specific targeted therapy for the treatment of neurodegenerative diseases.

2.1. Alzheimer disease

AD is a progressive neurodegenerative disease that causes memory and cognitive impairments. The pathological characteristics of AD are distinct from those of neurofibrillary tangles and neuritic plaques [63]. The progression of AD can be classified into three stages: preclinical, mild cognitive impairment, and dementia stages [64]. In patients with AD, neurodegeneration progresses until death [65]. Because of their ability to improve memory and cognitive symptoms, symptomatic agents remain the gold standard for treating treatment patients with AD; however, disease-modifying therapies that reduce biomarkers of AD pathogenesis including amyloid β (Aβ) accumulation and neuronal degeneration or injury have been developed and may be commercially available in the near future [64]. Unlike symptomatic agents, disease-modifying therapies can be used to treat AD in the preclinical stages to delay the onset and progression of dementia. The therapeutic effects of MSCs on the pathogenesis of AD have been investigated in preclinical and clinical studies. Farahzadi et al. showed that MSCs protected against Aβ-induced decreases in telomere length as a biomarker of AD associated neurodegeneration and prevented decreases in telomerase activity. MSC administration also attenuated the mTOR, AMPK, GSK-3β, and Wnt/β-catenin signaling pathways, which are related to AD [66]. Human umbilical cord MSCs attenuate neuronal damage induced by hyperphosphorylated tau, stimulating synaptic plasticity in the hippocampus of AD mice [67]. Intravenous transplantation of human umbilical cord MSCs decreased oxidative stress markers and upregulated antioxidant enzymes such as superoxide dismutase (SOD) and neuronal nitric oxide synthase, thus recovering cognitive function in a Tg2576 mouse AD model [68]. Human amniotic MSCs attenuated Aβ deposition, microglia activation, and neuroinflammation in the hippocampus of APP/PS1 mice [69]. Transplantation of human umbilical cord MSC-derived cholinergic-like neurons decreased Aβ expression and neuronal apoptosis in Aβ-induced AD rat model [70]. Many substrates, including resveratrol and melatonin, were reported to increase the efficiency of MSCs in the treatment of neurodegenerative diseases [71–73]. MSC-exos were found to attenuate Aβ expression and modulate neuroinflammation. MSC-exos also decreased Aβ levels in an AD cell model [74]. MSC-exos upregulate anti-inflammatory factors, such as IL-10 and tissue inhibitor matrix metalloproteinase 1 in AD, resulting in the reduction of M1 microglial polarization [75]. Accumulating evidence has revealed the role of MSC-exo-associated microRNAs. MSC-derived exo miR-223 inhibited neuronal apoptosis via the PTEN-PI3K/Akt pathway in an Aβ1–40 induced AD cell model [76]. Exosomal miR-146a secreted from bone marrow MSCs transferred into astrocytes reduced astrocytic inflammation induced by the inflammatory transcription factor NF-κB in AD model mice [77]. Several clinical trials confirmed the safety of MSC transplantation in patients with AD [78]. The most common adverse side effects include headache, nausea, and vomiting, which are typically not serious and subside within 36 h [79,80]. Nonetheless, further clinical trials are required to demonstrate the safety of MSCs and their effects on the AD brain.

2.2. Parkinson's disease

PD is clinically diagnosed based on the presence of bradykinesia in combination with at least one motor disorder symptom, such as rigidity or tremor, after considering the absolute exclusion and supportive criteria. Beyond motor disorders, non-motor symptoms include cognitive impairment, autonomic dysfunction, sleep–wake cycle deficits, and depression. The neuropathology of PD is characterized by neuronal loss in the substantia nigra compacta (SNc) and accumulation of intracellular protein (α-synuclein). Neuroinflammation has been implicated as a salient feature of PD [81]. Currently, there is no available treatment for PD that completely terminates the progression of neurodegeneration. Thus, methods for decelerating PD advancement are needed. Neuronal dysfunction in PD occurs long before the onset of motor symptoms in prodromal PD [82]. Pharmacological management of PD restores dopaminergic function and ameliorates motor symptoms but has no effect on non-motor symptoms and is difficult to use in the prodromal stage because of intolerable side effects [83]. MSC-based therapies have been investigated to improve the efficacy of PD treatment, with numerous experimental MSC-based therapies developed for use in animal models of PD. Pharmacological PD mouse models induced by neurotoxic agents, including methamphetamine (MA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), are widely used for screening of PD therapies. These agents induce loss of dopaminergic neurons in the SNc and striatum, mimicking brain damage in patients with PD [84,85]. SB623 MSC transplantation protected against MPTP-induced impairment of DA levels and tyrosine hydroxylase immunoreactivity in the striatum of mice [86]. Additionally, MSCs differentiated into dopaminergic neurons and significantly recovered striatal dopamine and dopamine metabolites in an MPTP-induced PD animal model [87]. MSCs migrated into the SNc and released TGF-β1, which downregulate microglial activation and neuroinflammation induced by MPTP [88]. MSCs attenuated MA-induced rotation behavior and protected against MA-induced tyrosine hydroxylase-positive cell loss in an animal model of PD [89]. Exosomes derived from MSCs exert neuroprotective effects against PD by stimulating cell proliferation and inhibiting apoptosis in the striata of PD mice [90]. Intraperitoneal injection of MSC-exos decreased α-synuclein aggregation and reduced MPTP-induced decreases in tyrosine hydroxylase immunoreactivity in the SNc [91].

2.3. Amyotrophic lateral sclerosis

ALS is characterized by the degeneration of motor neurons that project from the cortex to the brainstem or spinal cord, and from the brainstem or spinal cord to the muscle. A neuropathological characteristic of ALS is high accumulation of proteinaceous proteins. Preclinical studies revealed that the pathophysiology of ALS is associated with impairment in protein homeostasis caused by the deterioration of both transcriptional and translational processes. In addition, mitochondrial dysfunction and the regulation of astrocytic and microglial differentiation contribute to neuronal loss in ALS disease [92]. MSCs were reported to attenuate ALS pathology in a transgenic $SOD1^{G93A}$ animal model, which is the most common animal model for studying ALS. Intravenous administration of MSCs delayed the onset of ALS and extended the lifespan of $SOD1^{G93A}$ mice. MSC-treated $SOD1^{G93A}$ mice showed less severe motor deficits in both behavioral and neuropathological assessments [93]. After transplantation, MSCs can survive for several weeks [93,94]. While inside the central nervous system (CNS), MSCs are reported to exert neuroprotective effects mainly by controlling apoptosis and inflammatory markers, rather than by replacing dead neurons [94]. Despite the promising results achieved in preclinical studies, few clinical studies have reported significant improvements in patients with ALS [95]. Therefore, further studies are required to clarify the role of MSCs in patients with ALS.

2.4. Huntington's disease

HD is an inherited neurodegenerative disease associated with mutations in the huntingtin gene, which plays a pivotal role in the regulation of brain cell transcription. Mutation in the huntingtin gene leads to the dysfunction of transcription factors such as p53 and CREB, causing neuronal death, mitochondrial dysfunction, and disruption of the protein synthesis machinery [96]. Increasing doses of 3-nitropropionic acid in rodents induce HD-like mitochondrial oxidative stress and neurodegeneration. MSC transplantation significantly increases striatal neurotrophic factors and protect transplanted mice from motor deficits and striatal neuronal loss [97]. MSCs showed protective effects similar to those in an HD transgenic mouse model [98,99]. These results suggest that MSCs can be used as therapeutic agents for patients with HD.

2.5. Circadian rhythm and sleep disorder

Neuronal loss in neurodegenerative diseases can affect brain regions that regulate sleep-wake cycles and circadian rhythms. Sleep disorders accelerate neuronal apoptosis [24]. Numerous neurodegenerative diseases including AD, HD, PD, and ALS are associated with circadian disruptions [100–102]. Circadian rhythms are regulated by groups of clock genes, and alterations in clock gene expression can result in neurodegeneration, oxidative stress injuries, and activation of neuroinflammatory cells [103,104]. Bmal1 deletion induces synaptic terminal degeneration, increases reactive oxygen species formation, and alters mitochondrial redox homeostasis. Treatment with the antioxidant N-acetyl-L-cysteine rescued oxidative stress damage in aging Bmal1 knockout mice [103]. Therefore, Bmal1 deletion may interfere with the glutathione system and reduce the expression of glutathione peroxidase-1 (GPx-1). Evidence suggests that glutathione peroxidase-1 protects against neurodegenerative disease [105,106]. MSC administration upregulates the expression of antioxidant enzymes and may restores oxidative defense enzyme systems [107]. Preclinical and clinical studies reported the involvement of sleep disturbances in HD [108–110]. Yu-Taeger et al. showed that MSC treatment attenuated sleep disturbances in R6/2 HD transgenic mice. Sleep deprivation resulted in an increase in Aβ within microglia and exacerbated microglial activation; these changes were associated with Bmal1 expression [111]. Recent evidence revealed that the relationship between circadian clock genes and neurodegenerative diseases involve not only neuron loss but also disease pathogenesis. A presenilin 1 or APP/PS1 transgenic mouse model of AD showed that the accumulation of amyloid plaques began at the same time as sleep-wake cycle impairment. As amyloid plaques spread, sleep disorders become more severe [112]. Interstitial fluid tau levels were significantly increased by sleep deprivation in both mice and humans [113]. Chronic short sleep causes sustained increases in tau oligomer spreading and aggregation [114]. Similarly, α-synuclein accumulation increases with increased neuronal activity during wakefulness caused by sleep deprivation [115,116]. These findings raise the possibility of developing therapeutic interventions targeting sleep disorders to treat neurodegenerative diseases. MSCs overexpressing Bmal1 can reverse aging-induced downregulation of Bmal1 [117]. Interestingly, in a 6-OHDA induced PD rat model, MSC-exo administration increased dopamine and serotonin levels by elevating the mRNA levels of CLOCK, BMAL1, and PER2 [118]. Peroxisome proliferation-activated receptor γ (PPARγ) inhibition caused neurodegeneration in animal models of several neurodegenerative diseases such as AD and HD [119,120]. Recovery of circadian rhythm-associated gene expression not only attenuated PD-associated sleep disorder but also ameliorated neurodegeneration and mitochondrial deficits by increasing PPARγ activities. These pilot studies provide a foundation for developing treatments for neurodegenerative diseases and clarifying the effects of MSCs on the circadian rhythm and sleep-wake disorders.

3. The role of MSC-based therapy in correspondence with antibody drug-based therapy for treating neurodegenerative diseases

The CNS is well-known for its immune privileges. Immune privilege in the brain is conferred via the BBB. The BBB strictly regulates molecular transport into the brain and restricts antibody entry from the peripheral blood. Therefore, the CNS is considered off-limits to monoclonal antibody (mAb) therapeutics [121]. However, recently developed mAbs that can penetrate the BBB were shown to exert therapeutic effects on the brain parenchyma [121]. Antibodies against Aβ [122–124] and tau protein [125,126] showed inhibitory effects against AD in both preclinical and clinical studies. Anti-α-synuclein immunotherapy for PD also showed preliminary preclinical successes [121,127]. mAb therapies for the treatment of neurodegenerative diseases have consistently shown promising results. Lecanemab and aducanumab are two new mAbs approved in the USA for treating AD [128]. Although mAbs are now considered a therapeutic approach for neurodegenerative diseases, studies are needed to overcome many major limitations, such as poor penetration and adverse side effects.

The poor penetration of mAbs through the BBB is closely associated with adverse drug reactions. The most common adverse drug reactions associated with mAb drugs for AD, such as aducanumab and lecanemab, is amyloid-related imaging abnormalities (ARIA). Only 0.1 % of circulating antibodies cross the BBB and penetrate the brain via three mechanisms: (1) nonspecific absorptive-mediated endocytosis, (2) substrate-selective carrier-mediated transport, and (3) receptor-mediated transcytosis [129]. The easiest strategy for penetrating more mAb into the CNS is increasing the dose. However, this can lead to an increase in adverse drug reactions. Scientists have taken advantage of routes that transport substrates in a more specific manner to develop a method for therapeutic antibodies to pass through the BBB at better-tolerated doses. A more specific route to the brain parenchyma, including carrier-mediated transport and receptor-mediated transcytosis, may enable transport of mAbs at lower doses than those used in absorptive-mediated endocytosis [121,130]. However, specificity must be optimized to avoid lysosomal degradation [131–133]. Thus, decreasing the mAb dose by increasing its specificity remains a limitation. Application of MSC-exos as a transport route for drugs to pass through the BBB has been frequently reported and reviewed [134–136]. Tashima suggested that loaded MSC-based drug delivery systems can infiltrate the BBB and release antibodies inside the brain tissue [137]. Thus, MSC-based delivery systems may greatly contribute to the development of new antibody drugs.

4. Limitations of MSC-based therapy for neurodegenerative diseases

MSC-based therapies show potential for the treatment of neurodegenerative diseases. However, several limitations remain. MSCs can cause immune rejection. Methods for managing immune rejection should be developed along with the development of MSC-based therapies. Different approaches using mAbs have been attempted preclinically to replace immunosuppressive drugs but are associated with many adverse side effects [138]. Clinical studies of MSC-based therapy have provided inconsistent results because of the variability of patients, sources of MSCs, delivery routes, and outcomes [83]. The pathogenesis of neurodegenerative diseases should be extensively investigated to overcome these challenges (see Figs. 1–3).

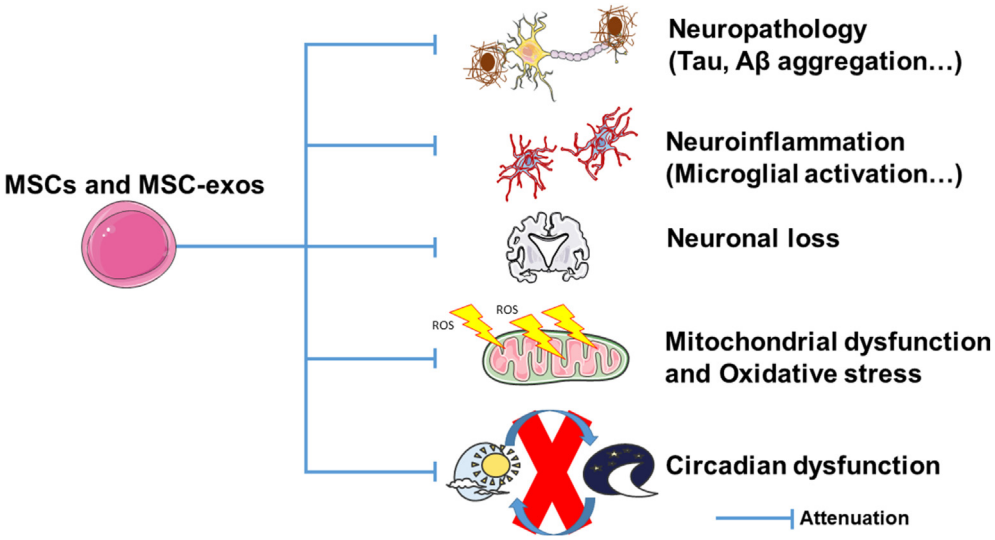

Fig. 1. Mechanism of MSCs and MSC-exos therapy in treatment of neurodegenerative diseases.

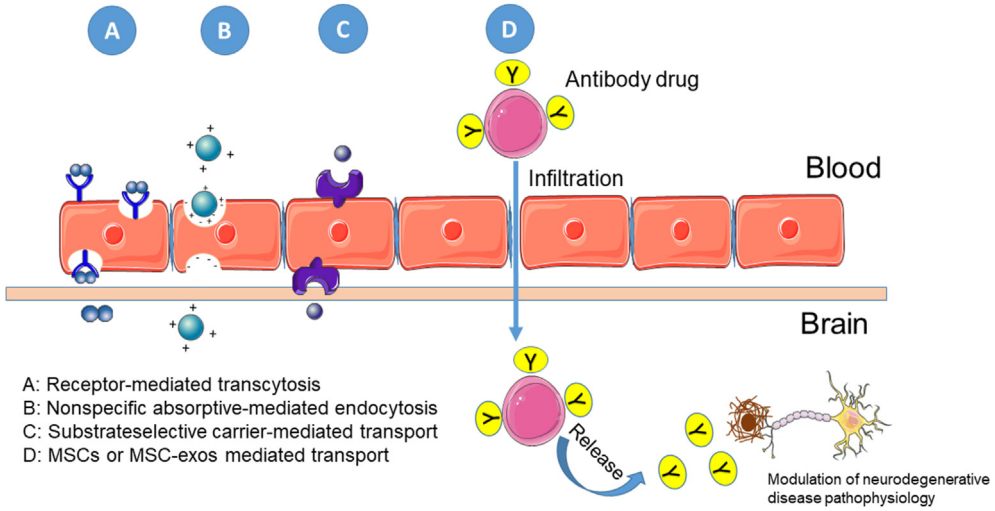

Fig. 2. MSCs application as antibody drug delivery system in treatment of neurodegenerative diseases.

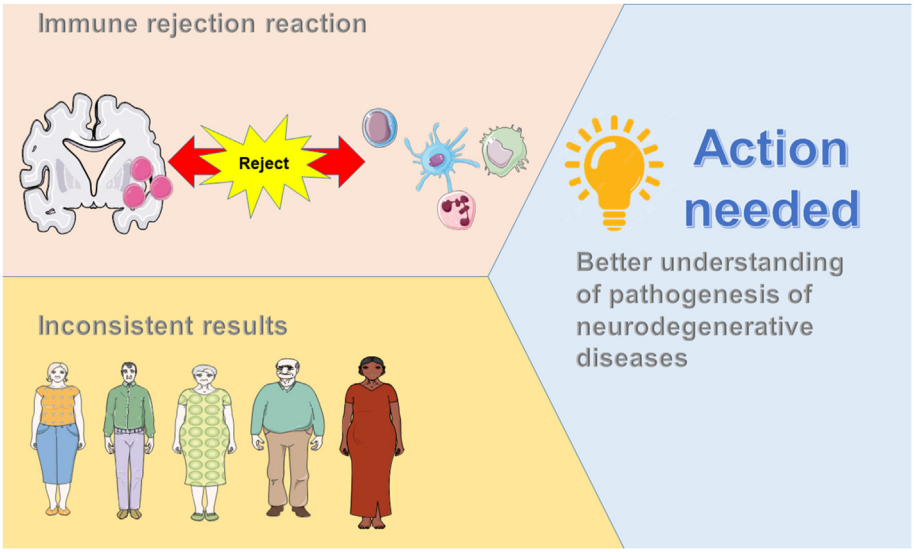

Fig. 3. Challenges of MSCs and MSC-exos therapy in treatment of neurodegenerative diseases in practice.

5. Conclusion

Regenerative medicine and stem cell transplantation have been developed and may serve as alternative treatments for neurodegenerative diseases. Numerous studies reported the positive effects of MSCs in the treatment of diverse neurodegenerative diseases, including AD, PD, ALS, and HD. In this study, we review several achievements in using MSCs in both preclinical and clinical studies. The protective effects of MSCs may be mainly exerted through their anti-inflammatory and anti-oxidative properties rather than their ability to replace lost neuronal cells. Therefore, the application of MSC-exos has been widely examined, and optimistic results indicate that progress is being made. In addition, circadian rhythm dysfunction linked to neurodegeneration was recently reported as a new target. Technology using MSC-exos may lead to new findings on the mechanism by which circadian clock genes mediate neurodegeneration and encourage new therapeutic approaches for better and safer treatments.

Declaration of competing interest

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

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