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Mesenchymal stem cells: As a multi-target cell therapy for clearing β-amyloid deposition in Alzheimer's disease

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Abstract: Extracellular β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) are the pathological hallmarks of Alzheimer's disease (AD). Studies have shown that aggregates of extracellular Aβ can induce neuroinflammation mediated neurotoxic signaling through microglial activation and release of pro-inflammatory factors. Thus, modulation of Aβ might be a potential therapeutic strategy for modifying disease progression. Recently, a large number of reports have confirmed the beneficial effects of mesenchymal stem cells (MSCs) on AD. It is believed to reduce neuroinflammation, reduce Aβ amyloid deposits and NFTs, increase acetylcholine levels, promote neurogenesis, reduce neuronal damage, and improve working memory and cognition. In this review, we focus on the role of MSCs in clearing Aβ deposition. MSCs have the potential to modulate Aβ-related microenvironments via enhancement of autophagy, proteolysis of Aβ aggregates, phagocytic clearance of Aβ by microglial M2 polarization, decrease oxidative stress (OS), and correction of abnormal sphingolipid (SL) metabolism. With advantages in clinical applications, these data suggest that the use of MSCs as a multi-target modulator of Aβ would be an effective therapeutic approach in AD.

Introduction

Alzheimer's disease (AD) is the most common chronic neurodegenerative disease, with increased life expectancy, this number is expected to rise in the future (Moonga and Likupe, 2016). AD is characterized by progressive memory deficits, cognitive impairment, and personality changes associated with the degeneration of multiple neuronal types and pathologically by synapse loss and the presence of β-amyloid (Aβ) plaques and NFTs (Karlawish *et al.*, 2005). All types of AD are characterized by the accumulation of Aβ, which triggers a series of neuroinflammation, culminating in neuronal dysfunction and death. Aβ plays a critical pathogenic role in AD and is related to the enhancement of oxidative stress (OS) in the brain, neuronal damage, synapse loss, and NFTs (Cunningham, 2013; Götz *et al.*, 2001).

Cell therapy has been regarded as one of the most promising novel therapies as a disease-modifying strategy for AD (Si *et al.*, 2011). Mesenchymal stem cells (MSCs), as a kind of stem cell that is easily available, has low immunogenicity, strong proliferation, and differentiation potential, have been used in the research of various diseases. Currently, we can isolate and prepare MSCs from bone marrow, fat, synovium, bone, muscle, lung, liver, pancreas, amniotic fluid, and umbilical cord blood. By using cell replacement or immunomodulation strategies, isolated MSCs have a beneficial effect on neurodegenerative diseases (including AD) in animal models (Sadan *et al.*, 2012; Gugliandolo *et al.*, 2019; Chen *et al.*, 2020b; Kim *et al.*, 2020; Reyhani *et al.*, 2020). Initially, people considered that it could replace the death and loss of AD neurons by differentiation into neurons (Mezey *et al.*, 2003). Since then, it has been suggested that in neuron replacement therapy, there are still several obstacles to be resolved, such as the transplantation pathway, tumorigenesis and mutation, and the efficiency of neuronal differentiation (Prockop *et al.*, 2003; Caruso and Parolini, 2015). However, with the in-depth study of stem cells, more and more evidence has supported that MSCs enter the blood-brain barrier (BBB) by paracrine with soluble factors to improve the brain microenvironment (Ma *et al.*, 2013; Lim *et al.*, 2020; Chen *et al.*, 2020a; Mehrabadi *et al.*, 2020).

The neuroprotective mechanism, by which MSCs indirectly modulate Aβ-related microenvironments, appears to be complex

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and pleiotropic. In this review, we provide evidence that MSCs clear Aβ via enhancement of autophagy-related proteins, autophagy-lysosome metabolism, and protein degrading enzyme levels, decrease of neuroinflammation, and controlling microglial polarization. We also discussed the implications of these findings for therapeutic interventions and the prospects for MSCs in the treatment of AD.

Structure and formation of β-amyloid

As we all know, Aβ is a hydrolysate of amyloid precursor protein (APP), and APP is continuously cleaved by β-/γ-secretase to form amyloid proteins (Masters and Selkoe, 2012). APP is hydrolyzed by β-secretase (also known as β-site amyloid cleavage enzyme, BACE) at the first amino acid position of the Aβ sequence to produce a large N-terminal fragment (sAPP β) and a small transmembrane fragment (C99), the latter acts on the 40/42 amino acid position of the Aβ sequence by γ secretase to produce a 39-42 amino acid peptide-Aβ and another intracellular fragment APP intracellular domain (AICD) (Caruso and Parolini, 2015; Nikolaev *et al*., 2009). Current studies have shown that the aggregation activity and toxicity of Aβ42 are the main pathogenic factors that promote the development of AD.

Part of the causes of β-amyloid deposits

Microglia-associated immune response

Under normal physiological conditions, neurons and glial cells in the central nervous system together maintain the homeostasis of the central nervous system. The stability of the content of Aβ in the brain depends on the balance between Aβ production and clearance, and the clearance of Aβ largely depends on the phagocytosis of microglia. After being activated by Aβ, microglia can phagocytose Aβ aggregates and necrotic nerve cells (Moore *et al*., 2002; Rogers *et al*., 2002). The clearance of Aβ also depends on the amyloid degrading enzymes (ADE) secreted after activation of microglia, such as neutral endopeptidase (NEP) and insulin-degrading enzyme (IDE) (Farris *et al*., 2003; Miller *et al*., 2003; Kim *et al*., 2020). Therefore, in the early stage of AD, microglia can effectively delay the development of AD through phagocytosis and production of degrading enzymes. However, in the late stage of AD, the physiological function of microglia cells is impaired (Morgan, 2018), resulting in excessive deposition of Aβ. Currently, amyloid deposits can bind to receptor proteins on the surface of microglia, such as TLR receptors and sweeper receptors, and enter cells through endocytosis. But at the same time, microglia are also activated abnormally, releasing neuroinflammatory cytokines and inflammatory mediators, further exacerbating local inflammatory responses and causing irreversible damage to neurons (Hong and Stevens, 2016).

Microglia can recognize various pathogens and endogenous cues. These cues in turn produce morphological changes, usually described as the M1 or M2 phenotype of microglia. Studies have shown that Aβ aggregates released from neurons directly induce microglia to transfer to the more reactive M1 phenotype, leading to inflammatory cascades (Neniskyte *et al*., 2016; Boche *et al*., 2013). Further increase of pro-inflammatory factors, such as IL-1, NO, and TNF, leads to the formation of amyloid plaques and neurodegenerative changes. In contrast, M2 polarized microglia is induced by IL-4 and/or IL-10, are believed to have anti-inflammatory effects, can promote phagocytosis, and are known to express arginase-1 (Arg-1), MRC1, and YM-1 (Ma *et al*., 2013). Furthermore, "M2 microglia" is indicated to increase the expression of the two main Aβ-degrading enzymes (IDE and NEP) in the brain (Wang *et al*., 2010; Edbauer *et al*., 2002). A large amount of evidence from AD studies shows that M2 polarization is closely related to β-amyloid clearance (Ma *et al*., 2013; Rogers *et al*., 2002; Hong and Stevens, 2016; Mandrekar-Colucci and Landreth, 2010). Therefore, it is important to modify microglial function, as a treatment mechanism to induce the clearance of Aβ before the formation of plaques, thereby improving the pathology of AD.

Autophagy failure: a novel factor in β-amyloid deposition

Autophagy is the process of transporting damaged, aging, or incorrectly aggregated proteins and organelles to lysosomes for degradation, to maintain the homeostasis of the intracellular environment. In the past five years, more and more wonderful reviews have summarized autophagy as a target for the treatment of neurodegenerative diseases (Park *et al*., 2020b; Suresh *et al*., 2020; Fujikake *et al*., 2018). The downregulation of autophagy was morphologically and genetically demonstrated in AD brains (Xiao *et al*., 1999). Morphologically, a large number of autophagic vacuoles (AVs) and lysosomes have accumulated in the brain of patients with AD with dystrophic neuritis (Lee *et al*., 2011; Whyte *et al*., 2017). Presenilin 1 (PSEN1/PS-1) is a component of the secretase complex that generates peptides (Saftig *et al*., 1998). A recent study showed that PS-1 is essential for v-ATPase targeting to lysosomes, lysosome acidification, and proteolysis during autophagy. The mutation of PS-1 in familial AD results in abnormal transport of v-ATP enzyme to lysosomes, which leads to lysosomal alkalization and autophagy-lysosome accumulation (Coffey *et al*., 2014; Lee *et al*., 2010c).

In general, studies have shown that rats lacking the Atg5/Atg7 gene have the AD phenotype (Hara *et al*., 2006). Furthermore, Beclin1, a key regulatory protein of autophagy, was identified as a causative molecule in AD pathology (Hara *et al*., 2006; Rocchi *et al*., 2017; Swaminathan *et al*., 2016). Vps34 is a mammalian class III PI3K enzyme, which mainly plays a role in the early stages of autophagy. Vps34 combines with Beclin1 in a variety of enzymatic reactions to form a Vps34/PI3K-Beclin1 complex, which participates in the maturation and transport of autophagic vesicles (AVs) and promotes the formation of autophagosomes under the action of Dapper1 regulatory factors (Ma *et al*., 2014). In AD, the complex is abnormal due to the decrease of Beclin1. This will lead to inhibition of the formation and maturation of autophagy vesicles and further reduce the occurrence of autophagy. This will lead to a decrease in Aβ clearance and induce AD (Jaeger *et al*., 2010) (Fig. 1). These studies indicate that Beclin1 plays a central role in the progression of AD and makes Beclin1 a target for improving Aβ starch deposition.

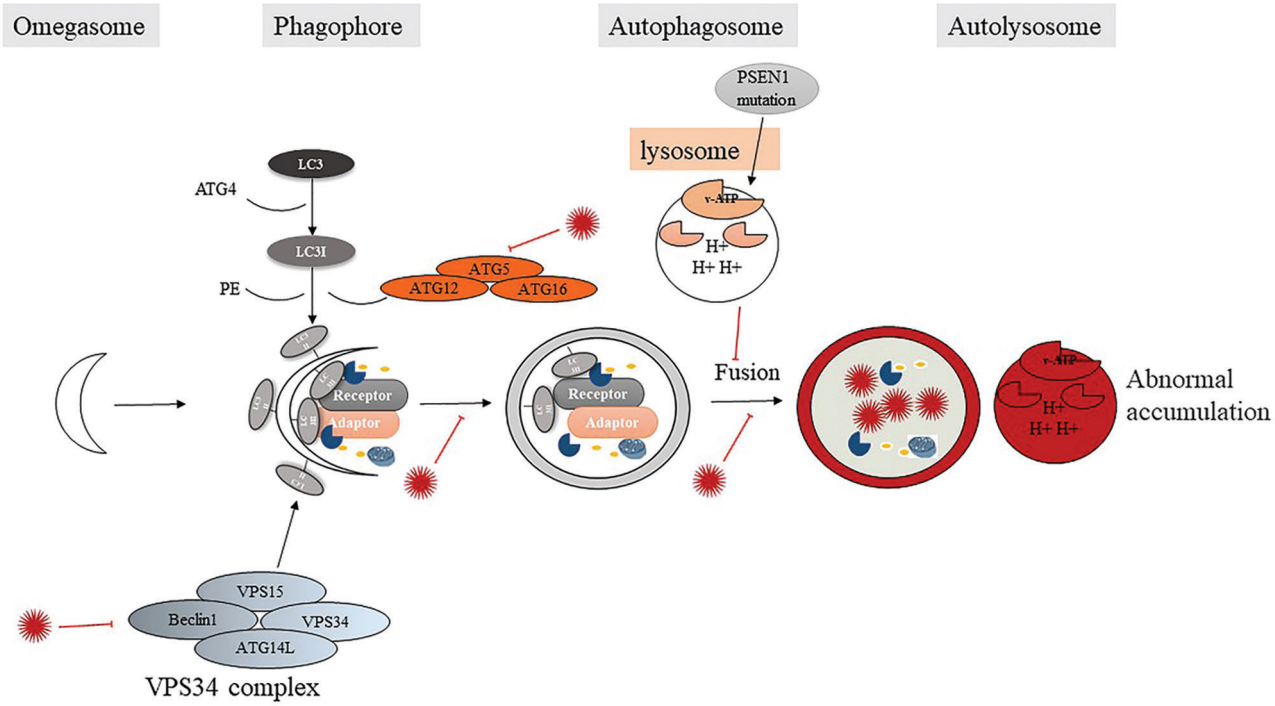

FIGURE 1. Autophagy failure: a novel factor in β-amyloid deposition.

Interactions between OS and β-amyloid

The aggregation of Aβ amyloid is related to the increase of OS. On the one hand, the increase of OS may be related to mitochondrial dysfunction and lipid peroxidation caused by amyloid aggregation (de la Monte and Wands, 2006). The aggregation of soluble Aβ induces reactive oxygen species (ROS), leading to synaptic damage and neuron loss in hippocampal neurons (de Felice *et al.*, 2007). These studies indicate that Aβ amyloid deposition contributes to the increase of OS in AD models.

On the other hand, the increase of OS in the brain further causes the accumulation of Aβ. The neurotoxicity of Aβ comes from the methionine residues of the peptide carbon segment, which can generate ROS, induce oxidation reactions, and produce peroxides, which can further cause the Aβ soluble body to transform into Aβ insoluble body, and finally constitute age spots. A study showed that OS can lead to an increase in Aβ levels in cultured neuroblastoma cells (Misonou *et al.*, 2000); it was reported that the loss of antioxidant function in Tg19959 mice overexpressing double-mutated APP caused an increase in OS and significantly increased Aβ levels and Aβ plaque deposition in the brain (Li *et al.*, 2004). Studies have shown that in differentiated human neuroblastoma cells, dual regulation of amyloid precursor protein metabolism is associated with downregulation of α-secretase and upregulation of γ-secretase, particularly β-secretase and JNK-dependent a β generation (Quiroz-Baez *et al.*, 2009). Since OS-mediated neurotoxicity and Aβ amyloid deposition are key factors leading to neurodegenerative diseases, the development of effective antioxidant protection is an attractive strategy for AD treatment.

Sphingolipid (SL) metabolism involved in β-amyloid

Previous studies have reported that abnormal SL patterns lead to SL-protein interactions, which to some extent lead to misfolding events, such as amyloid deposition in AD (Piccinini *et al.*, 2010; Matsuzaki, 2020). It is reported that brain glycosphingolipids (GSL) metabolism disorders have appeared in the brains of patients with AD and transgenic mouse models of the disease (Ariga *et al.*, 2008). GSL participates in the formation of β-amyloid in these ways: on the one hand, it regulates the functions of APP as a signal molecule and the proteolytic process of APP in the process of amyloidosis; on the other hand, it promotes the conversion of soluble β-starch into insoluble form (Piccinini *et al.*, 2010). Studies have analyzed several SL and SL hydrolases in brain samples of AD patients and age-matched normal individuals. The pattern of increased expression of acid sphingomyelinase (ASM) and acid ceramidase in AD was found, resulting in a decrease in sphingomyelin and an increase in ceramide. The downstream result of ASM activation is increased ceramide, activation of ceramidase, and sphingosine production. The decrease in sphingosine-1-phosphate (S1P) levels in the brain of patients with AD and the increase in ceramide levels may contribute to the pathogenesis of the disease (He *et al.*, 2010).

Mesenchymal stem cells

MSCs are known for their strong proliferation, multi-lineage differentiation, immune regulation, and a wide range of sources. They include bone marrow MSCs (BM-MSCs) (Lee *et al.*, 2010b), adipose-derived MSCs (AD-MSCs) (Ma *et al.*, 2013), umbilical cord MSCs (hUCMSCs) (Ding *et al.*, 2018), placental MSC and so on. They can differentiate into non-mesoderm cell types (including neuronal lineages) *in vivo* and *in vitro* (Li *et al.*, 2015). MSCs have strong immune regulation and regeneration capabilities, which stem from their ability to secrete a variety of chemokines, cytokines, and nutritional factors, and have been shown to have a

regulatory effect on the progression of AD under many different conditions (Ma *et al.*, 2013; Kim *et al.*, 2018a; Lee *et al.*, 2012b). The most important thing is that these small molecules can enter the brain through the BBB to regulate the microenvironment in the BBB (Wang *et al.*, 2018). At least it can be confirmed that MSCs can target the removal of Aβ protein deposits through the following aspects.

MSCs regulate β-amyloid degradation through a variety of pathways (Table 1)

MSCs reduce Aβ and neuroinflammation via microglia activation

Microglia is an immune regulatory cell of the nervous system, which initiates an immune response and induce neuroinflammation in the AD brains through toll-like receptors (TLR2, TLR4, TLR6, and TLR9) (Heneka *et al.*, 2015b; Heneka *et al.*, 2015a; Lee *et al.*, 2009). However, ATSCs-conditioned medium can reduce the excessive activation of microglia and reduce the secretion of pro-inflammatory factors IL-1β and TNF-α by reducing the activation of TLR2 and TLR4 receptors in microglia (Mehrabadi *et al.*, 2020). Lee *et al.* (2010b) implanted MSCs into the brains of APP/PS1 transgenic mice and found that the phenotype of microglia in the cerebral cortex and hippocampus of mice changed to M2 type (Lee *et al.*, 2010b). This effect was also demonstrated in the acutely induced AD mice model, BM-MSCs can prevent and/or eliminate Aβ deposition.

In addition, MSCs can also eliminate Aβ by enhancing the secretion of Aβ proteolytic enzymes in microglia or upregulating the expression of uptake Aβ receptors in activated microglia (Lee *et al.*, 2010b; Kim *et al.*, 2013; Yokokawa *et al.*, 2019; Kim *et al.*, 2018b; Zheng *et al.*, 2017; Zhao *et al.*, 2018; Lee *et al.*, 2009). On the one hand, M2 microglia enhanced the secretion of Aβ proteolytic enzymes NEP, IDE, and matrix metallopeptidase 9 (MMP9). On the other hand, it up-regulated the expression of Aβ protein binding receptor scavenger receptor B-1 (SCARB-1) and enhanced the uptake of Aβ amyloid (Kim *et al.*, 2013). Yokokawa *et al.* (2019) also confirmed in APdE9 transgenic mice that BM-MSCs can change the phenotype of microglia by up-regulating CD14, enhancing the uptake of Aβ and inhibiting the production of pro-inflammatory factors (Yokokawa *et al.*, 2019). And an *in vivo* experiment showed that Human umbilical cord blood-derived MSCs (hUCB-MSCs) treatment can significantly reduce the level of BACE-1 (Lee *et al.*, 2012a). MSCs regulate the function of microglia in AD by activating neuroprotective microglia (Fig. 2).

With the deepening of research on MSCs, more and more people are interested in the mechanism by which MSCs function. Due to its limited efficiency of directional differentiation into damaged neurons in AD models (Parr *et al.*, 2007), more people place their hopes on its paracrine mechanism or transplantation after directional differentiation *in vitro* (Ma *et al.*, 2013; Yokokawa *et al.*, 2019; Ding *et al.*, 2018; Losurdo *et al.*, 2020; Kim *et al.*, 2018b; Lee *et al.*, 2012b). Recent studies have demonstrated the immunomodulatory effect of MSCs-derived extracellular vesicles in different AD models (Ding *et al.*, 2018; Losurdo *et al.*, 2020). hUCMSCs-derived exosomes (hUCMSCs-Exo) improves the microenvironment by inducing the transformation of microglia into a neuro-protective phenotype, and by up-regulating NEP and IDE to reduce Aβ deposition and enhance the secretion of neuroprotective factors in microglia (Ding *et al.*, 2018). In addition, in the 3xTgAD model, nasal transplantation of BM-MSC-EV exerts an immunomodulatory effect promotes microglia to polarize towards an anti-inflammatory phenotype and improves synaptic loss (Losurdo *et al.*, 2020). However, after Yokokawa *et al.* (2019) filtered the BM-MSC culture medium with a 100 kDa ultrafilter to filter out the cell vesicles, the effect of activating microglia remained (Yokokawa *et al.*, 2019). After further filtering out more molecules with finer filtering conditions, this effect disappeared. The data showed that in addition to extracellular vesicles, the secretome secreted by MSCs also enhanced the uptake of Aβ deposition by microglia.

A recent report indicated that CCL-5 secreted by BM-MSCs can recruit bone marrow-derived microglia and induce the immune response of microglia to improve the neuropathology of AD.CCL-5, which can control the migration of T lymphocytes, mononuclear macrophages, and eosinophils (Ransohoff *et al.*, 2007), are widespread in neurodegenerative diseases (Mines *et al.*, 2007). Existing evidence suggests that this chemokine can promote the migration of M2 microglia instead of M1 in spinal cord injury. In the study of Jong Pil Lee, *in vitro* experiments found that when the microenvironment changes of the AD brain were simulated, the migration of microglia increased significantly after BM-MSCs treatment, and the level of CCL-5 also increased significantly (Lee *et al.*, 2012b). Secondly, in APP/PS1 animal experiments, it was found that endogenous microglia can clear Aβ by enhancing the secretion of Aβ degrading enzymes (including NEP and MMP). Interestingly, these effects will disappear after transfecting BM-MSCs with CCL-5 siRNA (Lee *et al.*, 2012b). In addition, Dong Hyun Kim verified the effect of GDF-15 secreted by hUCB-MSCs on Aβ amyloid in 5XFAD mice and *in vitro* models. GDF-15 is a therapeutic neurotrophic factor. In AD, it can promote the generation of hippocampal nerves and synaptic activity. The loss of GDF in neonatal mice is manifested as progressive loss of motor and sensory neurons (Kim *et al.*, 2018a). TGFβRII is a receptor involved in the GDF-15 pathway, which is related to the mechanism of clearing Aβ42. In this study, GDF-15 secreted by hUCB-MSCs mainly corrected the expression of TGFβRII receptor and the degrading enzyme IDE in microglia. After knocking out GDF-15 in hUCB-MSCs, these effects disappeared (Kim *et al.*, 2018a). These data indicate that MSCs can increase, through paracrine action, the ability of microglial cells to clear Aβ.

MSCs reduce Aβ and neuroinflammation via modulating autophagy

Research evidence shows that autophagy plays a key role in AD, and the disorder of autophagy function may lead to the accumulation of Aβ amyloid. Currently, researchers believe that the role of autophagy in MSCs includes two aspects: ① MSCs can regulate cell autophagy involved in diseases or regulate the expression of autophagy-related proteins to

TABLE 1

The mechanism by which mesenchymal stem cells reduce amyloid β

Cell/ animal model of AD	Cell type	Removing mechanisms of Aβ	Administration route	Effects	References
APP/PS1 mice	hUCMSC-exos	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity	IV	Aβ40, Aβ42↓ IDE, NEP, TGF-β, IL-10↑ IL-1β, TNF-α↓	(Ding *et al.*, 2018)
APP/PS1 mice	AD-MSCs	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity • Decreases pro-inflammatory cytokines	ICV	Aβ40, Aβ42, IL-1β, TNF-α↓ IDE, NEP, MMP9↑	(Ma *et al.*, 2013)
APP/PS1 mice	hUCB-MSCs	• Induces alternatively activated microglia • Reduce β-secretase 1 (BACE-1) levels	ICV	IL-1β, TNF-α BACE-1↓	(Lee *et al.*, 2012a)
APP/PS1 mice	BM-MSCs	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity	ICV	NEP, MMP9↑ TNF-α, TL-1β↓	(Lee *et al.*, 2012b)
APP/PS1 mice	BM-MSCs	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity	ICV	NEP, IDE, MMP9, SRB1↑ TNF-α, IL-1β↓	(JK Lee *et al.*, 2010c)
APP/PS1 mice	MenSCs (Human Menstrual Blood-Derived Mesenchymal Stem Cells)	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity	ICV	TNF-α, IL-1β, IL-6, COX-2↓ CD206, NEP, IDE↑	(Zhao *et al.*, 2018)
APP/PS1 mice	hAMSCs	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity • Increases anti-inflammatory cytokines • Decreases pro-inflammatory cytokines	ICV	TNF-α, IL-1β↓IL-10, TGF-β↑, IDE, NEP, MMP9, SYN↑	(Zheng *et al.*, 2017)
Tg2576-AD	hAMSCs	• Induces alternatively activated microglia which enhances Aβ-degrading enzyme activity	IV	MMP9, IDE, IL-10, TGF-β↑ IL-1β, TNF-α↓	(Kim *et al.*, 2013)
APdE9 mice	BM-MSCs	• Induces alternatively activated microglia • Enhanced phagocytosis of Aβ • Decreases pro-inflammatory cytokines and M1 microglia	IV	Aβ uptake↑ TNF-α↓	(Yokokawa *et al.*, 2019)
3xTg-AD mice	BM-MSC-EVs	• Induces alternatively activated microglia • Increases anti-inflammatory cytokines • Decreases pro-inflammatory cytokines	Intranasal route of administration	IL-10↑IL-6, IL-1β↓	(Losurdo *et al.*, 2020)
Aβ induced-AD mice	BM-MSCs	• Promoted the fusion of autophagosomes and lysosomes	IV	LC3II, Beclin1, CTSB, RAB1↑ Aβ↓	(Shin *et al.*, 2014)

(Continued)

Table 1 (continued).

Cell/ animal model of AD	Cell type	Removing mechanisms of Aβ	Administration route	Effects	References
Aβ induced-AD mice	ES-MSCs	• Promote the metabolism of autophagy lysosome to reduce deposition of A protein	External carotid artery and pterygopalatine artery	LC3II, LAMP2↑ Aβ↓	(Kim *et al.*, 2020a)
Aβ induced BV2 cell	UC-MSCs	• Enhance microglia autophagy • Increase the proteasome activity	Cell co-culture	LC3II, Beclin1, IDE, NEP↑P62, Aβ25-35↓	(Xu *et al.*, 2018)

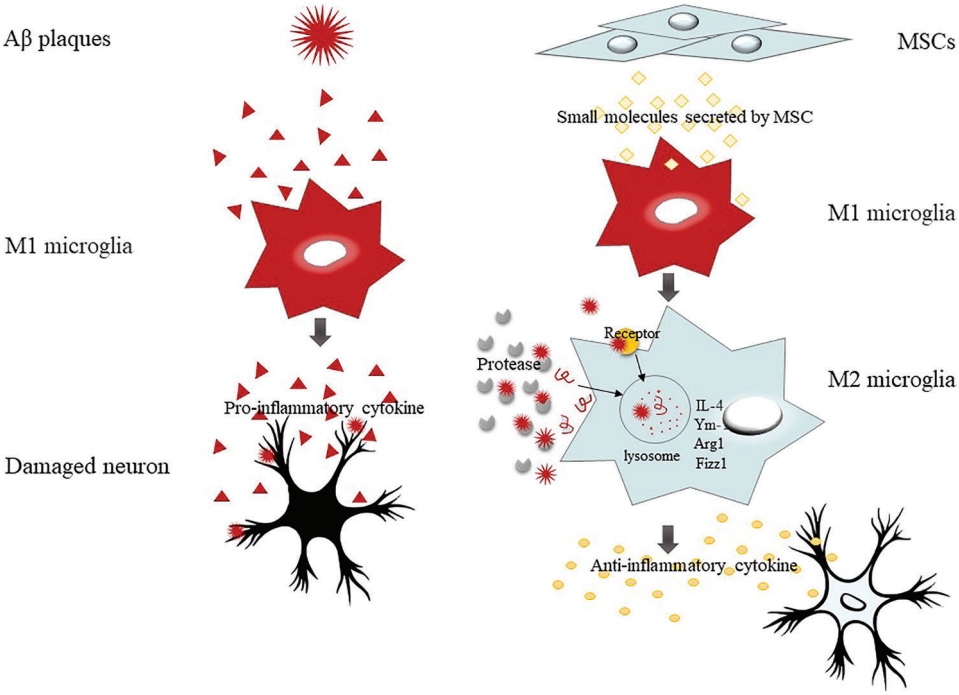

FIGURE 2. MSCs have immuno-regulatory properties, especially microglia polarization.

treat diseases (Fig. 3); ② Autophagy is maintained MSCs play a critical role in many aspects such as secretion, proliferation, migration, and differentiation (Fig. 4).

According to a report, in SH-SY5Y cells treated with Aβ, autophagolysosomal increased, and most autophagosomes did not fuse with lysosomes, which is an important cause of neuronal damage. However, after MSCs were co-cultured with SH-SY5Y cells treated with Aβ, the expression of LC3II and the major protease cathepsin B (CTSB) in the lysosomes increased, indicating an increase in the formation of autophagosomes. In addition, MSCs intervention also increased the expression of RAB7 (which is necessary for the final maturation of late AVs and fusion with lysosomes), proving that MSCs promoted the fusion of autophagosomes and lysosomes (Shin *et al.*, 2014). This means that under the treatment of Aβ, MSCs can significantly increase the formation of neuronal autophagosomes and promote the metabolism of lysosomes. In the Aβ-treated mice, the autophagy regulation effect of MSCs is more significant, mainly in inducing the formation of autophagosomes, promoting the maturation of AVs and fusion with lysosomes, and further down-regulating Aβ-treated mice Medium Aβ level, increase the survival rate of neurons. In addition, MSCs treatment can up-regulate the expression of Beclin1 *in vivo* and *in vitro* experiments (Shin *et al.*, 2014). Moreover, the efficacy of autophagy induction in ES-MSCs was comparable to that of BM-MSCs (Kim *et al.*, 2020a). A recent study proved that cytokines secreted by MSCs can enhance the expression of autophagy-related proteins in microglia. Umbilical cord mesenchymal stem cell-conditioned medium (ucMSCs-CM) was co-cultured with BV2 microglia (Xu *et al.*, 2018). It was found that ucMSCs-CM can increase Aβ25-35 phagocytosis by enhancing the autophagy of microglia compared with the control group without MSCs medium and changes the expression of autophagy-related proteins. Taken together, these findings suggest that, although the exact pathological role of autophagy in AD remains to be elucidated, MSCs can serve as autophagy inducer that may provide new effective therapeutic strategies through degrading Aβ in the early AD.

On the contrary, some scientists believe that MSCs need autophagy to maintain their function and improve cognitive

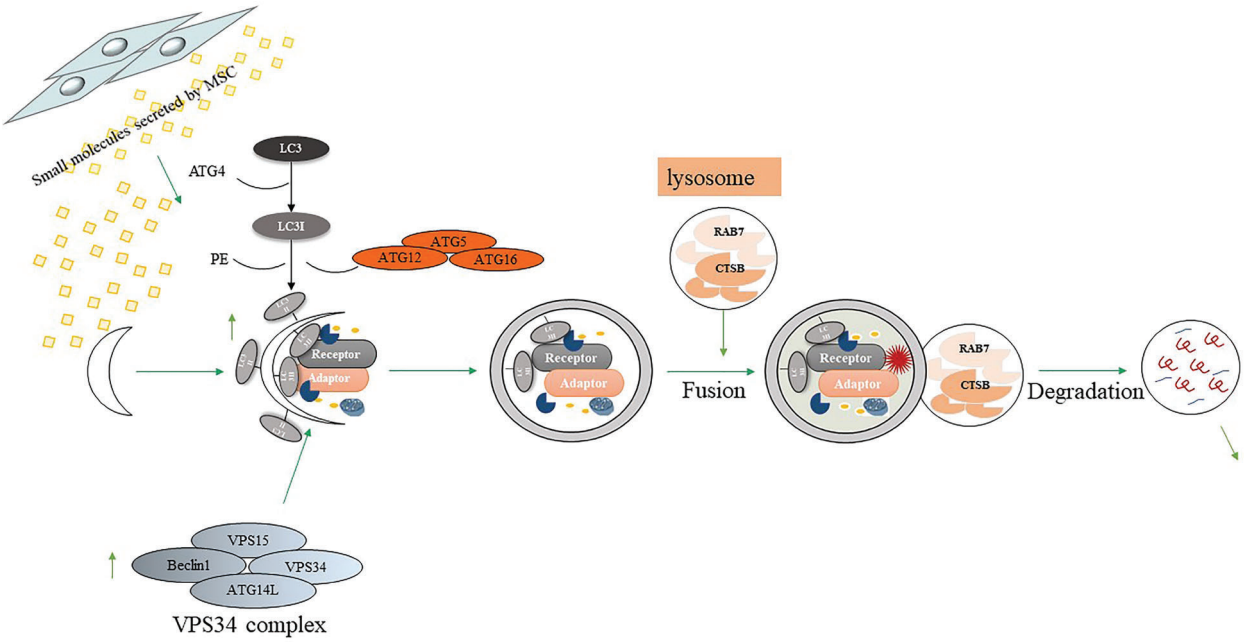

FIGURE 3. MSCs-derived small molecules enhance Aβ degradation by autophagy.

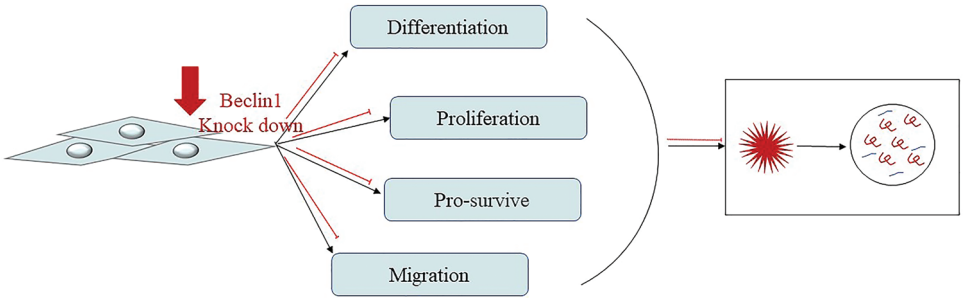

FIGURE 4. MSCs require autophagy to maintain their ability to proliferate, migrate, differentiate, and survive.

impairment in APP/PS1 mice. In order to study the role of autophagy in hUCMSCs, Li *et al.* (2018) knocked out Beclin1 in cells and found that in addition to changes in autophagy-related proteins (LC3, Beclin1, ATG7, and P62), migration and differentiation (SDF-1), stem cell key protein (Sox2), and apoptosis (caspase-3 and PARP) related proteins have also changed. It is proved that autophagy plays a vital role in maintaining the differentiation, migration, and survival of MSCs (Fig. 4). In addition, hUCMSCs transplantation can also improve the working memory and LTP of AD mice, while significantly inhibiting DEP, an indicator of reverse learning behavior. In the hippocampus and cerebral cortex, it reduces apoptosis and increases the new-born neuron. However, after inhibiting the autophagy of hUCMSCs, these effects all disappeared (Li *et al.*, 2018). A recent study showed that the regulation of autophagy may also affect the secretion capacity of BM-MSCs, thereby affecting their functions. In fact, subcutaneous injection of BM-MSCs pretreated with the autophagy inducer rapamycin can enhance the wound healing ability of BM-MSCs. On the contrary, the therapeutic effect of early Beclin1 silencing BM-MSCs was reduced (An *et al.*, 2018). These findings demonstrate that autophagy plays a key role in the treatment of MSCs, but now, more convincing evidence is still needed and still represents a stimulating field of research.

MSCs reduce Aβ by reducing OS

OS is considered to be an important factor of neurotoxicity. It occurs in the early stage of AD. Before the appearance of clinical and pathological symptoms, it is considered that it may be one of the causes of Aβ starch deposition (Jiao *et al.*, 2016). Previously, studies have confirmed that MSC can induce antioxidant effects in neurodegenerative diseases (Yokokawa *et al.*, 2019; Godoy *et al.*, 2018; Wang *et al.*, 2018). Godoy and his colleagues proposed that MSC-EVs exerts a neuroprotective effect due to the presence of antioxidant enzymes, anti-inflammatory, and/or nutritional molecules. Studies have shown that MSC-EVs contains and carries catalase, which makes EVs have ROS scavenging activity (Godoy *et al.*, 2018).

Glutathione (GSH) is a critical cellular antioxidant stressor, which may reduce from oxidation by hydrogen peroxide and hydroperoxides, and it protects the protein thiol (Behl, 2005). Glutathione is converted to GSSG through GPx, to detoxify peroxide, glutathione reductase can reduce the reaction. GSH/GSSG is an index to evaluate the anti-oxidation in the cell. SOD is an important antioxidant enzyme that catalyzes the generation of H_2O_2 from superoxide radical anions and induces the oxidation of polyunsaturated fatty acids and lipid peroxidation (Smith *et al.*, 2000). MDA is the final product of lipid peroxidation and has a toxic effect on neurons. A recent study showed

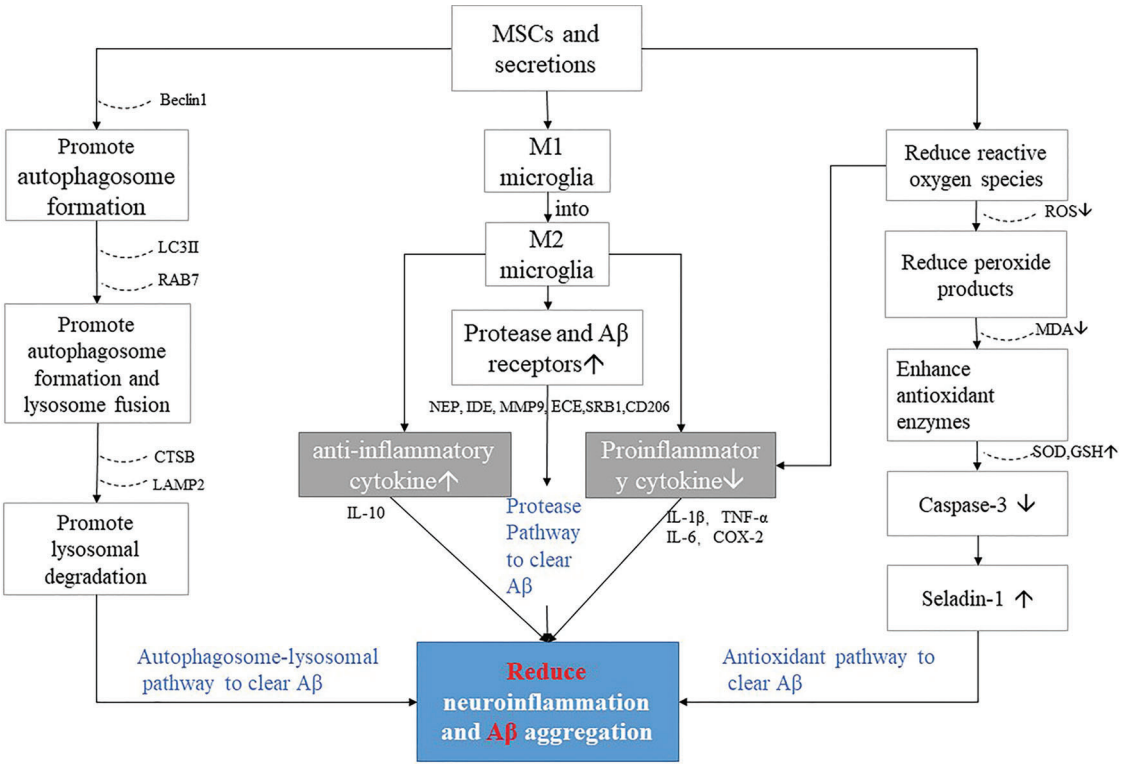

FIGURE 5. MSCs and secretions factors reduce pathways of neuroinflammation and Aβ aggregation in AD.

that the tail vein injection of human amniotic MSCs (hAMSCs) can alleviate OS by reducing lipid peroxide products and increasing the levels of antioxidant enzymes SOD and GSH (Jiao *et al.*, 2016). Compared with the PBS control group, hAMSCs treatment significantly increased the SOD activity in the brain of AD transgenic mice and reduced the MDA level.

Furthermore, in the normal brain, Selective Alzheimer's disease indicator-1 (seladin-1) protects neurons from OS (Greeve *et al.*, 2000). When OS in AD increases, seladin-1 is cleaved in a caspase-dependent manner (caspase 6 and caspase 3) and may be inactivated (Greeve *et al.*, 2000). Mo *et al.* reported that BM-MSCs significantly down-regulate the expression and activity of caspase-3, thereby protecting seladin-1 from lysis (Mo *et al.*, 2012). Research by Salem showed that BM-MSCs can repair damaged brains and significantly increase the levels of choline acetyltransferase (ChAT) and survivin expressing cells (Salem *et al.*, 2015). And it up-regulates the expression of selective seladin-1, Nestin, and further removes β amyloid plaques in the hippocampus And MSCs can improve biomarkers better than drugs (Salem *et al.*, 2015). In addition, studies have reported that *in vitro* induction of hMSCs to neurons (hMSCs-N) is more resistant to Aβ42 aggregates than undifferentiated MSCs (Cecchi *et al.*, 2011). hMSCs-N enhanced its resistance to Aβ toxicity by reducing the levels of membrane GM1, Ca^{2+}, and ROS in neurons (Cecchi *et al.*, 2011). These results indicate that MSCs as effective antioxidants reduce Aβ deposition better than drugs.

MSCs have the potential to correct SL metabolism

As AD progresses, abnormal SL metabolism is often observed. It is related to dysfunctional protein clearance, impaired lysosome production, and inflammation control functions, as well as Aβ production and autophagy (Takasugi *et al.*, 2011; Maceyka *et al.*, 2012; Czubowicz *et al.*, 2019). These experiments investigated the possibility of using stem cells to treat abnormal SL metabolism (Lee *et al.*, 2010a; Marfia *et al.*, 2016). The BM-MSCs were transplanted into the cerebellum of the Niemann-Pick type C disease mouse model, and the correction of S1P levels and the decrease of sphingosine accumulation were observed. Therefore, it can reduce cell apoptosis, restore calcium homeostasis, and prevent neuron loss (Lee *et al.*, 2010a). In another study, the conditioned medium of AD-MSCs controlled the sphingomyelin kinase/sphingomyelin-1-phosphate signaling pathway and inhibited the activation of microglia (Marfia *et al.*, 2016). These studies demonstrate that MSCs have the potential to correct SL metabolism abnormalities in mice. Although no one has yet studied the effect of MSCs on abnormal SL metabolism in AD brains, we believe that this is an area worthy of further study.

Conclusion and Future Perspective

As a promising method of treatment, MSCs therapies have become at the forefront of the field of neurodegeneration disease, especially in the area of AD. It is believed to reduce neuroinflammation, clear Aβ deposits, neurofibrillary tangles, increase acetylcholine levels, promote neurogenesis, reduce neuronal damage, improve working memory and cognition (Ma *et al.*, 2013; Ma *et al.*, 2020; Wang *et al.*, 2018). In almost all types of ADs, Aβ plays a key pathogenic role, and studies have connected Aβ plaques with the formation of intercellular tau tangles and neuroinflammation. Therefore, we focus on the degradation effect and mechanism of Aβ by

MSCs in this review. Considering that the number of MSCs differentiated into neuronal cells after transplantation *in vivo* is very small (Prockop *et al.*, 2003; Caruso and Parolini, 2015), the cell-free therapy using MSCs-derived secretome might constitute an alternative because of their advantages. Many studies suggest that MSC-secretomes act as an important mediator of the information exchange between MSCs and neurons in neurodegenerative diseases (Kim *et al.*, 2010; Lim *et al.*, 2020; Wang *et al.*, 2018). Specifically, MSC-secretomes contain neuroregulatory molecules known as potential therapeutic mediators against AD-related microenvironments. Recent studies have shown that clearance mechanisms of MSC-secretomes or exosomes in Aβ are likely multifaceted, including immune regulation, increased Aβ-degrading factors, enhanced autophagy, reduced OS, and correction of SL metabolism, which suggests the potential of clinical application for the treatment of AD (Fig. 5) (Yokokawa *et al.*, 2019; Kim *et al.*, 2018a; Shin *et al.*, 2014; Kim *et al.*, 2013; Park *et al.*, 2020a; Lee *et al.*, 2010a; Wang *et al.*, 2018; Marfia *et al.*, 2016; Jiao *et al.*, 2016; Kim *et al.*, 2020a).

The accumulation of Aβ is the result of many factors, so its clearance should also be multi-targeted. The fact that a huge amount of money has been put into the development of protein-based therapies in AD but has not achieved valid results supports this issue in part (Salloway *et al.*, 2014). Therefore, a strategy that can modulate multiple pathological factors of AD is important to achieve clinical benefits in the treatment of neurodegenerative disease, and MSCs would be a strong candidate for such a treatment strategy.

So far, a large number of studies have verified the effect of MSCs on multi-target clearance of Aβ amyloid from *in vitro* and *in vivo*, but the tumorigenicity of MSCs have also been widely discussed and become one of the most important risks of clinical treatment (Torsvik *et al.*, 2010). At present, there is no report that MSCs induce tumors. However, due to the self-proliferation and differentiation of MSCs are similar to cancer cells, the risk of tumorigenesis cannot be ignored. Therefore, future research will focus on identifying specific small molecules in MSCs that regulate neuroinflammation and induce autophagy to enhance Aβ clearance, which is significant to the development of clinical targets for AD. In addition, although the therapeutic effect of MSCs on AD has been gradually confirmed, to form a systematic treatment system, we must fully consider factors such as the optimal MSCs injection time point, cell concentration, and injection route. We are convinced that, although MSCs research is still in its infancy, the MSCs still have a great deal of hope for patients with AD.

Availability of Data and Materials: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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