Life Sciences 246 (2020) 117405

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Immunomodulatory role of mesenchymal stem cells in Alzheimer's disease

Lu Zhang[a,b,*], Zhi-fang Dong[a,b,**], Jie-yuan Zhang[c]

[a] Department of Pediatric Research Institute, Ministry of Education Key Laboratory of Child Development and Disorders, National Research Center for Child Health and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China

[b] Chongqing Key Laboratory of Translational Medical Research in Cognitive Development and Learning and Memory Disorders, China

[c] Research Institute of Surgery, Daping Hospital, Army Medical University, Chongqing, China

ARTICLE INFO

Keywords:
Mesenchymal stem cell
Alzheimer's disease
Microglia
Astrocyte
Neuroinflammation
Transcription factors
Immunoregulation

ABSTRACT

Alzheimer's disease (AD) is one of the most common causes of dementia and is characterized by gradual loss in memory, language, and cognitive function. The hallmarks of AD include extracellular amyloid deposition, intracellular neuronal fiber entanglement, and neuronal loss. Despite strenuous efforts toward improvement of AD, there remains a lack of effective treatment and current pharmaceutical therapies only alleviate the symptoms for a short period of time. Interestingly, some progress has been achieved in treatment of AD based on mesenchymal stem cell (MSC) transplantation in recent years. MSC transplantation, as a rising therapy, is used as an intervention in AD, because of the enormous potential of MSCs, including differentiation potency, immunoregulatory function, and no immunological rejection. Although numerous strategies have focused on the use of MSCs to replace apoptotic or degenerating neurons, recent studies have implied that MSC-immunoregulation, which modulates the activity state of microglia or astrocytes and mediates neuroinflammation via several transcription factors (NFs) signaling pathways, may act as a major mechanism for the therapeutic efficacy of MSC and be responsible for some of the satisfactory results. In this review, we will focus on the role of MSC-immunoregulation in MSC-based therapy for AD.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease of the brain characterized by progressive memory loss and other cognitive dysfunctions. In 2015, the Alzheimer's Association International Conference estimated that approximately 47 million people worldwide suffered from dementia, and that the number could exceed 131 million people by 2050 as populations age [1]. Currently, cholinesterase inhibitors like donepezil and rivastigmine and the *N*-methyl-D-aspartate (NMDA) receptor inhibitor memantine are mainly used as interventions in AD. Although these inhibitors can improve cognitive function in patients with AD, they consistently show side effects and toxicity after long-term use. To address these problems, stem cell therapy, especially mesenchymal stem cell (MSC) transplantation, has received much more attention in recent years. In view of their many advantages, including easy accessibility, immunoregulatory function, and no immunological rejection, MSCs have become extensively utilized in AD treatment, and have produced a growing number of fruitful results [2–4]. However, the underlying mechanisms of MSC therapy for AD remain unclear. Neuronal loss in AD is partly compensated by MSC transplantation, and this may be one of the mechanisms for MSC therapy in AD [5]. Nevertheless, the mechanisms for the compensation remain largely unclear. Importantly, neuroinflammation frequently occurs alongside the neuropathological hallmarks of AD, and MSCs may directly or indirectly regulate the state of astrocytes or microglia and depend on TFs signaling pathways to adjust the balance of inflammatory cytokines, including both pro-inflammatory and anti-inflammatory cytokines [6,7], thereby producing significant effects of MSC therapy in AD. Given that neuroinflammation in the brain is considered one of the major causes of the cognitive symptoms in AD [8], this inflammation may play a pivotal role in MSC therapy for AD. This review will focus on the role of MSC-mediated neuroinflammation in the treatment of AD.

* Correspondence to: Lu Zhang, Department of Pediatric Research Institute, Children's Hospital of Chongqing Medical University, Chongqing Key Laboratory of Translational Medical Research in Cognitive Development and Learning and Memory Disorders, 136 Zhongshan Er Road, Yuzhong District, Chongqing 400014, China.

** Correspondence to: Zhifang Dong, Children's Hospital of Chongqing Medical University, 136 Zhongshan Er Road, Yuzhong District, Chongqing 400014, China.
E-mail addresses: zlu_0524@hospital.cqmu.edu.cn (L. Zhang), zfdong@cqmu.edu.cn (Z.-f. Dong), zzzzz0456@sina.com (J.-y. Zhang).

https://doi.org/10.1016/j.lfs.2020.117405
Received 19 December 2019; Received in revised form 3 February 2020; Accepted 4 February 2020
Available online 05 February 2020

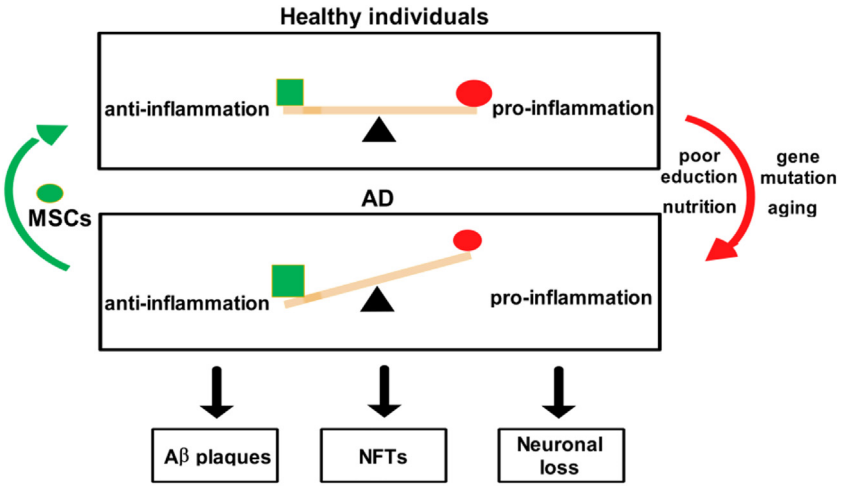

Fig. 1. Dynamic transformation of neuroinflammation in AD patients and healthy individuals. Healthy individuals show homeostasis, comprising a dynamic balance of anti-inflammation and pro-inflammation. The majority of AD cases are believed to be caused by multiple factors, including aging, nutrition, poor education, lifestyle, and chronic metabolic disorders. More importantly, the homeostasis of neuroinflammation becomes disrupted in AD patients, accompanied by Aβ plaques, NFTs, and neuronal loss. However, MSC therapy can rescue the homeostasis of neuroinflammation, and return the state to a healthy condition.

2. MSC-based therapies in AD

2.1. Gene mutation and other genetic information cause AD

Less than 5% of AD cases are early onset and familial, and such cases usually occur before the age of 65 years and arise from genetic alterations, such as pathogenic mutations in the amyloid-β precursor protein (*AβPP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes [96]. The majority of AD cases are late onset and sporadic, and are believed to be caused by multiple factors such as aging, nutrition, and lifestyle, as well as chronic metabolic disorders [9] (Fig. 1).

Familial and sporadic AD share the same neuropathological hallmarks in the brain, including extracellular amyloid β-peptide (Aβ) plaques, intraneuronal neurofibrillary tangles (NFTs), and synaptic/neuronal loss. In addition, the neuropathological hallmarks of AD are often accompanied by neuroinflammation, which is intended to protect the body, but also can contribute to aggravation of damage when it becomes excessive [10]. In the five familial AD (5 × FAD) mutations model in mice, reduction of microglia activation by galectin-3 inhibition or deletion slowed AD progression and improved cognitive behaviors [11]. Meanwhile, the treatment of neurotropin that restrained astrocyte activation, reduced pro-inflammatory cytokines (interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α) expression, decreased Aβ accumulation, and improved cognitive deficits in APP/PS1 mice [12]. Therefore, modulation of neuroinflammation may be an effective method for improvement of AD.

2.2. Different MSC-based therapies used in AD

However, there are currently no effective treatments for AD, although cholinesterase and NMDA receptor inhibitors can improve cognitive function in AD patients in the short term. With the failure to develop new drugs for AD, the number of studies on MSC transplantation has dramatically increased during the past few years, with notable effects on AD [13–15]. MSC is multipotent stem cells with properties of self-renewal, differentiation, and immunoregulation [16], just so which can be adopted for stem cell therapy in AD [17,18]. They is easily isolated from bone marrow [19], adipose tissue [20], amniotic fluid [21], umbilical cord [22], placenta [23], and dental pulp [24] without serious ethical or technical problems. Therefore, MSC-derived from various sources including human umbilical cord-derived MSC [25,26], bone marrow-derived MSC [27,28], adipose-derived MSC [29–31], and amniotic-derived MSC [32,33] has recently received increasing attention as a promising cell source for stem cell therapy in AD (Tables 1, 2).

3. AD and inflammation

The main pathological features of AD include Aβ plaques and intracellular NFTs (Fig. 1). Recently, emerging findings related to the initial steps of neuroinflammation have been considered late-phase responses to pathobiological events in AD [34]. Astrocytes and microglia, the main immune cells in the brain, play significant roles in neuroinflammation [35,97].

Aβ plaques are potent activators of microglia, which respond to cerebral amyloidosis by chronic pro-inflammatory response. Activated microglia are observed in AD, and characterized by short, thickened, and less ramified processes. Microglia have been shown to exert pro-inflammatory and anti-inflammatory effects. Many studies including those on the post-mortem human brain, neuroimaging analyses in AD patients, as well as transgenic rodent models have provided obvious evidence that microglia are attracted to nearby senile plaques in AD [36,37]. In addition, Aβ can activate microglia to produce cytokines and neurotoxins, thereby promoting neurodegeneration [38,39]. In contrast, another report suggested that microglia could secrete neurotrophic agents and eliminate toxic Aβ by phagocytosis, thus playing a neuroprotective role in AD [40]. The same study observed the existence of an age-dependent phenotypic change in microglial activation within the hippocampus of an AD mouse model from an alternative activation state (IL-4 expression) to a classic cytotoxic phenotype (IL-1β and TNF-α expression) [40]. Interestingly, recent work on an ischemic mouse model confirmed that microglia could switch phenotypes to become “alternatively activated” such that anti-inflammatory effects were predominant, and that the switch was promoted by adult stem cell transplantation [41]. The activated microglia were located near Aβ deposits, and their morphology changed from ramified to ameboid through the action of microglial phagocytosis [42].

Astrocytes are the most abundant type of glial cells in the central nervous system (CNS), and have many functions, including maintenance of ionic balance, blood-brain barrier (BBB), participation in synaptogenesis, neurogenesis, and synaptic transmission. Astrogliosis occurs in AD, and the degree of astrogliosis alterations is associated with cognitive impairment. Astrocytes express several receptors for chemokines and inflammatory cytokines including those like IL-1β and TNF-α [43]. IL-1β and TNF-α can activate astrocytes, which are important for Aβ clearance and degradation [44]. On the contrary, amyloid-β precursor protein (AβPP) can induce astrogliosis and neuronal death [45]. Moreover, astrocytes in AD induce deposition of Aβ, which aggravates the extent of AD pathology [46]. It is possible that the recruited astrocytes are involved in neuroinflammation and express inducible nitric oxide synthase (iNOS), resulting in NO-mediated toxicity. Likewise, observations of activated astrocytes in AD patients and

Table 1
Evaluation of MSCs therapy in AD model.

Stem cells	Model	Way	Functional evaluation	Molecular mechanism	Source
hUBC-MSC	APP/PS1, 5 × FAD	Intracardiac injection	MWM	Activated microglia and inflammatory factors [18,92,93]	Umbilical cord
BMSC	APP/PS1	Hippocampal injection	MWM	Activation of microglia [42,51,94,95]	Bone marrow
ADSC	APP/PS1	Hippocampal injection	MWM, NOR	Anti-inflammatory cytokines [29]	Adipose tissue
AMSC	APP/PS1, APPswe, 3XTg-AD	Hippocampal injection, intravenous injection	MWM, light/dark transition test	Immunomodulatory [32,33]	Amniotic fluid

MWM: Morris water maze; NOR: new object recognition; hUBC-MSC: human umbilical cord-derived mesenchymal stem cells; BMSC: bone marrow-derived mesenchymal stem cells; ADSC: adipose tissue-derived mesenchymal stem cells; AMSC: amniotic fluid-derived mesenchymal stem cells.

animal models further indicate a neuroinflammatory role of astrocytes in AD [47]. Briefly, neuroinflammation plays a significant role in the pathogenesis of AD, especially with respect to inflammation that activates microglia and astrocytes involved in AD pathogenesis.

4. MSC therapy for AD: microglia-mediated neuroinflammation

Because of their easy accessibility, lack of ethical concerns, and no immune rejection, MSCs have enormous potential for AD therapy. However, the underlying mechanisms of MSC therapy for AD require further exploration. MSCs have been transplanted into different animal models of AD (Table 1) and patients with AD (Table 2), and shown to play an immunomodulatory role in AD development by microglia [48] (Fig. 2).

For example, systemic transplantation of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) into APP/PS1 transgenic mice decreased the level of interferon-γ (IFN-γ) (pro-inflammatory cytokine), increased the levels of IL-10 and transforming growth factor (TGF)-β1 (anti-inflammatory cytokines) in the peripheral plasma, significantly ameliorated the cognition defects, and reduced Aβ plaque deposition as well as soluble Aβ, which may be related to activation of microglia [48]. Importantly, alternatively activated microglia are associated with Aβ plaques. The effect of hUCB-MSCs on reducing Aβ accumulation is likely attributed to inhibition of β-site APP-cleaving enzyme 1 (BACE1) expression via immunomodulation. Aβ is generated from APP, which is cleaved by BACE1. Placenta-derived MSCs (PD-MSCs) were reported to attenuate BACE1 expression as well as γ-secretase activity, and improve cognitive impairment in an $A\beta_{1-42}$-infused mouse model, which might result from the activated microglia [49]. In addition, the mechanisms of MSC therapy for AD may involve regulation of pro-inflammatory and anti-inflammatory cytokines through activated microglia. Previous studies showed that hUCB-MSC transplantation into APP/PS1 double-transgenic mice significantly reduced the levels of Aβ, BACE1, and Tau hyperphosphorylation and improved spatial learning and memory defects by up-regulating anti-inflammatory cytokines (IL-4, IL-10, TGF-β) and down-regulating pro-inflammatory cytokines (IL-1β, TNF-α) through activation of microglia [32,48,50,51]. In particular, MSC therapy promoted an increase in IL-4, which may induce microglia to produce insulin-like growth factor (IGF)-1 [52], reduce Aβ toxicity [53,54], and enhance Aβ phagocytosis [53]. MSCs transplanted into an AD model triggered microglia to become activated and convert into an amoeboid shape, and subsequently reach the area of inflammation [55].

Activated microglia have two phenotypes: M1 (classically activated) and M2 (alternatively activated). The terms M1 and M2 originally indicated macrophages [56,57], but can also be used for microglia, although microglia have more than just two activity states [58]. M1 microglia usually produce massive amounts of pro-inflammatory cytokines including IL-1β, IL-12, TNF-α, and iNOS, which often worsen the CNS damage [59]. M2 microglia respond to IL-4, IL-10, IL-13, and TGF-β, which have an anti-inflammatory impact on AD [3]. Excessive amounts of pro-inflammatory cytokines usually act for AD development. For example, a neutralizing antibody for IL-17 (pro-inflammatory cytokine) prevented the increase in pro-inflammatory mediators and improved memory function in the $A\beta_{1-42}$ mouse model [60]. Interestingly, transplantation of MSC line B10 cells decreased Aβ deposition and improved neurological function, but increased IL-1β mRNA and protein expression in an amyloid β-infused rat model [61]. Conversely, anti-inflammatory cytokines are considered to favor AD improvement [62]. Thus, it is imperative that MSCs regulate activation of microglia from M1 phenotype to M2 phenotype. Interestingly, alternatively activated microglia (M2 phenotype) may be activated by a pro-inflammatory cytokine (IL-β), thereby contributing to the suppression of pro-inflammatory cytokines [10,63]. Activated microglia may switch from M2 phenotype to M1 phenotype in AD [64,65]. Specifically, the microglia phenotype switched from a pro-inflammatory role to an anti-inflammatory role can be facilitated by the PI3/Akt pathway [98]. In addition, the modulatory effect of microglia polarization (from M1 state to M2 state) was partly mediated by LRP-1 receptor [99], NLRP3 inflammasome suppression [100], and steroid hormones (17β-estradiol, progesterone) [101]. Hence, the switch between M1 phenotype and M2 phenotype may be a dynamic process with a significant role in neuroinflammation [10].

A possible mechanism of MSC-based therapy for AD may be that MSCs regulate neuroinflammation by activation of microglia, and the activated microglia subsequently alleviate pathological features such as Aβ deposits and Tau hyperphosphorylation, and rescue the spatial learning and memory deficits.

5. MSC therapy for AD: astrocyte-mediated neuroinflammation

Recently, it was reported that exosomes derived from hypoxia-preconditioned MSCs and administered to APP/PS1 mice decreased proinflammatory cytokines (TNF-α, IL-1β) and increased anti-inflammatory cytokines (IL-4, IL-10) by modulating the activation of astrocytes, reduced Aβ plaque deposition, and finally rescued the cognition and memory impairments [66]. Likewise, brain-derived neurotrophic factor (BDNF)-modified human umbilical cord mesenchymal stem cells transplanted into an AD rat model enhanced the activation of astrocytes, reduced Aβ expression, and improved spatial learning and memory abilities [2]. Thus, MSCs may participate in neuroinflammation progression by regulating the state of astrocytes in AD, and may be helpful for AD therapy (Fig. 3).

Astrocytes comprise a specific cell type with a star-shaped morphology resembling inactivated microglia that are surrounded by nearby neurons and blood vessels, and have many important functions including metabolic effects [67] and modulatory effects on the neuronal microenvironment [68] under physiological conditions. Nevertheless, a large number of activated astrocytes have been found adjacent to Aβ plaques [69], supporting the concept that Aβ plaques can stimulate astrocytes, and that activated astrocytes, which regulate inflammatory cytokines, are involved in the neuropathology of AD, suggesting a complicated interaction between activated astrocytes and AD development [69]. Activated astrocytes are associated with NFTs, as another pathological feature of AD. For instance, the number of NFTs increases as the number of activated astrocytes increases [70], suggesting that

Table 2
MSC clinical trials in patients with Alzheimer's disease registered on Clinicaltrials.gov (National Institute of Health) as of December 2019.

NCT	Phase	Status	Conditions	Outcome measures	Study date	Locations
NCT02600130	Phase 1 (N = 33)	Active, not recruiting	Alzheimer's disease	Incidence of subjects with adverse events, ADAS-Cog 11, MMSE, NPI, UPSIT, GDS,QQL-AD,ADCS-ADL, Blood inflammatory and AD biomarkers, CSF inflammatory biomarkers, Tau, Aβ, MRI	2016.10–2020.9	Florida, US
NCT02833792	Phase 2 (N = 40)	Recruiting	Alzheimer dementia	Number of patients with adverse events, NIHSS	2016.6–2020.6	California, US
NCT04040348	Phase 1 (N = 10)	Recruiting	Alzheimer's disease	TE-SAEs, ADAS-Cog 11, MMSE, GDS, ADRQL-40, ADCS-ADL, NPI-Q, Aβ40/42, ApoE, Tau, MRI, Serum PRA	2019.10–2021.9	Florida, US
NCT02054208	Phase 1/2 (N = 45)	Recruiting	Alzheimer's disease	Number of subjects with adverse events, ADAS-Cog, S-IADL, K-MMSE, CGA-NPI, ADAS-cog Response Rate, CDR-SOB, FDG-PET, MRI, CSF biomakers	2014.2–2019.7	Seoul, Korea
NCT01297218	Phase 1 (N = 9)	Completed	Dementia of the Alzheimer's type	Number of subjects with adverse events, ADAS-cog 12, S-IADL, K-MMSE, CGA-NPI, Aβ, Tau, PIB-PET, FDG-PET	2011.2–2011.12	Seoul, Korea
NCT02672306	Phase 1/2 (N = 16)	Active, not recruiting	Alzheimer's disease	ADAS-Cog score, MMSE, CIBIC-plus, ADCS-ADL, NPI, Aβ	2017.10–2019.10	Guangzhou, China
NCT01547689	Phase 1/2 (N = 30)	Active, not recruiting	Alzheimer's disease	Number of subjects with adverse events, ADAS-cog, CIBIC, MMSE, ADL, NPI, Aβ, Tau, Th1/Th2 cytokines, serum transthyretin	2012.3–2016.12	Beijing, China
NCT03117738	Phase 1/2 (N = 21)	Active, not recruiting	Alzheimer's disease	Number of subjects with adverse events, ADAS-Cog, MMSE, CDR-SOB, NPI, GDS, ADCS-ADL, C-SSRS, MRI, Aβ40/42, AICD, sNRG-1	2017.4–2019.9	California, US
NCT03172117	Phase 1/2 (N = 45)	Recruiting	Alzheimer's disease	ADAS-Cog, S-IADL, K-MMSE, CGA-NPI, ADAS-Cog Response Rate, CDR-SOB, CIBIC-plus, FDG-PET, MRI, CSF biomarkers	2017.5–2021.12	Seoul, Korea
NCT02899091	Phase 1/2 (N = 24)	Recruiting	Alzheimer's disease	Number of adverse events, ADAS-Cog, K-MMSE, GDS, CDR,K-IADL, CGA-NPI, CIBIC-plus, SF-36, Aβ, Tau, MRI, CMRglc, SPM, PET, qEEG	2016.9–2021.12	Gyeonggi-do, Korea
NCT01696591	Unknown (N = 14)	Unknown	Alzheimer's disease, dementia	Incidence rate of adverse events, ADAS-Cog, S-IADL, K-MMSE, FDG-PET	2012.3–2013.9	Seoul, Korea

ADAS-Cog: Alzheimer's disease assessment scale-cognitive subscale; S-IADL: Seoul instrumental activities of daily living; MMSE: mini mental state examination; K-MMSE: mini mental state examination Korean version; FDG-PET: fluorodeoxyglucose positron emission tomography; GDS: global deterioration scale; CDR: clinical dementia rating; K-IADL: Korean instrumental activities of daily living; CGA-NPI: caregiver administered-neuropsychiatric inventory; CIBIC-plus: clinician interview based impression of change plus; Aβ: amyloid beta; MRI: magnetic resonance imaging; CMRglc: regional cerebral metabolic rate for glucose; SPM: statistical parametric mapping; qEEG: quantitative electroencephalography; CDR-SOB: clinical dementia rating-sum of box; CSF: cerebrospinal fluid; C-SSRS: Columbia suicide severity rating scale; AICD: amyloid precursor protein intracellular domain; sNRG-1: soluble neuregulin-1; NPI: neuropsychiatric inventory; TE-SAEs: treatment-emergent serious adverse events; ADRQL-40: Alzheimer's disease related quality of life 40; ADCS-ADL: Alzheimer's disease cooperative study activities of daily living; NPI-Q: neuropsychiatric inventory-Q; ApoE: apolipoprotein E; Serum PRA: Serum blood plasma renin activity; UPSIT: University of Pennsylvania smell identification test; QOL-AD: quality of life-Alzheimer's disease; NIHSS: National Institutes of Health stroke scale.

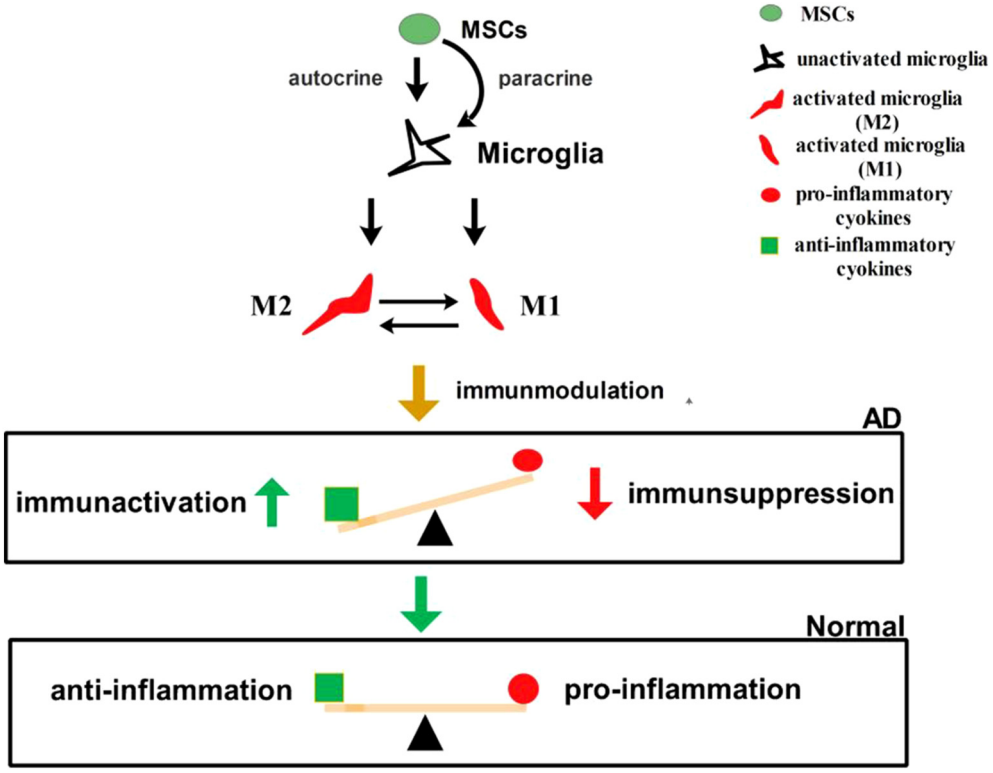

Fig. 2. Effects of MSC-immunomodulated microglia on AD progression. MSCs affect the activity state of microglia, M1 (classically activated) or M2 (alternatively activated), in autocrine or paracrine manners, and then immunomodulate the homeostasis of neuroinflammation for a return to the normal healthy condition.

activated astrocytes may lead to NFT formation and subsequently aggravate AD progress. However, many studies have confirmed that MSCs-derived from various tissues can be utilized for intervention in AD, and achieved some positive outcomes, specifically that MSCs can reduce Aβ plaque deposition [71] as well as NFT formation [13,72], and subsequently improve cognitive defects [15,73]. However, it is important to note that the mechanisms of MSC-based therapy for AD remain to be fully elucidated. Therefore, it is necessary to clarify

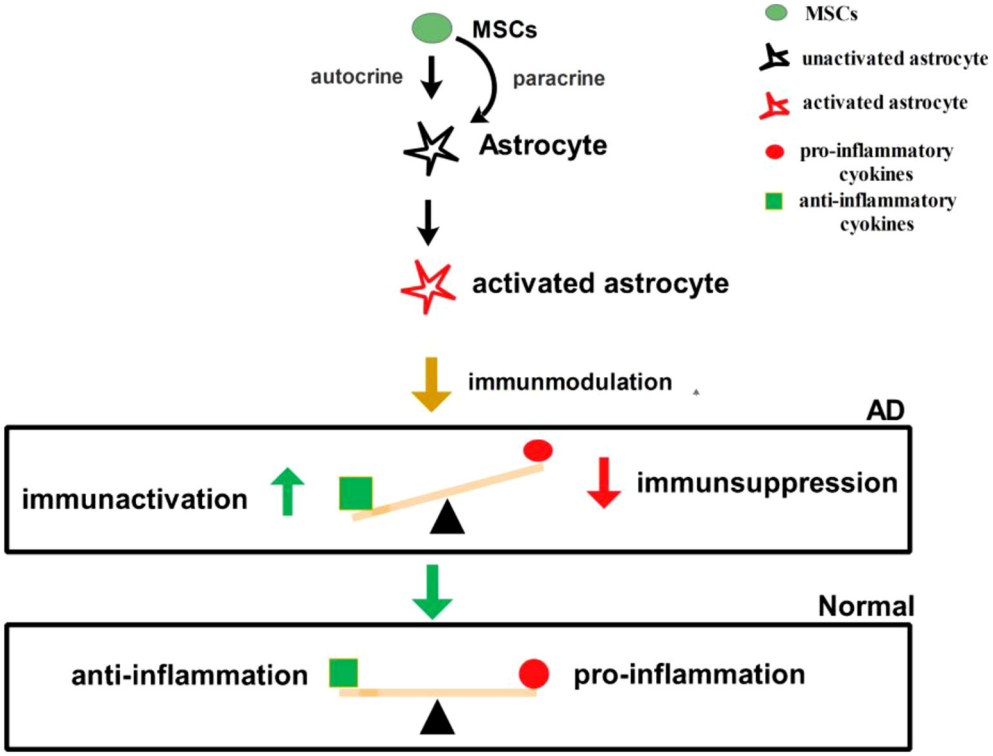

Fig. 3. Effect of MSC-immunomodulated astrocytes on AD progression. MSCs affect the activity state of astrocytes by autocrine or paracrine manners, and the activated astrocytes immunomodulate the homeostasis of neuroinflammation, and facilitate a return to the normal healthy condition.

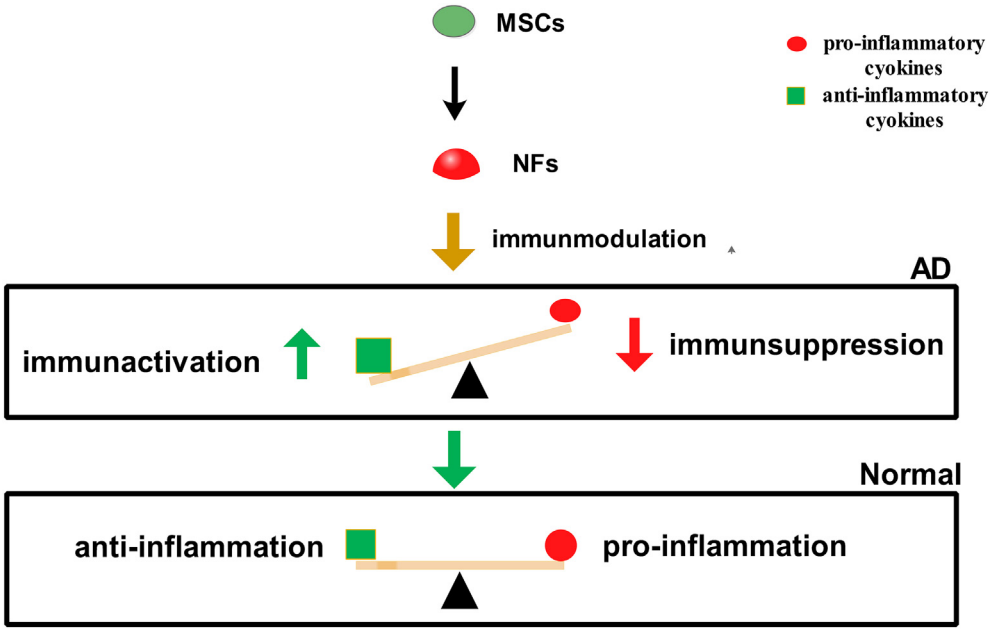

Fig. 4. Effect of MSC-immunomodulated via NFs pathways on AD progression. MSCs modulate inflammatory cytokines through NFs signaling pathways, which immunomodulate the homeostasis of neuroinflammation, and facilitate a return to the normal healthy condition. Abbreviation: NFs: transcription factors signaling pathways.

whether MSC-based therapy for AD exerts important effects by modulating the state of astrocytes. Recently, it was reported that MSC transplantation promoted the recovery of learning and memory function in neonatal rats with hypoxic-ischemic brain damage by reducing the proliferation of reactive astrocytes [74]. Based on these observations, we propose the hypothesis that exogenous MSCs may play a restorative role in AD by suppressing the activation of astrocytes. Moreover, once MSCs are applied to the microenvironment of injured tissues, they can produce various factors like TGF-β [75] and IGF-1 [76] that trigger the activation of astrocytes. Subsequently, the activated astrocytes can clear Aβ plaque deposition [44] and which also may secret TGF-β and IGF-1 as neuroprotective factors [104,105].

However, the activation of astrocytes has both pros and cons. On the one hand, excessive activation of astrocytes can lead to astrogliosis colocalized with amyloid plaques in AD [77] or glial scar formation after CNS damage [78], which hinder synaptic communication and axonal regeneration. On the other hand, moderate activation of astrocytes may be favorable for the improvement of AD. Astrocytes may be involved in the recognition and modulation of immune and inflammatory processes in AD [79], given that they express several receptors for inflammatory cytokines like IL-1β, TNF-α, and TGF-β that can activate astrocytes [43,80]. Activated astrocytes participate in Aβ clearance and degradation similar to phagocytic microglia [44]. In addition, MSCs are closely associated with Toll-like receptors (TLRs), by which MSCs could secret IL-10 and TGF-β1 [81,82]. Astrocytes can also express innate immunity receptors like TLRs, and when inflammatory cytokines secreted by MSCs activate TLRs, like TLR3, they trigger a comprehensive neuroprotective response by enhancing the production of anti-inflammatory cytokines, such as IL-9, IL-10, and IL-11, and downregulating pro-inflammatory cytokines like IL-12 [83]. Thus, MSCs may rescue AD by paracrine effects involving secreted inflammatory cytokines or growth factors to modulate the activation of astrocytes. Finally, MSCs can directly or indirectly modulate the state of astrocytes or microglia, and thus their manners of modulation are diverse.

In short, astrocytes or microglia modulated by MSCs may play more than individual roles. In AD, Aβ plaques are likely to activate astrocytes or microglia. It is possible that activation of microglia plays an important role in activation of astrocytes. It is likely that activation of astrocytes leads to activation of microglia. Therefore, the interaction between activation of microglia and activation of astroglia may be involved in the pathogenesis of AD. Similarly, the mechanism of MSC-based therapy for AD has complex modes by modulating the activation of microglia or astroglia.

6. MSC therapy for AD: transcription factors-mediated neuroinflammation

Transcription factors (TFs), such as nuclear factor-κB (NF-κB) [106], nuclear factor of activated T-cells (NFAT) [107], hypoxia-inducile factor (HIF) [108], and nuclear factor-erythroid 2-related factor (Nrf) [106], play a significant role in the stimulation of inflammatory mediators related to neuroinflammation. It been verified that [109,110] BMSCs can secrete IL-6 and VEGF, which are dependent on the classic NF-κB pathway. Therefore, MSCs therapy for AD may regulate inflammatory response via modulation of TFs signaling pathways. More important, It have reported that AD-MSCs transplanted into infracted hearts decreased inflammatory cytokines (TNF-α and IL-6) and increased growth factors through modulation of TLR4/NF-κB and kelch-like ECH-associated protein 1 (Keap-1)/Nrf-2 signaling pathways [106]. Treatment of hUCB-MSCs with $CoCl_2$ was reported to promote anti-inflammatory response and increase the expression of microRNA-146a (miR-146a). However, hypoxia-inducile factor-1α (HIF-1α) silencing and ERK inhibition abolished $CoCl_2$-induced miR-146a expression, suggesting that $CoCl_2$ may enhance the immunoregulation capacity of hUCB-MSCs via the ERK/HIF-1α signaling pathway [108]. Additionally, the administration of MSCs in pulmonary hypertension may suppress the expression of TNF-α by calcineurin (CaN)/NFAT signaling pathway [107]. Hence, these results indicate that MSCs are likely to regulate directly neuroinflammation by means of several TFs signaling pathways (Fig. 4).

7. Outlook

MSCs possess huge potentials for AD-based therapy since they can be readily obtained from various tissues including umbilical cord, bone marrow, adipose tissue, and amniotic fluid (Table 1), have no immune rejection, and exhibit multiple differentiation potentials as well as immunoregulatory properties compared with embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and neural stem cells [84]. MSC transplantation has been applied in various AD models (Table 1) and clinical trials (Table 2), all which showed positive effects to a certain

extent, although the mechanisms of MSC therapy for AD remain largely unknown. Currently, the most widely accepted hypothesis is that MSCs secrete neurotrophic factors like BDNF [33], nerve growth factor (NGF) [72], and vascular endothelial growth factor (VEGF) [85] to exert neuroprotective effects on AD. Certainly, MSCs can differentiate into neurons, which substitute for apoptotic or degenerative neurons, and improve the symptoms of AD [86]. Importantly, MSCs can also be employed to rescue cognitive impairments in AD by modulating neuroinflammation, because many studies have revealed that neuroinflammation plays a key role among the mechanisms of MSC therapy for AD [87,88]. This review has provided detailed information on ways to modulate the role of neuroinflammation in MSC therapy for AD.

Clearly, the mechanisms of MSC-based therapy for AD must be established before its use in clinical practice. Currently, peripheral administration of MSCs (via intravenous or intraperitoneal routes) is not considered one of the potential treatments for AD, although it can modulate the immune system globally with some moderate suppression of neuroinflammation. There are multiple issues for therapeutic approaches involving peripheral administration of MSCs for AD. However, administration of MSC-derived extracellular vesicles (EVs) is considered a better approach than administration of MSCs, because EVs can across the BBB and target neurons and glia, which protect neurons from damage induced by AD-linked Aβ oligomers, even after peripheral administration [89–91,102,103]. Besides, MSC therapy still has various obstacles, limitations, and unexpected risks for treatment of AD in its methods and applications. Because MSC therapy is still in the research stage (Table 2), the gap between knowledge and technology is the main obstacle to overcome for clinical success and treatment efficacy. In addition to these considerations, a variety of risk factors have been investigated, including biological distribution, differentiation type, allograft use, cell purity, and transplantation methods. These risks, limitations, and side effects need to be taken into account before clinical application of AD can be achieved.

The future of MSC therapy has many problems that scientists need to explore, and consequently this emerging field has great potentials for exploitation. The unpleasant fact is that effective treatment is not available because of the health industry's disastrous processes, which have a pronounced impact on public health costs. Stem cell research maintains a bright future for AD treatment. MSC therapy brings AD patients great hope, and has low immune responses and complications compared with ESCs or iPSCs. However, the optimal method for MSC transplantation remains uncertain. Regarding AD research, most of the work is carried out in animal models (Table 1), especially in consideration of potential translation to patients with AD, which lays the foundation for pre-clinical research. MSC therapy for AD can be repeated, measurable, and cost-effective to the point of easy availability.

8. Conclusions

MSC therapy for AD has great prospects, but is still developing. There is a large number of pre-clinical studies indicating the theoretical feasibility, but further studies are required to reveal the potential therapeutic mechanisms. In this review, we have summarized that MSCs can participate in treatment of AD pathology to a large extent, by modulating the role of neuroinflammation in AD. One theory is that MSC therapy for AD regulates the role of neuroinflammation by adjusting the activation of astrocytes, and another is that MSC therapy for AD regulates the role of neuroinflammation by adjusting the activation of microglia. Importantly, MSC-mediated neuroinflammation intervenes AD progression via TFs signaling pathways. Regardless of whether MSCs adjust the activity state of microglia or astrocytes and TFs signaling pathways, they modulate the homeostasis of pro-inflammatory and anti-inflammatory biomarkers in AD, and can improve the symptoms of the disease. Once the mechanism of MSC therapy for AD has been determined, MSC therapy is very likely to enter into clinical practice and alleviate the pain of AD patients.

Declaration of competing interest

The authors have declared no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant Nos. 81622015 to Z.D. and 81601676 to J.Z.). The authors thank Alison Sherwin, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac) for editing the English text of a draft of this manuscript.

Author contributions

LZ conceived the review and wrote the manuscript. ZFD revised the manuscript. JYZ gathered some original papers and modified the manuscript. All authors read and approved the final manuscript.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

References

[1] R. Brookmeyer, E. Johnson, K. Ziegler-Graham, H.M. Arrighi, Forecasting the global burden of Alzheimer's disease, Alzheimers Dement. 3 (2007) 186–191, https://doi.org/10.1016/j.jalz.2007.04.381.
[2] W. Hu, Z. Feng, J. Xu, Z. Jiang, M. Feng, Brain-derived neurotrophic factor modified human umbilical cord mesenchymal stem cells-derived cholinergic-like neurons improve spatial learning and memory ability in Alzheimer's disease rats, Brain Res. 1710 (2019) 61–73, https://doi.org/10.1016/j.brainres.2018.12.034.
[3] M. Ding, Y. Shen, P. Wang, Z. Xie, S. Xu, Z. Zhu, Y. Wang, Y. Lyu, D. Wang, L. Xu, J. Bi, H. Yang, Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyoid-beta deposition by modulating microglial activation in Alzheimer's disease, Neurochem. Res. 43 (2018) 2165–2177, https://doi.org/10.1007/s11064-018-2641-5.
[4] J. Lee, S.J. Kwon, J.H. Kim, H. Jang, N.K. Lee, J.W. Hwang, J.H. Kim, J.W. Chang, D.L. Na, Cerebrospinal fluid from Alzheimer's disease patients as an optimal formulation for therapeutic application of mesenchymal stem cells in Alzheimer's disease, Sci. Rep. 9 (2019) 564, https://doi.org/10.1038/s41598-018-37252-9.
[5] S.H. Oh, H.N. Kim, H.J. Park, J.Y. Shin, P.H. Lee, Mesenchymal stem cells increase hippocampal neurogenesis and neuronal differentiation by enhancing the Wnt signaling pathway in an Alzheimer's disease model, Cell Transplant. 24 (2015) 1097–1109, https://doi.org/10.3727/096368914X679237.
[6] Y.J. Kim, H.J. Park, G. Lee, Q.Y. Bang, Y.H. Ahn, E. Joe, H.O. Kim, P.H. Lee, Neuroprotective effects of human mesenchymal stem cells on dopaminergic neurons through anti-inflammatory action, Glia 57 (2009) 13–23, https://doi.org/10.1002/glia.20731.
[7] C. Zhou, C. Zhang, S. Chi, Y. Xu, J. Teng, H. Wang, Y. Song, R. Zhao, Effects of human marrow stromal cells on activation of microglial cells and production of inflammatory factors induced by lipopolysaccharide, Brain Res. 1269 (2009) 23–30, https://doi.org/10.1016/j.brainres.
[8] V. Calsolaro, P. Edison, Neuroinflammation in Alzheimer's disease: current evidence and future directions, Alzheimers Dement. 12 (2016) 719–732, https://doi.org/10.1016/j.jalz.2016.02.010.
[9] M. Rochoy, V. Rivas, E. Chazard, E. Decarpentry, G. Saudemont, P.A. Hazard, F. Puisieus, S. Gautier, R. Bordet, Factors associated with Alzheimer's disease: an overview of reviewers, J. Prev Alzheimers Dis. 6 (2019) 121–134, https://doi.org/10.14283/jpad.2019.7.
[10] M. Lyman, D.G. Lloyd, X. Ji, M.P. Vizcaychipi, D. Ma, Neuroinflammation: the role and consequences, Neurosci. Res. 79 (2014) 1–12, https://doi.org/10.1016/j.neures.2013.10.004.
[11] A. Boza-Serrano, R. Ruiz, R. Sanchez-Varo, J. García-Revilla, Y. Yang, I. Jimenez-Ferrer, A. Paulus, M. Wennstrom, A. Vlialta, D. Allendorf, J.C. Davila, J. Steqmayr, S. Jimenez, M.A. Roca-Ceballos, V. Navarro-Garrido, M. Swanberq, C.L. Hsieh, L.M. Real, E. Enqlund, S. lINSE, H. Leffler, U.J. Nilsson, G.C. Brown, A. Gutierrez, J. Vitorica, J. Venero, T. Deierborq, Galectin-3, a novel endogenous TREM2 ligand, detrimentally regulates inflammatory response in Alzheimer's disease, Acta Neuropathol. (2019), https://doi.org/10.1007/s00401-019-02013-z.
[12] W. Fang, W. Liao, Y. Zheng, X. Huang, X. Weng, S. Fan, X. Chen, X. Zhang, J. Chen, S. Xiao, A. Thea, P. Luan, J. Liu, Neurotropin reduces memory impairment and neuroinflammation via BDNF/NF-κB in a transgenic mouse model of Alzheimer's disease, Am. J. Transl. Res. 11 (2019) 1541–1554.
[13] Y. Zhao, X. Chen, Y. Wu, Y. Wang, Y. Li, C. Xiang, Transplantation of human menstrual blood-derived mesenchymal stem cells alleviates Alzhemer's disease-like pathology in APP/PS1 transgenic mice, Front. Mol. Neurosci. 11 (2018) 140, https://doi.org/10.3389/fnmol.2018.00140.

[14] W. Li, K. Li, J. Gao, Z. Yang, Autophagy is required for human umbilical cord mesenchymal stem cells to improve spatial working memory in APP/PS1 transgenic mouse model, Stem Cell Res Ther 9 (2018) 9, https://doi.org/10.1186/s13287-017-0756-2.
[15] S.S. Wang, J. Jia, Z. Wang, Mesenchymal stem cell-derived extracellular vesicles suppresses iNOS expression and ameliorates neural impairment in Alzheimer's disease mice, J. Alzheimers Dis. 61 (2018) 1005–1013, https://doi.org/10.3233/JAD-170848.
[16] P.W. de Oliverira, R. Pezato, J.S. Agudelo, C.A. Perez-Novo, W.V. Berghe, N.O. Camara, D.C. de Almeida, L.C. Greqorio, Nasal polyp-derived mesenchymal stromal cells exhibit lack of immune-associated molecules and high levels of stem/progenitor cells markers, Front. Immunol. 8 (2017) 39, https://doi.org/10.3389/fimmu.2017.00039.
[17] Y. Naaldijk, C. Jaeger, C. Fabian, C. Leovsky, A. Blüher, L. Rudolph, A. Hinze, A. Stolzing, Effect of systemic transplantation of bone marrow-derived mesenchymal stem cells on neuropathology markers in APP/PS1 Alzheimer mice, Neuropathol. Appl. Neurobiol. 43 (2017) 299–314, https://doi.org/10.1111/nan.12319.
[18] H. Yang, Z. Xie, L. Wei, H. Yang, S. Yang, Z. Zhu, P. Wang, C. Zhao, J. Bi, Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model, Stem Cell Res Ther 4 (2013) 76, https://doi.org/10.1186/scrt227.
[19] B.O. Zhou, R. Yue, M.M. Murphy, J.G. Peyer, S.J. Morrison, Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone fromed by adult bone marrow, Cell Stem Cell 15 (2014) 154–168, https://doi.org/10.1016/j.stem.2014.06.008.
[20] M. Part, F. Oltolina, S. Antonini, A. Zamperone, Isolation of stromal stem cells from adipose tissue, Methods Mol. Biol. 1553 (2017) 169–182, https://doi.org/10.1007/978-1-4939-6756-8_13.
[21] S.A. Steigman, D.O. Fauza, Isolation of mesenchymal stem cells from amniotic fluid and placenta, Curr. Protoc. Stem Cell Biol. (2007), https://doi.org/10.1002/9780470151808.sc01e02s1 (Chapter 1, Unit 1E.2).
[22] N. Beeravolu, C. Mckee, A. Alamri, S. Mikhael, C. Brown, M. Perez-Cruet, G.R. Chaudhry, Isolation and characterization of mesenchymal stromal cells from human umbilical cord and fetal placeta, J. Vis. Exp. 122 (2017), https://doi.org/10.3791/55224.
[23] C.B. Portmann-Lanz, A. Schoeberlein, A. Huber, R. Sager, A. Male, W. Holzgreve, D.V. Surbek, Placental mesenchymal stem cells as potential autologous graft for pre- and perinatal neuroregeneration, Am. J. Oynecol. 194 (2006) 664–673, https://doi.org/10.1016/j.ajog.2006.01.101.
[24] Al Tsai, H.H. Hong, W.R. Lin, J.F. Fu, C.C. Chang, I.K. Wang, W.H. Huang, C.H. Weng, C.W. Hsu, T.H. Yen, Isolation of mesenchymal stem cells from human deciduous teeth pulp, Biomed. Res. Int. 2851906 (2017), https://doi.org/10.1155/2017/2851906.
[25] E. Dantuma, S. Merchant, K. Sugaya, Stem cells for the treatment of neurodegenerative diseases, Stem Cell Res Ther 1 (2010) 37, https://doi.org/10.1186/scrt37.
[26] F.H. Moghadam, H. Alaie, K. Karbalaie, S. Tanhaei, M.H. Nasr Esfahani, H. Baharvand, Transplantation of primed or unprimed mouse embryonic stem cell-derived neural precursor cells improves cognitive function in Alzheimerian rats, Differentiation 78 (2009) 59–68, https://doi.org/10.1016/j.diff.2009.06.005.
[27] B. Huang, Y. Tabata, J.Q. Gao, Mesenchymal stem cells as therapeutic agents and potential targeted gene delivery vehicle for brain diseases, J. Control. Release 162 (2012) 464–473, https://doi.org/10.1016/j.jconrel.2012.07.034.
[28] Y. Yang, X. Wu, X. Qu, X. Wang, C. Luo, L. Li, K. Zhang, The effect of triggering receptor expressed by myeloid cells 2 modified bone marrow mesenchymal stem cells on Alzheimer's disease-mouse model, Ann. Clin. Sci. 49 (2019) 23–30.
[29] T. Ma, K. Gong, Q. Ao, Y. Yan, B. Song, H. Huang, X. Zhang, Y. Gong, Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice, Cell Transplant. 22 (Suppl. 1) (2013) S113–S126, https://doi.org/10.3727/096368913X672181.
[30] Y. Yan, T. Ma, K. Gong, Q. Ao, X. Zhang, Y. Gong, Adipose-derived mesenchymal stem cell transplantation promotes adult neurogenesis in the brains of Alzheimer's disease mice, Neural Regen. Res. 9 (2014) 798–805, https://doi.org/10.4103/1673-5374.131596.
[31] M. Lee, J.J. Ban, S. Yang, W. Im, M. Kim, The exosome of adipose-derived stem cells reduces β-amyloid pathology and apoptosis of neuronal cells derived from the transgenic mouse model of Alzheimer's disease, Brain Res. 1691 (2018) 87–93, https://doi.org/10.1016/j.brainres.2018.03.034.
[32] K.S. Kim, H.S. Kim, J.M. Park, H.W. Kim, M.K. Park, H.S. Lee, D.S. Lim, T.H. Lee, M. Chopp, J. Moon, Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model, Neurobiol. Aging 34 (2013) 2408–2420, https://doi.org/10.1016/j.neurobiolaging.2013.03.029.
[33] X.Y. Zheng, Q.Q. Wan, C.Y. Zheng, H.L. Zhou, X.Y. Dong, Q.S. Deng, H. Yao, Q. Fu, M. Gao, Z.J. Yan, S.S. Wang, Y. You, J. Lv, X.Y. Wang, K.E. Chen, M.Y. Zhang, R.X. Xu, Amniotic mesenchymal stem cells decrease Aβ deposition and improve memory in APP/PS1 transgenic mice, Neurochem. Res. 42 (2017) 2191–2207, https://doi.org/10.1007/s11064-017-2226-8.
[34] A. Le Page, H. Garneau, G. Dupuis, E.H. Frost, A. Larbi, J.M. Witkowski, G. Pawelec, T. Fülop, Differential phenotypes of myeloid-derived suppressor and T regulatory cells and cytokine levels in amnestic mild cognitive impairment subjects compared to mild alzheimer diseased patients, Front. Immunol. 8 (2017) 783, https://doi.org/10.3389/fimmu.2017.00783.
[35] M.H. Ahmad, M. Fatima, A.C. Mondal, Influence of microglia and astrocyte activation in the neuroinflammatory pathogenesis of Alzheimer's disease: rational insights for the therapeutic approaches, J. Clin. Neurosci. 59 (2019) 6–11, https://doi.org/10.1016/j.jocn.2018.10.034.
[36] T. Van Groen, I. Kadish, K. Wiesehan, S.A. Funke, D. Willbold, In vitro and in vivo staining characteristics of small, fluorescent, Abeta42-binding D-enantiomeric peptides in transgenic AD mouse models, ChemMedChem 4 (2009) 276–282, https://doi.org/10.1002/cmdc.200800289.
[37] C.A. Wiley, B.J. Lopresti, S. Venneti, J. Price, W.E. Klunk, S.T. DeKosky, C.A. Mathis, Carbon 11-labeled Pittsburgh compound B and carbon 11-labeled (R)-PK11195 positron emission tomographic imaging in Alzheimer disease, Arch. Neurol. 66 (2009) 60–67, https://doi.org/10.1001/archneurol.2008.511.
[38] J.B. EI Khoury, K.J. Moore, T.K. Means, J. Leung, K. Terad, M. Tofta, M.W. Freeman, A.D. Luster, CD36 mediates the innate host response to beta-amyloid, J. Exp. Med. 197 (2003) 1657–1666, https://doi.org/10.1084/jem.20021546.
[39] A.R. Simard, D. Soulet, G. Gowing, J.P. Julien, S. Rivest, Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease, Neuron 49 (2006) 489–502, https://doi.org/10.1016/j.neuron.2006.01.022.
[40] S. Jimenez, D. Baglietto-Vargas, C. Caballero, I. Moreno-Gonzalez, M. Torres, R. Sanchez-Varo, D. Ruano, M. Vizuete, A. Gutierrez, J. Vitorica, Inflammatory response in the hippocampus of PS1M146L/APP751SL mouse model of Alzheimer's disease: age-dependent switch in the microglial phenotype from alternative to classic, J. Neurosci. 28 (2008) 11650–11661, https://doi.org/10.1523/JNEUROSCI.3024-08.2008.
[41] H. Ohtaki, J.H. Ylostalo, J.E. Foraker, A.P. Robinson, R.L. Reger, S. Shioda, D.J. Prockop, Stem/progenitor cells from bone marrow decrease neuronal death in global ischemia by modulation of inflammatory/immune responses, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14638–14643, https://doi.org/10.1073/pnas.0803670105.
[42] J.K. Lee, H.K. Jin, J.S. Bae, Bone marrow-derived mesenchymal stem cells reduce brain amyloid-beta deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model, Neurosci. Lett. 450 (2009) 136–141, https://doi.org/10.1016/j.neulet.2008.11.059.
[43] I. Morales, L. Guzman-Martinez, C. Cerda-Troncoso, G.A. Farías, R.B. Maccioni, Neuroinflammation in the pathogenesis of Alzherimer's disease. A rational framework for the search of novel therapeutic approaches, Front. Cell. Neurosci. 8 (2014) 112, https://doi.org/10.3389/fncel.2014.00112.
[44] E.C. Philips, C.L. Croft, K. Kurbatskaya, M.J. ONeill, M.L. Hutton, D.P. Hanger, C.J. Garwood, W. Noble, Astrocytes and neuroinflammation in Alzheimer's disease, Biochem. Soc. Trans. 42 (2014) 1321–1325, https://doi.org/10.1042/BST20140155.
[45] M. Sastre, T. Klockgether, M.T. Heneka, Contribution of inflammatory processes to Alzherimer's disease: molecular mechanisms, Int. J. Dev. Neurosci. 24 (2006) 167–176, https://doi.org/10.1016/j.bbadis.2019.04.016.
[46] R.G. Nagele, M.R. D'Andrea, H. Lee, V. Venkataraman, H.Y. Wang, Astrocytes accumulate A beta 42 and give rise to astrocytic amyoid plaques in Alzheimer's disease brains, Brain Res. 971 (2003) 197–209, https://doi.org/10.1016/s0006-8993(03)02361-8.
[47] J. Rogers, L.F. Lue, D.G. Walker, S.D. Yan, D. Stern, R. Strohmeyer, C.J. Kovelowski, Elucidating molecular mechanisms of Alzheimer's disease in microglial cultures, Ernst Schering Res. Found. Workshop 39 (2002) 25–44, https://doi.org/10.1007/978-3-662-05073-6_3.
[48] H. Yang, H. Yang, Z. Xie, L. Wei, J. Bi, Systemic transplantation of human umbilical cord derived mesenchymal stem cells-educated T regulatory cells improved the impaired cognition in AβPPswe/PS1dE9 transgenic mice, PLoS One 8 (2013) e69129, , https://doi.org/10.1371/journal.pone.0069129.
[49] H.M. Yun, H.S. Kim, K.R. Park, J.M. Shin, A.R. Kang, K. Ii Lee, S. Song, Y.B. Kim, S.B. Han, H.M. Chung, J.T. Hong, Placenta-derived mesenchymal stem cells improve memory dysfunction in an Aβ1-42-infused mouse model of Alzhimer's disease, Cell Death Dis. 4 (2013) e958, , https://doi.org/10.1038/cddis.2013.490.
[50] H.J. Lee, J.K. Lee, H. Lee, J.E. Carter, J.W. Chang, W. Oh, Y.S. Yang, J.G. Suh, B.H. Lee, H.K. Jin, J.S. Bae, Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation, Neurobiol. Aging 33 (2012) 588–602, https://doi.org/10.1016/j.neurobiolaging.2010.03.024.
[51] J.K. Lee, H.K. Jin, S. Endo, E.H. Schuchman, J.E. Carter, J.S. Bae, Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses, Stem Cells 28 (2010) 329–343, https://doi.org/10.1002/stem.277.
[52] J. Koenigsknecht-Talboo, G.E. Landreth, Microglia phagocytosis induced by fibrillar beta-amyloid and IgGs are differentially regulated by proinflammatory cytokines, J. Neurosci. 25 (2005) 8240–8249, https://doi.org/10.1523/JNEUROSCI.1808-05.2005.
[53] O. Butovsky, M. Koronyo-Hamaoui, G. Kunis, E. Ophir, G. Landa, H. Cohen, M. Schwartz, Glatiramer acetate fights against Alzheimer's disease by inducing dendritic-like microglia expressing insulin-like growth factor 1, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 11784–11789, https://doi.org/10.1073/pnas.0604681103.
[54] W. Zhao, W. Xie, Q. Xiao, D.R. Beers, S.H. Appel, Protective effects of an anti-inflammatory cytokine, interleukin-4, on motoeuron toxicity induced by activated microglia, J. Neurochem. 99 (2006) 1176–1187, https://doi.org/10.1111/j.1471-4159.2006.04172.x.
[55] U.K. Hanisch, H. Kettenmann, Microglia: active sensor and versatile effector cells in the normal and pathologic brain, Nat. Neurosci. 10 (2007) 1387–1394, https://doi.org/10.1038/nn1997.

[56] S. Gordon, Alternative activation of macrophages, Nat. Rev. Immunol. 3 (2003) 23–35, https://doi.org/10.1038/nri978.

[57] D.M. Mosser, J.P. Edwards, Exploring the full spectrum of macrophage activation, Nat. Rev. Immunol. 8 (2008) 958–969, https://doi.org/10.1038/nri2448.

[58] H. Kettenmann, U.K. Hanisch, M. Noda, A. Verkhratsky, Physiology of microglia, Physiol. Rev. 91 (2011) 461–553, https://doi.org/10.1152/physrev.00011.2010.

[59] B. Liu, J.S. Hong, Role of microglia in inflammation-mediated neurodegenerative disease: mechanisms and strategies for therapeutic intervention, J. Pharmacol. Exp. Ther. 304 (2003) 1–7, https://doi.org/10.1124/jpet.102.035048.

[60] C. Cristiano, F. Volpicelli, P. Lippiello, P. Buono, F. Raucci, M. Piccolo, A.J. Iqbal, C. Irace, M.C. Miniaci, C. Perrone Capano, A. Caliqnano, N. Mascolo, F. Maione, Neutralization of IL-17 rescues amyloid-β-induced neuroinflammation and memory impairment, Br. J. Pharmacol. (2019), https://doi.org/10.1111/bph.14586.

[61] M.A. Haque, A.M. Sheikh, A. Al Mamun, S. Yano, M. Hashimoto, O. Shido, A. Nagai, A mesenchymal stem cell line transplantation improves neurological function and angiogensis in intraventricular amyloid β-infused rats, Curr. Alzheimer Res. 15 (2018) 1331–1342, https://doi.org/10.2174/1567205015666180911145159.

[62] G. Mudo, M. Frinchi, D. Nuzzo, P. Scaduto, F. Plescia, M.F. Massenti, M. Di Carlo, C. Cannizzaro, G. Cassata, L. Cicero, M. Ruscica, N. Belluardo, L.M. Grimaldi, Anti-inflammatory and cognitive effects of interferon-β1a (IFNβ1a) in a rat model of Alzheimer's disease, J. Neuroinflammation 16 (2019) 44, https://doi.org/10.1186/s12974-019-1417-4.

[63] C. Cunningham, Microglia and neurodegeneration: the role of systemic inflammation, Glia 61 (2013) 71–90, https://doi.org/10.1002/glia.22350.

[64] M.M. Varnum, T. Ikezu, The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain, Arch. Immunol. Ther. Exp. 60 (2012) 251–266, https://doi.org/10.1007/s00005-012-0181-2.

[65] C. Cunningham, D.C. Wilcockson, S. Campion, K. Lunnon, V.H. Perry, Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration, J. Neurosci. 25 (2005) 9275–9284, https://doi.org/10.1523/JNEUROSCI.2614-05.2005.

[66] G.H. Cui, J. Wu, F.F. Mou, W.H. Xie, F.B. Wang, Q.L. Wang, J. Fang, Y.W. Xu, Y.R. Dong, J.R. Liu, H.D. Guo, Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice, FASEB J. 32 (2018) 654–668, https://doi.org/10.1096/fj.201700600R.

[67] D.D. Wang, A. Bordey, The astrocyte odyssey, Prog. Neurobiol. 86 (2008) 342–367, https://doi.org/10.1016/j.pneurobio.2008.09.015.

[68] R.C. Frederickson, Astroglia in Alzheimer's disease, Neurobiol. Aging 13 (1992) 239–253, https://doi.org/10.1016/0197-4580(92)90036-w.

[69] J.E. Simpson, P.G. Ince, G. Lace, G. Forster, P.J. Shaw, F. Matthews, G. Savva, C. Brayne, S.B. Wharton, MRC, Cognitive Function and Ageing Neuropathology Study Group, Astrocyte phenotype in relation to Alzheimer's-type pathology in the ageing brain, Neurobiol. Aging 31 (2010) 578–590, https://doi.org/10.1016/j.neurobiolaging.2008.05.015.

[70] J.G. Sheng, R.E. Mrak, W.S. Griffin, Glial-neuronal interactions in Alzheimer disease: progressive association of IL-1alpha+ microglia and S100beta+ astrocytes with neurofibrillary tangle stages, J. Neuropathol. Exp. Neurol. 56 (1997) 285–290.

[71] Z.H. Xie, Z. Liu, X.R. Zhang, H. Yang, L.F. Wei, Y. Wang, S.L. Xu, L. Sun, C. Lai, J.Z. Bi, X.Y. Wang, Wharton's jelly-derived mesenchymal stem cells alleviate memory deficits and reduce amyloid-β deposition in an APP/PS1 transgenic mouse model, Clin. Exp. Med. 16 (2016) 89–98, https://doi.org/10.1007/s10238-015-0375-0.

[72] M.M. Safar, H.H. Arab, S.M. Rizk, S.A. EI-Maraghy, Bone marrow-derived endothelial progenitor cells protect against scopolamine-induced Alzheimer's-like pathological aberrations, Mol. Neurobiol. 53 (2016) 1403–1418, https://doi.org/10.1007/s12035-014-9051-8.

[73] Y. Cui, S. Ma, C. Zhang, W. Cao, M. Liu, D. Li, P. Lv, Q. Xing, R. Qu, N. Yao, B. Yang, F. Guan, Human umbilical cord mesenchymal stem cells transplantation improves cognitive function in Alzheimer's disease mice by decreasing oxidative and promoting hippocampal neurogenesis, Behav. Brain Res. 320 (2017) 291–301, https://doi.org/10.1016/j.bbr.2016.12.021.

[74] M. He, X. Shi, M. Yang, T. Yang, T. Li, J. Chen, Mesenchymal stem cells-derived IL-6 activates AMPK/mTOR signaling to inhibit the proliferation of reactive astrocytes indused by hypoxic-ischemic brain damage, Exp. Neurol. 311 (2019) 15–32, https://doi.org/10.1016/j.expneurol.2018.09.006.

[75] S.P. Hung, M.H. Yang, K.F. Tseng, O.K. Lee, Hypoxia-induced secretion of TGF-β1 in mesenchymal stem cell promotes breast cancer cell progression, Cell Transplant. 22 (2013) 1869–1882, https://doi.org/10.3727/096368912X657954.

[76] J. Hou, X. Peng, J. Wang, H. Zhang, J. Xia, Q. Ge, X. Wang, X. Chen, X. Wu, Mesenchymal stem cells promote endothelial progenitor cell proliferation by secreting insulin-like growth factor-1, Mol. Med. Rep. 16 (2017) 1502–1508, https://doi.org/10.3892/mmr.2017.6741.

[77] G. Manocha, A. Ghatak, K. Puig, C. Combs, Anti-α4β1 integrin antibodies attenuated brain inflammatory changes in a mouse model of Alzheimer's disease, Curr. Alzheimer Res. 15 (2018) 1123–1135, https://doi.org/10.2174/1567205015666180801111033.

[78] M. Pekny, M. Pekna, Astrocyte reactivity and reactive astrogliosis: costs and benefits, Physiol. Rev. 94 (2014) 1077–1098, https://doi.org/10.1152/physrev.00041.2013.

[79] S. Fuller, G. Munch, M. Steele, Activated astrocytes: a therapeutic target in Alzheimer's disease? Expert. Rev. Neurother. 9 (2009) 1585–1594, https://doi.org/10.1586/ern.09.111.

[80] J.F. Reilly, P.A. Mather, V.G. Kumari, Regulation of astrocyte GFAP expression by TGF-β1 and FGF-2, Glia 22 (1998) 202–210, https://doi.org/10.1002/(sici)1098-1136(199802)22:2<202::aid-glia11>3.0.co;2-1.

[81] DelaRosa, O., & Lombardo, E., Modulation of adult mesenchymal stem cells activity by toll-like receptors: implications on therapeutic potential. Mediat. Inflamm. 2010, 865601, doi:https://doi.org/10.1155/2010/865601 (2010).

[82] A.B. Speio, G.B. Chiarotto, A.D.F. Ferreira, D.A. Gomes, R.S. Ferreira Jr., B. Barraviera, A.L.R. Oliveira, Neuroprotection and immunomodulation following intraspinal axotomy of motoneurons by treatment with adult mesenchymal stem cells, J. Neuroinflammation 15 (2018) 230, https://doi.org/10.1186/s12974-018-1268-4.

[83] M. Bsibsi, C. Persoon-Deen, R.W. Verwer, S. Meeuwsen, R. Ravid, Van, J.M. Noort, Toll-like receptor 3 on adult human astrocytes triggers production of neuroprotective mediators, Glia 53 (2006) 688–695, https://doi.org/10.1002/glia.20328.

[84] S. Ma, N. Xie, W. Li, B. Yuan, Y. Shi, Y. Wang, Immunobiology of mesenchymal stem cells, Cell Death Differ. 21 (2014) 216–225, https://doi.org/10.1038/cdd.2013.158.

[85] K.O. Garcia, F.L. Ornellas, P.K. Martin, C.L. Patti, L.E. Mello, R. Frussa-Filho, S.W. Han, B.M. Lonqo, Therapeutic effects of the transplantation of VEGF overexpressioning bone marrow mesenchymal stem cells in the hippocampus of murine model of Alzheimer's disease, Front. Aging Neurosci. 6 (2014) 30, https://doi.org/10.3389/fnagi.2014.00030.

[86] E.E. Reza-Zaldivar, M.A. Hernandz-Sapiens, Y.K. Gutierrea-Mercado, S. Sandoval-Avila, U. Gomez-Pinedo, A.L. Marquez-Aquirre, E. Vazquez-Mendez, E. Padilla-Camberos, A.A. Canales-Aquirre, Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease, Neural Regen. Res. 14 (2019) 1626–1634, https://doi.org/10.4103/1673-5374.255978.

[87] P. Aqostinho, R.A. Cunha, C. Oliveira, Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease, Curr. Pharm. Des. 16 (2010) 2766–2778, https://doi.org/10.2174/138161210793176572.

[88] M. Fakhoury, Microglia and astrocytes in Alzheimer's disease: implications for therapy, Curr. Neuropharmacol. 16 (2018) 508–518, https://doi.org/10.2174/1570159X15666170720095240.

[89] L.C. Liew, T. Katsuda, L. Gailhouste, H. Nakaqama, T. Ochiya, Mesenchymal stem cell-derived extracellular vesicles: a glimmer of hope in treating Alzheimer's disease, Int. Immunol. 29 (2017) 11–19, https://doi.org/10.1093/intimm/dxx002.

[90] Q.L. Yuan, Y.G. Zhang, Q. Chen, Mesenchymal stem cell (MSC)-derived extracellular vesicles: potential therapeutics as MSC trophic mediators in regenerative medicine, Anat. Rec. (Hoboken) (2019), https://doi.org/10.1002/ar.24186.

[91] T. Katsuda, K. Oki, T. Ochiya, Potential application of extracellular vesicles of human adipose tissue-derived mesenchymal stem cells in Alzheimer's disease therapeutics, Methods Mol. Biol. 1212 (2015) 171–181, https://doi.org/10.1007/7651_2014_98.

[92] S.E. Park, N.K. Lee, J. Lee, J.W. Hwang, S.J. Choi, H. Hwang, B. Hyung, J.W. Chang, D.L. Na, Distribution of human umbilical cord blood-derived mesenchymal stem cells in the Alzheimer's disease transgenic mouse after a single intravenous injection, Neuroreport 27 (2016) 235–241, https://doi.org/10.1097/WNR.0000000000000526.

[93] M. Son, S. Oh, H. Park, H. Ahn, J. Choi, H. Kim, H.S. Lee, S. Lee, H.J. Park, S.U. Kim, B. Lee, K. Byun, Protection against RAGE-mediated neuronal cell death by sRAGE-secreting human mesenchymal stem cells in 5×FAD transgenic mouse model, Brain Behav. Immun. 66 (2017) 347–358, https://doi.org/10.1016/j.bbi.2017.07.158.

[94] L. Danielyan, S. Beer-Hammer, A. Stolzing, R. Schafer, G. Siegel, C. Fabian, P. Kahle, T. Biedermann, A. Lourhmati, M. Buadze, A. Novakovic, B. Proksch, C.H. Gleiter, W.H. Frey, M. Schwab, Intranasal delivery of Bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in mouse models of Alzheimer's and Parkinson's disease, Cell Transplant. 23 (Suppl) (2014) S123–S139, https://doi.org/10.3727/096368914X684970.

[95] K. Wu, R. Zhang, Y. Lu, L. Wen, Y. Li, R. Duan, Y. Yao, Y. Jia, Lin28B regulates the fate of grafted mesenchymal stem cells and enhances their protective effects against Alzheimer's disease by upregulating IGF-2, J. Cell. Physiol. 234 (2019) 21860–21876, https://doi.org/10.1002/jcp.28750.

[96] J. Hardy, A hundred years of Alzheimer's disease research, Neuron 52 (2006) 3–13, https://doi.org/10.1016/j.neuron.2006.09.016.

[97] L.F. Lue, R. Rydel, E.F. Brigham, L.B. Yang, H. Hampei, G.M. Murphy Jr., L. Brachoval, S.D. Yan, D.G. Walker, Y. Shen, J. Rogers, Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro, Glia 35 (2001) 72–79, https://doi.org/10.1002/glia.1072.

[98] L. Tarassishin, H.S. Suh, S.C. Lee, Interferon regulatory factor 3 plays an anti-inflammatory role in microglia by activating the PI3/Akt pathway, J. Neuroinflammation 8 (2011) 187, https://doi.org/10.1186/1742-2094-8-187.

[99] D. Han, Z. Yu, W. Liu, D. Yin, Y. Pu, J. Feng, Y. Yuan, A. Huang, L. Cao, C. He, Plasma Hemopexin ameliorates murine spinal cord injury by switching microglia from the M1 state to the M2 state, Cell Death Dis. 9 (2018) 181, https://doi.org/10.1038/s41419-017-0236-8.

[100] R. Aryanpour, P. Pasbakhsh, K. Zibara, Z. Namjoo, Beigi, F. Boroujeni, S. Shahbeigi, I.R. Kashani, C. Beyer, A. Zendehdel, Progesterone therapy induces an M1 to M2 switch in microglia phenotype and suppresses NLRP3 inflammasome in a cuprizone-induced demyelination mouse model, Int. Immunopharmacol. 51 (2017) 131–139, https://doi.org/10.1016/j.intimp.2017.08.007.

[101] P. Habib, A. Slowik, A. Zendedel, S. Johann, J. Dang, C. Beyer, Regulation of hypoxia-induced inflammatory responses and M1-M2 phenotype switch of primary rat microglia by sex steroids, J. Mol. Neurosci. 52 (2014) 277–285, https://doi.org/10.1007/s12031-013-0137-y.

[102] V. Bodart-Santos, L.R.P. de Carvalho, M.A. de Godoy, A.F. Batista, L.M. Saraiva, L.G. Lima, C.A. Abreu, F.G. De Felice, A. Galina, R. Mendea-Otero, S.T. Ferreira, Extracellular vesicles derived from human Wharton's jelly mesenchymal stem cells protect hippocampal neuron from oxidative stress and synapse damage induced by amyloid-β oligomers, Stem Cell Res Ther 10 (2019) 332, https://doi.org/10.1186/s13287-019-1432-5.

[103] M.A. de Godoy, L.M. Saraiva, L.R.P. de Carvalho, A. Vasconcelos-Dos-Santos, H.J.V. Beiral, A.B. Ramos, L.R.P. Silva, R.B. Leal, V.H.S. Monteiro, C.V. Barga, C.A. de Araujo-Silva, L.C. Sinis, V. Bodart-Santos, T.H. Kasai-Brunswick, C.L. Alcantara, A.P.C.A. Lima, E. da Cunha-, N.L. Silva, A. Galina, A. Vieyra, F.G. De Felice, R. Mendea-Otero, S.T. Ferreira, Mesenchymal stem cells and cell-derived extracellular vesicles protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers, J. Biol. Chem. 293 (2018) 1957–1975, https://doi.org/10.1074/jbc.M117.807180.

[104] L.P. Diniz, V. Tortelli, I. Matias, J. Morgado, Bergamo, A.P. Arauio, H.M. Melo, G.S. Seixas da Silva, S.V. Alves-Leon, J.M. de Souza, S.T. Ferreira, F.G. De Felice, F.C.A. Gomes, Astrocyte transforming growth factor beta 1 protects synapses against Aβ oligomers in Alzheimer's disease model, J. Neurosci. 37 (2017) 6797–6809, https://doi.org/10.1523/JNEUROSCI.3351-16.2017.

[105] J. Pitt, K.C. Wilcox, V. Tortelli, L.P. Diniz, M.S. Oliveira, C. Dobbins, X.W. Yu, S. Nandamuri, F.C.A. Gomes, N. DiNunno, K.L. Viola, F.G. De Felice, S.T. Ferreira, W.L. Klein, Neuroprotective astrocyte-derived insulin/insulin-like growth factor 1 stimulates endocytic processing and extracellular release of neuron-bound Aβ oligomers, Mol. Biol. Cell 28 (2017) 2623–2636, https://doi.org/10.1091/mbc.E17-06-0416.

[106] Y. Wang, C. Li, K. Cheng, R. Zhang, K. Narsinh, X. Li, X. Qin, R. Zhang, C. Li, T. Su, J. Chen, F. Cao, Activation of liver X receptor improves viability of adipose-derived mesenchymal stem cells to attenuate myocardial ischemia injury through TLR4/NF-κB and Kkeap-1/Nrf-2 signaling pathways, Antioxid. Redox Signal. 21 (2014) 2543–2557, https://doi.org/10.1089/ars.2013.5683.

[107] J. Liu, Z. Han, Z. Han, Z. He, Mesenchymal stem cells suppress CaN/NFAT expression in the pulmonary arteries of rats with pulmonary hypertension, Exp. Ther. Med. 10 (2015) 1657–1664, https://doi.org/10.3892/etm.2015.2722.

[108] Kwa, J., Choi, S.J., Oh, W., Yang, Y.S., Jeon, H.B., Jeon E.S., Cobalt chloride enhances the anti-inflammatory potency of human umbilical cord blood-derived mesenchymal stem cells through the ERK-HIF-1α-MicroRNA-146a-mediated signaling pathway. Stem Cells Int. 2018, 4978763, doi:https://doi.org/10.1155/2018/4978763 (2018).

[109] N.M. Novotny, T.A. Maret, P.R. Crisostomo, D.R. Meldrum, Differetial IL-6 and VEGF secretion in adult and neonatal mesenchymal stem cells: role of NFκB, Cytokine 43 (2008) 215–219, https://doi.org/10.1016/j.cyto.2008.05.015.

[110] P.R. Crisostomo, Y. Wang, T.A. Marel, M. Wang, T. Lahm, D.R. Meldrum, Human mesenchymal stem cells stimulated by TNF-alpha, LPS, or hypoxia produce growth factors by an NF kappa B- but not JNK-dependent mechanism, Am. J. Physiol. Cell Physiol. 294 (2008) C675–C682, https://doi.org/10.1152/ajpcell.00437.2007.