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Astrocytes in Pathogenesis of Multiple Sclerosis and Potential Translation into Clinic

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Abstract

Astrocytes are the most abundant glial cells in the central nervous system (CNS) and play a pivotal role in CNS homeostasis and functionality. Malfunction of astrocytes was implicated in multiple neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and multiple sclerosis (MS). The involvement of astrocytes in the pathology of neurodegenerative disorders supports the rationale of transplantation of healthy human astrocytes that can potentially compensate for diseased endogenous astrocytes. In this review, we will focus on the roles of astrocytes in the healthy CNS and under MS conditions. We will describe the cell sources and current cell-based therapies for MS with a focus on the potential of astrocyte transplantation. In addition, we will cover emerging early-stage clinical trials in MS that are currently being conducted using cell-based therapies.

Keywords: astrocytes, multiple sclerosis, neurodegenerative diseases, autologous hematopoietic stem cells (AHSC), mesenchymal stem cells (MSC)

1. Multiple sclerosis

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and degenerative disease of the CNS. The disease leads to permanent neurological disability, including limb weakness, sensory loss, vision disturbances, pain, and muscle spasms [1]. MS is affecting more than 2 million people worldwide, most of them are females between the age of 20 and 40 years. The most prevalent clinical course of the disease (approximately 80% of the cases) is relapsing-remitting MS (RRMS), characterized by a period of functional disability (relapses) and followed by spontaneous improvements (remissions) [1]. With the progression of the disease, most of the patients will develop a course of secondary progressive MS (SPMS), characterized by a steady decline in neurological function, with no phases of remissions [2]. A less common form of MS is primary progressive MS (PPMS), representing approximately 10% of MS cases. PPMS is characterized by a development of gradual progressive disease with no remission phases [2, 3]. Currently, 15 disease-modifying treatments (DMTs) are approved by the FDA for the treatment of MS [4]. The mechanisms of action of these DMTs are diverse; however, they all aim to modulate or suppress the immune system. The current DMTs have benefit in reducing frequency and severeness of relapses and buildup of disability in RRMS; nevertheless, they have only limited impact on the progressive forms of MS [2, 5, 6].

2. Astrocytes in the naive CNS

Although the major players in the onset and development of MS are immune cells, oligodendrocytes, and neurons, astrocytes also play a crucial role in all stages of the pathogenesis of the disease [7]. Astrocytes are the most abundant glial cells in the CNS, making at least 30% of its cell mass in mammals, having a pivotal role in maintaining the physiologic functions in the CNS [8–10]. Astrocytes can be classified based on their morphological and structural characteristics into two subtypes, namely, protoplasmic and fibrous. Protoplasmic astrocytes are widely distributed in the gray matter, extending processes from their soma to neurons and blood vessels [11]. Their extended end feet are associated with blood vessels to form the glial limiting membrane of the blood-brain barrier (BBB). They also interact with synapses and play an important role in modulation of synaptic functions and uptake of glutamate [12–14]. Conversely, fibrous astrocytes have a starlike appearance, and they are found mainly in the white matter, sending long and thin processes through axonal bundle [15]. Fibrous astrocytes express higher levels of the intermediate filament glial fibrillary acidic protein (GFAP) as compared to protoplasmic astrocyte. Despite the differences in morphology and distribution, both subtypes of astrocytes share many similar functions [16–18].

Astrocytes provide functional support to neurons by maintaining levels of glutamate, extracellular ions, energetic metabolism, pH, and water homeostasis [10, 19]. Astrocytes are also involved in the creation, elimination, and modulation of synapses [20–22]. They modulate the synaptic transmission of neurons by the formation of tripartite synapses that regulate the release of neurotransmitters such as glutamate, d-serine, and gamma-aminobutyric acid (GABA) and by buffering extracellular potassium ions [23–26]. They can also regulate synaptic activity by uptake of neurotransmitters from the synaptic cleft [27, 28]. Astrocytes are important in maintaining the survival of neurons in the CNS, as they secrete neurotrophic and neuroprotective factors such as glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) that directly support neuronal survival [29, 30]. Astrocytes play a pivotal role in formation and maintenance of the blood-brain barrier (BBB), a highly selective physical border that separates the CNS parenchyma from blood circulation through extension of processes of an end-foot membrane that surrounds CNS capillaries [31]. The end-foot membrane contains the channel protein aquaporin-4 (AQP4) and the gap junction protein connexin 43 (Cx43) that allow astrocytes to tightly regulate the selective exchange of water-soluble molecules and ions with blood vessels [32]. In a healthy state, astrocytes constitutively secrete low basal levels of the anti-inflammatory cytokines including transforming growth factor- β (TGF- β) [33] and interleukin-10 (IL-10) [34] to maintain a stable noninflammatory environment. In an inflammatory state, astrocytes change the permeability of the BBB by releasing cytokines such as IL-6, IL-1 β , and tumor necrosis factor- α (TNF- α), specifically acting on the endothelial tight junctions of the BBB [35–37]. The close vicinity to blood vessels also allows astrocytes to transfer glucose from the blood to neurons as a source of energy [38]. Astrocytes can also protect neurons from oxidative stress by secretion of antioxidants, such as glutathione and thioredoxin to their coupled neurons [39, 40].

3. Reactive astrocytes

Activation of astrocytes, known also as astrogliosis, is a process that is characterized by proliferation of astrocytes, accompanied by profound morphological

and functional changes [41]. Astrocytes become active in response to changes in the CNS homeostasis or under pathological conditions. Cues that lead to astrogliosis include (i) CNS injury that causes the release of damage-associated molecular patterns (DAMPs), (ii) pro-inflammatory cytokines in response to damaged CNS tissue, (iii) pathogen-associated molecular patterns (PAMPs) produced by microbial infection, and (iv) oxidative or chemical stress [42–44]. Although all reactive astrocytes share similar attributes, they can still be distinguished by two different phenotypes, A1 and A2, resembling the M1/M2 states of macrophages [45]. The A1 astrocytes are neurotoxic and induced in response to inflammatory microglia, e.g., those found in neurodegenerative disease such as Huntington's disease (HD) and Parkinson's disease (PD) but also in MS [45, 46]. The A2 reactive astrocytes are formed in response to ischemic damage and, in contrast to the A1-type astrocytes, exhibit anti-inflammatory properties and secrete neurotrophic factors such as BDNF and nerve growth factor (NGF) [93, 45]. Yet, the definition of these two types of reactive astrocytes may be quite elusive, as intermediate phenotypes with mixed characteristics of A1/A2 states were also observed [41]. A1 and A2 astrocytes can appear during different phases of a pathological process and sometimes may even coexist. Their distinct functions allow to attract microglia and T cells by A1 astrocytes at the first stages of the pathology and to support tissue repair by inhibiting inflammation and secreting neurotrophic factors at a later recovery stage [41].

Depending on the severity of the injury, astrogliosis can lead to the formation of a glial scar. The glial scar isolates the inflamed area, restricts the damage to the lesion, and provides structural support to the CNS parenchyma [16]. Based on their environmental cues, reactive astrocytes produce pro- and anti-inflammatory cytokines including IL-1, IL-6, TNF- α , IL-10, and TGF- β [47]. They can also attract circulating leukocytes by secreting chemokines such as CXCL8, CXCL10, CCL2, CCL5, and CCL20 from their end feet at the surface membrane of blood vessels of the BBB [47–49]. Reactive astrocytes also present cell adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1), which are important for migration of T cells [50]. Reactive astrocytes can also protect neurons by secretion of neurotrophic factors such as NGF, BDNF, GDNF, and VEGF [51–53]. Although the morphology and activities of reactive astrocytes are well defined, there is no exclusive marker that clearly distinguishes between reactive and nonreactive astrocytes. The major marker of astrogliosis is the intermediate filament GFAP, which is abundant in all astrocyte populations but upregulated upon activation. However, the functional contribution of GFAP in the activation process is still not clear yet [54]. In addition to GFAP, expression of other astrocytic markers is also upregulated in reactive astrocytes, including glutamine synthetase 1, aldehyde dehydrogenase 1 (ALDH1), and S100 β [55, 56].

4. Reactive astrocytes in MS

Astrocytes are involved in all stages of the formation and development of the plaques in MS. Their contribution starts already at a very early stage of the lesion, before demyelination is actually seen [57].

Lesions in MS can be classified in four categories.

- i. Early pre-active lesions do not show demyelination damage yet. However, the presence of reactive astrocytes and microglia is the indication for a development of pathological process in the area [58]. Studies in experimental

autoimmune encephalomyelitis (EAE) mice suggest that activation of astrocytes can actually occur even before the immune cells cross the BBB into the CNS parenchyma [59].

- ii. Active-acute lesions contain hypertrophic astrocytes with enlarged soma and processes comprising high levels of GFAP filaments. In the active-acute plaque, the astrocytes are in close proximity to oligodendrocytes, probably interacting with them. Although the nature of this oligodendrocyte-astrocyte interaction is not completely understood [60–62], it is suggested that astrocytes clear debris of myelin by phagocytosis [63]. Reactive astrocytes in MS may also lose their surface contact with blood vessels of the BBB, enhancing the infiltration of leukocytes to the CNS [57]. The hypertrophic astrocytes also recruit T cells, macrophages, and microglia to the lesion by expressing a set of cell adhesion molecules and chemokines such as ICAM-1 and CCL2 [64–67].
- iii. Active-chronic lesions contain a plaque core with a profound active demyelination, which is accompanied by remyelination activity and infiltration of immune cells, especially at the periphery of the lesion. Astrocytes in this type of lesions can be of either A1 or A2 types, and it is suggested that they contribute to the clearance of tissue debris from damaged areas and protect remaining intact regions [45].

In the lesion, reactive astrocytes produce matrix metalloproteinases (MMP), extracellular matrix-remodeling proteins, that changes BBB permeability, allowing immune cell infiltration to the CNS parenchyma and thus inhibiting repair processes [68]. On the other hand, reactive astrocytes also secrete tissue inhibitors of metalloproteinases (TIMPs) in the lesioned area that inhibit the activity of MMPs, help to stabilize BBB permeability, and eventually to promote remyelination [69–71]. Thus, the balance between TIMP and MMP expression can influence the ratio between demyelination and remyelination.

Reactive astrocytes in MS also express a variety of trophic factors that mediate protective and repairing processes in the lesion. Examples of neurotrophic factors which are secreted by astrocytes include neuroprotective factors such as *vascular endothelial growth factor* (VEGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), and insulin-like growth factor-1 (IGF-1) [72, 73]. Reactive astrocytes secrete the cytokine IL-6 that, in addition to its pro-inflammatory activity, also promotes remyelination and neuroprotection [74, 75].

- iv. Inactive lesions contain astrocytes with a small cytoplasm and elongated thin processes. The astrocytes in the inactive lesion are rich in GFAP and form a glial scar around the core of the plaque, while occasionally they can be found also within the core [76].

With the progression of MS pathogenesis, reactive hypertrophic astrocytes form a glial scar, which is the most severe grade of astrogliosis, around the core of the demyelinated plaque [10]. The astrocytes in the glial scar form a compact structure that is held by tight junctions on their filament-rich processes [77, 78]. The scar primarily serves as a physical barrier surrounding the demyelinated area, and this prevents widespread of the damage to the surrounding parenchyma [79, 80]. The glial scar also maintains the structure of the BBB, provides structural support, and prevents immune cell infiltration [10, 57]. The glial scar is generally considered as a non-supporting environment for remyelination

since it prevents oligodendrocyte progenitor cells (OPCs) from approaching the demyelinated axons surrounded by the glial scar [81, 82].

5. Cell-based therapy

Currently, the available DMTs for MS focus on targeting inflammation processes. These therapies can be divided into two main groups: drugs for the treatment of acute relapses (corticosteroids) [83] and drugs which affect the course of the disease [84]. The second group can be further subdivided into immunosuppressive drugs (e.g., methotrexate and mitoxantrone) and drugs with immunomodulatory activity (e.g., interferon- β [84] and antibodies) [85]. Although these treatments are effective in treating relapsing-remitting MS (RRMS), they show no significant therapeutic benefits in the progressive forms of the disease. A new therapeutic approach with a dual mode of action that is based on tissue repair in addition to immunomodulation has an enormous potential to further attenuate the progression of the disease and to prevent the transition to the progressive course. Cell-based therapies might serve as promising candidates for such a therapy.

The mechanisms of action (MOA) by which therapeutic cells can exert their activities in the CNS include (i) secretion of neurotrophic factors that promote neuronal survival and outgrowth, (ii) reduction of oxidative stress in lesioned areas, (iii) clearance of toxic factors from the CNS environment, (iv) promotion of remyelination, and (v) immunomodulation. In this context, astrocytes hold a promising therapeutic potential, as they share these mechanisms of action [86].

During the last two decades, cell-based therapies from different cell sources were tested in EAE models, and some of them have been further evaluated in clinical trials.

6. Sources of cells for treatment of MS

6.1 Autologous hematopoietic stem cell (AHSC)

Increasing scientific evidence demonstrate that antigen-specific immune response mediates the inflammation process in MS. The immune milieu that depicts MS inflammation include (i) immunoglobulins (oligoclonal Igs) that are found in the CSF of the majority of MS patients, but not in their serum [87]; (ii) common clonal T-cell populations in the peripheral blood, cerebrospinal fluid (CSF), and CNS parenchyma [88]; (iii) MHC class II HLA-DRB1 that plays a role in the development of MS [89, 90]; and (iv) specific T-cell receptor (TCR) repertoire in distinct lesions as found in postmortem brains of MS patients [91]. Silent nucleotide exchanges within the V-CDR3-J region of TCR suggest that the corresponding T-cell clones were recruited and stimulated by particular antigens. It was demonstrated that some of the pervasive T-cell clones belonged to the CD8⁺ compartment, supporting the pathogenic relevance of this T-cell subset [88, 91, 92]. Studies in EAE models and the presence of Th1 and Th17 cells contributed to the notion that self-reactive lymphocytes induce inflammation in response to myelin epitopes [93–95].

One of the approaches to reset the immune system in MS is to use a myeloablative protocol and transplant autologous hematopoietic stem cells (AHSC) similarly to those used in hematologic malignancies [96, 97]. However, immunoablation and reconstitution of the immune system that reset the autoreactive immunoinflammatory process and restore self-tolerance are still considered as an intensive approach as compared to the current DMTs in MS [97, 98].

6.1.1 Clinical data

One explanation for the therapeutic effect by autologous hematopoietic stem cell transplantation (AHSCT) is reset of the immune system by immune reconstitution following their transplantation. This effect is obtained through deletion of pathogenic clones by a combination of direct ablation and induction of a lymphopenic state. Another explanation might be that the immunosuppression regimen depletes T-cell populations for a long period. AHSCT therapy after immunoablation has been studied for the last 20 years [98]. The results of thousands of patients who have received AHSCT for different types of MS were collected by international transplant registries and showed benefits in a subset of patients with highly active relapsing forms of MS. For instance, recently, a study that was performed in 110 RRMS patients who received AHSCT along with cyclophosphamide (immunosuppressant) and anti-thymocyte globulin, or disease-modifying treatments, was found to prolong the time to disease progression. In the first year, mean of expanded disability status scale (EDSS) scores decreased (improved) from 3.38 to 2.36 in the AHSCT group and increased (worsened) from 3.31 to 3.98 in the DMT group [99]. Other recent trials in MS, mainly in RRMS [99–102], demonstrated a degree of disease stabilization after AHSCT. In addition, recent publications showed a sustained disease remission following AHSCT in a subset of patients with highly active inflammatory disease [103].

The process of immunoablation and reconstitution of the immune system is complicated and includes multiple steps: mobilization of hematopoietic stem cells (HSC), collection and preservation of CD34+ HSCs, immunoablative conditioning, infusion of HSCs, and posttransplant care [104]. It is important to note that immunoablation strategies are also associated with infertility and short-term higher rate of cerebral atrophy that might lead to neurological disability, and hence optimizing treatment regimen is required in order to minimize mortality and morbidity. In addition, this treatment was not found effective for the treatment of primary or secondary progressive MS [105].

6.2 Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent, non-hematopoietic, stromal cells that can differentiate into mesodermal lineage including osteoblasts, chondrocytes, and adipocytes as well as into ectodermal cells (neurons and glia) and endodermal cells (hepatocytes) [106, 107]. Typically, the bone marrow is used as the source of MSCs. These bone marrow stem cells do not contribute to the formation of blood cells and do not express the hematopoietic stem cell marker CD34 [108]. Alternative tissues that can be used as a source for MSCs include umbilical cord cells that consist of young and most primitive MSCs, adipose tissue, developing tooth bud (molar cells), and the amniotic fluid [109–111]. MSCs present immunomodulatory properties such as activation of regulatory T cells, maturation of dendritic cells, suppression of B- and T-cell proliferation, and inhibition of natural killer functionality. The hypothesis is that the immunomodulatory effect is mediated by paracrine signals and homing of MSCs to the damaged area [112]. Injection of MSCs to EAE animal models demonstrated a slowdown in disease progression, lesser immune cell infiltration, and a decline in demyelination and axonal damage [113, 114]. MSCs were found to possess immunomodulatory effect when administered intraventricular (IVT), intravenously (IV), intrathecally (IT), and intraperitoneally (IP) [113, 115, 116].

6.2.1 Clinical data

In 2007, Mohyeddin et al. were the first to publish their clinical results using MSCs for treatment of MS [117]. The aim of the study was to evaluate the safety and therapeutic potential of autologous MSCs to ameliorate clinical manifestations in MS patients. In this study, 10 MS patients were injected intrathecally with MSCs. The results of the study showed that the use of MSCs is safe, but no significant clinical benefits were observed. In order to provide MSCs with neuromodulatory properties, in addition to their immunomodulatory properties, a few groups differentiated the MSCs into neural-like cells or glial-like cells that secrete neurotrophic factors. IT transplantation of these autologous cells to MS patients demonstrated their safety profile and tolerability [118–120]. Recently, Harris et al. [121] also reported that IT injection of neural-like cells derived from MSCs was safe and well tolerated. The 20 subjects in the clinical trial completed all 60 planned treatments without having serious adverse events. The minor adverse events included transient fever and mild headaches. Posttreatment disability score analysis demonstrated improvement in median EDSS. The beneficial affect was greater in a subset of SPMS patients and in ambulatory subjects ($\text{EDSS} \leq 6.5$). In addition, 70 and 50% of the subjects demonstrated improved muscle strength and bladder function, respectively [121].

6.3 Neural stem cells and oligodendrocyte precursor cells

In the recent years, clinical trials using cell therapies in MS patients were mainly based on autologous transplantation of MSCs and AHSCs [122]. While showing promising clinical effects, the transplantation of autologous cells is limited to the donor. It would therefore be advantageous to develop allogeneic cell treatments as shelf-products that could be used for large populations of patients. In addition, the potential therapeutic effect of AHSCs and MSCs on MS is mostly mediated through immunomodulatory cues. Finding a cell source that triggers remyelination and tissue, in addition to immunosuppression properties, has a great DMT potential. Neural stem cells (NSCs) can migrate to demyelinated areas and differentiate into neurons and glial-restricted cells (i.e., oligodendrocytes and astrocytes) [7]. NSCs can differentiate to oligodendrocytes that can potentially remyelinate demyelinated axons in MS [123]. The benefits of NSCs might arise not only from their potential to differentiate into oligodendrocytes but also from their capacity to differentiate into astrocytes and neurons, the former having neurotrophic and immunomodulatory properties [86, 123]. Endogenous NSCs are found in germinal niches, such as the subgranular zone (SGZ) of the dentate gyrus and subventricular zone (SVZ) of the lateral ventricles [124, 125]. These NSCs play a pivotal role in early stages of MS, but fail to do so in later stages of the disease. Thus, replenishing endogenous NSCs with allogeneic NSCs has a great therapeutic potential. Transplantation of NSCs in EAE animal models demonstrated that the cells can migrate into inflamed white matter plaques and differentiate into oligodendrocytes [126, 127]. Another study showed that transplantation of NSCs derived from induced-pluripotent stem cells (iPSCs) reduced T-cell infiltration as well as white matter damage [128]. To date, no clinical trial in MS evaluated NSCs in MS. A few groups used pluripotent stem cells (human embryonic stem cells or induced-pluripotent stem cells) as a source for neural lineage following an in vitro differentiating protocol [129]. Transplanted hESC-derived NSCs in EAE MS animal models demonstrated neuroprotective and immunosuppressive effect; however, remyelination was not observed [127, 130]. Another study showed that transplantation of iPSC-derived NSCs to

EAE model significantly reduced infiltration of T cells to the lesion and reduced demyelination areas. Consistent with this histopathological improvement, the clinical score of the disease was also rescued in the iPSC-NSC-treated group of mice [128]. Transplantation of hESC-derived OPCs (A2B5⁺) demonstrated that these cells remyelinate brains of shiverer mice and partially rescue their clinical deficiencies [131–133]. The platelet-derived growth factor α receptor (PDGFR)-positive OPCs presented even a greater myelinogenic potential [134, 135]. Similarly, intracortical implantation of iPSC-derived OPCs to a nonhuman primate model of progressive multiple sclerosis (MS) showed that the cells can migrate to the lesions and remyelinate denuded axons [136].

6.4 Astrocyte progenitor cells

As discussed above, astrocytes have multiple roles in maintaining the homeostasis of the CNS. Some of the mechanisms of action, which are crucial for the maintenance of the CNS, are postulated to contribute also to the treatment in MS. The diverse modes of action of astrocytes may be more effective in treating MS compared to a single pathway-based drug. Transplantation of healthy astrocytes was proven effective in other neurodegenerative diseases such as ALS [137, 138]. In ALS animal model, it was shown that intrathecal injections of human astrocytes significantly delayed disease onset and improved motor performance compared to sham-injected animals. In this study, the astrocytes were found to secrete various neurotrophic factors and decrease glutamate neurotoxicity [138]. In spinal cord injury (SCI) model, it was demonstrated that transplantation of human astrocytes promotes functional recovery [139–141]. In addition, transplantation of subtype of astroglia was found to possess protective effects against ischemic brain injury [142, 143].

There are several cell sources for human astrocytes. Glial-restricted progenitors (GRPs) represent early cell population of the CNS that can self-renew and give rise to astrocytes and oligodendrocytes. GRPs can be isolated from human fetal tissues [144]. In vivo transplantation of human GRPs into the spinal cord-injured animals showed that the cells can survive and differentiate into astrocytes [139, 140]. However, human astrocytes from primary brain tissue, obtained from cadaveric donors, are challenging due to limited availability and robustness.

Other sources for derivation of astrocytes include pluripotent stem cells (PSC) such as embryonic stem cells and induced-pluripotent stem cells (iPSCs) [145]. These sources potentially provide unlimited supply of cells for clinical use. Methods for producing neural precursor cells from PSCs and their further differentiation into glial lineage were demonstrated in pioneering studies in animal models of neurodevelopment. In these studies, the key steps for neural commitment in vivo were identified and recapitulated in a stepwise process in culture. Specific commitment of pluripotent stem cells toward astrocytes can be achieved using factors such as sonic hedgehog (SHH), Wnt proteins, fibroblast growth factors (FGFs), epidermal growth factors (EGFs), retinoic acid (RA), and bone morphogenetic protein (BMP) [146–150]. Most recently, direct-reprogramming approaches of somatic cells into neural cells and astrocytes, including transduction of specified transcription factors or by using a combination of defined chemical, have been reported [151]. Caiazzo et al. [152] described a conversion of mouse fibroblast into astrocytes (iAstrocytes), which are comparable to endogenous astrocytes. This was carried out by transducing the transcription factors *nuclear factors* IA and IB (NFIA, NFIB) and SOX9. Another approach for direct conversion or reprogramming of mammalian fibroblasts into astrocytes is by culturing the cells in the presence of a cocktail of small molecules that includes histone deacetylase inhibitor VPA, TGF β , and GSK3 β inhibitor CHIR99021, among other factors [153].

7. Conclusions

MS is a multifactorial disease involving dysregulation of molecular pathways and immunomodulatory processes. Transplantation of healthy functional cells that can affect the CNS via diverse mechanisms of action that work in parallel such as anti-inflammatory, immunomodulatory, clearance of the toxic environment, secretion of neurotrophic factors, and triggering remyelination has great therapeutic potential in treating multiple sclerosis. Yet, bringing new cell-based therapies to the clinic faces a few challenges, e.g., what is the optimal injection site in the CNS, and what cell dose will be effective? In MS the demyelinated lesions are spread throughout the CNS, and it is still not clear whether the transplanted cells have long-distance migratory capacity to reach these plaques from their injection site. Once the cells reach to lesion, it is still questionable whether they can remyelinate axons under a hostile inflammatory environment. Finally, the safety profile of transplanted cells and their long-term tumorigenic potential should be further tested.

Abbreviations

AD	Alzheimer’s disease
AHSC	autologous hematopoietic stem cell
ALDH1	aldehyde dehydrogenase
ALS	amyotrophic lateral sclerosis
AQP4	aquaporin-4
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BMP	bone morphogenetic protein
CCL2	chemokine C-C motif ligand
CNS	central nervous system
CSF	cerebrospinal fluid
Cx43	connexin 43
CXCL	chemokine C-X-C motif ligand
DAMP	damage-associated molecular pattern
DMT	disease-modifying treatment
EAE	experimental autoimmune encephalomyelitis
EDSS	expanded disability status scale
EGF	epidermal growth factor
FGF	fibroblast growth factor
GABA	gamma-aminobutyric acid
GDNF	glial cell line-derived neurotrophic factor
GFAP	glial fibrillary acidic protein
HD	Huntington’s disease
HSC	hematopoietic stem cells
ICAM-1	intercellular adhesion molecule 1
IGF-1	insulin-like growth factor-1
IL	interleukin
IP	intraperitoneally
iPSC	induced-pluripotent stem cell
IT	intrathecally
IV	intravenously
IVT	intraventricular
MMP	matrix metalloproteinases
MOA	mechanisms of action

MS	multiple sclerosis
MSC	mesenchymal stem cells
NFI	nuclear factor I
NGF	nerve growth factor
NSC	neural stem cell
NT-3	neurotrophin-3
PAMP	pathogen-associated molecular pattern
PD	Parkinson's disease
PPMS	primary progressive multiple sclerosis
PSC	pluripotent stem cell
RA	retinoic acid
RRMS	relapsing-remitting multiple sclerosis
SCI	spinal cord injury
SGZ	sub granular zone
SHH	sonic hedgehog
SPMS	secondary progressive multiple sclerosis
SVZ	subventricular zone
TCR	T-cell receptor
TGF- β	transforming growth factor- β
TIMP	tissue inhibitors of metalloproteinases
TNF- α	tumor necrosis factor- α
VCAM-1	vascular cell adhesion protein 1
VEGF	vascular endothelial growth factor

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References

- [1] Kobelt G et al. New insights into the burden and costs of multiple sclerosis in Europe. *Multiple Sclerosis*. 2017;**23**(8):1123-1136
- [2] Lublin FD et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. 2014;**83**(3):278-286
- [3] Polman CH et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*. 2011;**69**(2):292-302
- [4] Cree BAC, Mares J, Hartung HP. Current therapeutic landscape in multiple sclerosis: An evolving treatment paradigm. *Current Opinion in Neurology*. 2019;**32**(3):365-377
- [5] Wingerchuk DM, Carter JL. Multiple sclerosis: Current and emerging disease-modifying therapies and treatment strategies. *Mayo Clinic Proceedings*. 2014;**89**(2):225-240
- [6] Kutzelnigg A, Lassmann H. Pathology of multiple sclerosis and related inflammatory demyelinating diseases. *Handbook of Clinical Neurology*. 2014;**122**:15-58
- [7] Fitzner D, Simons M. Chronic progressive multiple sclerosis: Pathogenesis of neurodegeneration and therapeutic strategies. *Current Neuropharmacology*. 2010;**8**(3):305-315
- [8] Lundgaard I et al. White matter astrocytes in health and disease. *Neuroscience*. 2014;**276**:161-173
- [9] Barres BA. The mystery and magic of glia: A perspective on their roles in health and disease. *Neuron*. 2008;**60**(3):430-440
- [10] Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. *Acta Neuropathologica*. 2010;**119**(1):7-35
- [11] Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: Redefining the functional architecture of the brain. *Trends in Neurosciences*. 2003;**26**(10):523-530
- [12] Olie SH, Piet R, Poulain DA. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. *Science*. 2001;**292**(5518):923-926
- [13] Rothstein JD et al. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron*. 1996;**16**(3):675-686
- [14] Henneberger C et al. Long-term potentiation depends on release of D-serine from astrocytes. *Nature*. 2010;**463**(7278):232-236
- [15] Butt AM, Duncan A, Berry M. Astrocyte associations with nodes of Ranvier: Ultrastructural analysis of HRP-filled astrocytes in the mouse optic nerve. *Journal of Neurocytology*. 1994;**23**(8):486-499
- [16] McKinnon PJ, Margolskee RF. SC1: A marker for astrocytes in the adult rodent brain is upregulated during reactive astrogliosis. *Brain Research*. 1996;**709**(1):27-36
- [17] Brown AM, Ransom BR. Astrocyte glycogen and brain energy metabolism. *Glia*. 2007;**55**(12):1263-1271
- [18] Marin-Padilla M. Prenatal development of fibrous (white matter), protoplasmic (gray matter), and layer I astrocytes in the human cerebral cortex: A Golgi study. *The Journal of Comparative Neurology*. 1995;**357**(4):554-572

- [19] Browne EC, Abbott BM. Recent progress towards an effective treatment of amyotrophic lateral sclerosis using the SOD1 mouse model in a preclinical setting. *European Journal of Medicinal Chemistry*. 2016;**121**:918-925
- [20] Fields RD. Oligodendrocytes changing the rules: Action potentials in glia and oligodendrocytes controlling action potentials. *The Neuroscientist*. 2008;**14**(6):540-543
- [21] Hong S et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*. 2016;**352**(6286):712-716
- [22] Adamsky A et al. Astrocytic activation generates de novo neuronal potentiation and memory enhancement. *Cell*. 2018;**174**(1):59-71 e14
- [23] Bezzi P, Volterra A. A neuron-glia signalling network in the active brain. *Current Opinion in Neurobiology*. 2001;**11**(3):387-394
- [24] Ventura R, Harris KM. Three-dimensional relationships between hippocampal synapses and astrocytes. *The Journal of Neuroscience*. 1999;**19**(16):6897-6906
- [25] Santello M, Volterra A. Neuroscience: Astrocytes as aide-memoires. *Nature*. 2010;**463**(7278):169-170
- [26] Sun W et al. Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. *Science*. 2013;**339**(6116):197-200
- [27] Kang J et al. Astrocyte-mediated potentiation of inhibitory synaptic transmission. *Nature Neuroscience*. 1998;**1**(8):683-692
- [28] Haydon PG. Neuroglial networks: Neurons and glia talk to each other. *Current Biology*. 2000;**10**(19):R712-R714
- [29] Ludwin SK et al. Astrocytes in multiple sclerosis. *Multiple Sclerosis*. 2016;**22**(9):1114-1124
- [30] Magistretti PJ. Neuron-glia metabolic coupling and plasticity. *The Journal of Experimental Biology*. 2006;**209**(Pt 12):2304-2311
- [31] Iliff JJ et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Science Translational Medicine*. 2012;**4**(147):147ra111
- [32] Brambilla R. The contribution of astrocytes to the neuroinflammatory response in multiple sclerosis and experimental autoimmune encephalomyelitis. *Acta Neuropathologica*. 2019;**137**(5):757-783
- [33] John GR, Lee SC, Brosnan CF. Cytokines: Powerful regulators of glial cell activation. *The Neuroscientist*. 2003;**9**(1):10-22
- [34] Cannella B, Raine CS. The adhesion molecule and cytokine profile of multiple sclerosis lesions. *Annals of Neurology*. 1995;**37**(4):424-435
- [35] Kim JH et al. Blood-neural barrier: Intercellular communication at glio-vascular interface. *Journal of Biochemistry and Molecular Biology*. 2006;**39**(4):339-345
- [36] Didier N et al. Secretion of interleukin-1beta by astrocytes mediates endothelin-1 and tumour necrosis factor-alpha effects on human brain microvascular endothelial cell permeability. *Journal of Neurochemistry*. 2003;**86**(1):246-254
- [37] Schwaninger M et al. Bradykinin induces interleukin-6 expression in astrocytes through activation of nuclear factor-kappa B. *Journal of Neurochemistry*. 1999;**73**(4):1461-1466

- [38] Villarroya H et al. Myelin-induced experimental allergic encephalomyelitis in Lewis rats: Tumor necrosis factor alpha levels in serum and cerebrospinal fluid immunohistochemical expression in glial cells and macrophages of optic nerve and spinal cord. *Journal of Neuroimmunology*. 1996;**64**(1):55-61
- [39] Masutani H et al. Thioredoxin as a neurotrophic cofactor and an important regulator of neuroprotection. *Molecular Neurobiology*. 2004;**29**(3):229-242
- [40] Anderson CM, Bergher JP, Swanson RA. ATP-induced ATP release from astrocytes. *Journal of Neurochemistry*. 2004;**88**(1):246-256
- [41] Pekny M et al. Astrocytes: A central element in neurological diseases. *Acta Neuropathologica*. 2016;**131**(3):323-345
- [42] Rothhammer V, Quintana FJ. Control of autoimmune CNS inflammation by astrocytes. *Seminars in Immunopathology*. 2015;**37**(6):625-638
- [43] Jensen CJ, Massie A, De Keyser J. Immune players in the CNS: The astrocyte. *Journal of Neuroimmune Pharmacology*. 2013;**8**(4):824-839
- [44] Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. *Trends in Immunology*. 2007;**28**(3):138-145
- [45] Liddelow SA, Barres BA. Reactive astrocytes: Production, function, and therapeutic potential. *Immunity*. 2017;**46**(6):957-967
- [46] Liddelow SA et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;**541**(7638):481-487
- [47] Dong Y, Benveniste EN. Immune function of astrocytes. *Glia*. 2001;**36**(2):180-190
- [48] Williams WM et al. Do beta-defensins and other antimicrobial peptides play a role in neuroimmune function and neurodegeneration? *Scientific World Journal*. 2012;**2012**:905785
- [49] Mahida YR, Cunliffe RN. Defensins and mucosal protection. *Novartis Foundation Symposium*. 2004;**263**:71-77; discussion 77-84, 211-218
- [50] Lee SJ, Benveniste EN. Adhesion molecule expression and regulation on cells of the central nervous system. *Journal of Neuroimmunology*. 1999;**98**(2):77-88
- [51] Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. *Trends in Neurosciences*. 2009;**32**(12):638-647
- [52] Gimenez MA, Sim JE, Russell JH. TNFR1-dependent VCAM-1 expression by astrocytes exposes the CNS to destructive inflammation. *Journal of Neuroimmunology*. 2004;**151**(1-2):116-125
- [53] Ransohoff RM, Kivisakk P, Kidd G. Three or more routes for leukocyte migration into the central nervous system. *Nature Reviews. Immunology*. 2003;**3**(7):569-581
- [54] Korfias S et al. Serum S-100B protein as a biochemical marker of brain injury: A review of current concepts. *Current Medicinal Chemistry*. 2006;**13**(30):3719-3731
- [55] Khakh BS, Sofroniew MV. Diversity of astrocyte functions and phenotypes in neural circuits. *Nature Neuroscience*. 2015;**18**(7):942-952
- [56] Yang Y et al. Molecular comparison of GLT1+ and ALDH1L1+ astrocytes *in vivo* in astroglial reporter mice. *Glia*. 2011;**59**(2):200-207

- [57] Brosnan CF, Raine CS. The astrocyte in multiple sclerosis revisited. *Glia*. 2013;**61**(4):453-465
- [58] Alvarez JI et al. Focal disturbances in the blood-brain barrier are associated with formation of neuroinflammatory lesions. *Neurobiology of Disease*. 2015;**74**:14-24
- [59] Pham H et al. The astrocytic response in early experimental autoimmune encephalomyelitis occurs across both the grey and white matter compartments. *Journal of Neuroimmunology*. 2009;**208**(1-2):30-39
- [60] Victor J et al. Pharmacokinetics and efficacy of delayed-action hydroquinidine in patients with ventricular extrasystole. *Annales de cardiologie et d'angéiologie (Paris)*. 1987;**36**(3):163-166
- [61] Popiela A, Zdrojewicz Z, Kasiak J. Clinical problems related to postmenopausal osteoporosis. *Polski Tygodnik Lekarski*. 1991;**46**(30-31):568-570
- [62] Ludwin SK. An autoradiographic study of cellular proliferation in remyelination of the central nervous system. *The American Journal of Pathology*. 1979;**95**(3):683-696
- [63] Skripuletz T et al. Astrocytes regulate myelin clearance through recruitment of microglia during cuprizone-induced demyelination. *Brain*. 2013;**136**(Pt 1):147-167
- [64] Bullard DC et al. Intercellular adhesion molecule-1 expression is required on multiple cell types for the development of experimental autoimmune encephalomyelitis. *Journal of Immunology*. 2007;**178**(2):851-857
- [65] Sorensen TL et al. Expression of specific chemokines and chemokine receptors in the central nervous system of multiple sclerosis patients. *The Journal of Clinical Investigation*. 1999;**103**(6):807-815
- [66] Ponath G et al. Myelin phagocytosis by astrocytes after myelin damage promotes lesion pathology. *Brain*. 2017;**140**(2):399-413
- [67] Kim RY et al. Astrocyte CCL2 sustains immune cell infiltration in chronic experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology*. 2014;**274**(1-2):53-61
- [68] Gardner J, Ghorpade A. Tissue inhibitor of metalloproteinase (TIMP)-1: The TIMPed balance of matrix metalloproteinases in the central nervous system. *Journal of Neuroscience Research*. 2003;**74**(6):801-806
- [69] Moore CS et al. How factors secreted from astrocytes impact myelin repair. *Journal of Neuroscience Research*. 2011;**89**(1):13-21
- [70] Moore CS et al. Astrocytic tissue inhibitor of metalloproteinase-1 (TIMP-1) promotes oligodendrocyte differentiation and enhances CNS myelination. *The Journal of Neuroscience*. 2011;**31**(16):6247-6254
- [71] Pagenstecher A et al. Differential expression of matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase genes in the mouse central nervous system in normal and inflammatory states. *The American Journal of Pathology*. 1998;**152**(3):729-741
- [72] Ludwin SK. The pathogenesis of multiple sclerosis: Relating human pathology to experimental studies. *Journal of Neuropathology and Experimental Neurology*. 2006;**65**(4):305-318
- [73] Nair A, Frederick TJ, Miller SD. Astrocytes in multiple sclerosis: A product of their environment.

Cellular and Molecular Life Sciences.
 2008;**65**(17):2702-2720

[74] Willenborg DO et al. Cytokines and murine autoimmune encephalomyelitis: Inhibition or enhancement of disease with antibodies to select cytokines, or by delivery of exogenous cytokines using a recombinant vaccinia virus system. *Scandinavian Journal of Immunology*. 1995;**41**(1):31-41

[75] Rodriguez M et al. Recombinant human IL-6 suppresses demyelination in a viral model of multiple sclerosis. *Journal of Immunology*. 1994;**153**(8):3811-3821

[76] Raine CS. Membrane specialisations between demyelinated axons and astroglia in chronic EAE lesions and multiple sclerosis plaques. *Nature*. 1978;**275**(5678):326-327

[77] Reier PJ, Houle JD. The glial scar: Its bearing on axonal elongation and transplantation approaches to CNS repair. *Advances in Neurology*. 1988;**47**:87-138

[78] Eng LF, Reier PJ, Houle JD. Astrocyte activation and fibrous gliosis: Glial fibrillary acidic protein immunostaining of astrocytes following intraspinal cord grafting of fetal CNS tissue. *Progress in Brain Research*. 1987;**71**:439-455

[79] Holley JE et al. Astrocyte characterization in the multiple sclerosis glial scar. *Neuropathology and Applied Neurobiology*. 2003;**29**(5):434-444

[80] Smith ME, Eng LF. Glial fibrillary acidic protein in chronic relapsing experimental allergic encephalomyelitis in SJL/J mice. *Journal of Neuroscience Research*. 1987;**18**(1):203-208

[81] Franklin RJ, Gilson JM, Blakemore WF. Local recruitment of remyelinating cells in the repair of demyelination in the central nervous

system. *Journal of Neuroscience Research*. 1997;**50**(2):337-344

[82] Bannerman P et al. Astrogliosis in EAE spinal cord: Derivation from radial glia, and relationships to oligodendroglia. *Glia*. 2007;**55**(1):57-64

[83] Sloka JS, Stefanelli M. The mechanism of action of methylprednisolone in the treatment of multiple sclerosis. *Multiple Sclerosis*. 2005;**11**(4):425-432

[84] Revel M. Interferon-beta in the treatment of relapsing-remitting multiple sclerosis. *Pharmacology & Therapeutics*. 2003;**100**(1):49-62

[85] Berger JR, Koralnik IJ. Progressive multifocal leukoencephalopathy and natalizumab—Unforeseen consequences. *The New England Journal of Medicine*. 2005;**353**(4):414-416

[86] Izrael M et al. Astrocytes in pathogenesis of ALS disease and potential translation into clinic. In: Gentile MT, D'Amato LC, editors. *Astrocyte - Physiology and Pathology*. London: IntechOpen; 2018. pp. 93-118. ISBN 978-953-51-5760-1

[87] Link H, Huang YM. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: An update on methodology and clinical usefulness. *Journal of Neuroimmunology*. 2006;**180**(1-2):17-28

[88] Salou M et al. Expanded CD8 T-cell sharing between periphery and CNS in multiple sclerosis. *Annals of Clinical Translational Neurology*. 2015;**2**(6):609-622

[89] Sawcer S et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 2011;**476**(7359):214-219

[90] Parnell GP, Booth DR. The multiple sclerosis (MS) genetic risk factors indicate both acquired and innate

immune cell subsets contribute to MS pathogenesis and identify novel therapeutic opportunities. *Frontiers in Immunology*. 2017;**8**:425

[91] Junker A et al. Multiple sclerosis: T-cell receptor expression in distinct brain regions. *Brain*. 2007;**130**(Pt 11):2789-2799

[92] Alves Sousa AP et al. Comprehensive analysis of TCR-beta repertoire in patients with neurological immune-mediated disorders. *Scientific Reports*. 2019;**9**(1):344

[93] Kitze B et al. Myelin-specific T lymphocytes in multiple sclerosis patients and healthy individuals. *Journal of Neuroimmunology*. 1988;**20**(2-3):237

[94] Lourbopoulos A et al. Cyclization of PLP139-151 peptide reduces its encephalitogenic potential in experimental autoimmune encephalomyelitis. *Bioorganic & Medicinal Chemistry*. 2018;**26**(9):2221-2228

[95] Arneth B. Early activation of CD4+ and CD8+ T lymphocytes by myelin basic protein in subjects with MS. *Journal of Translational Medicine*. 2015;**13**:341

[96] Cohen JA et al. Autologous hematopoietic cell transplantation for treatment-refractory relapsing multiple sclerosis: Position statement from the american society for blood and marrow transplantation. *Biology of Blood and Marrow Transplantation*. May 2019;**25**(5):845-854

[97] Alexander T et al. Hematopoietic stem cell therapy for autoimmune diseases: Clinical experience and mechanisms. *Journal of Autoimmunity*. 2018;**92**:35-46

[98] Fassas A et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: First

results of a pilot study. *Bone Marrow Transplantation*. 1997;**20**(8):631-638

[99] Burt RK et al. Effect of Nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: A randomized clinical trial. *JAMA*. 2019;**321**(2):165-174

[100] Atkins HL et al. Immunoablation and autologous haematopoietic stem-cell transplantation for aggressive multiple sclerosis: A multicentre single-group phase 2 trial. *Lancet*. 2016;**388**(10044):576-585

[101] Burman J et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: The Swedish experience. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2014;**85**(10):1116-1121

[102] Chen B et al. Long-term efficacy of autologous haematopoietic stem cell transplantation in multiple sclerosis at a single institution in China. *Neurological Sciences*. 2012;**33**(4):881-886

[103] Moore JJ et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2019;**90**(5):514-521

[104] Curro D, Mancardi G. Autologous hematopoietic stem cell transplantation in multiple sclerosis: 20 years of experience. *Neurological Sciences*. 2016;**37**(6):857-865

[105] Muraro PA et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. *Nature Reviews. Neurology*. 2017;**13**(7):391-405

[106] Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells:

Immune evasive, not immune privileged. *Nature Biotechnology*. 2014;**32**(3):252-260

promote endogenous repair in animal models of multiple sclerosis. *Glia*. 2009;**57**(11):1192-1203

[107] Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. *International Journal of Cell Biology*. 2016;**2016**:6940283

[115] Kassis I et al. Neuroprotection and immunomodulation with mesenchymal stem cells in chronic experimental autoimmune encephalomyelitis. *Archives of Neurology*. 2008;**65**(6):753-761

[108] Dominici M et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;**8**(4):315-317

[116] Gordon D et al. Human mesenchymal stem cells abrogate experimental allergic encephalomyelitis after intraperitoneal injection, and with sparse CNS infiltration. *Neuroscience Letters*. 2008;**448**(1):71-73

[109] Abbasi-Kangevari M et al. Potential therapeutic features of human amniotic Mesenchymal stem cells in multiple sclerosis: Immunomodulation, inflammation suppression, angiogenesis promotion, oxidative stress inhibition, neurogenesis induction, MMPs regulation, and remyelination stimulation. *Frontiers in Immunology*. 2019;**10**:238

[117] Mohyeddin Bonab M et al. Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study. *Iranian Journal of Immunology*. 2007;**4**(1):50-57

[110] Gregory CA, Prockop DJ, Spees JL. Non-hematopoietic bone marrow stem cells: Molecular control of expansion and differentiation. *Experimental Cell Research*. 2005;**306**(2):330-335

[118] Harris VK, Sadiq SA. Stem cell therapy in multiple sclerosis: A future perspective. *Neurodegenerative Disease Management*. 2015;**5**(3):167-170

[111] Zhang X et al. Transplantation of autologous adipose stem cells lacks therapeutic efficacy in the experimental autoimmune encephalomyelitis model. *PLoS One*. 2014;**9**(1):e85007

[119] Harris VK et al. Clinical and pathological effects of intrathecal injection of mesenchymal stem cell-derived neural progenitors in an experimental model of multiple sclerosis. *Journal of the Neurological Sciences*. 2012;**313**(1-2):167-177

[112] Wilkins A et al. Human bone marrow-derived mesenchymal stem cells secrete brain-derived neurotrophic factor which promotes neuronal survival *in vitro*. *Stem Cell Research*. 2009;**3**(1):63-70

[120] Harris VK, Vyshkina T, Sadiq SA. Clinical safety of intrathecal administration of mesenchymal stromal cell-derived neural progenitors in multiple sclerosis. *Cytotherapy*. 2016;**18**(12):1476-1482

[113] Zhang J et al. Human bone marrow stromal cell treatment improves neurological functional recovery in EAE mice. *Experimental Neurology*. 2005;**195**(1):16-26

[121] Harris VK et al. Phase I trial of intrathecal mesenchymal stem cell-derived neural progenitors in progressive multiple sclerosis. *EBioMedicine*. 2018;**29**:23-30

[114] Bai L et al. Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and

[122] Scolding NJ et al. Cell-based therapeutic strategies for multiple sclerosis. *Brain*. 2017;**140**(11):2776-2796

- [123] Temple S, Alvarez-Buylla A. Stem cells in the adult mammalian central nervous system. *Current Opinion in Neurobiology*. 1999;**9**(1):135-141
- [124] Blakemore WF, Keirstead HS. The origin of remyelinating cells in the central nervous system. *Journal of Neuroimmunology*. 1999;**98**(1):69-76
- [125] Ming GL, Song H. Adult neurogenesis in the mammalian brain: Significant answers and significant questions. *Neuron*. 2011;**70**(4):687-702
- [126] Ben-Hur T et al. Transplanted multipotential neural precursor cells migrate into the inflamed white matter in response to experimental autoimmune encephalomyelitis. *Glia*. 2003;**41**(1):73-80
- [127] Einstein O et al. Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression. *Annals of Neurology*. 2007;**61**(3):209-218
- [128] Zhang C et al. Treatment of multiple sclerosis by transplantation of neural stem cells derived from induced pluripotent stem cells. *Science China. Life Sciences*. 2016;**59**(9):950-957
- [129] Izrael M et al. Human oligodendrocytes derived from embryonic stem cells: Effect of noggin on phenotypic differentiation *in vitro* and on myelination *in vivo*. *Molecular and Cellular Neurosciences*. 2007;**34**(3):310-323
- [130] Einstein O et al. Transplanted neural precursor cells reduce brain inflammation to attenuate chronic experimental autoimmune encephalomyelitis. *Experimental Neurology*. 2006;**198**(2):275-284
- [131] Goldman SA, Windrem MS. Cell replacement therapy in neurological disease. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. 2006;**361**(1473):1463-1475
- [132] Windrem MS et al. Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. *Nature Medicine*. 2004;**10**(1):93-97
- [133] Windrem MS et al. Neonatal chimerization with human glial progenitor cells can both remyelinate and rescue the otherwise lethally hypomyelinated shiverer mouse. *Cell Stem Cell*. 2008;**2**(6):553-565
- [134] Sim FJ et al. CD140a identifies a population of highly myelinogenic, migration-competent and efficiently engrafting human oligodendrocyte progenitor cells. *Nature Biotechnology*. 2011;**29**(10):934-941
- [135] Goldman SA, Nedergaard M, Windrem MS. Glial progenitor cell-based treatment and modeling of neurological disease. *Science*. 2012;**338**(6106):491-495
- [136] Thiruvalluvan A et al. Survival and functionality of human induced pluripotent stem cell-derived oligodendrocytes in a nonhuman primate model for multiple sclerosis. *Stem Cells Translational Medicine*. 2016;**5**(11):1550-1561
- [137] Lepore AC et al. Human glial-restricted progenitor transplantation into cervical spinal cord of the SOD1 mouse model of ALS. *PLoS One*. 2011;**6**(10):e25968
- [138] Izrael M et al. Safety and efficacy of human embryonic stem cell-derived astrocytes following intrathecal transplantation in SOD1(G93A) and NSG animal models. *Stem Cell Research & Therapy*. 2018;**9**(1):152
- [139] Davies JE et al. Transplanted astrocytes derived from BMP- or CNTF-treated glial-restricted precursors

have opposite effects on recovery and allodynia after spinal cord injury. *Journal of Biology*. 2008;7(7):24

[140] Davies SJ et al. Transplantation of specific human astrocytes promotes functional recovery after spinal cord injury. *PLoS One*. 2011;6(3):e17328

[141] Noble M et al. Precursor cell biology and the development of astrocyte transplantation therapies: Lessons from spinal cord injury. *Neurotherapeutics*. 2011;8(4):677-693

[142] Jiang P et al. Human iPSC-derived immature astroglia promote oligodendrogenesis by increasing TIMP-1 secretion. *Cell Reports*. 2016;15(6):1303-1315

[143] Jiang P et al. hESC-derived Olig2+ progenitors generate a subtype of astroglia with protective effects against ischaemic brain injury. *Nature Communications*. 2013;4:2196

[144] Haas C, Fischer I. Human astrocytes derived from glial restricted progenitors support regeneration of the injured spinal cord. *Journal of Neurotrauma*. 2013;30(12):1035-1052

[145] Chandrasekaran A et al. Astrocyte differentiation of human pluripotent stem cells: New tools for neurological disorder research. *Frontiers in Cellular Neuroscience*. 2016;10:215

[146] Ciani L, Salinas PC. WNTs in the vertebrate nervous system: From patterning to neuronal connectivity. *Nature Reviews. Neuroscience*. 2005;6(5):351-362

[147] Krencik R et al. Specification of transplantable astroglial subtypes from human pluripotent stem cells. *Nature Biotechnology*. 2011;29(6):528-534

[148] Krencik R, Zhang SC. Directed differentiation of functional astroglial subtypes from human pluripotent

stem cells. *Nature Protocols*. 2011;6(11):1710-1717

[149] Tcw J et al. An efficient platform for astrocyte differentiation from human induced pluripotent stem cells. *Stem Cell Reports*. 2017;9(2):600-614

[150] Zhang PW et al. Generation of GFAP::GFP astrocyte reporter lines from human adult fibroblast-derived iPS cells using zinc-finger nuclease technology. *Glia*. 2016;64(1):63-75

[151] Peljto M, Wichterle H. Programming embryonic stem cells to neuronal subtypes. *Current Opinion in Neurobiology*. 2011;21(1):43-51

[152] Caiazzo M et al. Direct conversion of fibroblasts into functional astrocytes by defined transcription factors. *Stem Cell Reports*. 2015;4(1):25-36

[153] Tian E et al. Small-molecule-based lineage reprogramming creates functional astrocytes. *Cell Reports*. 2016;16(3):781-792