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Chapter

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 immerging 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 mammalians, 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-1β, 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 S100β [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 no 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 milieus that depict 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 attention 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 (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 allogenic 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 (PDGFAR)-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, TGFβ, and GSK3β 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 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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