Chapter

Therapeutic Features of Mesenchymal Stem Cells and Human Amniotic Epithelial Cells in Multiple Sclerosis

Reza ArefNezhad and Hossein Motedayyen

Abstract

Imbalance in immune responses plays an indispensable role in pathogenesis and development of multiple sclerosis (MS), as a neurodegenerative disorder. Current treatments are not always successful in preventing MS development and treating the disease. Stem cell-based cell therapy has provided a new window for treating neurodegenerative disorders. Stem cells can regulate the immune system and improve axonal remyelination. They can be isolated from different origins such as bone marrow, embryonic, neural, and adipose tissues. However, there is a challenge in choosing the best cell source for stem cell therapy. Mesenchymal stem cells (MSCs) derived from different origins have significant immunoregulatory impacts on different cells from the immune system. A growing body of evidence indicates that adipose tissue and umbilical cord can be a suitable source for obtaining MSCs. Moreover, human amniotic epithelial cell (hAEC), as a novel stem cell with immunoregulatory effects, regenerative effects, and low antigenicity, can be a candidate for MS treatment. This chapter discusses therapeutic impacts of MSCs and hAECs in MS disease.

Keywords: multiple sclerosis, mesenchymal stem cell, human amniotic epithelial cell, regenerative impacts, immunomodulatory effects

1. Introduction

Neurodegenerative disorders are considered as a chronic and progressive inflammatory condition resulting in the deposition of abnormal forms of specific proteins in the nervous system and destruction of neurons in motor, sensory, or cognitive systems [1, 2]. These disorders mainly involve women and are observed in subjects with age ranging from 20 to 30 years [3]. It is reported that more than 2.5 million individuals suffer from multiple sclerosis (MS) around the world who require effective therapeutic approaches to control disability and recover the central nervous system (CNS) functions [3]. The major problem of the management of the disease is the lack of successful regeneration of neurons [4].

Until now, several therapeutic approaches for MS have been suggested to control abnormal immune responses including natalizumab, interferon-β (IFN-β), glatiramer acetate, and fingolimod (FTY720). These treatments mainly exert their inhibitory effects on immune reactions and thereby reduce the number of relapses and modulate the progression of neurologic disability. However, they have not been consistently successful and are suitable in arresting the disease in approximately 30% of relapsing-remitting (RR) MS patients as the most common form of MS [5, 6]. It is reported that these treatments fail to control the degeneration of nerve tissue in an aggressive form of MS [7]. Among these approaches, stem cell-based therapies show a hopeful outlook for decreasing neural damages in the neurological diseases through regenerative roles for remyelination, the secretions of neurotrophic mediators with immunomodulatory impacts, and differentiation into astrocytes and oligodendrocytes effectively *in vivo* and *in vitro* [8]. Previous studies have shown some challenges for using stem cells as a curative treatment in clinical trials such as tumorigenicity and immunogenicity [9, 10]. However, extensive data of the literature have indicated that stem cell therapy exerts positive effects on animal models with neurological disorders [11, 12]. Clinical uses of adult stem cells, particularly mesenchymal stem cells (MSCs) and human amniotic epithelial cells (hAEC), have been recommended for the management of neurological diseases such as MS [13–15]. Several advantages have been reported for their therapeutic applications including the following: (1) their relative safety and low immunogenicity in comparison with other stem cell sources [16, 17]; (2) the ease of their accessibility, isolation, expansion, and manipulation *ex vivo* [18]; (3) their potency in differentiation into mesodermal lineages [16]; and (4) their capability to transport from the blood to damaged sites. Hereby, this chapter aimed to describe and discuss evidence regarding MSC- and hAEC-based therapies and their mechanisms for treating MS.

2. MS and its pathogenesis

Multiple sclerosis (MS) is the most common non-traumatic disabling disease, resulting in axonal loss and myelin disruption. The frequent features of MS are formations of lesions and sclerotic plaques in the central nervous system (CNS) and the cerebrospinal cord. The immune system plays a critical role in neural evolution through regulating oligodendrogenesis, neurogenesis, and synaptic organization. Therefore, immune cells can participate in the pathogenesis and development of MS [19, 20]. The pathogenesis of MS is largely related to hormone, environmental, and genetic factors. It is reported that alterations in expressions and functions of some immune agents such as major histocompatibility complex (MHC), immunoglobulin (Ig), T-cell receptor (TCR), and cytokines can contribute to the increased risk of MS [6, 21]. Today, studies on MS have indicated that autoreactive T-cell migration to the CNS occurs upon autoimmune cascade initiation and blood-brain barrier (BBB) disruption, which leads to destroy myelin sheath and creates sclerotic lesions and plaques [6, 22]. Destruction of the myelin sheath, which plays a significant role in survival and integration of axon, is a major reason for the development of MS [3]. T helper 1 (Th1) and T helper 17 (Th17) cells are the main effector cells that participate in the demyelination and destruction of the CNS [19, 20]. Th1 and Th17 produce some pro-inflammatory cytokines, including inerleukine-1 (IL-1), IL-17, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) [23]. Moreover, CD8+ T cells are found in MS lesions, especially around the blood vessels. Previous studies

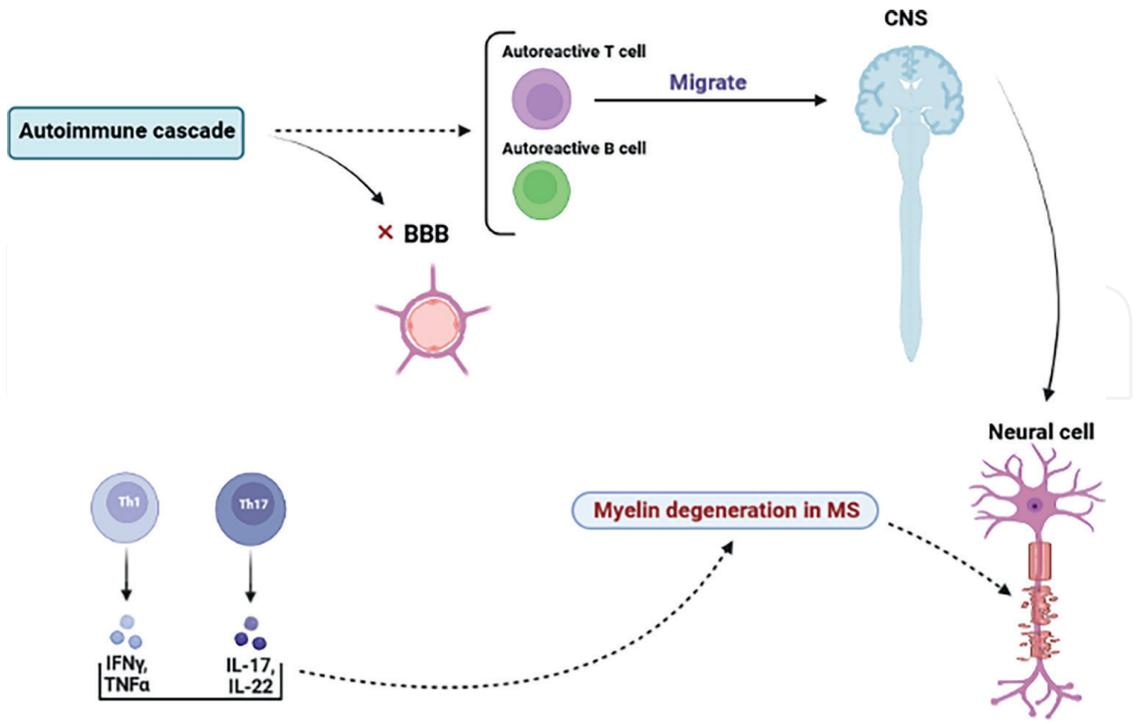

Figure 1.
The impacts of immune responses in MS pathogenesis.

have revealed that the proliferation of CD8+ T cell in patients with MS is more than CD4+ T cell, which is largely associated with axon injury [1]. Besides the roles of T cells in the pathogenesis of MS, other immune cells play important roles in the formations of lesions and plaques. The activation of macrophage by Th1 cytokines leads to the destruction of the myelin and thereby exposes more CNS antigens. Although it is demonstrated that autoreactive T cells are the major effector cells for the pathogenesis of MS, some reports have indicated that autoreactive B cells have critical roles in disappearing the myelin sheaths and axonal loss, through cytokine secretions, antigen presentations, and autoantibody productions [24]. Autoantibodies can be major immune mediators that can be found in MS plaques. There are some reports pointing toward the association of immunoglobulin G (IgG) with MS signs. Furthermore, it is shown that IgG, especially IgG against proteolipid proteins (PLP) and myelin basic proteins (MBP), can be considered as the features of the disease, although their roles in MS pathogenesis are not well identified yet (**Figure 1**) [25].

3. Mesenchymal stem cells

MSCs can be obtained from different tissues such as bone marrow, adipose tissue, umbilical cord, brain, dental tissue, and fetal lung [26–28]. MSCs can differentiate into monocytes and neurons *in vitro* and *in vivo* [29]. These cells can migrate to injured tissue *via* expressions of the receptors for chemokines such as CXCR4, CXCR5, CXCR6, CCR1, and some growth factors [7]. In line with potential therapeutic effects of MSCs, it is revealed that these cells possess anti-oxidant and anti-apoptotic impacts and are able to secrete trophic factors, which can contribute to support axon and increase neural stability [30]. They improve neural cell differentiation, promote angiogenesis, inhibit neuron apoptosis, and repair the CNS in MS patients [25].

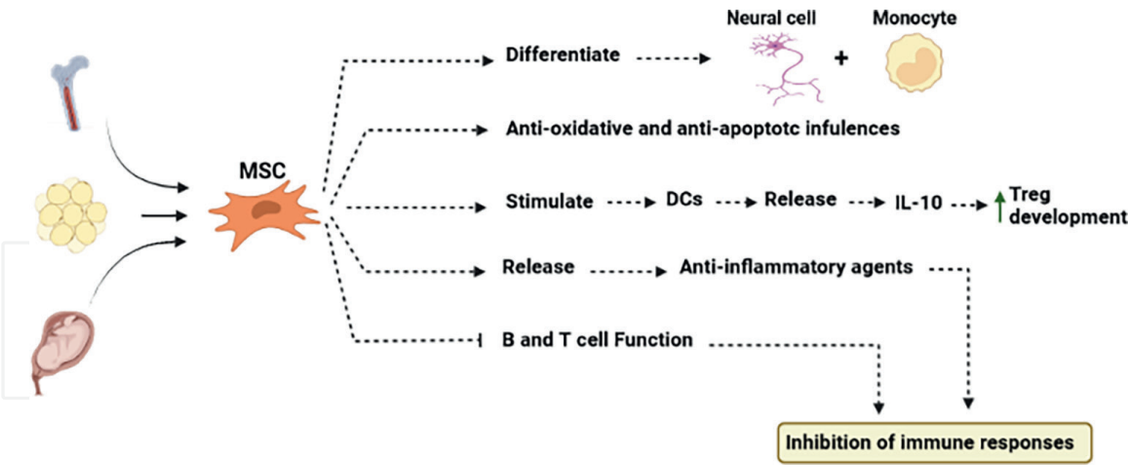

Figure 2.
Immunoregulatory and therapeutic effects of MSCs.

Furthermore, these cells can recruit oligodendrocyte precursors to the CNS and induce their differentiation into neuronal cells [31, 32]. MSCs exert immunomodulatory impacts through suppressing the activity of B, T, and other immune cells [33]. Intravascular MSC therapy improves CNS tissue repair through the induction of T-cell tolerance to myelin glycoproteins [34]. Studies on experimental autoimmune encephalomyelitis (EAE), an animal model of MS, indicated that intravenous injection of syngeneic MSCs induces tolerance in MOG-specific T cells and thereby reduces immune cell infiltrations to the CNS and increases the clinical course [35, 36]. Others have revealed that the immunoinhibitory effects of MSCs are mediated through the secretions of anti-inflammatory cytokines such as TGF-β, prostaglandinE-2 (PGE-2), and indoleamine-pyrrole 2, 3-dioxygenase (IDO) [37]. Previous studies have demonstrated that MSCs can impair B-cell proliferation and antibody production through inhibiting the activation and proliferation of Th1 cells [38]. These cells also improve the activation of suppressor of cytokine signaling 3 (SOCS3) and decrease the differentiation of Th17 via the IFN-γ pathway [39]. IDO, as a mechanism used by MSC for controlling immune responses, depletes tryptophan from the environment of lymphocytes, which plays a key role in lymphocyte activations [40]. MSC participates in the development of regulatory T cells (Treg) through inducing IL-10 secretion of peripheral dendritic cells (DCs) [40]. In line with the improvement of peripheral tolerance, it is reported that MSCs inhibit the differentiation and function of DCs, resulting in the inhibition of clonal expansion of autoreactive T cells via the reduction of antigen presentation [41]. Hepatocyte growth factor (HGF) produced by MSC increases tolerogenic DCs [42]. MSCs with HGF can reduce immune cell infiltrations and CNS inflammation in EAE mice [42]. Thus, HGF derived from MSC may be effective in MS treatment. Several studies on genetically modified MSCs have shown that over-expressed anti-inflammatory cytokines such as IL-10 and IL-4 can participate in suppressing immune responses, reducing BBB injury, and improving remyelination of neurons in EAE mice (**Figure 2**) [43].

4. Human bone marrow-derived MSCs (hBM-MSCs)

MSCs obtained from bone marrow have multiple properties, which make them an attractive cell source for therapeutic applications (**Table 1**). These cells are the most

Different sources of MSCs	Advantages	Disadvantages
hBM-MSCs	1. Colony formations that contribute to hemopoiesis [44]. 2. Differentiation into mesodermal lineage cells [44]. 3. Secretion of brain-derived neurotrophic factor (BDNF) and enhancement of oligodendrogenesis. 4. Immunomodulatory impacts in animal models of neurodegenerative disorders, especially in the early stages of MS [16].	1. Invasive and painful techniques with low efficiency for its isolation [45]. 2. Low efficiency in controlling disease progression in the stabilized stage of MS [16]. 3. The probability of malignant transformation and immune rejection after clinical applications [46, 47].
hUC-MSCs	1. Less-invasive techniques for its isolation [48]. 2. Less ethical issues for its isolation [48]. 3. High proliferation ability [48]. 4. Low immunogenicity potential [48]. 5. Differentiation capacity into various lineages [48] 6. Immunoregulatory impacts in animal models of autoimmune disorders [49]. 7. Production of nerve growth factors [50].	1. Tumorigenic potential and immune rejection after clinical use [51]. 2. Procoagulant properties that may contribute to pulmonary embolism [52]. 3. The risk of viral and prion transmission after administration [53, 54].
AD-MSCs	1. Easy isolation with high efficiency of adipose tissue [53]. 2. Adipogenic, cardiogenic, neurogenic, myogenic, chondrogenic, and osteogenic features [53]. 3. Migration to different organs through expression of α4 integrin [55]. 4. Production of different growth factors [56].	1. Tumorigenic potential and immune rejection after their clinical use [57]. 2. Nephrotoxicity potential [49, 57]. 3. Procoagulant properties [52].
hAECs	1. Easy isolation with high efficiency of the amniotic membrane [58]. 2. Pluripotency and self-renewal properties [18, 59]. 3. Differentiation into the cells originating from three germinal layers [18]. 4. Production of neurotrophic mediators [59, 60]. 5. Immunomodulatory impacts in animal models of inflammatory neurological disorders [61, 62]. 6. Low tumorigenic and immunogenicity potential [15, 18, 63].	1. The controversial formation of teratomas upon hAEC-derived neural cell engraftment [64]. 2. Are not described as stem cells because they do not show long-term self-renewal and fail to grow the cells from single-cell clones [17].

Table 1.
The pros and cons of MSC-based therapies.

frequent cell sources used in clinical settings [49]. Given therapeutic features of hBM-MSCs in neurological disorders, it is revealed that they can promote disease recovery in relapsing-remitting and chronic types of MS in EAE mice, due perhaps to reduce demyelination regions and inflammatory infiltrates, induce oligodendrogenesis, and

enhance brain-derived neurotrophic factor (BDNF) production [65]. Several studies have reported that BM-MSCs have immunomodulatory effects in EAE through preventing the maturation of antigen-presenting cells (APCs) and proliferation of B and T cells [39]. These immunosuppressive impacts are mainly mediated by releasing various bioactive mediators [66]. Moreover, their neuroprotective effects can induce local progenitor cells and suppress scar creation, gliosis, and neuron apoptosis [67]. Besides having immunomodulatory impacts, they have the ability to differentiate into the neurons and improve the replacement of the cells [67]. Nonetheless, the isolation of BM-MSC is painful, invasive, and low efficiency [45], which may be considered a disadvantage in their clinical applications. In the first phase of clinical trial using autologous *ex vivo* expanded BM-MSCs on patients with advanced MS, it was reported that 30% of patients were unable to grow an acceptable number of these cells ($< 2 \times 10^6$) despite several bone marrow aspirations. This observation has reflected an inherent deficiency of MSCs in the bone marrow of participants [67]. Thus, MSCs derived from other tissues can be considered for MS treatment. In EAE, BM-MSCs are notable curative effects if they are used before disease initiation due to a significant suppression on effector T cells and the induction of peripheral tolerance. However, these cells fail to control disease development in the stabilized stage of MS [16].

5. Human umbilical cord (hUC)-MSCs

HUC-MSCs have significant characteristics, which distinguish them from other sources of MSCs (**Table 1**). Several lines of evidence suggest the administration of hUC-MSCs in autoimmune disorders such as encephalomyelitis, type 1 diabetes, and rheumatoid arthritis due to its immunoregulatory impacts [68–71]. Immunomodulatory effects of these cells have fundamental roles in tissue recovery [72]. They have the decreased expression of HLA-I, increased capacity of proliferation, and more rapid growth *in vitro*, compared with BM-MSCs [73]. *In vitro* and *in vivo* studies have indicated that hUC-MSCs have a positive effect on Treg proliferation [74]. hUC-MSCs can increase behavioral activities and reduce the histopathological impairments of EAE. Furthermore, they exert a positive effect on the productions of IL-4 and IL-10, unlike IL-1 and IL-6 [70]. *In vitro* studies have demonstrated that hUC-MSCs can enhance the frequency of Treg and secretion of anti-inflammatory

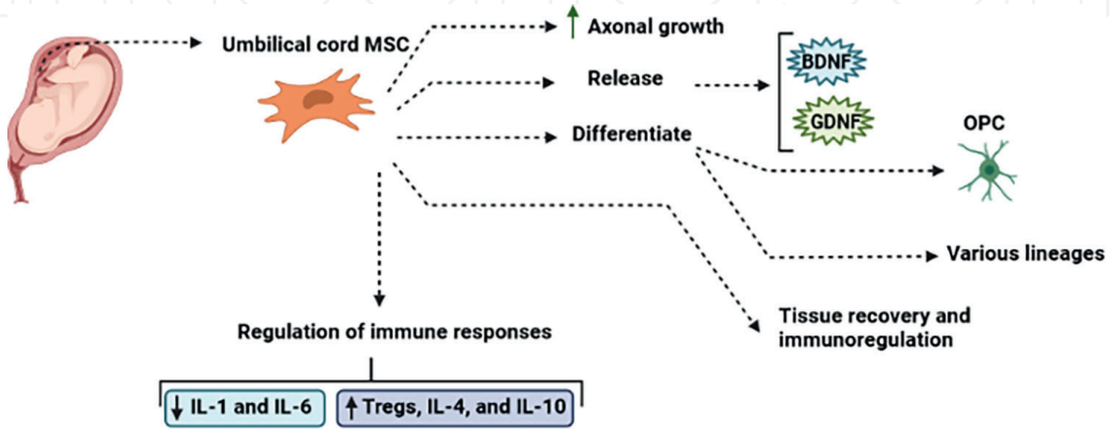

Figure 3.
Immunomodulatory and therapeutic impacts of hUC-MSCs.

cytokines of peripheral blood mononuclear cells (PBMCs) (**Figure 3**) [74, 75]. In addition to their immunoregulatory effects, this source of stem cells is able to release several nerve growth factors, for example, glial cell-derived neurotrophic factor (GDNF) and BDNF. Moreover, their capacity to differentiate into oligodendrocyte precursor cells can improve axonal growth [50].

6. Human adipose-derived MSCs (AD-MSCs)

AD-MSC can be obtained from adipose tissue by collagenase digests. Adipose tissue contains high levels of MSCs (approximately 100–1000 MSCs per gram of fat) and is easily accessible for use. Thus, this tissue is an important source of the cell for cellular therapy. AD-MSCs show the adipogenic, cardiogenic, neurogenic, myogenic, chondrogenic, and osteogenic features *in vitro*, which make them a fantastic cell source for stem cell therapy [8, 76]. Unlike BM-MSCs, these cells are able to migrate to different organs due to express α4 integrin, an adhesive molecule [55]. It is suggested that autologous and allogeneic AD-MSCs are effective in the treatment of the diseases with immunopathogenesis such as MS and autoimmune encephalomyelitis [77–80]. Study on EAE mice revealed that intravascular AD-MSC participates in the reduction of immune infiltration in the CNS and decreases demyelination and axonal loss [9]. Various growth factors released from AD-MSCs, such as anti-apoptotic, angiogenic, and neurotrophic mediators, play critical roles in cell differentiation, proliferation, and maturation [56]. It is thought that AD-MSCs have more capabilities for stem cell-based cell therapy, due perhaps to the expression of integrin α4β1; pass the BBB; and exert their anti-inflammatory, immunoregulatory, and neurodegenerative impacts (**Figure 4**) [7]. Until now, several studies have been performed to find a standard method for the treatment of MS by these cells [81, 82]. Nonetheless, there are some concerns regarding the clinical application of MSCs such as tumorigenesis and immune rejection after use that must be addressed in future studies.

7. Human amniotic epithelial cells (hAECs)

hAECs are easily isolated from the amniotic membrane, the inner layer of the fetal membranes, and possess some stem cell-like properties [83–86]. These cells express

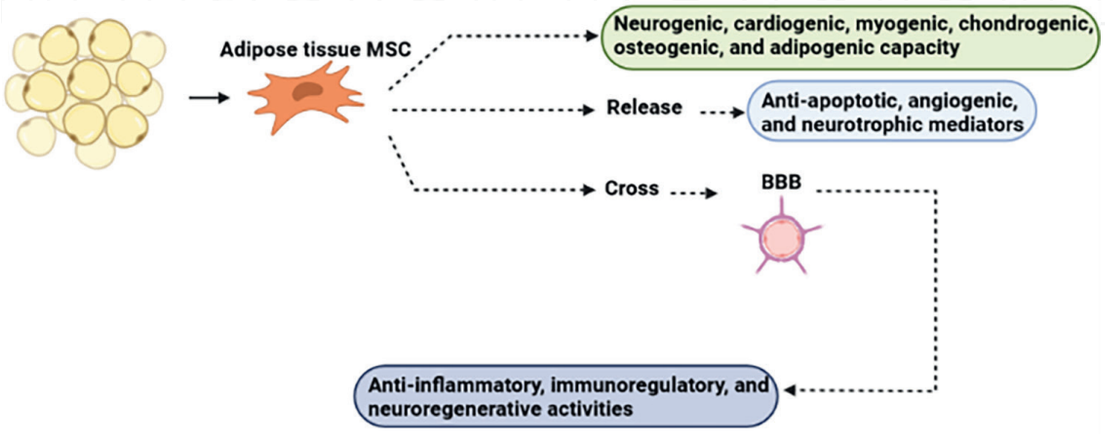

Figure 4.
Immunoregulatory and therapeutic impacts of AD-MSCs in degenerative disorders.

some markers of pluripotent stem cells, including FGF-T, Sox-2, Nanog, Rex-1, SSEA-4, and Oct4. Some of these markers have important roles in pluripotency and self-renewal properties in induced pluripotent stem (iPS) cells and embryonic stem cells (ESCs) [87]. hAEC can differentiate into different cells such as the pancreatic cells, neural cells, hepatocytes, cardiomyocytes, adipocytes, and myocytes, which originate from the endoderm, ectoderm, and mesoderm [18]. It is reported that hAECs have immunomodulatory impacts on adaptive and innate immune systems [17, 88, 89]. They exert suppressive effects on the activations of natural killer (NK) and CD4+ T cells, migrations of neutrophil and macrophage, secretions of pro-inflammatory cytokines of CD4+ T cells, and proliferation of B cells [23, 61, 90, 91]. These impacts are primarily mediated through the productions of immunoregulatory mediators, such as IL-4, PG-E2, and transforming growth factor-beta (TGF-β), which may participate in the increase of Tregs and Th2 cells, inhibition of pathogenic T-cell reactions, and protection of the peripheral naive CD4+ T-cell source [61, 63, 92–95]. These effects suggest that hAECs may be considered as an effective cell source for MS treatment [62, 95]. To support this notion, they can contribute to a shift from Th1-type responses to Th2-type responses [95]. EAE mice treated with hAECs experienced significant reductions in demyelination and immune infiltration into the CNS [95]. It is indicated that hAECs have a negative effect on Th17 differentiation through reducing the productions of TGF-β and IL-6, which play indispensable roles in the differentiation of these cells [88]. Studies on animal models of MS have revealed that alpha-fetoprotein (AFP) produced from hAECs participates in the reduction of lymphocyte function and neuroinflammation [96, 97]. Others have indicated that these cells can reduce gray and white matter damages through residing in inflammation locations such as the brain [98]. Furthermore, they can release neurotrophic agents such as neurotrophin-3 (NT-3), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) (**Figure 5**) [59, 60]. These features along

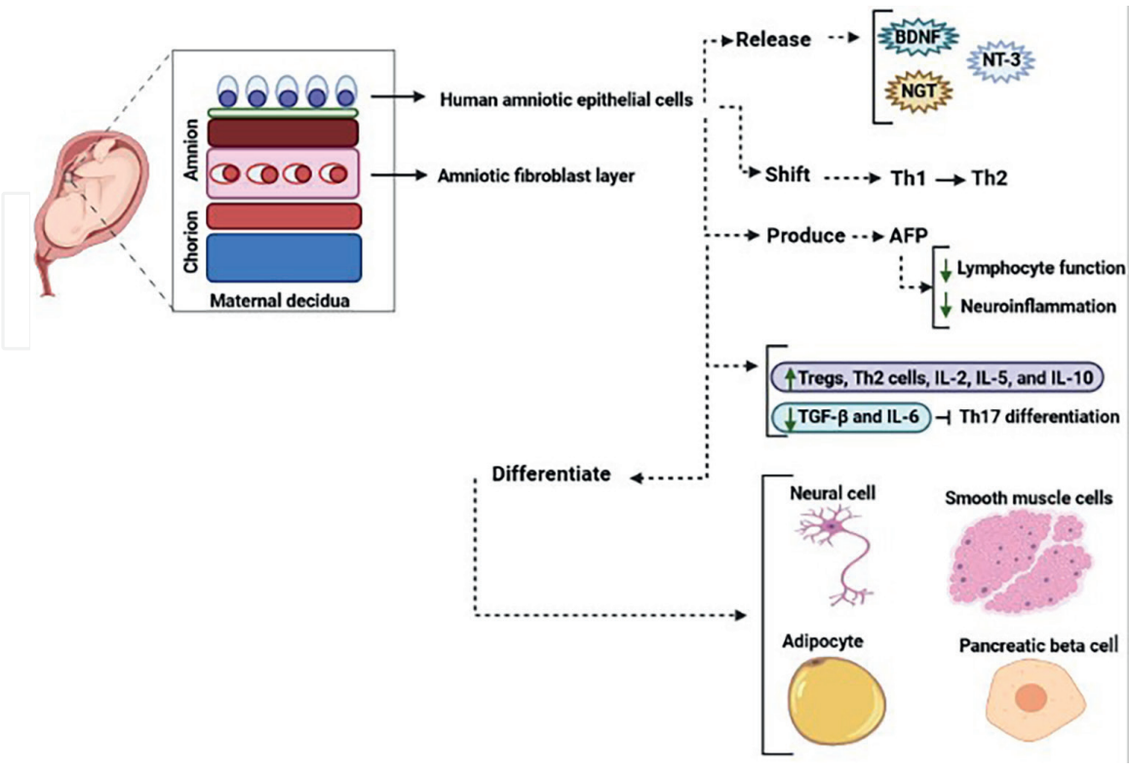

Figure 5.
Immunomodulatory and stem cell characteristics of hAECs.

with low antigenicity provide additional confirmations to clarify therapeutic properties of hAECs in the treatment and management of inflammatory neurological disorders such as MS [99]. hAECs possess a limited proliferative potential due perhaps to the lack of telomerase [87, 92, 100, 101], which helps to reduce potential tumorigenicity of stem cell-based therapies. Nevertheless, it should be noted that further works and more information are needed to illustrate the possible capability of these cells in treating diseases with immune pathophysiology.

8. Comparison of hAECs with MSCs derived from different sources

There are some differences and similarities between hAECs and MSCs derived from different sources, for example, morphologic and tumorigenic properties, immunoregulatory characteristics, angiogenesis capacities, and ethical issues associated with their isolations and applications [45, 102]. In line with morphology, hAECs show a cobblestone-like morphology, while the cultured hAMSCs have a spindle fibroblast-like morphology [103]. The morphologic feature of the cultured MSCs derived from BM can range from fibroblast-like spindle-shaped cells to large flat cells [104]. MSCs from other sources, such as AD-MSCs and hUC-MSCs, indicate spindle shapes in the culture [105, 106]. The amniotic membrane can be collected by standard isolation methods following cesarean section, which is not invasive and does not have unfavorable effects on human embryos and ethical issues [102]. The isolation of amniotic cells can simply be performed upon prenatal testing. However, there are some ethical problems in regard to clinical applications of MSCs and the isolation of some sources of MSCs [104, 107]. As mentioned above, the isolation of hBM-MSCs is done by invasive techniques with low efficiency, which is painful [45]. Today, there is no document pointing to the tumorigenicity of amnion membrane or membrane-originated cells after clinical applications [17]. However, some reports have shown that MSCs may raise tumor growth in some cancer mouse models [108]. Several lines of evidence propose that hAECs, BM-MSCs, and AD-MSCs participate in enhancing angiogenesis through the productions of some cytokines and angiogenic factors, such as VEGF, HGF, and EGF, and mechanisms associated with protease [103, 109]. According to evidence, hAECs possess better immunomodulatory impacts but lesser osteogenic effects than BM-MSCs and MSCs derived from the human amniotic fluid (hAF) [110]. hAECs express some MSC markers such as CD90, CD44, and CD105. However, the levels of SSEA4 and SSEA3 expressions are higher on hAECs than those on hBM-MSCs and hAFMSC, revealing more multipotent potential of these cells [17, 111]. Furthermore, hAECs and hAFMSC possess higher levels of PD-L1 and PD-L2 than hBM-MSCs, which may make them more successful in providing peripheral tolerance in immune cells [110, 112].

9. Mesenchymal stem cell-based cell therapy and clinical trials

Until now, several clinical trials were carried out using MSCs as a therapeutic approach for MS. In a phase II clinical trial, intravascular MSCs were employed in the treatment of nine relapsing-remitting multiple sclerosis (RRMS) patients. After 6 months, the results revealed a significant reduction in MS lesions in magnetic resonance imaging (MRI) [67]. In a phase IIa clinical trial, autologous BM-MSCs were injected to one RRMS and nine secondary progressive multiple sclerosis (SPMS)

patients. After 3 months to 1 year, authors observed that BM-MSCs improved clinical features in the treated patients. In this clinical trial, 10 SPMS patients were treated with intravascular MSCs for 6 months, and the results revealed neuroprotection effect of MSCs and remyelination [67]. Furthermore, in a study conducted by Bonab et al., in 2007, therapeutic impacts of intrathecal injection of MSC were studied on 10 MS patients. This study indicated that the disease progression was gradually reduced in half of the participants [113]. Another study on 22 patients with primary progressive multiple sclerosis (PPMS) demonstrated that intravascular and intrathecal injections of BM-MSCs were effective in MS treatment [35]. In a triple-blind and placebo-controlled study on 30 patients with SPMS, the researchers indicated that AD-MSC injection is a possible and safe method in the treatment of SPMS patients [114]. Staff et al. reported the safety of intrathecal administration of AD-MSCs in amyotrophic lateral sclerosis (ALS) patients [115]. In a study conducted by Li et al., it was demonstrated that hUC-MSC transplantation is able to reduce MS symptoms and relapse occurrence in comparison with control individuals. In addition, the researchers observed that hUC-MSC administration results in a shift in Th1 responses toward Th2 immunity [116]. In line with the therapeutic impacts of MSCs, Riordan et al. indicated that hUC-MSC transplantation is safe and exerts suitable impacts on life quality and brain lesion in MS patients [117].

10. Conclusion

There are many documents pointing to stem cell-based cell therapy as a treatment for MS and other neurological disorders. However, an inconsistency in the results of these studies is observed. Among different types of stem cells, MSCs are more possible to consider as a therapeutic approach for MS treatment because they utilize different mechanisms involved in regulating immune responses and repairing CNS damages. Furthermore, MSCs have anti-oxidant and anti-apoptotic properties and trophic factor secretion, which exert positive effects on the axon and neural stability. Numerous studies have recommended that MSCs derived from umbilical cord and adipose tissue can be more effective for stem cell therapy. Moreover, hAECs are mentioned as a novel source of the cells, which have immunoregulatory effects and show a potential for differentiation into the cells originating from three germinal layers. Consequently, hAECs may be considered a therapeutic method to manage and control MS. However, more experimental studies should be done to illustrate their efficiency and mechanisms involved in the treatment of MS.

Finding

This study was not financially supported and was performed in personal capacity.

Conflicts of interest

The authors declare that there is no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.110221

Author details

Reza ArefNezhad[1] and Hossein Motedayyen[2*]

1 Department of Anatomy, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

2 Autoimmune Diseases Research Center, Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran

*Address all correspondence to: hmotedayyen@gmail.com

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