6

Stem Cell Therapy: A Promising Therapeutic Approach for Multiple Sclerosis

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Doi: http://dx.doi.org/10.15586/codon.multiplesclerosis.2017.ch6

Abstract: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system which is accompanied by demyelination of the nerves, axonal loss, and disability. Currently, no definitive treatment is recognized for MS. Stem-cell therapy for MS has shown promising results and has attracted attention as an alternative therapeutic option. Various stem cell sources such as mesenchymal, embryonic, and neural have been identified. This chapter gives an overview of the advances made in our understanding of these stem cells under two broad categories: exogenous and endogenous. Stem-cell therapy in MS and the substantial literature regarding their

In: *Multiple Sclerosis: Perspectives in Treatment and Pathogenesis*. Ian S. Zagon and Patricia J. McLaughlin (Editors), Codon Publications, Brisbane, Australia. ISBN: 978-0-9944381-3-3; Doi: http://dx.doi.org/10.15586/codon.multiplesclerosis.2017

therapeutic potential for MS are discussed. Much of the promising data are still in experimental stage, and further clinical trials are needed to rigorously evaluate the safety, validity, and feasibility of these stem cells for the treatment of MS.

Key words: Endogenous stem cells; Mesenchymal stem cells; Multiple sclerosis; Pluripotent stem cells; Stem-cell therapy.

Introduction

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system (CNS) and leads to demyelination of neural fibers, severe neurological symptoms, and progressive disability (1, 2). None of the currently available drugs are effective in supporting regeneration of the demyelinated areas, and preventing disease progression (2). Stem cells, because of their self-renewal and differentiation capacity into various cell types, appear to be suitable candidates for alternative therapeutic strategies for MS (3, 4). A wide variety of stem cells that have therapeutic potential in neurodegenerative diseases have been identified; these include, but are not limited to, mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and neural stem cells (NSCs) (3–5).This chapter gives an overview of stem cells and their therapeutic potential for MS.

Exogenous Stem Cell Therapy in MS

BONE MARROW MESENCHYMAL STEM CELLS

Bone marrow mesenchymal stem cells (BMSCs) are multipotent stem cells that are derived from the bone marrow and have chondrogenic, osteogenic, and adipogenic differentiation capacities. They can also differentiate into neurons and glial cells (6, 7). The anti-inflammatory, low immunogenicity, and multipotency characteristics of BMSCs render them as a desirable cell source in regenerative medicine (6, 7). Unlike other source of stem cells, ethical concerns or tumorigenic activity is not a concern with BMSCs. They can be cultured and propagated easily *in vitro*, and autologous transplantation can be achieved without rejection (8, 9). BMSCs exhibit migration and homing ability into damaged parts of CNS. Transplantation of this cell population into damaged neural tissues leads to functional improvement via formation of glia and neurons that is identifiable at molecular and cellular levels (10–12). Furthermore, BMSCs have the ability to secrete many autocrine and/or paracrine factors that prevent apoptosis, and mediate neurogenesis and angiogenesis (13, 14). These neurotrophic and neuroprotective factors increase viability and proliferation of neuroglial cells and promote repair and recovery (15, 16). Several studies have confirmed the capacity of BMSCs to improve remyelination following experimental autoimmune encephalomyelitis (EAE) (17, 18). These results suggest that BMSCs are promising cell sources for functional recovery in MS patients. Auto transplantation of BMSCs in patients leads to significant recovery, and limits disability (19, 20).

The transplantation of differentiated BMSCs results in better glial cell engraftment than undifferentiated BMSCs. Transplantation of neuroglial progenitors derived from BMSCs enhances the homing and functional maturation rate of the cells (21, 22). Although the mechanisms that control neuroglial differentiation of BMSCs are not clearly understood, they can be differentiated into neuroglial phenotypes using growth factors, retinoic acid, and cytokines (23, 24). Recovery of the demyelinated areas and promotion of remyelination following transplantation of glial progenitors derived from BMSCs in animal MS models have been documented (25, 26). In experimental animal models, BMSCs have been shown to reduce immune attack to myelin sheets by suppressing T-lymphocyte proliferation (27, 28), diminishing inflammation and demyelination, inducing oligodendrogenesis (12), and improving remyelination (29) and tissue regeneration (10). Clinical trials suggest that BMSCs have the potential to reduce infiltration, decrease demyelinated areas, and improve axonal formation and functional recovery (30).

HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells are isolated from bone marrow and give rise to hematopoietic and lymphopoietic precursor cells, and lymphoid to myeloid lineage cells. Cell-therapy strategies based on engraftment of hematopoietic stem cells have been shown to result in neurological regeneration and repopulation of the immune system (31–35). In animal models, similar positive effects have been reported; however, controversial results also exist (36, 37). Engraftment of hematopoietic stem cells causes clinical improvement in MS patients (38, 39), and auto transplantation of hematopoietic stem cells show positive results in the management of progressive MS (40, 41). Some systematic reviews show that hematopoietic stem-cell therapy in patients with progressive MS leads to recovery of neurological function and prevents mortality of patients (42–45).

UMBILICAL CORD MSCS

Several studies have shown the therapeutic potential of human umbilical cord–derived mesenchymal stem cells (hUC-MSC) in MS patients. hUC-MSCs are promising candidate sources of MSCs that can be collected without pain. They have a faster self-renewal ability compared to other MSCs (46), and they differentiate into a variety of cell types such as bone, cartilage, adipose, muscle, cardiomyocyte, neuron, astrocyte, and oligodendrocyte (47). There is compelling evidence that hUC-MSCs, compared to BM-MSCs, have higher proliferation and differentiation abilities, and stronger immune tolerance because of lower human leukocyte antigen-1 (HLA-1) expression (48, 49). hUC-MSCs can improve clinical manifestations in the animal model of EAE. hUC-MSC-treated EAE mice showed long-term (50 days) recovery of behavioral functions and improvement of histopathological characteristics, including suppression of perivascular immune cell infiltrations and reduction of demyelination in the spinal cord (50). The first report of successful treatment of an MS patient with hUC-MSC was published in 2009 (51). After transplantation of hUC-MSC in a patient with refractory progressive MS, the disease course was stabilized with signs of improved sensory function

and muscle strength, and the patient could even stagger along with the help of family (51). In subsequent clinical experiments, during a 1-year observation period, no significant adverse effects were found in groups treated with hUC-MSC, indicating a better safety profile of these stem cells (52). Administration of hUC-MSC showed lower relapse occurrence and EDSS (Expanded Disability Status Scale) scores in MS patients. Assessment of inflammatory cytokines demonstrated a shift from Th1 to Th2 immunity in treated patients. An increase in HGF was also observed in hUC-MSC-treated group which may have played a role in the improvement of MS. HGF is a multifunctional cytokine which is important for tissue regeneration with its ability to stimulate mitogenesis, cell motility, and matrix invasion (52). According to a case report, a 25-year-old MS patient, throughout the 4-year treatment period (2008–2012) with BM and UC-MSC, was completely free of clinical and radiological disease activity. Also, the patient had good recovery from severe relapse and was able to walk unaided. No new lesions were observed on the MRI performed at the end of the treatment period, and many lesions had resolved (53).

HUMAN WHARTON'S JELLY MSCS

Wharton's jelly is a mucoid connective tissue that surrounds the umbilical vessels. Human Wharton's jelly–derived mesenchymal stem cells (hWJ-MSCs) are a valuable alternative to BM-derived stem cells (54). They can differentiate into many different cell types, including fat, bone, cartilage, and neural cells (29, 55–58). In an experimental model of EAE, transplantation of hWJ-MSCs-derived oligodendrocyte progenitor cells into the brain ventricles of mice reduced the clinical signs of EAE and significantly increased remyelination (59). In another study on rat EAE model, hWJ-MSC suppressed proliferation of activated T-cells with contact-dependent and paracrine mechanisms. Indoleamine 2,3-dioxygenase 1 was shown as the major effector molecule responsible for T-cell suppression (60).

ADIPOSE-DERIVED MSCS

Adipose tissue is an abundant and accessible source of MSCs that can be obtained easily in sufficient quantities with a minimal invasive procedure. These adipose-derived mesenchymal stem cells (AdMSCs) are multipotent and differentiate into chondrocyte, myocyte, neuronal, and osteoblast lineages (61, 62), and are effective in the treatment of immune-related diseases, including GVHD, MS, and rheumatic disease (63).The differentiation and immunomodulatory potencies of AdMSCs are equivalent to that of BMSCs. Whereas hAdMSC derived from elderly and young donors showed similar proliferation, differentiation, and senescence marker patterns, BMSCs from the elderly showed reduced proliferation, decreased differentiation, and increased senescence (64). The therapeutic potential of AdMSCs in a mouse model of peripheral nerve sciatic crush has been demonstrated (65). The therapeutic efficacy of AdMSCs isolated from lean and obese persons indicated that obesity reduces the anti-inflammatory effects of human AdMSCs such that they may not be a suitable cell source for the treatment of autoimmune diseases (66). AdMSCs are a valuable source of adult MSC with neuronal differentiation ability, and are a useful remedy to treat neurodegenerative diseases (67).

Recent studies suggest that AdMSCs have a significant beneficial effect on chronic EAE model, both in the preclinical phase of the disease and after the disease has entered an irreversible clinical course (68). In EAE lesions, the amelioration of clinical scores was accompanied by a strong reduction of spinal cord inflammation as well as demyelination and axonal damage. Administration of AdMSCs in chronic EAE induces a Th2-type cytokine shift in T-cells. The penetration of AdMSCs within demyelinated areas is accompanied by increased number of endogenous oligodendrocyte progenitors (69). Additional studies showed that murine AdMSCs (mASCs) suppress T-cell proliferation via inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) activities. mASCs also prevented lipopolysaccharide (LPS)-induced maturation of dendritic cells (DCs) (70). The efficacy of intravenous AdMSCs transplantation in remyelination, in mouse cuprizone model of MS, can be significantly enhanced by 17β-estradiol (E2) administration (71). AdMSCs can upregulate immunomodulatory cytokines, such as TGF-β, and downregulate inflammatory cytokines, such as IFN-γ, and transcription factors, such as t-bet (72). Brains and lymph nodes of EAE rats treated with AdMSCs show a significant expression of human leukocyte antigen G (HLA-G) gene. The immunomodulatory effects of AdMSCs may be related to their secretion of HLA-G (73). Engineering of AdMSCs as carriers for IFN-β delivery, or secretors of IL-10, has shown beneficial effects in experimental models of MS (74, 75).

NEURAL STEM CELLS

NSCs are unipotent stem cells found in the subventricular zone (SVZ) of the lateral ventricle. This part of the CNS is routinely used for isolation of NSCs (76, 77). The unipotency and migratory properties of NSCs help to repopulate neural cells in the CNS following inflammation (4, 78). The potential of NSCs to differentiate into neuroglial cells and oligodendrocytes suggests their application as a beneficial method for the treatment of MS (79–84). NSCs can also be derived from bone marrow, and these cells also exhibit the capacity for neuroglial differentiation (81, 82).

ENDOMETRIAL STEM CELLS

Human endometrium contains a small number of endometrial stem cells (hEnSCs) that can be considered as a source of MSCs for cell-based tissue engineering applications to repair bone, neural cells, osteoblasts, cartilage, and muscle (85). It is well understood that endometrial stem cells (EnSCs) are responsible for the remarkable regenerative capacity of endometrium (86). hEnSCs can differentiate into high-efficiency cholinergic and dopaminergic neurons with confirmed formation of functional neurons (87). EnScs alleviate neuroinflammation through the impairment of Th17 and Th1 CD4 cells (88). hEnSCs can be differentiated into Schwann cells (SCs) in both 2D and 3D cultures. These differentiated cells in fibrin gel could present new opportunities for tissue engineering approaches and subsequent treatment of neurodegenerative disorders (89). hEnSCs can differentiate into oligodendrocyte progenitors with characteristic oligodendroglial precursor cells (OPCs) morphology, and express markers such as PDGFRα, Sox10, A2B5, Olig2, and O4 (90). hEnSCs reduced perivascular

infiltrate and EAE scores, and improved overall tissue appearance (91) in experimental mice. Intravenous or intrathecal administration of hEnSCs to four patients showed a good safety profile. After 1 year of follow-up, the patients showed no immunological reactions or treatment-associated adverse effects; based on radiological and functional assessment as reported by radiologists, no disease progression was observed (92).

EMBRYONIC STEM CELLS

ESCs are derived from the inner cell mass of blastocyst-stage embryos. ESCs are totipotent cells that can differentiate into all tissues and cell types, including hematopoietic precursors, heart and skeletal muscles, and neural cells. ES cells can be considered as a valuable source of cells for deriving glial precursors that can interact with host neurons and efficiently myelinate axons in brain and spinal cord and also promote improvement of motor function (93, 94). Human embryonic stem cells (hESCs) have proved a promising source for the generation and replacement of mature oligodendrocytes (95). Accordingly, hESC-derived oligodendrocytes can play a supportive role in the repair of CNS injuries (96). Intracerebroventricular transplanted hESC-derived oligodendroglial progenitor (hESC-OPs) cells ameliorated the clinical symptoms and promoted recovery from EA E paralysis. EAE mice that received hESC-OPs induced Foxp3-positive T-regulatory cells and produced a new population of TREM2-positive cells that has anti-inflammatory and tissue regeneration promoting properties (97). Also, transplanted hESC-derived neural precursor cells into the brain ventricles significantly reduced the clinical signs of EAE mice. Transplanted neural precursors migrated into the host white matter; however, differentiation into mature oligodendrocytes and remyelination were insignificant (3). In the EAE model of MS, the therapeutic effect of hES-MSCs, including reduction of clinical symptoms and prevention of neuronal demyelination, was significantly higher than BM-MSCs (98). Transplantation of ESCs in adult rat spinal cord had the ability to survive, migrate, and differentiate into mature myelin-producing cells in areas of demyelination (99). Clinical reports of transplantation of hESC in patients with MS and Lyme disease have shown remarkable improvement in their functional skills, overall stamina, cognitive abilities, and muscle strength (100).

INDUCED PLURIPOTENT STEM CELLS

Induced pluripotent stem cells (iPSCs) are generated via reprogramming of mouse fibroblasts into ESCs that overexpress four genes: *Sox2,Oct3/4*, *Klf4,* and *c-Myc* (101, 102). iPSCs exhibit similar phenotype of ESC, and proliferate and differentiate into all cell types of the body as well as teratomas formation (103, 104). Remyelination activity of iPSCs was assessed in mouse EAE models. The formation of oligoprogenitor cells and myelinating oligodendrocyte confirms the therapeutic effects of cell therapy based on iPSCs. Also, iPSCs have the neuroprotective effects via secretion of growth factors such as LIF that amplify the viability of endogenous oligoprogenitor stem cells and remyelination (105, 106). iPS cells can provide the allogeneic and autologous stem cell therapy and hold promise for specific treatment.

SPERMATOGONIA STEM CELLS

Spermatogonia stem cells (SSCs) are derived from seminiferous tubules in testes, and *in vitro* studies show the pluripotency of these cells (22, 107–109). They differentiate into ES-like cells, with a similar phenotype and differentiation capacity (110–112). They can be considered an alternative cell source to ESCs without the ethical limitation and immunological problems associated with ESCs. Neural and glial differentiation of ES-like cells derived from testes have been reported by several groups. The efficiency of neural differentiation was confirmed using action potentials recorded by Patch-clamp electrophysiological examinations, and the capacity of SSCs to form functional neurons and oligodendrocytes has been reported. Our findings showed functional recovery and significant remyelination, following transplantation of oligoprogenitor cells derived from mouse SSCs, in an animal model of demyelination (22). Further investigations should be done to confirm the recovery outcome of this novel pluripotent cell source in animal models of MS.

Endogenous Stem Cell Niches Reactivation in MS

Apart from the exogenous sources of stem cells described above, the endogenous stem cell population opens up a new perspective for MS treatment (113). Studies on patient brain tissue samples and animal models of MS show that in the adult CNS, endogenous regeneration activities exist; however, repair efficacy is low and tends to diminish during disease progression (114, 115). Mature oligodendrocytes are extremely degenerative due to primary insult, or secondary to oxidative and excitotoxic stress; thus, they do not participate in myelin repair activities (116). However, resident OPCs (117) or adult neural stem cells (aNSCs) (118–120) become activated and are recruited to lesion sites in order to perform remyelination and restore axonal functionality. There is evidence that OPCs produce the vast majority of remyelinating oligodendrocytes (121), which can also originate from the stem and precursor cells of adult SVZ (122). In response to injury or demyelination, OPCs in the surrounding area convert from a quiescent state to a regenerative phenotype (123). Injury to the CNS activates microglia and astrocyte cell types and disturbs tissue homeostasis, resulting in OPC activation (124). These two cell types are the main factors that induce proliferation and migration of OPCs to the site of injury in demyelinating insults (124, 125). During the regeneration phase of demyelination, some factors have been shown to contribute to the regulation of OPC differentiation into myelinating oligodendrocytes (126). Several studies have provided evidence for the inhibitory effects of some factors such as semaphorin 3A (127), Nogo receptor (128), LINGO-1 (129, 130), and wnt signaling pathway (131) on OPCs differentiation during development and remyelination. Remyelination can occur in demyelination conditions but is very limited. Remyelination failure is due to the impact of numerous inhibitory mechanisms (132, 133). To improve functional recovery, therapeutic approaches should be developed by either potentiating endogenous stem cell populations or by providing exogenous source of repair-mediating cells for the injured CNS. In this section, we describe recent studies related to the

endogenous stem cells of the central and peripheral nervous systems, and their potential therapeutic application for the treatment of MS.

CNS Neural Stem Cell pools

Within the adult mammalian brain, NSCs are located in the SVZ of lateral ventricles, hippocampal subgranular zone (SGZ), and the central canal (CC) of the spinal cord where they divide and give rise to new neurons in a process termed adult neurogenesis (4, 134, 135). Other germinal regions have been identified in the third ventricle, hypothalamus, the subpial layer of the cerebellum, and the meninges (136, 137). NSCs located in very specific microenvironments, called niche, and their cellular makeup have been shown to consist of a variety of cells including NSCs and their immature progeny accompanied by endothelial, astroglial, and ependymal cells (138, 139). They receive structural and trophic signals from cell-to-cell and cell-to-extracellular matrix (ECM) contact. This communication provides critical spatial and temporal information, which in turn allows stem cells to act in response to both physiological and pathological stimuli (138, 140).

SVZ OF LATERAL VENTRICLES

SVZ is the largest neurogenic niche in the adult CNS that is capable of sustaining neurogenesis throughout life (141). The adult SVZ displays a high degree of organization with stem cells and other cell types which is an important feature of the neurogenic region of SVZ (142). The SVZ is composed of heterogeneous cell types including nondividing ependymal cells (E1) with a large apical surface and multiple long cilia (143), astrocyte-like type B cells (B1) (slow dividing) that give rise to type C cells (fast dividing), which in turn differentiate into neuroblasts (type A) and migrate to olfactory bulb and provide new interneurons (144, 145). The en face view of the lateral ventricle revealed that the apical cilium of one or more B1 cells was surrounded by E1 cells in striking pinwheel architecture which is specific to neurogenic area (142). B1 cells contact the ventricle via their apical cilium and blood vessels at the basal processes. They are quiescent and slowly proliferate in normal condition but can become activated in different pathologies (146).

Intense research in the last decades on animal models of MS and tissue samples of MS patients has shown that the adult SVZ niche is reactivated in response to various types of proximal insults by producing new progenitors that migrate toward the injury site and differentiate into oligodendrocytes (118, 147–149). In addition, it has been reported that type B (150), type C (147), and type A cells (151) have all been indicated as sources of newly generated oligodendrocytes in physiological and pathological conditions. Furthermore, we recently found that ventricular pinwheel organization and structure are modified and E1 cells are reactivated in response to inflammatory demyelination (152). However, SVZ progenitor's recruitment into the lesion site in the demyelination condition was relatively poor and their differentiation potential to oligodendrocyte is limited because of some inhibitory factors in mature environments during MS.

SGZ OF THE HIPPOCAMPUS

The second major region that sustains neurogenesis in the adult brain throughout life is the SGZ of the hippocampus, which is located at the border of the granule cell layer (GCL) and the hilus of dentate gyrus (DG) (153). Neurogenesis in the adult hippocampus occurs throughout life and mainly contributes to the processes involved in learning and memory; however, the ultimate function of neurogenesis in DG remains to be clarified (154). Radial glia-like cells (RGL) in DG represent a quiescent population which may be provoked to generate the proliferative precursors identified as intermediate progenitors, namely, IPC1 and IPC2 cells (155). These cells produce novel immature granule neurons (type 3 cells), which migrate into the inner GCL and differentiate into granule cells of the DG (153). They extend their dendrites and axons toward the CA3 region and become functionally integrated into host circuitry (119).

Cognitive impairment and memory dysfunction affect more than 60% of MS patients (156). It has been reported that cognitive dysfunction is correlated with hippocampal demyelination (157). Although the molecular mechanisms that control hippocampal NSC proliferation and differentiation in physiology and pathological conditions are unknown, recent findings reveal that acute inflammatory demyelination in animal model of MS could provoke the hippocampal stem cell niche and enhance proliferation of NPCs in SGZ (158). Thus, inflammatory factors such as cytokines and chemokines can affect the proliferative capacity of NSCs and alter neurogenesis in the SGZ (159). Huehnchen et al. (2011) reported that NPC proliferation in the DG increases not only in the acute phase but also in the chronic phase of the disease(160). Furthermore, it has been found that the neurogenic niche of the hippocampus was reactivated in animal models of MS (161).

CENTRAL CANAL OF THE SPINAL CORD

The spinal cord is the caudal part of CNS that consists of 33 nerve segments, from the cervical to coccygeal sections. There is a central canal at the center of the spinal cord which contains the cerebrospinal fluid (CSF) (134). The ependymal layer of the spinal cord has an important role in embryonic development and is well known for its function as a neuroprogenitor niche (162). In the late 1990s, multipotent stem cells were discovered in the adult mammalian spinal cord. Isolated NSC from central canal of rat and mouse can produce neurospheres that are able to self-renew, proliferate, and differentiate into the three major CNS cell types (163). Moreover, it was shown that NSC resides at the central canal and is able to self-renew and generate mature oligodendrocytes during injury (164). The adult central canal stem cells are quiescent under physiological conditions; however, some proliferation has been observed at the dorsal and ventral tip of the CC that contacts the lumen or the subependymal position (135, 164). Dorsal ependymal cells show radial glial morphology and express GFAP, nestin, CD15, and/or brain lipid–binding protein (BLBP) (165). It has currently been shown that ependymal cells at both dorsal and ventral point of the central canal are able to generate progeny of multiple fates under physiological and pathological conditions (166). Further research is needed to fully unravel the neurogenic properties and/or potential of the central canal in MS.

OTHER GERMINAL AREAS OF THE CNS

Beyond the classic NSC niches referenced above, other germinal niches have been identified. These germinal regions include the hypothalamus, the third ventricle, the meninges, and the subpial layer of the cerebellum (167). The parenchyma of the cerebral cortex and spinal cord are mainly comprised of restricted neuroglia precursors and these niche are referred to as nongerminal regions of CNS (168). These neurogenic niches are composed of a heterogeneous population of NSC that is able to self-renew and give rise to most of the neuronal and glial precursors (4). Several studies showed that the third ventricle and hypothalamus neurogenic zone contain multipotent cells that can give rise to neurons, oligodendrocytes, and astrocytes *in vitro* and *in vivo* (169–171). Xu and others reported that the third ventricle ependymal layer cells were able to migrate into hypothalamic parenchymal regions and differentiate into functional neurons in response to injury (172). Our previous study also showed that progenitor cells in the third ventricle surroundings could be reactivated by local demyelination in the optic chiasm (128, 171). Also nestin and DCX-positive cells have been found in the meninges of the brain and spinal cord (138, 173). We concluded that there are widespread sources of stem cells in the CNS that can be activated in different pathological situations, especially in MS.

Peripheral Endogenous Stem Cells and Their Role in MS

SCHWANN CELLS

In the peripheral nervous system (PNS), a different source of cells has been identified that can be used for the treatment of CNS diseases like MS. SCs have been intensely studied in CNS repair and have been shown to support and myelinate regenerating axons (174). Several studies that transplanted neonate or adult SCs in different animal models of CNS demyelination had shown that SCs efficiently remyelinate CNS axons (175). The myelin formed by a grafted SC was stable for up to 5 months post-graft and improved conduction of demyelinated axons (176, 177). Neuroregenerative effect of SCs has also been reported in spinal trauma models which highlighted the ability of these cells to regenerate axons in the injured area (178). However, the important limitation concerning the use of SCs as a therapeutic approach to promote remyelination in MS is their inability to migrate efficiently when grafted in injured CNS (179). Modifying SC-intrinsic properties, like boosting expression of neurotrophins (e.g., BDNF and NT3), promote SC migration and myelinating potentials (180, 181). Also, SC-mediated myelination and axonal regeneration increased when the environment of the SC was modified (182).

OLFACTORY ENSHEATHING CELLS

Olfactory ensheathing cells (OEC) are very similar to SCs and belong to the peripheral olfactory system that ensheathes the axon of the first cranial nerve but does not myelinate it (183). Recently, it was shown that the origin of OEC

during development was from neural crest cells (NCCs) (184). Although OEC does not usually myelinate axons of the first cranial nerve, the vast studies have shown that OECs are capable of extensive functional remyelination when grafted into demyelinated lesions (185, 186). Numerous studies proposed that OEC migrates better than SC when faced with CNS elements (187, 188). From a therapeutic point of view, OEC transplantation appears to be better than SC.

PNS PROGENITORS

PNS progenitors include Schwann cell precursors (SCps), boundary cap cells (BCs), and olfactory epithelial progenitors (OEps) that all originate from NCCs (175). It has been reported that SCp has greater capacity for remyelination after grafting in demyelinated CNS or spinal cord injury (189). BC is the potential stem cell of spinal roots (190) that could migrate freely in the demyelinated CNS and compete with endogenous myelin-forming cells to remyelinate axons of far distant lesions (191). BC can also differentiate into central myelin-forming cells *in vitro* and *in vivo* (192). OEp was extracted from olfactory epithelium with a less invasive method and when pieces of olfactory lamina containing OEp were grafted into injured rat spinal cord, they promoted functional recovery in paraplegic rats (193). OEp provided extensive remyelination upon transplantation into demyelinated lesion (194).

Endogenous Neural Stem Cell Niche Modulation as a Therapeutic Approach

The niche microenvironment regulates NSC survival, proliferation, and differentiation during health and disease (142, 152). Therefore, different molecular strategies have been studied in an effort to enhance the NSC niche potential for facilitating repair and aiding in functional recovery of various neurodegenerative disorders by using new pharmacological targets (138). Administration of exogenous growth factors such as EGF, PEDF, HGF, and CNTF in mice has been reported to enhance NSC proliferation (195, 197). In addition, other factors such as bFGF, EGF, and BDNF have also been shown to enhance neurogenesis and eventually enhance functional recovery in animal models of neurological disease (198–200). Administration of valproic acid has been shown to attenuate symptoms of EAE, and increase endogenous myelin repair by recruiting NSCs and oligodendrocyte progenitors to the lesion sites (201). Moreover, treatment of EAE animals with polymerized nanocurcumin showed promising results in enhancing neuroprotection and myelin repair (202). Certain antidepressants like fluoxetine have been revealed to be capable of increasing neurogenesis (203). Administration of small interfering RNA (siRNA) or specific antibodies against various inhibitory targets such as Nogo, Nogo receptor (NgR), LINGO1, and Sema3A in different animal models of MS and spinal cord injury enhance proliferation, migration, and differentiation potential of endogenous stem cells and facilitate axonal regeneration, myelin repair, and functional recovery (128, 204–207). Khezri and coworkers reported that administration of cyclic AMP inhibits the progression of EAE disease and potentiates recruitment of endogenous NSCs and myelin repair (208).

Conclusion

The existence of NSCs and neurogenic niches in the adult mammalian CNS is clearly recognized. The functional implication of adult neurogenesis and gliogenesis continues to grow as new researches describe their critical roles in both health and disease. In spite of this growing body of evidence and progress in our understanding of NSC and niche functions in physiological and pathologic situations, several critical issues remain to be answered. The main issue is the translational relevance of the basic biology, that has been described in animal models, to human neurogenesis, and clinical trials. Moreover, the ultimate molecular mechanisms that influence endogenous stem cell migration will also be a key in developing appropriate treatments and strategies to prevent, alleviate, and treat MS. Further studies to identify the definitive nature, location, and behavior of NSC are warranted to realize the full therapeutic potential of these stem cells for the treatment of MS.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this chapter.

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