REVIEW

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Promoting exogenous repair in multiple sclerosis: myelin regeneration

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Purpose of the review
Despite the significant progress in the development of disease-modifying treatments for multiple sclerosis (MS), repair of existing damage is still poorly addressed. Current research focuses on stem cell-based therapies as a suitable alternative or complement to current drug therapies.

Recent findings
Myelin damage is a hallmark of multiple sclerosis, and novel approaches leading to remyelination represent a promising tool to prevent neurodegeneration of the underlying axon. With increasing evidence of diminishing remyelination capacity of the MS brain with ageing and disease progression, exogenous cell transplantation is a promising therapeutic approach for restoration of oligodendrocyte precursor cell pool reserve and myelin regeneration.

Summary
The present review summarizes recent developments of remyelinating therapies in multiple sclerosis, focusing on exogenous cell-based strategies and discussing related scientific, practical, and ethical concerns.

Keywords
exogenous repair, multiple sclerosis, remyelination, stem cells

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelination and primary or secondary axonal degeneration [1]. The pathogenetic mechanisms involved in the disease development [2] are highly heterogeneous and are closely related to the clinical disease phenotypes [3]. Demyelination in MS is caused by a dysregulation of myelin-specific self-tolerance, CNS recruitment and activation of inflammatory cells, such as lymphocytes, microglia, and macrophages, resulting in myelin damage. Progressive MS (PMS) is primarily characterized by neurodegeneration, however, it is still unclear whether early neurodegeneration drives autoimmune injury or ongoing inflammation reaches a threshold to trigger the neurodegeneration [4]. Most of the ongoing clinical trials for PMS are focused on testing the repurposed drugs, unfortunately, none of these studies achieved significant results, lacking clinical efficacy due to the paucity of the tailored targets [5]. The failure of clinical trials may indicate that exclusively targeting axonal resilience or only enhancing remyelination might not be sufficient to achieve neuroprotection and revert or delay MS progression. Effective management of PMS represents an unmet need for alternative therapeutic strategies modulating chronic inflammation, inducing neuroprotection, and potentiating intrinsic regenerative CNS properties, altogether impeding the irreversible progression of disability. Myelin damage is a hallmark of MS, and novel approaches leading to remyelination represent a promising tool to prevent neurodegeneration of the underlying axon. Although

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KEY POINTS

- Neuroprotection and remyelination are the unmet clinical needs in multiple sclerosis.
- Endogenous remyelination is spontaneous but is inefficient and highly heterogeneous, especially in progressive multiple sclerosis patients.
- Stem cell therapy might serve as a suitable alternative or complement to current drug therapies in multiple sclerosis.
- Exogenous remyelination therapies can be mediated by restoring the stem cell pool reserve or by a bystander effect of beneficial trophic factors release promoting the generation of new oligodendrocytes.

remyelination is common in MS where completely remyelinated lesions or shadow plaques are detectable by magnetic resonance imaging (MRI) and present all along the course of the disease with similar frequencies [6], the newly-generated myelin is mostly thin and predisposed to secondary demyelination [7,8]. A recent study by Neely *et al.* [9▪▪] have demonstrated that oligodendrocytes (OLs) surviving demyelination have a reduced capacity to generate functional myelin, compared to newly formed OLs. Moreover, the remyelination capacity of the MS brain diminishes with ageing and during disease progression [10]. This suggests that future therapeutic approaches for potentiation of remyelination by pharmacological improvement of endogenous oligodendrocyte precursors cells (OPCs) remyelination capability or by transplantation of exogenous OPCs are the promising strategies in demyelinating diseases like MS [11].

This short review discusses the potential of remyelinating therapies in MS, focusing on cell-based strategies and discussing related scientific, practical, and ethical concerns.

STEM CELLS SOURCES FOR REMYELINATION THERAPIES

Cell-based remyelination therapies hold great potential for demyelinating diseases like MS and can serve as a suitable alternative or complement to current drug therapies. The therapeutic effect of transplanted stem cell progenitors or their derivatives can be mediated either through the restoration of the stem cell pool reserve by direct cell replacement or via a bystander effect of beneficial trophic factors release. Among the adult stem cell sources for transplantation, hematopoietic (HSCs) and nonhematopoietic (nHSCs) stem cells have been investigated in the last decade. HSCs represent the only cellular therapy validated in the clinical practice, which is used as a standard of care in patients with highly active relapsing-remitting MS (RRMS) [12]. Despite HSCs transplantation represents a highly effective treatment in RRMS, it exerts a poor pro-regenerative effect on the CNS.

In the context of nHSCs, two main stem cells populations have been studied: mesenchymal stromal cells (MSCs) and neural stem/precursor cells (NSCs/NPCs). The latter includes the use of fetal NPCs (fNPC), iPSC-derived NPCs, and directly reprogrammed iNPCs from the patient somatic cells (Fig. 1). Several preclinical studies have demonstrated the ability of MSCs to transdifferentiate into neural cells and migrate into the CNS. These properties led to the assessment of MSCs efficacy in experimental autoimmune encephalomyelitis (EAE). Pro-regenerative and immunomodulatory MSCs functions are mediated mainly by MSCs secretome. Indeed, MSCs secrete paracrine molecules via extracellular vesicles (EVs) to mediate the therapeutic effects on neuroregeneration and remyelination [13].

The transplantation of NPCs has several advantages compared to other stem cell sources due to their inherent commitment to the neural lineage, lack of pluripotency and, therefore, low tumorigenicity. NPCs can be isolated from donated fetal tissues or can be differentiated from iPSCs, maintained, and expanded *in vitro* as a cell line by continuous stimulation with growth factors, and cryopreserved. NPCs maintain a steady growth profile and have the potential to differentiate into postmitotic daughter neural cells. Transplanted, NPCs engraft into the adult CNS exerting neurogenic and nonneurogenic functions [14], which have been extensively studied in preclinical models of MS. Transplanted NPCs reach the site of injury, shape their fate to the microenvironmental needs and promote CNS repair through heterogeneous mechanisms, displaying both pro-regenerative and by-stander neurotrophic and immunomodulatory potential [15]. In a neurodegenerative milieu, transplanted cells differentiate and replace damaged neural and oligodendroglia cells [15,16]. In contrast, when neuroinflammation prevails, NPCs maintain an undifferentiated phenotype exerting trophic support, immunomodulation and metabolic signaling through paracrine mechanisms and cell-to-cell interaction, promoting tissue repair and re-establishing the functional interactions between neural and glial cells [17,18].

PRECLINICAL AND CLINICAL TRIALS OF STEM CELL-BASED REGENERATIVE CNS THERAPIES

Preclinical studies of MSCs transplantation in MS animal models demonstrated their neuroprotective,

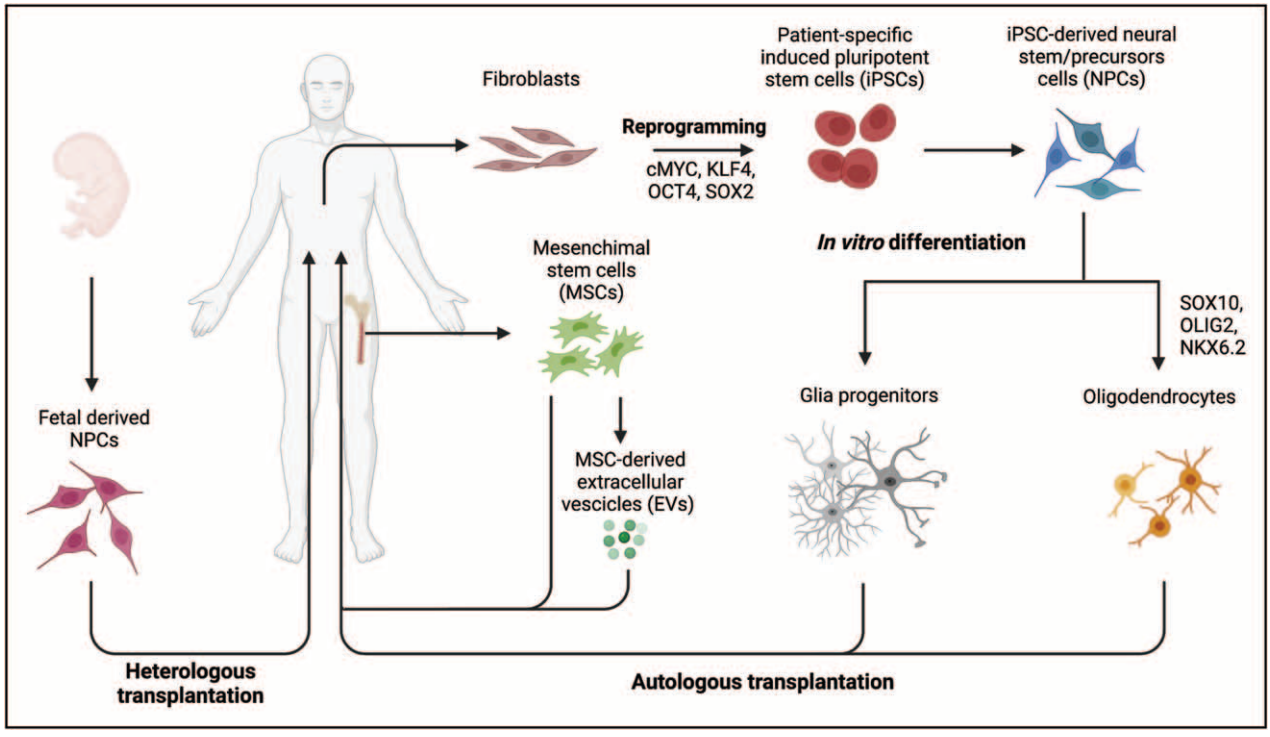

FIGURE 1. Stem cells sources for remyelination therapies. Cell-based remyelination therapies can be obtained from autologous and heterologous sources. Fetal neural precursor cells (fNPC) can be derived from the fetal brain tissue at 10–12 weeks of gestational age obtained from an elective pregnancy interruption. Besides the major ethical issues, transplantation of heterologous fNPCs requires immunosuppressant therapies to prevent cells rejection. The autologous stem cell sources for transplantation obviate the need for immunosuppression; among the optimal sources are mesenchymal stromal cells (MSCs) and patient-specific induced pluripotent stem cells (iPSCs). Since MSCs secrete paracrine molecules via extracellular vesicles (EVs) release, MSC-derived EVs (MSC-EVs) have been recently employed as therapeutic vehicles. NPCs can be differentiated from iPSCs (iPSC-derived NPCs) or directly reprogrammed from patient somatic cells (iNPCs). Finally, iPSCs can be guided towards *in vitro* differentiation to oligodendrocytes and glial progenitors.

immunomodulatory and remyelinating properties [19,20]. MSC transplantation improved the EAE clinical course fostering endogenous neurogenesis and remyelination. MSC exert their effect by stimulation of OPC and OL proliferation, and enhancement of myelinogenesis through the release of brain-derived neurotrophic factor (BDNF) that supports neuronal survival and regulates dendritic growth [21]. These effects have been associated with reduced encephalitogenic T cells migration and activation and enhanced tolerance against myelin proteins [22]. About thirty clinical trials based on MSCs transplantation have been conducted so far in patients with MS [23], demonstrating safety and tolerability of the procedure and short-term benefits by inhibiting disease progression, especially in patients with previously active disease [24,25▪]. However, the outcome of the MESEMS study, which evaluated the activity of MSCs on MRI (gadolinium-enhancing lesions) and clinical (annualized relapse rate) surrogate markers of efficacy, do not support their use in patients with multiple sclerosis with ongoing inflammation [26▪▪]. Additional large cohort trials are necessary to assess the bona fide neuroprotective and tissue-healing properties of MSCs in patients with PMS and sustained disability. MSC-derived EVs (MSC-EVs) have been recently employed as therapeutic vehicles due to their capability to cross the BBB [27]. In addition to the encouraging safety profile [28], MSC-EVs efficacy has been shown to ameliorate the functional outcome in EAE mice by reducing demyelination and the number of inflammatory infiltrates [29].

Cell-based therapies are still in their early experimental phase, and strict ethical issues about easily accessible and readily available sources of NPCs for clinical trials should be considered. Different cell types have been recognized as sources of neural progenitor for brain regeneration, such as fetal neural precursor cells (fNPCs) or iPSCs [30,31]. Although fNPCs can be maintained and expanded *in vitro* without losing their self-renewing and neurogenic capacity for an extended period, they have a low proliferation rate and, therefore, limited use. Besides,

their fetal tissue source of origin brings major ethical issues. In addition, fNPCs are heterologous, and immunosuppressant therapies are needed to prevent cell rejection. To overcome ethical concerns, patient-specific iPSC-derived NPCs and iNSCs are the alternative cellular therapy candidates that demonstrated preclinical efficacy in MS-relevant animal models ameliorating chronic neuroinflammation, reducing astrogliosis and demyelination through release, for instance, of leukemia-inhibiting factor (LIF) and transforming growth factor (TGF)-β2, confirming their bystander effect activity [25▪,32,33]. Ad hoc engineered *in vitro* iPSC-derived NPCs hold a great promise to maximize the bystander effect of transplanted NPCs in promoting remyelination and neuroprotection, for example, by targeting TGFβ2 expression through Tbx21 promoter boosting the immunomodulatory potential, or by overexpression of Sox10, Sema3F or Chi3l3/Ym1 [34,35,36▪] to promote remyelination.

iPSCs, generated by genetic reprogramming of adult somatic cells [31], are pluripotent and, therefore, can be differentiated virtually into any cell type. Advanced technologies for guiding iPSCs toward *in vitro* differentiation to multiple neuronal subtypes, oligodendrocytes and astrocytes offer the possibility of autologous transplantation, obviating the need for immunosuppression [37]. Transplantation of cells committed to oligodendrocyte precursor state (iPSC-derived OPCs) represents an ideal autologous source to promote remyelination. Recent technological advancements exploiting the introduction of three transcription factors (SOX10, OLIG2, NKX6.2) in iPSCs-NPCs allows generating human induced oligodendrocytes (hiOL) with high efficiency in a relatively short time [38]. hiOLs from MS patients showed their full ability to integrate and establish functional cellular connections *in vivo* [39], qualifying them as an ideal source for personalized autologous cellular therapies to promote remyelination in MS. Although human iPSC-derived OPCs (hOPCs) or hiOL have not yet been tested in early clinical trials, their repair efficacy and safety were evaluated after transplantation into mice with congenital demyelination [40]. In addition, the transplantation of hiPSC-derived OLs in the myelin mutant Shi/Shi $Rag2^{-/-}$ mice was developed to study the therapeutic potential of novel pro-myelinating compounds on human-derived myelin *in vivo* [41▪]. The humanized chimera models provide a unique opportunity for studying human demyelinating diseases and hold the promise to bridge the gap in the translation of preclinical discoveries to the clinic [42].

The first phase I clinical study of intracerebral injections of hOPCs into multiple locations in patients with secondary progressive MS (SPMS) is currently planned by the New York Consortium for the Treatment of Myelin Disease (https://stemcell.ny.gov/nystem-consortia). Additionally, early clinical trials had investigated the safety and efficacy of human embryonic stem cell (hESC)-derived OPCs and neural progenitor transplantation in spinal cord injury and congenital demyelinating Pelizeaus-Merzbacher disease [43].

Despite great promise, several challenges have been associated with iPSC-derived stem cell therapy in clinical settings, including their potential immunogenicity, tumorigenicity, and heterogeneity [44] due to genetic modifications introduced during reprogramming, including aberrant DNA methylation and potential cancer-related genetic mutations [45]. These issues should be carefully addressed before advancing iPSC-based therapies into routine clinical settings. Regardless of certain limitations, NPCs transplantation may represent one of the most promising approaches to generate new therapeutic options for a wide range of still incurable chronic neurological disorders [46▪▪], including PMS. The multifactorial effect of NPCs has been assessed in preclinical models of MS, both in rodents and non-human primates. In EAE, injected NPCs can migrate to demyelinating areas leading to a significant amelioration of EAE impairment evaluated through clinical and neurophysiological measures [47]. NPCs attenuate EAE clinical course by either differentiating into mature brain cells, decreasing demyelination and axonal loss rates [47], or maintaining an undifferentiated regulatory phenotype. Undifferentiated NPCs express various secreted and transmembrane molecules that exert immunomodulatory and neurotrophic factors. Indeed, NPCs inhibited the perivascular activation of proinflammatory infiltrating $CD3^+$ T cells, increased the number of $CD25^+$ and $CD62L^+$ regulatory T cells [48], and induced apoptosis of CNS infiltrating Th1 cells [49] after transplantation in EAE mice. These effects were mediated by the expression of death receptor ligands (FasL, Trail, Apo3L) and by the secretion of molecules involved in apoptosis regulation (NO, IFN-γ, LIF, and glial cell line-derived neurotrophic factor (GDNF).

Interestingly, pathology studies have demonstrated that transplanted NPCs displayed a pathotropic distribution pattern, located closely proximal to the demyelinated or remyelinated axons. Only a few NPCs were found in regions with a preserved myelin architecture. The engrafted cells differentiate into OPCs which are involved in active remyelination processes, as demonstrated by their distribution in close contact with axons with poorly compacted myelin sheets and by the expression of platelet-derived growth factor-α (PDGF α) receptor [47].

Since the EAE model in nonhuman primates resembles the hallmarks of human MS more closely than murine EAE, the therapeutic properties of hNPCs transplantation have been demonstrated in a preclinical study of the EAE marmoset [50]. The EAE marmosets transplanted with hNPCs showed remarkable amelioration from EAE-related neurological deficits in terms of cumulative score, number of relapses per day at follow-up and number of EAE-related deaths, compared to the sham-treated control. The transplantation of hNPCs decreased CNS inflammation, demyelination, and axonal loss [50]. No adverse events were ever observed. In addition, the pathological evaluation identified transplanted hNPCs within the perivascular CNS areas. These cells displayed round or bipolar morphology, suggesting their undifferentiated state, whereas only rare cells expressed differentiation markers. The marmoset study represents a preclinical proof-of-principle of hNPCs transplantation feasibility in MS patients. Indeed, this preclinical evidence led to the first clinical phase I trial in patients with PMS, the STEMS study (ClinicalTrials.gov: NCT03269071). This is a prospective, not randomized, open-label, single dose-escalation phase I clinical trial, performed at San Raffaele Scientific Institute, Milan, Italy aimed at evaluating the feasibility, safety, and tolerability of intrathecally transplanted human fetal NPCs (hfNPCs) in 12 patients with PMS. Patients were divided into four treatment cohorts and received a single escalating dose of cells. Enrolled patients were under immunosuppressive treatment to prevent hfNPCs rejection and have received adequate antibiotic and antiviral prophylaxis. To reduce hypersensitivity reactions, premedication with steroids was given immediately before the slow intrathecal infusion of hNPCs, performed through a lumbar puncture. Follow up was conducted for 2 years after transplantation with clinical monitoring for survival, safety, tolerability, and overall changes in the neurological status, assessed through neurological, neuroradiological and neurophysiological examinations.

Additionally, two phase-II clinical trials (ClinicalTrials.gov: NCT03355365, NCT03822858) will investigate potential benefits of autologous mesenchymal stem cell-derived neural progenitors (MSC-NPs) transplantation, a specific MSC subpopulation primed towards neuroectodermal lineage, in PMS patients. Phase I safety clinical study by Harris and colleagues demonstrated improvement in expanded disability status scale (EDSS) in a subset of ambulatory SPMS patients (EDSS $\leq$ 6.5), together with improvement in bladder and muscle strength functions after intrathecal administration of MSC-NPs [51]. The transplantation was well tolerable and safe, resulting in sustained EDSS improvement or disease stabilization in 13 out of 20 patients over a 2-year follow-up period [52▪▪].

Results from these ongoing trials will provide indisputable evidence for the future development of new treatment strategies based on NPC transplantation in MS.

CONCLUSION

Although stem cell therapies have shown encouraging results in preclinical and early clinical studies [53▪▪], the field of stem cell-based regenerative medicine is still in its relative infancy, and more advanced, well designed, and rigorously controlled studies are required to establish the stem cell repair potential in MS [54▪].

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Conflicts of interest

There are no conflicts of interest.

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