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REVIEW

Cell Therapy for Multiple Sclerosis

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Abstract The spontaneous recovery observed in the early stages of multiple sclerosis (MS) is substituted with a later progressive course and failure of endogenous processes of repair and remyelination. Although this is the basic rationale for cell therapy, it is not clear yet to what degree the MS brain is amenable for repair and whether cell therapy has an advantage in comparison to other strategies to enhance endogenous remyelination. Central to the promise of stem cell therapy is the therapeutic plasticity, by which neural precursors can replace damaged oligodendrocytes and myelin, and also effectively attenuate the autoimmune process in a local, nonsystemic manner to protect brain cells from further injury, as well as facilitate the intrinsic capacity of the brain for recovery. These fundamental immunomodulatory and neurotrophic properties are shared by stem cells of different sources. By using different routes of delivery, cells may target both affected white matter tracts and the perivascular niche where the trafficking of immune cells occur. It is unclear yet whether the therapeutic properties of transplanted cells are maintained with the duration of time. The application of neural stem cell therapy (derived from fetal brain or from human embryonic stem cells) will be realized once their purification, mass generation, and safety are guaranteed. However, previous clinical experience with bone marrow stromal (mesenchymal) stem cells and the relative easy expansion of autologous cells have opened the way to their experimental application in MS. An initial clinical trial has established the probable safety of their intravenous and intrathecal delivery. Short-term follow-up observed immunomodulatory effects and clinical benefit justifying further clinical trials.

Key Words Multiple sclerosis, stem cell, transplantation, remyelination, immunomodulation.

Introduction

Although current therapy in multiple sclerosis (MS) is directed at the underlying autoimmune pathogenic process, cell therapy has been advocated as a means of regenerative medicine. In this review, the complexity, advantages, and difficulties in cell therapy will be discussed.

Is Cell Therapy a Valid Option for MS?

Any discussion of cell therapy for MS needs to first take a look at the endogenous processes of brain repair and their failure to build a rationale for the feasibility and prospects of treatment by cell transplantation.

Glial Progenitor Cells in the Adult Central Nervous System

The identification of neural precursor cells and neurogenesis in the adult central nervous system (CNS) [1–3], including that of humans [4–6], and the identification of persistent neural stem cells (NSCs) as the parental cells from which new neurons are derived [7–14], has revolutionized our concepts of the adult brain as structurally immutable. There are several niches in the adult brain in

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which NSCs persist throughout life and can respond to injurious processes [15–18]. New neurons are continuously generated in the anterior subventricular zone (SVZ) of adult rodents, from which they migrate via the rostral migratory stream to the olfactory bulb [19–23], and in the subgranular zone of the hippocampal dentate gyrus of both adult rodents [24–27] and humans [6, 28]. The subependymal cell layer of the ventricles [29] and spinal cord [30] contains stem cells that give rise to both neurons and glia. Multi-potential precursors are abundant in many regions of the adult brain parenchyma [31–34]. In particular, oligodendrocyte progenitor cells (OPCs) were isolated from various regions of the adult rodent CNS [35–37], and were identified also in the adult human brain [38–42] and spinal cord [43]. OPCs are identified by expression of chondroitin-sulfate proteoglycan NG2+ and of platelet-derived growth factor receptor-α are highly abundant in the adult CNS, comprising up to 5% of its cells [37].

Adult Precursor Cells can Generate Remyelinating Oligodendrocytes

The origin of endogenous remyelinating cells in the adult CNS has been subject to multiple studies (for more detail see Franklin and Ffrench-Constant [44]). Differentiated postmitotic oligodendrocytes are unable to rebuild myelin sheaths [45–47] and remyelination is dependent on cycling cells [47, 48]. The notion that OPCs are the main remyelinating cells of the adult CNS emerged from studies showing remyelination after focal demyelination by resident progenitor cells [49, 50]. Tissue OPCs expressing NG2 and platelet-derived growth factor receptor-α on their cell surface are mobilized in response to demyelination [49, 51–53]. Recent studies provided the definitive proof that these cells are indeed the main remyelinating cell in the CNS following a demyelinating injury [54, 55]. In addition, neural precursor cells (NPCs) of the adult SVZ expressing the embryonic polysialylated form of the neural cell adhesion molecule (PSA-NCAM) react to inflammation and demyelination with proliferation, and migration into the tissue and glial differentiation, generating both astrocytes and remyelinating oligodendrocytes [56–59].

Myelin Regeneration Fails in MS

In MS, the inflammatory process in the CNS leads to demyelination. The affected demyelinated regions can undergo partial remyelination, leading to structural repair and recovery of function [60–63]. Attempts to regenerate myelin can be recognized pathologically in brains of MS patients by the existence of shadow plaques, which are partially remyelinated lesions. Analysis of brain tissue from MS patients suggests there are several different pathological patterns of demyelination [64]. In some patients, there was progressive loss of oligodendrocytes and myelin without reactive remyelination, whereas in others, who exhibited strong T-cell and macrophage activity, there was robust remyelination, indicating the important role of tissue support to the remyelinating response [65]. The sequential involvement of these processes underlies the clinical course, characterized by episodes of relapses, which after full remissions early in the course of disease, eventually leave persistent deficits, and finally deteriorate into a secondary chronic progressive phase. Moreover, remyelination is typically incomplete and ultimately fails in the setting of recurrent episodes contributing to the progressive demyelination, gliosis, axonal damage, and neurodegeneration typically noted in MS [66, 67]. Several studies have indicated that axonal pathology is the best correlate of chronic neurological impairment in MS and its animal model, experimental autoimmune encephalomyelitis (EAE) [68–73].

It is unclear why remyelination fails in time with MS [44, 67]. Some studies showed a depletion of progenitor cells after focal demyelination in experimental animals [52, 74], whereas others showed that repeated episodes of demyelination did not slow down remyelination [75]. In pathological specimens of chronic MS lesions in human patients, neither decrease nor reactive increase was observed relative to normal white matter [39, 76–78]. This suggests that the response of the progenitor cell population to the demyelinating process in the human brain is deficient. In the adult and aging brain, OPC recruitment and differentiation is impaired, resulting in slowed remyelination [79]. This is attributable to age-dependent deficiency in histone deacetylase, allowing the accumulation of transcriptional inhibitors that prevent myelin gene expression [80]. In addition cell migration seems to be another limiting factor in myelin regeneration. Progenitor cells that reside at the margins of experimental lesions migrate into the lesion core and remyelinate it, but long distance migration does not occur in the brain parenchyma [50, 81]. The limited recruitment of adult CNS OPCs into demyelinated lesions may be also related to their apparent dormant state. Adult OPCs are very slow cyclers [82], and they require prolonged exposure to multiple growth factors before they convert into rapidly proliferating cells [34, 83]. Thus, precursors derived from the developing CNS may have superior migratory and remyelinating capabilities than endogenous precursors.

The questions of whether remyelination failure originates from malfunction of resident OPCs or is due to the lack of permissiveness of the adult CNS, and whether the causes to failure are reversible, represent crucial issues in the discussion on the prospects of replacement cell therapy in MS. For example, there is evidence that extensive axonal transections already occurs in acute MS lesions [84]. Remyelination cannot effectively proceed in the absence

of sufficient intact axonal substrate, so that it may be effectively rate-limited by the extent of underlying axonal loss. Therefore, achieving remyelination prior to development of axonal damage is crucial to any therapeutic strategy. Alternatively, if reversible cell autonomous factors or inhibitory factors that are expressed in the demyelinated tissue limit OPC differentiation into remyelinating oligodendrocytes, then the rationale treatment would be to target them directly. Active inhibition of resident OPCs is suggested by the sharp border of demyelinated plaque, surrounded by OPCs [39, 76, 77]. It was suggested, for example, that re-expression of Notch1, a regulator of oligodendrocyte progenitor differentiation, inhibits remyelination in MS [85]. Yet targeted ablation of Notch1 did not enhance remyelination in experimental animals [86]. It was further recently shown that failure of OPC differentiation was due to cytoplasmic entrapment of the intracellular domain of Notch1 as a result of abnormal expression of TAT-interacting protein 30 kDa (TIP30), an inhibitor of importin-mediated nuclear transport [87]. Several strategies have been proposed to overcome the intrinsic block or extrinsic inhibition of OPC response to facilitate the endogenous process of myelin repair. One approach is to increase the recruitment and number of cycling OPCs by growth factor treatment. Candidates include platelet-derived growth factor [88–90], neuregulin-1, which is not essential for myelination in the CNS but can induce hypermyelination when overexpressed [91], and epidermal growth factor [59]. In addition, sonic hedgehog signaling stimulates the maintenance and renewal of neural precursors in the neurogenic niches of the adult brain [92, 93]. Recruitment and mobilization of OPCs and multipotential neural precursors in the models of MS have been mainly attributed to the inflammatory process. Brain inflammation attracts the migration of both endogenous [57] and transplanted [94–97] precursor cells. Various inflammatory cytokines can induce neural/oligodendrocyte precursor cell migration. Transforming growth factor-β induces microglia to release hepatocyte growth factor, which increases OPC migration [98]. Tumor necrosis factor-α increases the motility of neural precursors *in vitro* [99]. The chemokine stromal derived factor 1 (CXCL12) induces neural stem/precursor cell migration in models of stroke [100, 101], viral-induced demyelination [102], and trauma [103]. In addition, the injection of inflammatory stimuli in an *ex vivo* model of hippocampal slices attracted neural precursors, depending of monocyte chemoattractant protein (MCP-1) signaling via the CCR2 receptor [104]. Moreover, inflammation stimulates the remyelinating process [105, 106]. The apparent link between the acute inflammatory phase and setting of regenerative processes in motion may define a narrow time window when remyelination is feasible. The necessity to remyelinate before axonal damage occurs, and the limited time window of opportunity in face of the dormant state of resident progenitors, may cause a temporal mismatch underlying remyelination failure [105]. However, although this time window may be too narrow for adequate endogenous progenitor cell mobilization, it may suffice for therapeutic cell transplantation. Another approach to push remyelination is to force OPC differentiation. Among several neurotrophic factors tested, the ciliary neurotrophic factor family was found to promote oligodendrocyte differentiation and remyelination [107]. More recently, pharmacologic induction of OPC differentiation by inhibition of RhoA-Rho-kinase II (ROCK-II), and/or protein kinase C signaling [108], or by anti-Leucine-rich repeats and Ig domain-containing, neurite outgrowth inhibitor (Nogo) receptor-interacting protein-1 (LINGO1) antibodies [109, 110] accelerated remyelination. Statins and inhibitors of receptor tyrosine phosphatases are other pharmacologic agents that induce rodent [111] and human [112] oligodendrocyte differentiation. However, when tested in the cuprizone model of demyelination *in vivo*, statin therapy inhibited remyelination [113]. Olig1 is an important transcription factor in early oligodendrocyte specification and differentiation. Its induction may stimulate remyelination [114]. Analysis of gene expression profiles during development in the normal adult brain and during demyelination identified several novel regulatory pathways of oligodendrocyte differentiation. These studies showed that oligodendrocyte differentiation and remyelination are dependent on retinoid-X receptor-gamma receptor agonists [115] and on Wnt-beta-catenin signaling [116]. In addition, type 2 cyclin dependent kinase (also known as cdk2), which controls the cell cycle, does not interfere with myelination during development, but its knock-out facilitates remyelination [117]. These exciting findings open novel therapeutic targets for enhancing remyelination. In addition, they highlight the discussion on whether the preferable regenerative therapeutic strategy in MS will be by cell transplantation or by boosting up endogenous remyelination, or both.

The Therapeutic Plasticity of Stem Cells

Cell Replacement

Transplantation of both rodent and human OPCs and various types of neural precursor cells has shown their potential in remyelinating the CNS. This has been established both in models of genetic dysmyelinating disorders (for more details see Goldman et al. [118]) and models of acquired demyelination in the adult rodent CNS (for more details see Ben-Hur and Goldman [119], Yang et al. [120], Miron et al. [121], and Martino [122].

Early studies focused on oligodendrocyte progenitors with the notion of cell replacement (i.e., remyelination)

therapy in mind. Although postmitotic oligodendrocytes have poor remyelinating capacity [123], their immediate progenitors exhibit greater mitotic, migratory, and regenerative properties in both genetic dysmyelinating and adult focal demyelinating models of disease [124–127]. Transplanted rodent OPCs myelinated nude axons and restored nerve conduction velocity to near normal values in the spinal cord of *md* rats [128], and canine OPCs repaired large brain areas in the *sh* pup [126].

Human OPCs showed similar properties as their rodent counterparts, and myelinated efficiently in models of focal demyelination [127, 129] and of congenital dysmyelination [42]. The *in vitro* propagation of glial precursors necessitates continuous mitogenic exposure to obtain a sufficient amount of cells. An alternative approach that may circumvent the potential negative effects of prolonged *in vitro* cell expansion may be by high scale selective isolation of precursor cells. For example, precursor cells could be isolated from dissociated fetal and adult CNS tissue by transfection with a plasmid encoding green fluorescent protein (GFP) placed under the control of the 2′,3′-cyclic nucleotide 3′-phosphodiesterase-2 (CNP2) promoter, a regulatory element activated in early oligodendrocyte progenitor cells, followed by fluorescence activated cell sorting [40, 42, 127]. Alternatively, fluorescence–activated or immunomagnetic sorting were used to isolate A2B5(+)/poly-sialic acid-neural cell adhesion molecule (PSA-NCAM)(−) fetal and adult human glial progenitors [42]. Highly efficient and widespread donor-derived myelination was obtained with these human precursors within a month of transplant to newborn shiverer mice [42], which are congenitally deficient in myelin basic protein [130]. Additional intracerebellar injection resulted in substantial infiltration and myelination of cerebellar white matter, peduncles, and dorsal brainstem [131]. Importantly, the transplanted shiverers lived significantly longer than their un-transplanted controls, and a fraction of the mice appeared to be completely rescued in terms of survival and neurological disability [131]. In correlation, donor-derived myelin sheaths had the ultra-structural architecture of compact and functional myelin [131]. Interestingly, fetal and adult-derived human glial precursors demonstrated different functional properties; fetal progenitors emigrated more widely and engrafted more efficiently than adult cells, but the adult progenitors generated oligodendrocytes more efficiently, and myelinated recipient brains much more rapidly and with more axons per donor cell than did fetal cells [42].

Several studies examined whether earlier stages of neural precursor cell development also may be valuable for remyelinating therapy. The potential advantages in NSCs are as nontransformed cells that are able to self-renew indefinitely, allowing their expansion in large quantities. As discussed, mammalian multi-potential NSCs support neurogenesis and gliogenesis within specific areas of the CNS during development and adulthood, and can be isolated from fetal and adult brains [10, 132, 133]. The notion that glial committed neural stem cells may combine the capacity for self-renewal and plasticity of stem cells, together with the remyelinating properties of OPCs, led to identification of such precursors in the developing brain [134]. Expression of PSA-NCAM on the cell membrane has been associated with stem cell commitment to neuronal or glial fate, depending on time and place in development [135–137]. Indeed, such PSA-NCAM+ glial precursors, growing as neurospheres and also termed as oligospheres [135, 138], efficiently myelinated the brains of *shi* mice [138–140], remyelinated 95 to 100% of axons following local injection into the dorsal columns of rats [141], and efficiently migrated along inflamed white matter tracts of rats with EAE [94, 95]. Similarly, adult human SVZ precursors remyelinated the adult rat spinal cord [142]. Finally, multipotential NSC also showed a capacity to perform efficient myelination in the spinal cords of shiverer mouse, *md* rat, and *sh* pup [143–145], as well as in adult animals with traumatic spinal cord injury [146, 147]. However, before discussing which cell type is the optimal remyelinating cell for clinical translation in MS, it is important to point out that many of these studies have not yet established the necessary proof-of-concept for cell therapy-based myelin repair in MS. When focal demyelinated lesions were induced by myelinotoxic chemicals, such as ethidium-bromide, lysolecithin, or cuprizone [148–150], it was followed by a rapid process of remyelination by endogenous cells. In fact, a prerequisite in all of these models to be able to show transplant-derived remyelination was the prior removal of endogenous OPCs, by means such as X-irradiation. Moreover, transplantation experiments have been typically performed during the acute phase, immediately after lesion induction. Obviously, these experimental models do not represent the complexity of the chronic MS brain, in which resident OPCs are present, but fail to perform their duties. EAE is considered the closest animal model to human MS, and served for the development of several immunotherapies. However, EAE has not proven useful for developing the cell transplantation approach for remyelination. A central problem is that the existing chronic EAE models have an extensive axonal pathology at the early acute phase, which does not allow any myelin repair [151]. Thus, there is urgent need for a clinical relevant model of remyelination failure where the potential of cell therapy may be examined properly. In particular, such models would serve to both develop and test therapeutic approaches to accelerate remyelination in the adult CNS and to examine whether the supply of exogenous myelin-forming cells has any advantage in comparison to endogenous precursors.

Although cell therapy was originally believed to be primarily a means of replacing damaged cells in the CNS,

transplantation experiments in several pre-clinical models of neurological disorders showed that the remarkable functional recovery obtained at NPC transplantation does not correlate with the amount of terminally differentiated neural cells originating from transplanted NPCs (for more details see Martino and Pluchino [152]). Multiple studies have pointed at other powerful mechanisms of actions by which transplanted cells exhibit a beneficial effect, termed collectively as therapeutic plasticity of stem cells.

Trophic Support by Transplanted Precursor Cells

Recent studies have focused on several bystander neuroprotective and neurotrophic properties of transplanted NPCs. The NPCs seeded on a synthetic biodegradable scaffold and grafted into the cord of hemi-sectioned rats induced significant clinical recovery, which was associated with reduced necrosis and limited secondary cell loss, inflammation, and glial scar formation of the surrounding parenchyma [153]. Moreover, the NPC graft induced a permissive environment for axonal regeneration [153]. Injection of biodegradable scaffolds loaded with NPCs into hypoxic brain regions induced substantial endogenous reconstitution of the brain structural connectivity [154]. A similar effect was observed following intracerebral transplantation of NPCs after ischemia/reperfusion injury in mice [155]. In a Parkinson's disease model, transplanted NPCs rescued endogenous dopaminergic neurons of the mesostriatal system [156], and in models of amyotrophic lateral sclerosis transplanted NPCs prevented motor neurons from dying [157–159]. Transplantation experiments in models of spinal cord injury have provided several insights to the basic biological mechanisms by which the various types of precursor cells exhibit their therapeutic functions (for more detail see Einstein and Ben-Hur [160]). First, neural and mesenchymal stem and progenitor cells reduce the acute deleterious inflammatory process and induce a permissive environment for axonal regeneration after spinal cord injury [161]. They produce a myriad of neurotrophic growth factors [162], and induce matrix metalloproteinases that degrade the extracellular matrix and cell surface molecules that impede axonal regeneration, thus enabling axons to extend through the glial scar [163]. In addition, the increased bioavailability of neurotrophins, such as nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, and glial-derived neurotrophic factor [162], attributes to the NPCs-driven bystander effect in increasing the survival and/or functions of endogenous glial and neuronal progenitors surviving to the pathological insult. Also, cell transplantation into the injured spinal cord provides proper realignment and guidance to enable axonal regeneration along long fiber tracts [164], and induces angiogenesis in the lesioned tissue, which provides trophic support and enables tissue repair [165]. Finally, transplanted cells increase remyelination in the lesion by both endogenous and graft-derived myelin forming cells to enhance action potential conduction and limit secondary axonal degeneration [166].

Recent work has also indicated that transplanted stem cells, including NPCs, can enhance endogenous neurogenesis in certain physiological and pathological conditions [167, 168]. Mice exposed prenatally to opioids display impaired learning associated with reduced neurogenesis, and transplantation of NPCs improves learning functions, as well as host brain-derived neurogenesis in the dentate gyrus of the hippocampus [169]. A similar neurotrophic effect was also reported in physiological aging. Although neurogenesis in the dentate gyrus declines severely by middle age, transplantation of NPCs stimulates the endogenous NPCs in the subgranular zone to produce new dentate granule cells [167]. With more direct relevance to remyelination failure, a recent study of a chronic cuprizone-induced demyelination model in aging mice showed that transplanted NPCs facilitated the endogenous process of remyelination [170]. This effect was mediated by induction of resident OPCs proliferation and their differentiation [170].

Thus, transplanted NPCs may enhance the adult CNS capacity to repair itself by restoring the ability of endogenous progenitors to respond properly to the diseased state and replace damaged CNS cells. In particular, stem/precursor cell therapy may serve as an approach to overcome the failure of endogenous remyelination in MS.

Immune Modulation

The first indication of a novel anti-inflammatory effect of NPCs was obtained when neurospheres were transplanted intracerebroventricularly (ICV) in acute spinal cord homogenate-induced EAE Lewis rats [171]. This model manifests with acute reversible paralytic disease that is the result of disseminated CNS inflammation without demyelination or axonal injury [172]. NPC transplantation in spinal cord homogenate-induced EAE Lewis rats attenuated the inflammatory brain process and clinical severity of disease [171]. Follow-up studies examined the effect of NPC transplantation on either ICV or intravenous cell injection in the myelin oligodendrocyte glycoprotein (MOG) 35–55 peptide-induced EAE in C57BL/6 mice. In this model, a T cell-mediated autoimmune process causes an acute paralytic disease due to severe axonal injury and demyelination. Subsequently, the mice remain in a fixed neurological sequel, the severity of which is correlated with the extent of axonal loss [73]. NPC transplantation in MOG35-55-induced EAE mice attenuated brain inflammation, reduced acute and chronic axonal injury and demyelination, and improved the overall clinical and neurophysiological performance of the

CNS of the mice [173, 174]. Finally, such immune regulatory properties were also shown for human embryonic-stem cell-derived NPCs in rodents [151] and for somatic NPCs in primates [175]. Again, the therapeutic effects of both these latter NPC sources was not related to graft- or host-driven remyelination, but rather were mediated by an immune regulatory mechanism that protected the CNS from immune-mediated injury [151].

In the CNS, NPC-mediated bystander immune regulation may take place in the ventricular space and white matter tracts [176], as well as at the level of the atypical perivascular niches [97, 152, 173]. Following systemic delivery, immune regulation by NPCs occurs in secondary lymphoid organs, such as the lymph nodes [177] or the spleen [178].

Several mechanisms were suggested to explain how transplanted NPCs attenuate CNS inflammation. One school of thought was suggested that NPCs induce apoptosis of Th1 cells, but not Th2 cells, selectively, via the inflammation-driven up-regulation of membrane expression of functional death receptor ligands (e.g., Fas Ligand, TNF-related apoptosis-inducing ligand-TRAIL, Apo3 ligand) on NPCs [173]. Alternatively, it has been suggested that NPCs inhibit T-cell activation and proliferation by a nonspecific, bystander immune suppressive action [177]. This notion emerged from co-culture experiments that showed a striking inhibition of the activation and proliferation of EAE-derived, as well as naive, T cells by NPCs, following stimulation by various stimuli [171, 177, 179]. The suppressive effect of NPCs on T cells was accompanied by a significant suppression of proinflammatory cytokines, such as interleukin (IL)-2, tumor necrosis factor-α, and interferon-γ [177]. Moreover, NPCs inhibited multiple inflammatory signals, as exemplified by attenuation of the T-cell receptor IL-2- and IL-6-mediated immune cell activation and/or proliferation [179]. The relevance of such NPC/T-cell interaction was first suggested when NPCs were intravenously injected prior to EAE disease onset (e.g., at 8 days after the immunization) and were transiently found in peripheral lymphoid organs, where they interacted with T cells to reduce their encephalitogenicity [177]. In a similar fashion, when NPCs were subcutaneously injected they targeted secondary lymphoid organs, where they interacted with immune cells and stably modified (e.g., for more than 2 months after cell injection) the perivascular microenvironment. Within this context, surviving NPCs stalled the activation of myeloid dendritic cells via a bone morphogenetic protein-4-dependent mechanism, which was completely reverted by the bone morphogenetic protein antagonist Noggin [180].

Therapeutic Plasticity of Non-Neural Stem Cells

Neurotrophic and immune regulatory properties seem to be a common property of stem cells from various sources. This was most thoroughly studied in bone marrow stromal (mesenchymal) stem cells (BMSC). These cells form the bone marrow stroma that support hematopoiesis [181] and serve as precursors of the various bone cell types (adipocytes, myocytes, and chondrocytes) [182]. They do not express hematopoietic markers and can be identified by expression of CD105, CD44, CD 90, and others. The neurotrophic properties of these cells were demonstrated in several models of neurological diseases, including stroke [183] and trauma [184]. BMSC possess wide immunomodulatory functions; they inhibit maturation of monocytes into dendritic cells [185], they impair the antigen-presenting function of dendritic cells [186, 187], they inhibit T-cell proliferation in a non-major histocompatibility complex (MHC) restricted manner [188–190], they induce a shift of T cells to an anti-inflammatory (IL-4 producing) phenotype [190], and they inhibit B-cell proliferation and differentiation [191]. Several soluble factors have been implicated in the immunomodulatory functions of BMSC, such as indoleamine 2,3-dioxygenase, transforming growth factor-β1, hepatocyte growth factor, IL-10, and others, but these effects were also partially dependent on cell-cell contact (for more details see Uccelli et al. [192]). Clearly, there is no single factor that is responsible for the diverse BMSC effects. BMSC exhibited powerful immunomodulatory effects in various conditions *in vivo*. Specifically, intravenously injected BMSC effectively attenuated EAE [193, 194], resulting in efficient protection of the CNS from tissue injury [195].

In conclusion, the observation that stem cell (from various sources) transplantation attenuates the clinical course of EAE ignited clinical translation and application of cell therapies in MS. Different types of stem cells share common immunomodulatory and neurotrophic properties, which can be exploited both systemically and in the CNS. When delivered directly into the CNS, then cell therapy may provide trophic support and induce repair, as well as a broad acting, yet tissue specific immunomodulatory effect, as compared to all other systemic immune therapies (Fig. 1).

Practical Aspects of Cell Therapy Are Issues for Basic Research

In genetic dysmyelinating diseases transplanted cells integrate into the normal developmental program of the CNS. This leaves us essentially with choosing the optimal myelin-forming cell for transplantation and producing the large mass of cell necessary for widespread CNS myelination. The chronic and multi-focal nature of MS along with hindrances to repair in the adult brain raise several additional crucial issues of timing, route of cell delivery, and long-term survival of grafted cells in such a "hostile environment." The basic biological mechanisms governing

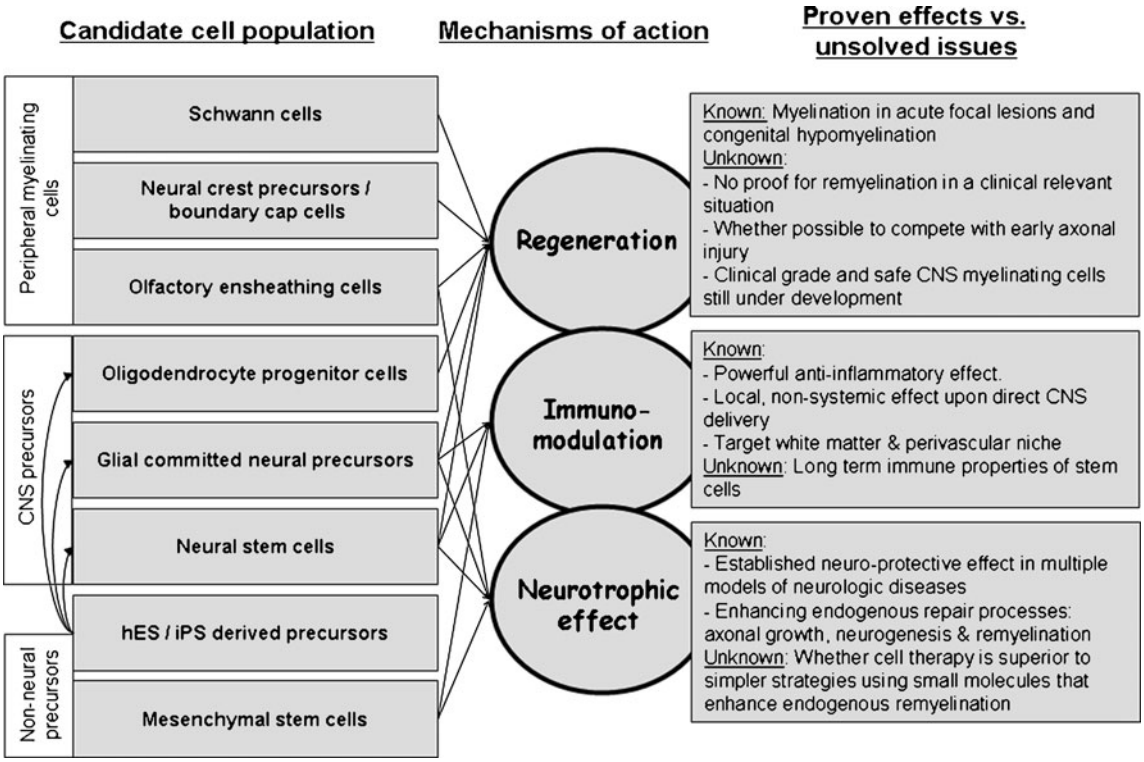

Fig. 1 Using the therapeutic plasticity of stem cells and myelin-forming cells in multiple sclerosis, each candidate cell type should be evaluated in terms of its regenerative capabilities, immunomodulatory properties, and trophic effects. The arrows show proven mechanisms of action by the various cell types. Although the therapeutic effects achieved by each of these mechanisms have been studied, there are still many "unknowns." These unknowns represent important areas of future research. CNS=central nervous system; hES=human embryonic stem; iPS = induced pluripotent stem cells

these aspects need to be studied to bring the therapeutic cell transplantation approach closer to clinical reality.

What Type of Cell to Transplant?

Various cell types have been considered as candidates for therapeutic transplantation in MS. These include immediate glial progenitors of the oligodendrocyte lineage, earlier neural precursor and stem cells, non-CNS myelin forming cells, and non-neural cell populations. There is still no consensus regarding the optimal donor cell phenotype, but some generalities can be made to compare the relative merits of various candidate cell populations.

Neural Stem and (Oligodendro-) Glial Precursor Cells

In view of the multiple mechanisms by which neural precursor cells may induce beneficial effects in MS, including their regenerative potential, their trophic, immunomodulatory, and neuroprotective properties, they seem to be an excellent candidate for cell therapy. Specifically, they may have an advantage on committed myelin forming cells that might not possess other stem cell properties, and on non-neural cells that cannot perform remyelination. However, these hypotheses need to be examined in clinically relevant models, as previously discussed. In addition, the value of transplanting purified cell populations *versus* a mixture of stem cells and OPCs that need to be directly compared.

Embryonic Stem and Induced Pluripotential Cells

The practical limitations in getting sufficient human oligodendrocytes prompted research on deriving tissue-specific progenitor cells from human embryonic stem cells. Embryonic stem (ES) cells are derived from the inner cell mass of blastocyst-stage embryos, and are pluripotent cells that are able to generate the entire repertoire of cell types in the body. Glial precursors with myelinogenic properties were derived from mouse ES cells [196–198]. Human ES cells [199, 200] can be directed into neural fate [201, 202]. Recent studies have discovered the means to mimic the tightly controlled human embryonic developmental program to produce highly enriched populations of specific neurons [203–206] and oligodendrocytes [207, 208]. Human embryonic stem cell-derived oligodendrocytes appear functional and capable of myelination [207, 209]. Clinical translation will need to deal with the much feared

potential for tumorigenesis [210]. In particular, human embryonic stem cell-based therapies might give rise to teratomas, growing from persistent undifferentiated ES cells in the graft [211], or neuroepithelial tumors arising from incompletely differentiated neural cells [212]. Purification of clinical grade and "safe" human ESC-derived glial precursors may be achieved by the same technologies that were developed for isolating these cells from the human brain [42, 131].

Although the use of ES cells dictates an allogeneic donor cell source, the recent generation of induced pluripotential stem (iPS) cells from somatic mouse [213] cells and from human [214, 215] cells may alleviate this limitation. iPS cells are similar to ES cells in their pluripotency, as defined by their ability to generate cells of all major germ layers and teratomas *in vivo*. Importantly, initial reports have validated their ability to generate functional postmitotic neurons [216–218] and oligodendrocytes [219, 220]. It will now be necessary to explore the potential for generating populations of iPS-derived oligodendrocytes for autologous grafting in the myelin disorders.

Non-CNS Myelin Forming Cells

Schwann Cells

These peripheral myelin-forming cells can myelinate CNS axons very efficiently [221–223]. Their transplantation into the CNS resulted in production of compact myelin [223, 224] and restoration of normal conduction velocity in the dorsal columns of the spinal cord, predicting functional recovery [221, 225–228]. They can be isolated from a sural nerve biopsy, expanded in culture, and eventually delivered as an autologous graft to a demyelinated focus in the CNS. As autologous cells, they might obviate the need for immunosuppressives, while concurrently escaping the autoimmune attack of MS, which is typically directed against the central myelin antigens. A clinical trial of Schwann cell transplantation was performed into single demyelinating lesions in 3 MS patients in 2001 at Yale University. The surgical procedure proved to be safe, but the study was discontinued in early 2003, after follow-up brain biopsies could not demonstrate either Schwann cell survival or new myelin formation. It is not known whether this failure resulted from poor cell preparation, autoimmune attack, or if it was due to a lack of integration of peripheral myelinating cells in the adult human brain environment. Although this study has dampened further clinical experimentation with Schwann cell transplants, recent reports renewed interest in using Schwann cell precursors isolated from the neural crest. These cells, and specifically boundary cap cells, which form the border between the developing peripheral and CNS, generate myelinating Schwann cells [229]. Their increased migratory and myelinating properties [230], as well as their potential to also generate myelinating oligodendrocyte [231], make Schwann cells another promising candidate for cell replacement therapy in myelin disorders.

Olfactory Nerve Ensheathing Cells

Olfactory nerve ensheathing cells (OECs) display properties of both astrocytes and Schwann cells. These cells are unique in that they continue to arise in the olfactory epithelium from which they can migrate to the olfactory bulb throughout life [232–234]. Rodent and human OECs generate Schwann-cell-like myelin and improve conduction properties when transplanted to areas of demyelination in the brain or spinal cord [227, 233, 235–240]. OECs also have the capacity to promote axonal growth [241] and to secrete neurotrophic molecules [242, 243]. Thus, the relative availability of these cells, their apparent myelinating properties and their trophic effect on axonal growth make them another promising candidate for autologous therapeutic transplantation. It is not known whether OECs posess any immunologic properties.

Non-Neural Stem Cells

Bone Marrow Stromal Cells

BMSCs are nonhematopoietic mesenchymal stem cells that give rise to bone, tendon, and fat progeny. These type of cells burst into the regenerative neuroscience field with the suggestion that promiscuity of stem cells may allow them to transdifferentiate into mature cells of other tissues [244, 245]. Specifically, a number of investigators have reported that adult mouse and human BMSCs can differentiate *in vitro* into other cell types, including muscle, skin, liver, lung, and neural cells [246–250]. It was also suggested that bone marrow-derived stromal cells can generate astrocytes [251], as wedll as produce myelin and remyelinate a demyelinated lesion of the spinal cord of the rat [252, 253]. The potential of stromal cells for cell replacement therapy is still controversial in view of reports showing that stromal cells may rather fuse with existing neurons and glia, resulting in the formation of heterokaryons [248, 254]. Although the potential of BMSCs to remyelinate is controversial, a large volume of research has demonstrated their powerfull neurotrophic and immunomodulatory properties, as previously described. Thus, BMSCs may serve as an easily expandable, autologous source of cells with powerful therapeutic capabilities and probably a safe profile. These properties make them a good candidate for relatively straigtforward translation into clinical practice.

Route of Cell Delivery

For a multi-focal disease like MS, the route of cell delivery becomes a primary consideration, raising 2 main questions: 1) what are the anatomic–biologic targets of cell therapy? The 2 main targets that may be contemplated include the white matter tracts, where immune-mediated demyelination should be halted and repair processes activated, and also the perivascular niche, where trafficking of immune cells occurs; and 2) to reach these targets, cell migration is crucial. Therefore, the cellular and environmental determinants of directed migration of transplanted cells into the proper sites need to be identified. Indeed, cell migration is a major limiting factor in endogenous remyelination. Intraventricular transplantation of various types of rodent precursor cells led to widespread myelination in the genetic dysmyelinating models of the *shi* mouse [143, 255] and the *md* rat [196]. Human oligodendrocyte progenitors showed similar capacity to disseminate white matter throughout the brain in these models [131]. However, in the lesioned adult CNS, there is limited migration of endogenous remyelinating cells resulting in local remyelination that may be insufficient for widespread lesions [50, 256].

The inflammatory process in the CNS of EAE animals was found to be a powerful stimulus stimulating subventricular PSA-NCAM+ cells [56, 57] and attracting targeted migration of transplanted neural and oligodendroglial precursor cells [94, 95, 257]. Following ICV transplantation of neurospheres, cells migrated into inflamed periventricular white matter tracts, and differentiated mainly into glial progeny. The greatest degree of migration occurred early in the course of disease [96], suggesting that transplantation may be optimally effective during a relatively narrow time window following the onset of an acute demyelinating episode. Importantly, transplanted precursors were found to possess superior migratory capabilities over endogenous precursors [81]. Thus, a major rationale for ICV route of cell delivery is that most white matter tracts that are involved in MS are in close proximity to the ventricular and spinal subarachnoid spaces. Following ICV injection, transplanted neural precursors may disseminate throughout the ventricular and subarachnoid space, enabling their inflammation-induced targeted migration into the white matter. By this, intraventricular and intrathecal transplantation may bring the remyelinating cells closest to the multiple foci of disease in MS without a separating barrier. Notably, when human embryonic stem cell-derived neural precursors were transplanted ICV, they also responded to inflammation by migration into the involved white matter tracts [96]. The observation that human neural precursors respond to tissue signals in an MS model in a very similar fashion to rodent cells is obviously indicative for the potential of clinical translation of cell therapy.

Various cytokines and growth factors, such as platelet derived growth factor [258, 259], fibroblast growth factor 2 [260], class 3 semaphorins [261, 262], Sonic hedgehog [263], stem cell factor [264], the chemokine stromal derived factor 1 (CXCL12) [265–269], epidermal growth factor [270], and vascular endothelial growth factor [271] increased the migration of progenitor cells of the oligodendrocyte or neuronal lineages *in vitro*, and were implicated in CNS development *in vivo*. Very little is known, however, on the molecular signals that control neural stem and progenitor cell migration in inflammation. *In vitro* studies showed that transforming growth factor-β induces microglia to release hepatocyte growth factor, which increases OPC migration [98]. Tumor necrosis factor-α increased the motility of neural precursors *in vitro* [99]. Several chemokines were shown to be expressed in the inflamed brain [272]. Among these, stromal derived factor 1 was shown to induce neural stem/precursor cells migration in stroke [100, 101], viral-induced demyelination [102], and trauma [103]. MCP-1 and its receptor CCR2 were shown to modulate neural precursor cell migration following cerebral ischemia [169]. In addition, injection of inflammatory stimuli in an *ex vivo* model of hippocampal slices attracted neural precursor depending of MCP-1 signaling via the CCR2 receptor [104].

Targeting the perivascular niche has been suggested mainly by the intravenous route of cell delivery from which the cells may cross the blood-brain-barrier [253, 273, 274]. The specific homing of NSCs to the brain was explained in part by the constitutive expression of a wide array of adhesion molecules (integrins, selectins, and so forth) and chemokine receptors by the transplanted cells [273, 275]. Integrins promote selective CNS homing through the interaction between transplanted cells and integrin receptor-expressing activated endothelial and ependymal cells surrounding inflamed brain tissues [276, 277]. Specifically, transendothelial migration was related to the expression of very late antigen-4 (VLA-4) and CD44 on NPCs, interacting with vascular cell adhesion molecule-1 (VCAM-1) and hyaluronic acid, respectively [173, 278]. This was shown to occur at a specific time window during the acute phase of EAE [273]. Recently, ICV transplanted NPCs were also shown to target the perivascular niche. Although cell migration was evident mostly in white matter tracts, cells also migrated in a radial fashion toward the cortex, along inflamed blood vessels [97]. Thus, transplanted NPCs may exhibit combined immunomodulatory, trophic, and regenerative properties in the involved white matter tracts, as well as at the perivascular spaces, which serve as junctions of inflammatory cell trafficking.

For the clinical application of BMSC transplantation, using their neurotrophic and immunomodulatory properties,

similar targets should be considered, as discussed for neural precursors. BMSC can extravasate from the blood vessels into the tissue in a cell-adhesion molecule-dependent manner, similar to immune cells [279]. Therefore, intravenously administered BMSCs may arrive at the site of active disease in the inflamed CNS [194]. Alternatively, BMSCs can be delivered into the ventricular and subarachnoid space from which they inhibit EAE [195]. Several studies addressed the issue of BMSC migration within CNS tissue [280, 281], but it is not yet clear whether this occurs efficiently in EAE.

When to Transplant

In a chronic-relapsing disease like MS, timing of transplantation may be crucial, as cells that are introduced into the CNS during nonactive phases of the disease might not survive, whereas if they are introduced after the onset of relapse, it may be too late. The developing brain is highly permissive to transplanted neural stem and progenitor cells. In these circumstances, their target of migration and lineage fate are directed by the normal pattern of development at that stage. Accordingly, human multipotential NSCs that were transplanted into the embryonic rat brain generated mostly neurons [282], but when transplanted into the newborn brain, a stage in which neurogenesis is complete and gliogenesis is in action, the stem cells generated mostly glia [283]. In contrast, the adult CNS does not support the survival of transplanted cells [284]. Transplanted cells may integrate significantly better in acutely lesioned tissue. When oligodendrocyte progenitor cells were transplanted into the spinal cord of animals with experimental EAE and an ongoing inflammatory process, they survived much better *in vivo* [257]. It is not well understood what tissue factors support graft survival and integration, and that is an important direction of further basic research to develop improved cell transplantation strategies in chronic and degenerative brain conditions. One approach may be to promote self support of transplanted NSCs, independent of the CNS environment. It has been shown that in the form of spheres, NSCs may survive for a prolonged period of time both *in vitro* and *in vivo* in the lack of any exogenous growth factors [285]. After ICV transplantation, neurospheres survived for months in the ventricular space and retained their ability to migrate into the brain parenchyma in response to delayed induction of EAE. However, graft survival is also dependent also on it not being attacked by the autoimmune process or the host immune system in case of allogeneic transplantation. These issues are as yet unsolved, and in particular, whether or not the immunomodulatory properties of stem cells are sufficient to protect them from rejection.

Clinical Translation

Although clinical translation of neural/oligodendrocyte precursor cell therapy awaits the mass production of clinical grade cells with proven safety, BMSC therapy has already been implemented. Initial promising studies on the use of BMSC for improving hematopoietic stem cell transplantation and for prevention of graft *versus* host disease were not confirmed in controlled trials (for more details see Caimi et al. [286]). However, this clinical experience opened the way for a trial of BMSC transplantation in MS. As previously discussed, the rationale for BMSC therapy was to exploit their immunomodulatory and trophic properties in a CNS-targeted manner. In a phase I/II open-safety clinical trial [287], BMSC were delivered intravenously and intrathecally into patients with chronic MS that had failed conventional treatments, and to patients with amyotrophic lateral sclerosis. There were transient side effects of headache and low grade fever, attributable to meningeal irritation, but no major side effects. Clinical follow-up showed that no patient worsened, and there was improvement in mean expanded disability score scale in the MS patients. Short-term immunological studies confirmed a systemic immunomodulatory effect of the intravenous treatment in these patients. Thus, we have entered an exciting new era of clinical experimentation of cell therapy in MS. Further studies are warranted to be able to define the efficacy of various cellular platforms, optimal dose, route of cell delivery, and timing of therapy.

Acknowledgements Full conflict of interest disclosure is available in the electronic supplementary material for this article.

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