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Adult mesenchymal stem cell therapy for myelin repair in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a demyelinating immune-mediated disease of the central nervous system (CNS). It is the most frequent neurological disease in young adults and affects over 2 million people worldwide. Current treatments reduce the relapse rate and the formation of inflammatory lesions in the CNS, but with only temporary and limited success. Despite the presence of endogenous oligodendroglial progenitors (OPCs) and of spontaneous remyelination, at least in early MS its levels and its qualities are apparently insufficient for a sustained endogenous functional repair. Therefore, novel MS therapies should consider not only immunemodulatory but also myelin repair activities. Mesenchymal stem cells (MSCs) represent an attractive alternative to develop a cell-based therapy for MS. MSCs display stromal features and exert bystander immunemodulatory and neuroprotective activities. Importantly, MSCs induce oligodendrocyte fate decision and differentiation/maturation of adult neural progenitors, suggesting the existence of MSC-derived remyelination activity. Moreover, transplanted MSCs promote functional recovery and myelin repair in different MS animal models. Here, we summarize the current knowledge on endogenous mechanisms for remyelination and proposed autologous MSC therapy as a promising strategy for MS treatment.

Key words: multiple sclerosis, remyelination, oligodendrocyte progenitor cells, mesenchymal stem cell therapy and functional recovery.

1. MULTIPLE SCLEROSIS: ETIOLOGY AND CLASSIFICATION

Oligodendrocytes are the myelin-producing cells of the central nervous system (CNS) and are responsible for electrical insulation and protection of axons. Electrical insulation is required for a salutatory conduction along the axons. Demyelination in the CNS as a consequence of a number of different pathologies leads to a variety of dysfunctions that cause a wide range of neurological symptoms resulting in physical and cognitive disabilities.

Multiple Sclerosis (MS) represents the most frequent demyelinating disease, and in young adults it is the major cause of neurological disabilities. There are approximately 2.5 million MS patients worldwide. MS primarily affects the Caucasian population from the Northern Hemisphere with a higher frequency in central and northern compared to southern Europe (Ebers and Sadovnick, 1993; Noseworthy et al., 2000). MS has a gender bias, since it appears more frequently in females than in males (Alonso and Hernan, 2008; Orton et al., 2006; Ramagopalan et al., 2010). The reason for this is unclear, but the higher MS incidence in females might be more related to specific female physiology (i.e. hormones) rather than to an MS-associated X-linked gene (Whitacre, 2001). MS patients suffer several neurological symptoms such as weakness, changes in sensation, spasticity, visual problems, fatigue and depression, acute/chronic pain, and paralysis.

Although the MS etiology is still under debate, it certainly involves an autoimmune response in which T and B cells react against CNS myelin. This causes inflammatory lesions in the CNS and culminates in the loss of oligodendroglia and in axonal degeneration (Kornek and Lassmann, 2003; Lassmann, 1998; Lassmann, 1999; Lassmann et al., 2007; Noseworthy et al., 2000; Siffrin et al.; Sospedra and Martin, 2005). The current concepts on MS etiology include i) dysregulation of the immune system and induction of an autoimmune response, ii) viral infections as the initial trigger, and iii) genetic and environmental risk factors (Ebers and Sadovnick, 1994; Noseworthy et al., 2000; Rodriguez, 2007; Sadovnick and Ebers, 1993; Sadovnick et al., 1996). For example, specific alleles of genes related to the immune response such as antigen-presentation (HLA, specifically DR genes), cell-adhesion (CD58), and cytokine receptors (IL7RA, IL2RA) have been described as genetic risk factors for MS (De Jager et al., 2009; Fugger et al., 2009; Svejgaard, 2008). In addition, smoking, lack of sunlight and vitamin D deficiency have been identified as environmental MS predisposing factors (Ascherio et al.; Hedstrom et al., 2009).

Based on the mode of progression, MS is classified in three major clinical forms: primary progressive (PP), secondary progressive (SP), and relapsing-remitting (RR) MS (Lublin and Reingold, 1996). The RR is the most frequent type, which is characterized by acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability (remission). While RR-MS and SP-MS are most likely distinct phases of the same disease, PP-MS may imply completely different processes. More than 50% of the RR-MS patients eventually develop progressive neurological symptoms and sustained deterioration without a clear remission period. This form is called the SP variety of MS (Lublin and Reingold, 1996). Finally, between 10 and 15% of MS patients suffer form the PP type, which is characterized by the absence of remission periods (Lublin and Reingold, 1996).

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Patients with PP-MS worsen at similar speeds, while those with the RR-MS may have very different clinical courses.

2. REMYELINATION: THE PHYSIOLOGICAL RESPONSE TO MYELIN DAMAGE

The CNS is generally referred to as an organ with a limited capacity for regeneration. As a consequence, traumatic injuries, demyelinating or degenerative diseases generally result in irreversible deficits. However, endogenous repair activities exist and can be activated in order to regain structure and function. The first evocative suggestion that remyelination exists in the CNS was made by Joseph Babinski at the end of the nineteenth century. In his studies on MS pathology he illustrated demyelinated axons that displayed short areas with thin myelin sheaths, which he interpreted as remyelination. Today, it is evident that myelin sheaths are re-established along demyelinated axons, restoring structure and function (Franklin and Ffrench-Constant, 2008; Lassmann et al., 1997; Smith et al., 1979; Woodruff and Franklin, 1999).

Research on animal models has provided a substantial contribution to our knowledge of the cellular and molecular mechanisms of remyelination. Animal models to study remyelination use mainly drugs that specifically induce demyelination. Cuprizone (bis-cyclohexanone-oxaldihydrazone) is one of the toxins widely used in preclinical research. It is easily administrated orally through food pellets, and once in the organism it chelates copper, resulting in a systemic copper deficiency. For still unknown reasons, the cuprizone-induced copper deficiency affects in particular oligodendrocytes and induces a synchronous and rapid demyelination in various brain regions such as the corpus callosum (CC), superior cerebellar peduncles, cortex, olfactory bulb, hippocampus, optic chiasm, brainstem, etc (Blakemore, 1972; Blakemore, 1973; Kesterson and Carlton, 1971; Komoly et al., 1987; Ludwin, 1978; Matsushima and Morell, 2001; Silvestroff et al.; Skripuletz et al., 2008). Remyelination is quite evident one to two weeks after cuprizone removal and largely complete after four weeks (Matsushima and Morell, 2001; Silvestroff et al.). Other toxic agents that are used to investigate de- and remyelination are lysophosphatidylcholine (lysolecithin) and ethidium bromide (EtBr). These are, in contrast to the systemic application of cuprizone, injected locally into the desired site of demyelination. Lysolecithin is a membrane-dissolving agent which acts mainly on myelin-producing cells, while EtBr is a DNA intercalating agent that damages not only oligodendrocytes but also astrocytes (Woodruff and Franklin, 1999). The substances are generally injected into white matter CNS regions such as caudal cerebellar peduncle, spinal cord or CC, provoking a rapid local demyelination (Jablonska et al., 2010; Woodruff and Franklin, 1999; Zawadzka et al., 2010).

Myelin repair represents a crucial therapeutic goal for the treatment of MS. Therefore it is critical to understand how this reparative phenomenon occurs in adult CNS. Which are the cells responsible for remyelination? What is the molecular and cellular mechanism that underlies this process? One would expect that adult remyelination might recapitulate the full program of developmental myelination. However, for still unknown reasons, remyelinated sheaths end up thinner than the myelin sheaths produced during development (Blakemore, 1974; Ludwin and Maitland, 1984). Two hypotheses which might explain this observation are currently under discussion: i) since myelination depends on the coordinated interaction between oligodendrocytes and axons, the thin myelin sheath formation might be a consequence of differences in the axonal properties (Franklin and Hinks, 1999); ii) alternatively, the intrinsic remyelination capability of adult oligodendroglial progenitors might be weaker compared to those of developmental progenitors. The different proliferation rates and migratory capacities of developmental versus adult progenitors might contribute to this possibility (Wolswijk and Noble, 1989). Although neither of these hypotheses has yet been confirmed, it is more likely that myelination and remyelination display relatively different cellular and molecular mechanisms.

At least two different cellular sources for newly generated myelinating oligodendrocytes have been identified: i) oligodendroglial precursor/progenitor cells and ii) subventricular zone-derived neural stem/progenitor cells. In the early 1980s, Martin Raff and co-workers identified for the first time oligodendroglial precursor/progenitor cells (OPCs). Optic nerve-derived OPCs are proliferating cells capable of differentiating into oligodendrocytes and type 2 astrocytes (also termed O-2A progenitors) (Raff et al., 1983; Raff et al., 1984). OPCs are widely spread throughout the CNS in the white and grey matter, representing 5 to 8% of total glial cells (Levine et al., 2001). OPCs can be identified through the expression of specific markers such as ganglioside antigens recognized by the A2B5 antibody (Wolswijk and Noble, 1989), chondroitin sulfate NG2 (Dawson et al., 2000; Keirstead et al., 1998), platelet-derived growth factor receptor-α (PDGFRα) (Redwine and Armstrong, 1998) and the transcription factor olig1 (Arnett et al., 2004). There is substantial evidence that OPCs are the major source of new myelinating oligodendrocytes in adult CNS (Franklin and Kotter, 2008). First, *lacZ*-encoding retroviral tracing studies demonstrated focal lysolecithin-induced demyelination in the white matter labeled proliferating cells that give rise to remyelinating oligodendrocytes (Gensert and Goldman, 1997). Second, transplanting adult OPCs into a myelin-deficient (md) rat was shown to remyelinate nude axons (Zhang et al., 1999). Third, after focal demyelination OPC repopulation was observed before new mature oligodendrocytes appeared (Levine and Reynolds, 1999; Sim et al., 2002; Watanabe et al., 2002). Finally, the existence of cells with a transitional expression of markers for OPCs and mature oligodendrocytes argues for OPCs being the source of newly generated myelin in the adult CNS (Fancy et al., 2004; Zawadzka et al., 2010). Although Schwann cells have been thought to remyelinate solely axons of the peripheral nervous system, they can also be a source for CNS myelin (Dusart et al., 1992; Felts et al., 2005). Conversely, a recent report using a genetic fate mapping strategy demonstrated that CNS-resident PDGFRα/NG2-expressing cells (OPCs) give rise to remyelinating oligodendrocytes and to Schwann cells after chemical-induced demyelination (Zawadzka et al., 2010).

The process of OPC-derived remyelination may be divided into three steps: OPC activation, recruitment and differentiation (Bruce et al.; Franklin and Kotter, 2008). Each individual step is tightly regulated by extrinsic and intrinsic factors that act as either remyelination inhibitors or activators (Rivera et al., 2010). Upon demyelination, OPCs become mitotically active and induce the expression of oligodendrogenic genes such as Olig2 and Nkx2.2 (Fancy et al., 2004; Levine and Reynolds,

1999; Reynolds et al., 2002). The proliferation stimulus is mediated via astrocytes and microglia, which are activated upon demyelination to release mitogens that act on OPCs (Olah et al., 2012; Redwine and Armstrong, 1998; Schonrock et al., 1998; Wilson et al., 2006). OPC recruitment is intrinsically modulated by the cell cycle regulatory protein p27Kip1 (Crockett et al., 2005) and promoted by platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) (Murtie et al., 2005; Woodruff et al., 2004; Zhou et al., 2006). Also, the coordinated interaction between cell surface molecules and extracellular matrix (ECM) is crucial for OPC recruitment (Larsen et al., 2003). Oligodendroglial differentiation and maturation is further subdivided into the following steps: first, OPCs establish contact with bare axons, then OPCs activate myelin genes and generate the myelin membrane that finally wraps compactly around the axons forming the myelin sheath (Franklin and Kotter, 2008).

Apparently, OPCs are not the only immature cells within the adult CNS which can generate new oligodendrocytes. The original findings of newly generated neurons in the adult brain by Altman and Das (Altman, 1969; Altman and Das, 1965; Altman and Das, 1964) evoked the hypothesis of neural stem cells that are the source of new neurons in the adult brain. Neural stem/progenitor cells (NPCs) reside in a particular cellular and extracellular microenvironment called the stem cell niche, in the subgranular zone (SGZ) in the dentate gyrus of the hippocampus and in the subventricular zone (SVZ) of the wall of the lateral ventricles (Alvarez-Buylla and Garcia-Verdugo, 2002; Doetsch and Scharff, 2001; Gage, 2000). In the SVZ NPCs divide and differentiate into neuronal precursors, migrating along the rostral migratory stream (RMS) to the olfactory bulb (OB), where they functionally integrate and differentiate into granule and periglomerular neurons (Carleton et al., 2003; Doetsch and Scharff, 2001; Lois et al., 1996). SVZ-derived NPCs generate not only neurons but also oligodendrocytes. Retroviral tracing has demonstrated that NPCs give rise to a small subpopulation of Olig2-expressing transit-amplifying precursor cells that in turn generate PSA-NCAM/PDGFRα-positive cells (Menn et al., 2006). These cells migrate towards the corpus callosum (CC), the striatum and to the fimbria fornix, where they differentiate into oligodendrocytes (Menn et al., 2006). SVZ-derived NPCs also respond to demyelinating lesions that enhance basal oligodendrogenesis. For example, the number of SVZ-derived newly generated oligodendrocytes was significantly increased after lysolecithin-induced demyelination (Menn et al., 2006). Moreover, SVZ-derived EGF-responsive NPCs migrate to the lesion area and differentiate into remyelinating oligodendrocytes (Gonzalez-Perez et al., 2009). Upon lysolecithin-induced demyelination of the CC, SVZ-derived PSA-NCAM-expressing progenitors in the RMS increased their proliferation rate, migrated towards the injured CC and differentiated into oligodendrocytes and astrocytes (Nait-Oumesmar et al., 1999). The shift towards the oligodendroglial fate apparently involves the BMP antagonist chordin, since chordin is upregulated in the SVZ after demyelination, and elevated levels of chordin inhibit the generation of GAD65-positive and DCX-positive cells and redirect the newly generated cells towards the CC, where they differentiate into oligodendrocytes (Jablonska et al., 2010). SVZ-derived progenitors also respond to chronic demyelination as it is presented in a MS animal model. Here, SVZ-derived remyelinating oligodendrocytes were found in CC, fimbria and striatum. In white matter areas remote from SVZ such as the cerebellum, however, no SVZ-derived newly generated oligodendrocytes were found (Picard-Riera et al., 2002), suggesting that unlike OPCs, SVZ-derived oligodendrogenesis is restricted to the SVZ near regions. In conclusion, the SVZ stem cell niche constitutes a source for new oligodendrocytes. A number of crucial questions are yet to be answered: i) how similar are SVZ-derived remyelinating cells and OPCs? ii) what are the molecular mechanisms of the neuronal-oligodendroglial fate switch?

Remyelination is a reparative response to myelin damage; however during MS this phenomenon largely fails. Although some MS patients generate autoantibodies against OPC epitopes such as NG2 and might destroy OPCs (Niehaus et al., 2000), the majority of data supports a failure of OPC differentiation and maturation in MS. OPCs are typically found in demyelinated areas, but they fail to differentiate and to remyelinate (Chang et al., 2002; Kuhlmann et al., 2008; Reynolds et al., 2002; Wolswijk, 1998). Also, the proliferation of glial progenitors in the SVZ and in demyelinated lesions in MS brains is 2 to 3-fold higher than in controls (Nait-Oumesmar et al., 2007) indicating that the number of OPCs is not a limiting factor for remyelination in MS. In the acute situation, the large number of immune cells and inflammatory cytokines facilitate and promote remyelination. However, chronic MS brains show microenvironmental changes that limit remyelination. These changes include a lower level of inflammatory responses, which are required for successful remyelination (Franklin, 2002). Therefore, an impaired OPC differentiation ability and variations in the CNS inflammatory status restrict remyelination capability during MS.

3. THE OLIGODENDROGENIC PROGRAM: MOLECULAR MODULATION OF OLIGODENDROGENESIS AND MYELIN REPAIR

The generation of new myelinating oligodendrocytes (oligodendrogenesis) is a process composed of several hierarchically structured events (de Castro and Bribian, 2005; Franklin and Kotter, 2008; Liu and Rao, 2004; Miller, 2002). During oligodendrogenesis, each step is tightly regulated by context-dependent stimulatory as well as inhibitory signals that are orchestrated in an oligodendrogenic program (Rivera et al., 2010).

Several molecular signals involved in the activation of oligodendrogenesis such as PDGF and thyroid hormone (TH) have been identified. The role of PDGF in oligodendrocyte development is well established. PDGF stimulates the proliferation of OPCs, and in the absence of PDGF, OPCs exit the cell cycle and differentiate pre-maturely (Barres et al., 1994; Raff et al., 1988). PDGF might also play an important role in the process of myelination. Excess PDGF increases the number of OPCs within demyelinating lesions (Woodruff et al., 2004), and accelerates remyelination (Allamargot et al., 2001). However, PDGF infusion also induces SVZ type B cell proliferation and tumor initiation (Jackson et al., 2006). In summary, although PDGF is an attractive candidate to enhance remyelination in MS, it might have detrimental side effects such as tumor formation. Another molecule that stimulates endogenous myelin repair is TH. This hormone induces proliferation of OPCs, promotes their differentiation and finally enhances morphological and functional maturation of post-mitotic oligodendrocytes (Ahlgren et al., 1997; Billon et al., 2001;

Rodríguez-Peña, 1999). Indeed, inhibition of this hormone leads to a decrease in oligodendrocyte numbers (Ahlgren et al., 1997; Koper et al., 1986). Consistent with these findings, TH also affects myelination and remyelination. Thus it has been shown *in vivo* in different demyelination and MS animal models that TH enhances and accelerates remyelination by promoting neural progenitor differentiation into OPCs and oligodendrocytes (Calza et al., 2002; Calzà et al., 2005; Franco et al., 2008). In conclusion, TH induces OPC differentiation, maturation and enhances remyelination.

In addition to oligodendrogenesis-promoting factors, a number of molecules and transduction pathways that inhibit oligodendrogenesis and remyelination have been identified. For instance, bone morphogenetic proteins (BMPs) are rapidly up-regulated after CNS injuries and are involved in astrogliosis and glial scar formation (Fuller et al., 2007; Setoguchi et al., 2001). Upon BMP stimulation, OPCs upregulate Id2 and Id4, which sequester the pro-oligodendrogenic Olig factors and prevent them from translocating into the nucleus and thereby block their activity (Samanta and Kessler, 2004). Besides BMPs, Notch signaling has been implicated in inhibition of oligodendrogenesis. The Notch downstream targets Hes1 and Hes5 (Jarriault et al., 1998; Wang et al., 1998) inhibits neuronal and oligodendroglial differentiation and promotes astrocyte fate decision in neural progenitor cells (Artavanis-Tsakonas et al., 1999; Kageyama and Ohtsuka, 1999; Kageyama et al., 2005; Ohtsuka et al., 2001; Tanigaki et al., 2001; Wang et al., 1998; Wu et al., 2003). Notch also inhibits the expression of genes relevant for oligodendroglial maturation and myelination (Givogri et al., 2002; Jessen and Mirsky, 2008; Woodhoo et al., 2009). Therefore, Notch signaling inhibits oligodendrocyte fate decision as well as oligodendroglial differentiation, maturation and myelination. A further interesting target for remyelinating therapies is the cyclin-dependent kinase inhibitor p57kip2. In addition to cell cycle control, p57kip2 is involved in oligodendrogenesis. It has been demonstrated that in Schwann cells suppression of endogenous p57kip2 levels uncouples cellular differentiation from axonal contact (Heinen et al., 2008). A similar role for p57kip2 has now been revealed during the oligodendroglial differentiation process. Although oligodendrocytes –in contrast to Schwann cells– showed spontaneous differentiation in culture, long-term p57kip2 suppression accelerated morphological maturation as well as myelin protein expression. Moreover, p57kip2 is dynamically regulated during MS and inhibits oligodendroglial maturation (Kremer et al., 2009). Furthermore, p57kip2 regulates glial fate choice in adult NPCs, since after p57kip2 suppression a significant increase in oligodendrogenesis at the expense of astrogenesis has been noticed (Jadasz et al., 2012). Therefore, p57kip2 blocks oligodendrocyte fate decision, differentiation and maturation. Finally, Wnt signaling was shown to interfere with oligodendrogenesis during development as well as during adult CNS remyelination (Fancy et al., 2009; Shimizu et al., 2005). It has been shown that stabilization of Axin2, a negative regulator of Wnt signaling, accelerated oligodendrocyte differentiation and remyelination (Fancy et al., 2011). In summary, Wnt is an inhibitory signal for oligodendrogenesis, affecting differentiation and maturation as well as remyelination.

There are several other molecular key regulators of oligodendrogenesis and remyelination, however, a review of all factors would be beyond the scope of this review. Nevertheless, therapeutic strategies aiming to enhance pro-oligodendrogenic activities and/or to suppress anti-oligodendrogenic signals might represent an attractive possibility for the treatment of demyelinating diseases such as MS.

4. INNOVATIVE THERAPIES FOR REMYELINATION AND MS TREATMENT

Current MS treatments use disease-modifying drugs, which have proven to have only limited efficacy, primarily in the RR type of MS. These include the immune-suppressive cytokines interferon beta-1a and interferon beta-1b, the immune-modulating drug glatiramer acetate and the immune-suppressant mitoxantrone. A novel and frequently used drug is the monoclonal anti alpha4-integrin antibody natalizumab, which reduces the ability of immune cells to cross the blood-brain-barrier (BBB). All these MS treatments have major side effects, have only minor effects in the progressive forms of MS, and most likely have no repair-promoting activity.

Preclinical development of novel MS therapies widely uses the experimental autoimmune encephalomyelitis (EAE) animal model (Lassmann, 2007a). This was first described in monkeys (Rivers et al., 1933), but now mainly rodent species are used. EAE is induced by active immunization with myelin-derived antigens such as myelin oligodendrocyte protein (MOG), myelin basic protein (MBP), myelin proteolipid protein (PLP), or with immunodominant peptides from these antigens such as MOG_{35-55}. Alternatively, EAE can also be evoked through the adoptive transfer of myelin-reactive T lymphocytes (Kabat et al., 1951; Kuchroo et al., 2002). A typical susceptible rodent will debut with the first clinical symptoms around 2 weeks after immunization and develop a RR EAE. Besides the clinical symptoms, the EAE models also resemble most, if not all the pathological characteristics of MS such as demyelination, inflammation and neurodegeneration, which makes this model particularly attractive for the development of new MS therapies.

A molecular therapy might not be sufficient to target all different aspects of MS pathogenesis. MS is a multi-factorial disease with inflammatory, myelin- and axon-degenerative components. Moreover, this disease is progressive, initiating with acute episodes characterized by T and B cell infiltration and subsequent inflammatory reactions that ultimately lead to a chronic situation encompassing an anti-regenerative microenvironment (Franklin, 2002; Lassmann, 2007b). Therefore the diseased microenvironment as well as the pathogenic parameters change during the course of MS, thus it is unlikely that a single molecular therapy would be able to cover the entire range of MS pathogenesis and provide sufficient structural and functional repair. Ideally, a MS therapy should: i) target the autoimmune-inflammatory component and exert an immunemodulatory activity, ii) target the neurodegenerative component and be neuroprotective, and iii) promote structural and functional repair mechanisms such as remyelination. In this respect, a cell therapy strategy that provides all these activities might represent an attractive therapy for MS treatment.

5. MESENCHYMAL STEM CELLS TRANSPLANTATION: AN ATTRACTIVE AND PROMISING THERAPY FOR MS TREATMENT

Adult mesenchymal stem cells (MSCs) reside in the bone marrow and in most connective tissues within the body (da

Silva Meirelles et al., 2006; Minguell et al., 2001). MSCs are characterized by their capability to differentiate into cells and tissue of the mesenchymal lineage such as bone, adipose tissue, cartilage, tendons, and muscle (Minguell et al., 2001). In bone marrow MSCs also display stromal cell properties, since they regulate the activity and fate of hematopoietic stem cells (HSCs), presumably through paracrine mechanisms (Minguell et al., 2001). Therefore the dual nature of MSCs as stem and stromal cells represents an advantage for these cells to "adapt" to neural microenvironments that arise from pathological conditions such as MS. In contrast to NPCs and OPCs that are embedded in the adult CNS and thus require invasive techniques to obtain them, MSCs are highly accessible. Altogether, MSCs are multipotent, stromal and accessible cells that might represent an attractive alternative to develop an autologous cell therapy for MS treatment.

During the last decades, several research groups have evaluated the effect of MSC transplantation into the diseased CNS. MSC transplantation promotes neuroprotection and regeneration in the lesioned areas of different animal experimental models (Dezawa et al., 2001; Gerdoni et al., 2007; Hofstetter et al., 2002; Lu et al., 2005; Neuhuber et al., 2005; Zhang et al., 2005; Zhang et al., 2004). Importantly, in the case of MS, several studies have demonstrated that transplanted MSCs reduce demyelination, increase neuroprotection, modulate inflammation and enhance functional recovery in the EAE animal model (Bai et al., 2009; Barhum et al., 2010; Gerdoni et al., 2007; Gordon et al., 2008; Gordon et al., 2010; Kassis et al., 2008; Kemp et al., 2010; Lanza et al., 2009; Lu et al., 2009; Rafei et al., 2009a; Rafei et al., 2009b; Zappia et al., 2005; Zhang et al., 2009; Zhang et al., 2005; Zhang et al., 2006). A list of these studies with the most relevant findings is summarized in Table I. It seems that systemic transplantation represents the best MSC administration route compared to others. For instance, while no negative side effects have been reported when MSCs were intravenously administrated into an EAE model, MSC-derived ectopic connective tissue has been detected within the CNS of EAE mice after intracerebroventricular transplantation (Grigoriadis et al., 2011). Clinical trials are currently ongoing with MSC autologous systemic transplantation into RR-, SP- and PP-MS patients (Freedman et al., 2010; Martino et al., 2010). Moreover, in a recent preliminary study in which autologous MSC transplantation was performed in SP-MS patients, a significant functional, structural and physiological visual improvement has been described (Connick et al., 2012). Although pre-clinical and clinical trials suggest MSC transplantation as a promising therapy for MS, more studies and long-term clinical trials are necessary to provide final conclusions.

The underlying mechanisms of the therapeutic effects of MSCs are still unknown, but they may involve one or more of the following possibilities: i) transdifferentiation of MSCs into functional integrated mature neurons and/or oligodendrocytes (MSC plasticity); ii) immunoregulatory effect of transplanted MSCs on host-derived immunoreactive cells (immunemodulation); iii) bystander effects of MSCs on the survival of damaged neurons and/or oligodendroglia (neuroprotection); iv) bystander effects of MSCs on the fate and differentiation of endogenous NPCs or OPCs present at the lesion site (remyelination).

5.1 MSC neural transdifferentiation: a fact or wishful thinking?

Several studies have considered and tested the hypothesis that transplanted adult MSCs might transdifferentiate into mature neurons or glial cells, which would integrate into the

TABLE I

Summary of the main findings (X) in studies where functional recovery has been reported after MSC transplantation into EAE mice

MSCs Source	Administration Route	IM	NP	RM	References
Human bone marrow	Intravenous	**X**	**X**		(Zhang et al., 2005)
Mouse bone marrow	Intravenous	**X**	**X**		(Gerdoni et al., 2007)
Human bone marrow	Intravenous	**X**		**X**	(Bai et al., 2009)
Human bone marrow (neurotrophic factor-producing MSCs)	Intracerebroventricular	**X**	**X**		(Barhum et al., 2010)
Human bone marrow	Intraperitoneal				(Gordon et al., 2008)
Human bone marrow	Intravenous		X		(Gordon et al., 2010)
Mouse bone marrow	Intravenous, Intraventricular	**X**	**X**	**X**	(Kassis et al., 2008)
Human (CNTF-overexpressing MSCs)	Intravenous	**X**	**X**	**X**	(Lu et al., 2009)
Mouse bone marrow	Intraperitoneal				(Rafei et al., 2009a)
Mouse bone marrow	Intravenous	**X**	**X**		(Zappia et al., 2005)
Mouse bone marrow	Intravenous		X		(Zhang et al., 2009)
Human bone marrow	Intravenous		X		(Zhang et al., 2006)
Mouse bone marrow	Intraperitoneal	**X**			(Rafei et al., 2009b)

Abbreviations: Immunemodulation (IM), Neuroprotection (NP), Remyelination (RM)

damaged CNS and promote functional recovery. For instance, MSCs that were injected into the mouse lateral ventricle were later detected in the cerebellum, hippocampus molecular layer and olfactory bulb. Surprisingly, transplanted MSCs were found to express markers specific for astrocytes and neuronal lineage. Moreover, after MSCs were placed into a CNS trauma, stroke or Parkinson mouse model, transplanted cells were found to express mature astrocyte- or neuronal-specific markers (Kopen et al., 1999; Li et al., 2001; Li et al., 2000; Mahmood et al., 2001). Together this *in vivo* evidence supported a MSC transdifferentiation mechanism; however, follow-up studies revealed the possibility of fusion events between transplanted stem/progenitors cells with endogenous differentiated cells (Álvarez-Dolado et al., 2003; Kemp et al., 2010; Terada et al., 2002). This observation clearly indicates caution when interpreting results and claiming conclusions. MSC transdifferentiation has been tested under both *in vivo* and *in vitro* conditions. A number of studies have shown that the induction of neural genes in MSCs could be achieved through stimulation with non-physiological substances such as betamercaptoethanol, dimethylsulfoxide, hydroxyanisole and butylated hydroxytoluene, etc (Deng et al., 2001; Munoz-Elias et al., 2003; Padovan et al., 2003; Rismanchi et al., 2003; Sánchez-Ramos et al., 2000; Woodbury et al., 2002; Woodbury et al., 2000). The criteria to assess MSC neural transdifferentiation properties of these compounds were based on the appearance of cells exhibiting a typical neural-like morphology and/or the expression of distinctive neural-specific genes. However, it has been observed that these non-physiological compounds induce a disruption of the actin cytoskeleton and may facilitate the outcome of neurite-resembling processes (Neuhuber et al., 2004). Moreover a study by Lu and coworkers demonstrated that morphological changes and increases in immunolabeling for certain neural markers upon "neural chemical induction" of MSCs are likely the result of cellular toxicity, cell shrinkage, and changes in the cytoskeleton and do not represent a true neural transdifferentiation phenomenon (Lu et al., 2004). Consequently, caution is recommended in the interpretation of results assessing the MSC neural transdifferentiation induced by non-physiological compounds. Therefore, to avoid misleading effects *in vitro* studies should focus on the investigation of physiological inductors for MSC neural differentiation. In this respect, we have shown that soluble

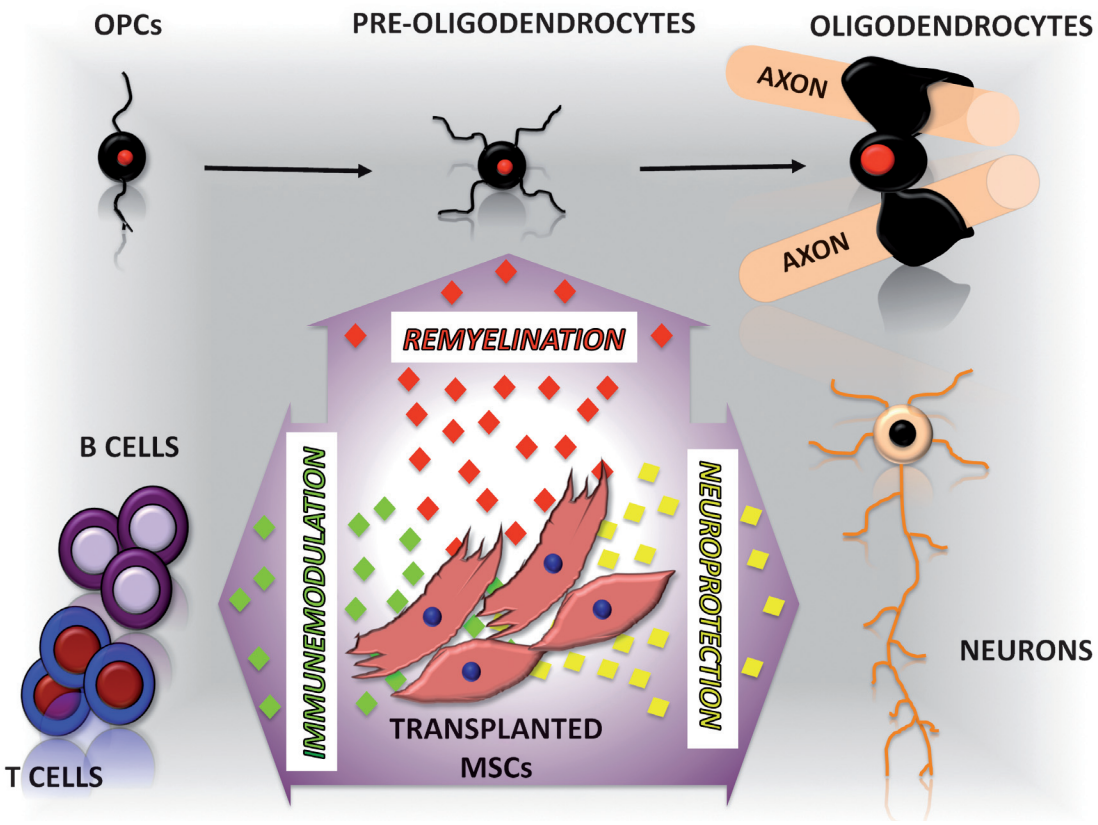

Figure 1. Therapeutic activities of transplanted MSCs in MS. Bone marrow-derived MSCs are accessible stromal multipotent cells that after transplantation display bystander therapeutic activities for MS treatment. It seems that mainly soluble factors (cytokines, growth factors, neurotrophins, etc) mediate the MSC-induced recovery in MS. Transplanted MSCs can home to and infiltrate the diseased CNS and lymph nodes. After transplantation, MSCs can modulate the immune system and inhibit encephalitogenic T and B cell activation (immunemodulatory activity (♦) in green). In addition, transplanted MSCs protect neurons and oligodendrocytes from cell death (neuroprotection activity (♦) in yellow). Finally, transplanted MSCs induce oligodendrocyte, stimulate endogenous OPCs differentiation and maturation that might enhance remyelination *in vivo* (remyelination activity (♦) in red). Therefore, MSC transplantation represents an attractive alternative to develop a novel therapeutic strategy for the treatment of MS. Abbreviations: Oligodendrocyte Progenitor Cells (OPCs), Mesenchymal Stem Cells (MSCs).

factors derived from adult hippocampus induce a neuronal-like phenotype in MSCs (Rivera et al., 2006a). However, differentiated MSCs did not display mature neuronal features. In conclusion, although some *in vivo* and *in vitro* studies indicate that MSCs might transdifferentiate into cells from the neural lineage, there is no convincing evidence and more studies are required to claim this conclusion.

Considering that MS is a CNS disease that mainly affects oligodendroglia, there is no substantial evidence showing that MSCs can transdifferentiate *in vivo* into mature remyelinating oligodendrocytes. In two different studies mouse and human-derived MSCs were systemically administrated into EAE mice. Although green fluorescent protein (GFP) labeled-MSCs were found in CNS demyelinating areas after intravenous infusion, no significant sign of MSC oligodendroglial transdifferentiation was observed (Gerdoni et al., 2007; Gordon et al., 2010). In summary, it is unlikely that neural transdifferentiation might be part of the transplanted MSC-derived repair mechanism in MS. Alternative mechanisms by which MSCs might enhance functional recovery in MS are mediated through bystander effects on the host immune system and CNS cells (Zhang et al., 2005). These activities involve CNS-homing, immunemodulation, neuroprotection and remyelination (Karussis et al., 2008).

5.2 Transplanted MSCs home into demyelinated CNS and exert immunemodulatory activity during MS

Interestingly, after systemic or intraperitoneal administration of GFP labeled MSCs, transplanted cells home and infiltrate into CNS demyelinated regions as well as into lymph nodes of EAE mice and promote functional recovery (Table I) (Gerdoni et al., 2007; Gordon et al., 2008; Gordon et al., 2010; Kassis et al., 2008; Zappia et al., 2005). These observations indicate that MSCs display CNS homing and immunemodulatory properties. The immunemodulatory effects of MSCs involve impairment of the maturation and function of dendritic cells (DCs) through the inhibition of molecules associated with antigen presentation and IL-12 release (Aggarwal and Pittenger, 2005). Additionally, MSCs inhibit the differentiation of monocytes into immature antigen-presenting myeloid DCs and modulate macrophage activity (Nemeth et al., 2009). The immunemodulatory effect of MSCs is not restricted to DCs and monocytes/macrophages, since they also influence B and T lymphocytes during MS. MSCs affect B cell proliferation and differentiation, promote T cell anergy and stimulate the production of regulatory T cells (Selmani et al., 2008; Uccelli et al., 2007; Uccelli et al., 2006). MSC-injected EAE mice display a reduction of CNS inflammatory infiltrates and a decrease in encephalitogenic T cell proliferation in lymph nodes with a subsequent reduction in demyelination (Kassis et al., 2008; Zappia et al., 2005). The MSC-derived inhibitory effect on encephalitogenic T cells has been also confirmed *in vitro* (Kassis et al., 2008; Zappia et al., 2005). Moreover, transplanted MSCs regulate the T cell phenotype and modulate the immune response in the EAE animal model (Bai et al., 2009; Liu et al., 2009; Rafei et al., 2009a; Rafei et al., 2009b). Intravenously injected MSCs inhibit Th1 and Th17 production with a concomitant increase in Th2 and anti-inflammatory cytokines, promoting functional recovery in EAE mice (Bai et al., 2009). Further studies have shown that transplanted MSCs inhibit the production of CD4 Th17 cells in a CCL-2-dependent manner (Rafei et al., 2009a; Rafei et al., 2009b). Interestingly, it seems that the immunemodulatory effect of MSCs during MS is mainly mediated through their secretome properties. In a recent study where conditioned medium derived from MSCs (MSC-CM) was infused into EAE mice, a significant decrease in pro-inflammatory cytokine (IFN-γ, IL-17, TNF-α, IL-2) expression together with a consequent increase in anti-inflammatory cytokine (IL-10, IL-14) expression has been observed (Bai et al., 2012). In this study, authors showed that at least partially, hepatocyte growth factor (HGF) signaling mediates these MSC-CM-induced changes in cytokine expression in EAE (Bai et al., 2012). Moreover, inhibition of HGF signaling decreased MSC-derived functional recovery in EAE. In summary, transplanted MSCs exert immunemodulatory activities by diverse mechanisms that might be involved in the functional recovery in MS (Figure 1).

5.3 Transplanted MSCs induce neuroprotection and enhance CNS remyelination during MS

The MSC-derived immunemodulatory activity is probably not sufficient to explain the functional recovery observed in EAE mice after MSCs transplantation. In a recent report, MSCs were transplanted into experimental autoimmune neuritis (EAN) mice, a non-MS autoimmune neuropathy. Contrary to EAE, although MSCs inhibited CD4+ T cell proliferation, transplanted cells failed to promote functional recovery in EAN (Sajic et al., 2012). This result suggests that the MSC-derived immunemodulatory activity is not sufficient to promote functional recovery in all autoimmune-based neuropathies, and therefore MSCs may exert other activities that provide better success in demyelinated diseases such as MS. Besides the immunemodulatory effects of MSCs, transplanted MSCs protect axons and oligodendrocytes from cell death. For instance, it has been shown that transplanted MSCs reduce axonal loss in EAE mice (Zhang et al., 2006). Moreover, transplanted MSCs decrease the cellular expression of proNGF and p75, reducing oligodendrocyte apoptosis and enhancing functional recovery in EAE model (Zhang et al., 2009). In addition to this, the neuroprotective effect of transplanted MSCs is endowed with a strong antioxidant effect in EAE (Lanza et al., 2009). In summary, transplanted MSCs enhance neuronal and oligodendroglial survival (Figure 1).

In addition to immunemodulatory and neuroprotective activities, MSCs display neuroreparative properties by affecting the fate of CNS endogenous progenitor cells. For example, it has been shown that transplanted MSCs enhanced endogenous oligodendrocyte differentiation and remyelination in EAE mice (Bai et al., 2009; Kassis et al., 2008; Lu et al., 2009). However, with this experimental setup (EAE model) is still not clear whether the MSC-derived regenerative effect is an indirect consequence of the MSC-mediated immunemodulation or whether MSCs could directly exert a bystander activity on endogenous progenitors. A recent study partially addressed this question by co-transplanting MSCs together with OPCs into the myelin deficient *shiverer* mouse strain (Cristofanilli et al., 2011). This study showed that MSCs enhanced OPC migration and maturation into oligodendrocytes promoting myelination in the corpus callosum. Consistent with this study, we have shown that *ex vivo* co-transplantation of MSCs together with NPCs onto hippocampal slice cultures (free of immune derived cells) induces NPCs to acquire an

oligodendrocytic phenotype, while NPCs transplanted alone generated mostly astrocytes (Rivera et al., 2009). Regarding the underlying mechanisms, we have studied the effects of MSCs on NPCs *in vitro* and demonstrated that soluble factors present in MSC-CM strongly activate oligodendrogenesis in postmitotic NPCs (Rivera et al., 2006b). First, we observed a strong increase in the number of GalC- and MBP-expressing cells in the MSC-CM treated cultures, indicating that MSC-CM promotes oligodendroglial differentiation and maturation. This was apparently at the expense of astrogenesis, since the number of GFAP-expressing cells was dramatically reduced. Moreover, we observed that MSC-CM augmented the expression of the pro-oligodendrogenic determinants Olig1/2, while it diminished the expression of Id2, a specific inhibitor of oligodendrogenesis. Therefore we suggested that MSC-CM not only promoted oligodendrocyte differentiation and maturation, but also induced oligodendrocyte fate decision, most likely through modulating the relative expression levels of Oligs/Ids (Rivera et al., 2006b). In agreement with this conclusion, we have recently published that MSC-CM primed or predisposed proliferating NPCs towards the oligodendrocyte lineage (Steffenhagen et al., 2011). Therefore, soluble factors derived from MSCs can activate NPC oligodendrogenesis at different progression stages. In the light of our findings, a recent report has shown in EAE mice that the MSCs derived oligodendrogenic and myelin repair activity or activities reside in soluble factors secreted by these cells (Bai et al., 2012). Thus, MSC-CM infusion into EAE mice enhanced oligodendrocyte development and remyelination. Hence the identification of the oligodendrogenic activity derived from MSCs becomes a priority to develop new remyelination therapies for MS treatment.

We performed a candidate approach in order to identify the MSC-derived oligodendrogenic activity. We have excluded a number of growth factors, cytokines and hormones as candidates for this activity: Insulin-like growth factor-1 (IGF-1), thyroid hormone (TH), fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), transforming growth factor beta-1 (TGFbeta-1), neurotrophin-3 (NT-3), sonic hegdehog (Shh), PDGF-AA, UDP-glucose and noggin (Rivera et al., 2006b; Rivera et al., 2008). Even though ciliary neurotrophic factor (CNTF) is expressed by MSCs and promotes oligodendrocyte differentiation of adult NPCs, it did not decrease astroglial differentiation (Rivera et al., 2008). Therefore it seems that, in contrast to MSC-CM, CNTF does not induce a change in the fate of NPCs from astrocytes towards oligodendrocytes. In experiments using neutralizing antibodies we demonstrated that CNTF, although expressed by MSCs, is not involved in the pro-oligodendrogenic effect triggered by MSCs (Rivera et al., 2008). A recent study concluded that HGF mediates MSC-induced recovery in MS (Bai et al., 2012). In addition, these authors showed that HGF accelerated remyelination of lysolecithin-induced demyelinated spinal cord. Although HGF seems to represent an attractive candidate for the MSC-CM derived oligodendrogenic activity, it does not induce oligodendrogenesis in NPCs and no decrease in the proportion of oligodendrocytes generated has been observed after blocking HGF in MSC-CM (unpublished observations). The nature of the MSC-CM-derived oligodendrogenic activity remains unclear at present, but molecules other than proteins might be considered. For example, recent studies demonstrated that MSCs secrete vesicles that contain miRNAs, which could exert effects on neighboring cells (Chen et al., 2010). In summary, MSCs might activate oligodendrogenesis and contribute to remyelination in MS, but this hypothesis requires further investigation (Figure 1).

6. CONCLUSION AND FINAL REMARKS

The CNS remyelination capacity is impaired during chronic MS, since neural progenitors are insufficiently recruited into the lesion site and fail to differentiate. Current MS treatments reduce the formation of inflammatory lesions within the CNS but do not enhance endogenous myelin repair. Therefore, in addition to immunemodulation, boosting endogenous oligodendrogenesis and remyelination through cell therapies is a highly attractive alternative, since it may cover several target mechanisms in one shot. Here, MSCs represent an attractive source to develop a cell therapy for MS. First, MSCs are accessible cells, easy to obtain and thus invasive techniques can be avoided. Second MSCs can be used in an autologous transplantation mode. Third, MSCs home into the demyelinated CNS and therefore systemic transplantation rather than invasive cell administration techniques could be used. Finally, MSCs exert stromal bystander immunemodulatory, neuroprotective and eventually remyelinating activities in the damaged CNS. Therefore, autologous MSC transplantation might be considered for developing novel therapeutic approaches for MS treatment (Figure 1).

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