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Promoting return of function in multiple sclerosis: An integrated approach

Mar Gacias^a and Patrizia Casaccia^{a,b,*}

^aDepartment of Neuroscience, Friedman Brain Institute, United States

^bDepartment of Genetics and Multiscale Biology, Department of Neurology Icahn School of Medicine at Mount Sinai, United States

Abstract

Multiple sclerosis is a disease characterized by inflammatory demyelination, axonal degeneration and progressive brain atrophy. Most of the currently available disease modifying agents proved to be very effective in managing the relapse rate, however progressive neuronal damage continues to occur and leads to progressive accumulation of irreversible disability. For this reason, any therapeutic strategy aimed at restoration of function must take into account not only immunomodulation, but also axonal protection and new myelin formation. We further highlight the importance of an holistic approach, which considers the variability of therapeutic responsiveness as the result of the interplay between genetic differences and the epigenome, which is in turn affected by gender, age and differences in life style including diet, exercise, smoking and social interaction.

Keywords

Multiple sclerosis; Repair; Neurodegeneration; Therapy; Epigenetics; Axonal damage; myelin

1. Introduction

Multiple sclerosis (MS) is considered the major cause of neurological disability among young adults affecting approximately 2.5 million people worldwide (Lassmann et al., 2007). The disease course in the majority of MS patients is relapsing remitting (RRMS) with acute relapses (demyelinating and inflammatory episodes) followed by periods of clinical remission, while in 15% of patients it is characterized by the absence of remissions characteristic of a progressive course (PPMS) (Debouverie et al., 2008). Eventually also 50-60% of RRMS patients will progress to a very debilitating form of the disease (SPMS) defined by sustained functional deterioration without periods of remission. Therefore, despite the definition of MS as inflammatory demyelinating disorder, it is clear that clinical disability is a prominent feature of this disorder and results from axonal damage and neurodegeneration (Trapp and Nave, 2008). Based on these considerations, any therapeutic approach aimed at restoring function in MS needs to target both axonal function and new myelin formation. In this manuscript we shall review the current knowledge on mechanisms of axonal damage and discuss potential therapeutic approaches, which include control of

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*Corresponding author at: Department of Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave Levy Place Box 1065, New York, NY 10029, United States. Tel.: +1 212 659 5988. patrizia.casaccia@mssm.edu. .

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inflammation and oxidative damage, support of mitochondrial energy production and enhanced remyelination. We shall then review mechanisms of myelin repair by providing a comprehensive review of the current knowledge and identifying potential molecular targets. Finally we acknowledge the importance of cell replacement therapies and suggest the importance of adopting a holistic approach, which includes management of patients' life style choices, such as smoking, diet, exercise and social stimulation.

2. Mechanism of axonal damage in MS

Despite the definition of MS as an autoimmune primarily demyelinating disorder, axonal damage has been recognized since the very first description of the disease by Charcot. Throughout the years this concept has evolved due to the progress of imaging techniques and molecular advances on the function of the axo-glial unit. A consideration of the most recent development in the field of axonal damage is crucial to the development of novel therapies, especially the distinction between damage occurring even in the presence of myelin (Fig. 1) and neurodegeneration consequent to myelin loss.

2.1. Acute axonal degeneration occurring independently of myelin damage

For over three decades, acute axonal damage has been considered the result of immune mediated events linked to the infiltration of cytotoxic T cells and recruitment of monocytes and resident microglia at the site of inflammation (Huitinga et al., 1990). Indeed acute axonal damage has been reported at the early stages of the disease (Kuhlmann et al., 2002; Trapp et al., 1998) and found both in white and gray matter lesions (Kutzelnigg et al., 2005). It was proposed that immune cells would directly affect axons via release of perforin (Howe et al., 2007) and cytotoxic cytokines, such as TNF α and release of nitric oxide (Siffrin et al., 2010). Immune cells and activated resident microglia have been linked to the production of nitric oxide (NO), glutamate and TNF α , and studies on the mechanism of action of these mediators have been instrumental in elucidating deficits occurring in the axonal compartment independent of the presence or absence of the myelin sheath. Acute axonal damage has been proposed to result from acute energetic impairment, defective axonal transport and/or direct damage to intracellular structures and organelles. Disruption of mitochondrial respiration can be directly caused by NO, due to its ability to compete with oxygen at the cytochrome C oxidase binding site and block the electron flow through the respiratory chain (Borutaite and Brown, 1998; Cleeter et al., 1994), thereby resulting in decreased ATP production and acute energy impairment in the axonal compartment. Impaired mitochondrial electron transfer and increased production of free radicals cause oxidation of cellular lipids, proteins and DNA (Bishop et al., 2009; Cross et al., 1998). Besides NO, activated microglia and recruited macrophages can also produce TNF α and glutamate, whose concentration is also dependent on the concomitant decrease of glutamate transporters and sustained electrical activity (Groom et al., 2003; Matute, 2011). Glutamate and TNF α have been shown to impair axonal transport by interfering with the phosphorylation of the adaptor molecule JIP (Horiuchi et al., 2007) or by modulating the binding of histone deacetylases to motor molecules (Kim and Casaccia, 2010). Glutamate and TNF α favor the nuclear export and accumulation of the histone deacetylase HDAC1 in the axoplasm, which binds to KIF2A and KIF5, thereby sequestering these key motor molecules and resulting in impaired mitochondrial movement (Kim et al., 2010). These results were also consistent with the detection of increased mitochondrial content in the brain of MS patients (Zamboni et al., 2011). Persistently elevated concentrations of glutamate and TNF α may also cause excessive intracellular calcium levels with subsequent activation of calcium-dependent proteases, responsible for cytoskeletal proteolysis and alter the mitochondrial permeability transition pore in neurons, thereby resulting in the release of pro-apoptotic molecules, such as cytochrome C (Su et al., 2009). Early signs of damage have been detected at axoglial junction, in the paranodal region and reveal the occurrence of

damage independent of myelin loss (Howell et al., 2010). Within myelinated axons, axonal swellings in live mice with EAE, could be detected in association with microglial production of reactive oxygen and nitrogen species and were reversed by treatment with specific radical scavengers (Nikic et al., 2011), thereby supporting the importance of anti-oxidants as neuroprotective strategies in MS. While there is general consensus on the importance of activated resident microglia as causative for axonal damage, there is accumulating *in vivo* evidence, in preclinical models, that activation may occur independently of immune infiltration (Davalos et al., 2012; Nikic et al., 2011). Recent studies have further shed some light on alternative recruitment mechanisms for microglia (Davalos et al., 2012) and shown that blood fibrinogen may be a primary cause for microglia clustering and activation with consequent axonal damage. Together these studies identify potential therapeutic targets for management of acute axonal damage independently of immunomodulation.

2.2. Damage consequent to myelin loss

Axonal damage in MS has for many decades been considered as the inevitable consequence of damage to the myelin sheath, with loss of its protective role and function. In physiological conditions, myelin segments contribute to the delineation of specialized regions of high energetic consumption and regulation of electrical transmission, called “nodes of Ranvier”, which are characterized by high density of sodium channels and mitochondria. Loss of myelin has been implicated as causal for the initial conduction block, consequent to loss of saltatory conduction, due to nodal disruption (Waxman et al., 1994). Adaptive mechanisms include the increased expression and redistribution of the NaV 1.2 and NaV 1.6 sodium channels and non-saltatory transmission of the action potential (Black et al., 2006; Waxman, 2006). Loss of the compartmentalized distribution of channels, together with the greater and more persistent sodium currents due to increased Nav1.6 subunit distribution (Craner et al., 2004) has also been associated with increased activity of the Na⁺/K⁺ ATPase along the demyelinated axon, in an attempt to maintain the membrane potential and to pump excess sodium ions out of the axon. Eventually, however, the intracellular accumulation of sodium leads to reversal of the Na⁺/Ca⁺⁺ exchanger thereby resulting in calcium influx (Stys et al., 1992) and activation of calcium-dependent enzymes (via calpain activation) and further aggravating mitochondrial impairment. Decreased mitochondrial function becomes even more challenging in a situation of sustained high energy demand, especially in the absence of myelin metabolic support. This is why remyelinating strategies maybe highly beneficial in preventing the long term deterioration of clinical conditions.

2.3. Therapeutic implications

The rapid acquisition of knowledge regarding mechanisms underlying axonal damage in MS has allowed the identification of a series of neuroprotective targets that are awaiting solid validation in preclinical models prior to being considered for human intervention. Among these new therapies is the use of nuclear export blockers, to prevent HDAC1-dependent damage, the use of dimethylfumarate to promote healthy mitochondrial function and counteract oxidative damage. In addition, based on the recently proposed role of myelin as major energy provider for long tract axons (Nave, 2010), it is becoming clear that therapies promoting remyelination are also essential for neuroprotection and improved of neurological disability.

3. Myelin repair

Remyelination is the regenerative process by which new myelin sheaths are generated around demyelinated axons in the adult CNS, restoring the saltatory conduction and resolving functional deficits (Duncan et al., 2009; Irvine and Blakemore, 2008; Franklin and Ffrench-Constant, 2008). It is widely accepted that CNS remyelination is driven by an

endogenous population of adult neural stem cells and by adult oligodendrocyte progenitor cells (OPCs), that are widely distributed throughout the CNS and constitute 5-8% of the adult brain cells (Dawson et al., 2003; Ffrench-Constant and Raff, 1986; Horner et al., 2000). Remyelination in MS is much more extensive than originally thought, although it is far from complete (Patrikios et al., 2006) and yet it has been shown that axonal damage might occur even in the presence of remyelination, possibly because the high energetic demand of the axons is not met by the newly formed myelin sheaths. Careful evaluation of animal models has indicated that remyelination requires the successful occurrence of multiple events, including expansion of the progenitor pool, their recruitment towards the lesion, followed by differentiation into myelinating oligodendrocytes and culminating with axonal wrapping (Fig. 2). We shall review these studies in detail, while using some caution in translating the potential translational application of these findings to humans, due to lack of direct data, possibly consequent to inadequate techniques of evaluation of remyelination.

3.1. Expansion of oligodendrocyte progenitor cells

The rapid proliferative response of OPCs to demyelination is modulated by the production of astrocyte and microglial-derived mitogens and cytokines (Wilson et al., 2006). Repeated episodes of demyelination-remyelination may result in depletion of the progenitor pool and decreased efficiency of repair and therefore emphasis has been placed on the reactivation of developmental pathways modulating the proliferative response after demyelination (Woodruff et al., 2004). Targeting these pathways has been considered a potential strategy to increase myelin repair.

Growth factors. Platelet-derived growth factor AA (PDGF-AA) is perhaps the best-characterized mitogen for OPC (Raff et al., 1988). The expression of PDGF-AA is critical in regulating the size of the progenitor pool during development (Fruttiger et al., 1999) and *Pdgfra* heterozygote mice displayed impaired OPC amplification and defective recruitment to focally demyelinated areas (Murtie et al., 2005b). Fibroblast Growth Factor 2 (FGF2) is another potent mitogen that enhances proliferation by rendering OPC more responsive to PDGF-AA (by inducing expression of its receptor levels) and inhibits differentiation (Bansal and Pfeiffer, 1997). Expression of these mitogens and their receptors is increased after demyelination (Messersmith et al., 2000; Woodruff et al., 2004) and experiments in knockout mice have revealed the importance of PDGF-AA to induce OPC proliferation and of FGF2 to avoid premature differentiation, during recruitment to the lesion site (Murtie et al., 2005a; Zhou et al., 2006). Other pathways, including EGFR pathway and IGF-1 signaling have also been shown to favor proliferation of OPC in response to injury (Aguirre et al., 2007; Mason et al., 2003). The detection of decreased EGF levels in CSF and plasma of MS patients is intriguing, although no human studies, to date have correlated EGF levels with efficiency of repair in MS brains. Combined treatment with several growth factors has been tested in experimental models of demyelination and shown promising results in attenuating EAE pathology (Frost et al., 2003; Kuhlmann et al., 2006) and favoring remyelination of focal demyelinated lesions (Aguirre et al., 2007). However, the systemic administration of these factors may have pleiotropic effects outside the CNS and their direct delivery to lesion may be hindered by the multifocal nature of MS. An additional consideration is that excessive and ectopic production of oligodendrocytes in response to overexpression of PDGF-AA was compensated by increased death of cells at an immature stage of differentiation. These results suggested that cell survival mechanisms may serve a compensatory function and override proliferation to control the final number and distribution of mature oligodendrocytes (Calver et al., 1998). These results underscore the relevance of appropriate timing of growth factor delivery during the remyelination phase and underscore the risks posed by continued delivery of growth factors as repair strategy.

3.2. Recruitment of OPCs to MS lesions

An additional limitation to full recovery is the inability of progenitors to migrate within the center of the lesion and completely remyelinate it. This has been best shown by the detection of high numbers of premyelinating oligodendrocytes at the edge, but not at the center of the lesion, thereby suggesting a deficiency of signals promoting OPC migration (Kuhlmann et al., 2008), a process that is exacerbated by aging (Chari et al., 2003).

Signaling pathways. Besides proliferation, PDGFR α and FGF2R have also been implicated in OPC migration (Vora et al., 2011), however the exact molecular mechanisms underlying OPC migration remain only partially defined. Several studies have suggested the MAPK cascade (Haines et al., 2008) and the Fyn-Cdk5-WAVE2 cascade (Miyamoto et al., 2008) as important modulators of OPC migration. Other studies have implicated activation of sphingosine-1-phosphate receptor5 and GABA-B receptors (Luyt et al., 2007; Novgorodov et al., 2007). The impact of GABAergic transmission on oligodendrocyte progenitors migration has been reported (Tong et al., 2009) and likely implies both, synaptic and extra-synaptic transmission possibly consequent to direct synaptic contact between GABAergic interneurons and OPCs (Velez-Fort et al., 2012).

Axonal guidance cues. Over the past decade, several short- and long-range axonal guidance cues have been implicated as regulators of OPC migration expressed in development and repair. Short cues include components of the extracellular matrix (ECM) such as tenascin-C, an inhibitor of OPC migration, which has also been detected in acute MS lesions (Jarjour and Kennedy, 2004; Sobel, 1998). The most important long-range guidance cues include netrins and semaphorins. Netrin-1 acts as chemorepellent for OPCs during embryonic development, and its effect is mediated by RhoA/ROCK signaling (Rajasekharan et al., 2010; Tsai et al., 2006). Semaphorin family members, in contrast, may act either as repellent (Sema 3A) or attractant (Sema 3F) of OPC migration during CNS development and their relative balance may modulate the success of progenitor recruitment during repair (Piaton et al., 2011; Syed et al., 2011). In animal models of demyelination Sema3A impaired OPC recruitment whereas Sema3F overexpression accelerated and enhanced remyelination (Piaton et al., 2011). In MS tissue, increased glial expression of *Sema3F* compared to *Sema3A* transcripts around and within active demyelinating lesions, but not in chronic plaques, has been reported. These results suggest that guidance cues may influence OPC recruitment, and therefore remyelination of MS lesions (Williams et al., 2007).

Chemokines—Local chemokine released by astrocytes and epithelial cells may also contribute to modulation of OPC migration during normal development and MS (Robinson et al., 1998). CXCL12 and CXCL1, for instance, act as inducers of OPC migration and differentiation (Carbajal et al., 2010; Omari et al., 2005). Decreased expression of these chemokines and their receptors in MS tissue has been proposed to contribute to remyelination failure (Calderon et al., 2006; McCandless et al., 2008). Promoting a shift towards a more favorable migratory environment around and within the demyelinated lesions might be highly desirable to increase repair in MS. However, promoting recruitment by up-regulation of PDGF-AA expression in aged animals with decreased remyelination rate, did not improve the overall remyelination efficiency (Woodruff et al., 2004). Development of new therapeutic approaches to favor OPCs recruitment and increase remyelination might require a modification of the molecular environment surrounding the lesions. This is an important therapeutic goal and yet difficult to achieve, due to the need specific and precise expression patterns of these cues and due to the multifocal nature of MS lesions.

3.3. Promoting myelin repair by enhancing OPC differentiation

Despite the evidence in support of progenitor pool exhaustion and deficient recruitment, the most accredited mechanism underlying remyelination failure is a differentiation block, supported by the detection of premyelinating cells in the proximity of the lesion (Chang et al., 2000; Kuhlmann et al., 2008). This block could result from excessive activation of pathways inhibiting differentiation and/or lack or deficient activation of pathways promoting myelin formation or changes of the intrinsic responsiveness of the cell, due to epigenetic changes occurring in oligodendrocytes (Shen et al., 2008).

3.3.1. Factors contributing to inefficient OPC differentiation—Besides mitogens, several highly conserved developmental pathways act as negative regulators of OPC differentiation and have been suggested as potential causes for remyelination failure.

Jagged-1/Notch Pathway: Activation of the canonical Notch/Jagged-1 pathway in OPCs has been shown to temporally and spatially coordinate proliferation and impair differentiation (Genoud et al., 2002). This is achieved by inducing expression of oligodendrocyte differentiation inhibitors (Hes1, Hes5, Hey1 and HeyL), which block OPC maturation by interfering with the transcriptional program of differentiation (Liu et al., 2006). Reactivation of this canonical pathway in response to TGF β has been described in active MS lesions and in EAE (John et al., 2002), even though Notch and Jagged-1 could be detected in completely remyelinated lesions (Seifert et al., 2007). In normal development, down-regulation of Jagged1 allows OPC differentiation to occur (Brosnan and John, 2009) and *in vitro* experimental evidence supported the hypothesis that blocking Notch canonical pathway enhances differentiation (John et al., 2002). However, *in vivo* studies revealed the importance of directing this strategy to the proper target cell, as *PLP-Cre*-driven ablation of Notch1 in oligodendrocytes yielded no differences in remyelination after cuprizone-induced demyelination (Stidworthy et al., 2004), while ablation in early oligodendrocyte progenitors resulted in accelerated and more extensive remyelination after a focal demyelinating insult (Zhang et al., 2009).

Wnt-signaling: Wnt signaling is another well-described developmental pathway implicated in preventing myelination during development and possibly preventing remyelination. Wnt signaling prevents OPC exit from the cell cycle and arrests their differentiation (Fancy et al., 2009). *In vivo* Wnt gain-of-function experiments resulted in delayed myelination and remyelination independent of deficits on OPC recruitment (Langseth et al., 2010). The study of the molecular mechanisms underlying Wnt inhibition of OPC differentiation, identified the transcription factor Tcf4 (aka Tcf712) as an important negative mediator of oligodendrocyte differentiation (Fancy et al., 2009; He et al., 2007; Ye et al., 2009). Upon Wnt activation, nuclear Tcf4 binds to phosphorylated β -catenin directing the expression of additional inhibitors of differentiation, such as Id2 and Id4, which have a direct role inhibiting of OPC differentiation (Chen et al., 2012; Samanta and Kessler, 2004). Unexpectedly, however, *in vivo* ablation of Tcf4 reduced oligodendrocyte differentiation and uncovered the need for additional research to clarify the role of this pathway in disease pathogenesis (Fu et al., 2009).

LRR-and Ig domain-containing Nogo receptor-interacting protein (LINGO-1): LINGO-1 is a CNS-specific trans-membrane glycoprotein, part of the NgR1 complex (Nogo-66 receptor complex) and belonging to a large family of Leucine-rich-domain Ig-containing proteins involved in neurogenesis, axon guidance and myelination during normal development (Mi et al., 2004). High levels of LINGO-1 were detected in OPCs and shown to inhibit differentiation, axonal regeneration and remyelination (McDonald et al., 2011; Mi et al., 2005). LINGO-1 knockout mice, in contrast, were characterized by precocious

myelination, and this led to the development of pharmacological inhibitors to promote remyelination and functional recovery (Mi et al., 2007, 2009). To date, two randomized, double-blind, placebo controlled phase-1 clinical trials to evaluate safety, tolerability, pharmacokinetic profile and the potential therapeutic utility of an anti-LINGO-1 monoclonal antibody have been completed, but not yet published ([Clinical Trial.gov](https://clinicaltrials.gov/ct2/show/study/NCT01052506) identifier: NCT01052506, NCT01244139). These trials were mostly focused on safety, rather than efficacy. However randomized controlled phase 2 trials are ongoing and it will be exciting to evaluate the results.

BMP4 pathway: Bone morphogenetic proteins (BMPs) are crucial regulators of neural development and oligodendrocyte specification (Liu and Niswander, 2005), that upon binding to their receptors, activate a transcriptional cascade involving Smads and other signaling pathways such as p38MAPK, LIM Kinase 1 (LIMK-1) or phosphatidylinositol-3 kinase (PI3K) (Fuller et al., 2007; Hocking et al., 2009). *In vitro* BMP as inhibitors of oligodendroglial lineage commitment, preventing the expression of myelin genes whereas promoting astrogliogenesis (See et al., 2004). In the adult CNS, BMPs are up-regulated after injury or demyelination (Cate et al., 2010; Fuller et al., 2007) and *in vivo* overexpression of BMP4 promoted the formation of a glial scar, which may serve as a barrier to factors favoring repair (Fuller et al., 2007). Glial scar formation and remyelination failure frequently co-exist in MS chronic lesions and have been correlated with increased expression of BMP4 and down-stream genes (Lock et al., 2002). This dual role of BMPs, inhibiting OPC differentiation and favoring astrocyte reactivation and glial scar formation may have direct relevance to remyelination and makes this pathway an important translational target for myelin repair in MS.

Hyaluronan-TLR2 pathway: The evidence of accumulated hyaluronan within demyelinated lesions in chronic MS lesions suggested a role for this molecule in preventing repair (Back et al., 2005; Sloane et al., 2010). A potential explanation is the hyaluronan-dependent activation of TLR2-MyD88 signaling resulting in inhibition of oligodendrocyte maturation. Up-regulated TLR2 in oligodendrocytes within the lesions was also described and the genetic ablation of *TLR2* in mice resulted in enhanced remyelination (Sloane et al., 2010). Thus, it has been proposed that small-molecules inhibiting the TLR2-MyD88 signaling pathway or its activation have the potential to improve remyelination.

Axonal-Oligodendrocyte contact: PSA-NCAM. An alternative possibility is that axons may signal directly to myelin forming cells (Coman et al., 2005), via post-translational modification of surface molecules. The presence of polysialic acid on NCAM, for instance, has been shown to decrease during postnatal development as myelination ensues, and it has been proposed it may serve the function of preventing premature myelination. The re-expression of PSA-NCAM in denuded axons within demyelinating regions has been described in MS lesions and compared with its lack on myelinated axons of the peri-plaque, normal appearing white matter and in remyelinated axons (Charles et al., 2002; Jakovcevski et al., 2007). Different strategies to mask or remove PSA determinants from axonal surfaces have succeed in promoting myelination both *in vitro* and *in vivo* (Charles et al., 2002) and suggested PSA-NCAM as an attractive pharmacological target to promote myelin repair. However, its expression in early migratory progenitors is important for migration and recruitment of OPC to the lesion. Hence, the therapeutic value of pharmacological approaches targeting PSA-NCAM expression in order to promote endogenous remyelination remains questionable.

Myelin debris: The presence of myelin debris clearly distinguishes the efficient process of postnatal myelination from the inefficient remyelination. Several lines of evidence support

the need for efficient phagocytic removal of myelin debris by macrophages prior to the formation of new myelin sheaths. Increased load of myelin debris in a toxic model of demyelination, for instance, severely impaired remyelination and was accompanied by defective oligodendrocyte maturation, even after normal recruitment of OPC and macrophages (Kotter et al., 2006).

Effect of aging: The progressive inability of oligodendrocytes to efficiently form new myelin in old mice with age (Sim et al., 2002) correlated with the detection of an aberrant epigenetic regulation of gene expression, including defective histone deacetylation (Shen et al., 2008). These mechanisms were previously shown to be critical to establish the oligodendrocyte cell-identity during development (Liu et al., 2007), and therefore their impairment was likely associated with inefficient differentiation of adult progenitors into mature oligodendrocyte and preferential choice of the astroglial lineage (Doucette et al., 2010). Decreased remyelination rate during has also been ascribed to poor macrophage response and delayed clearance of myelin debris (Zhao et al., 2006). Even though a detailed revision of the dynamics and role the different types of immune cells within the CNS and their potential role during remyelination is beyond the scope of this review it is important to take into consideration this dual role of microglial cells in axonal damage, axonal regeneration and in myelin repair. The development of approaches able to stimulate the beneficial roles of CNS inflammation without increasing the harmful aspects of macrophage/microglia activation is a challenging and promising field of future MS research. Exciting results were obtained in experiments in heterochronic parabiosis between young and old mice, which revealed that circulating monocytes from young mice had the ability to favorably restore repair in old mice (Ruckh et al., 2012).

3.3.2. Factors favoring OPC differentiation and myelin formation—Repair can only be achieved if the antagonism of inhibitory signals is counterbalanced by activation of pro-myelinating signals.

Growth factors: While mitogens may exert their beneficial effect by promoting the expansion of the progenitor pool, they may also activate survival pathways and favor survival of differentiated cells (McKinnon et al., 1993). Transgenic mice overexpressing human epidermal growth factor (hEGF) were also characterized by enhanced remyelination of focally demyelinated lesions (Aguirre et al., 2007). Insulin Growth Factor-1 (IGF-1) is also expressed during remyelination (Mason et al., 2003) and transgenic mice overexpressing IGF-1 have increased myelin thickness and number of myelinated axons (Luzi et al., 2004; Ye et al., 2004). Indeed, continue delivery of IGF-1 protected oligodendrocytes from apoptosis induced by cuprizone and in the EAE model, IGF-1 treatment had beneficial effects on clinical score and disease outcome (Cannella et al., 2000). Nevertheless, CNS targeted expression of IGF-1 failed to attenuate of EAE pathology and revealed a pleiotropic effects on immune cells (Genoud et al., 2005). Increased expression of IGF-1 alone was not sufficient to enhance remyelination of toxic-induced lesions in rats (Cannella et al., 2000; O'Leary et al., 2002) and a pilot study using recombinant IGF-1 in 7 MS patients did not show any significant differences between treated and untreated patients (Frank et al., 2002). However, the small sample size and the enrollment of secondary progressive MS patients could partially explained the lack of effectiveness. Additional studies are needed to define the potential use of IGF-1 for repair, possibly as combined treatment.

Non canonical Notch pathway: *F3/contactin signaling.* In contrast to the negative role of Notch/jagged-1 on OPC differentiation, the activation of Notch by the non-canonical ligand, F3/contactin, has been shown to promote maturation of OPC and myelination. A

dysfunctional non-canonical Notch signaling has been postulated as an alternative mechanism for ineffective remyelination in chronic silent MS lesions (Hu et al., 2003). In MS brains, it has been proposed that the pro-myelinating signal is blocked because the nuclear translocation of Notch1 intracellular domain (NICD) is defective due to increased expression of TIP30, a direct inhibitor of the nuclear transporter importin-B (Nakahara et al., 2009). Given the opposing effects of activating the canonical or non-canonical Notch pathways on oligodendrocyte differentiation the therapeutic value of pharmacological modulation of this pathway remains controversial and uncertain.

Nuclear receptor superfamily: The nuclear receptor superfamily is composed by transcription factors modulating key biological processes such as cell growth, cell cycle progression, differentiation, apoptosis and also OPC differentiation. With the exception of orphan receptors, nuclear receptors bind to small molecules amenable to modification by drug design and therefore, represent promising pharmacological targets (Gronemeyer et al., 2004). *In vitro* and *in vivo* experiments have involved retinoic acid receptors (RXR), peroxisome proliferator-activated receptors (PPARs) and some nuclear hormone receptors (thyroid hormone receptor, vitamin D receptor and estrogen receptors) in the differentiation program of oligodendrocytes.

Retinoid X receptors (RXR). The retinoid X receptor (RXR) is the obligatory heterodimerization partner for a range of nuclear hormone receptors, and is required for signaling through the pathways mediated by those receptors. Recently, Huang and coworkers identified higher levels of nuclear RXR- γ in oligodendrocyte lineage cells, macrophages and astrocytes within acute and remyelinating lesions but not in chronic silent MS lesions. OPCs from normal-appearing white matter of MS brains showed cytoplasmic localization of RXR- γ . Ablation of RXR- γ resulted in the accumulation of undifferentiated progenitors and fewer oligodendrocytes during repair after focal demyelination. Treatment with 9-cis-retinoic acid in contrast, lead to increased myelin thickness compared to controls (Huang et al., 2011). Besides the effect on oligodendrocyte lineage cells, retinoic acid also has immunomodulatory properties (Klemann et al., 2009) and these are promising features for MS treatment. In order to develop targeted therapies it would be of great interest to define cell-specific pathways downstream of RXR in distinct cell types.

Peroxisome proliferator-activated receptors (PPARs). Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors and key mediators of metabolism and energy balance (Desvergne et al., 2006). Three isotypes of PPARs have been described to date: PPAR α , PPAR γ , and PPAR δ (Ziouzenkova et al., 2002). In line with their various developmental and physiological functions, PPARs exhibit broad, but isotype-specific, tissue expression patterns (Braissant et al., 1996). Within the CNS, PPAR δ is known to be expressed in oligodendrocytes and neurons (Hall et al., 2008; Woods et al., 2003). Even though its precise function within the CNS has not been clearly elucidated several evidences suggest that this nuclear receptor may play a role in myelination. Highest PPAR δ expression levels occur at myelination onset (Braissant and Wahli, 1998) and ablation of PPAR δ in mice results in hypomyelination of the corpus callosum (Peters et al., 2000). Accordingly, *in vitro* experiments have demonstrated that PPAR δ agonists favor the formation of myelin sheaths (Granneman et al., 1998; Saluja et al., 2001). PPAR agonists have provided clinical benefits also in preclinical models of MS (Dasgupta et al., 2007; Lovett-Racke et al., 2004; Polak et al., 2005) with PPAR α and PPAR γ agonists reducing both the clinical and histological signs of EAE (Diab et al., 2004; Natarajan and Bright, 2002), in part due to their immunomodulatory effects (Drew et al., 2006; Xu et al., 2007). PPAR δ has also been studied in experimental models of demyelination and CNS injury (Almad and McTigue, 2010) and treatment with the PPAR δ agonist, GW0742 at peak of EAE was accompanied by reduced lesion load, neuronal damage and glial inflammation

(Polak et al., 2005) and increased myelin gene expression. More recently, GW0742 was also shown to increase the expression of the BMP inhibitor, noggin and reducing BMP2 and BMP4 levels thereby further enhancing oligodendrocyte maturation (Vittoria Simonini et al., 2010). In addition to the beneficial effect on oligodendrocyte development and survival in EAE models, PPAR δ agonists are neuroprotective *in vitro* and in several disease models such as Parkinson disease and ischemia (Iwashita et al., 2007). Small pilot studies in humans using PPAR agonists have shown promising results (Kaiser et al., 2009). The possibility to regulate PPAR activity with selective agonists and the growing body of evidences supporting a positive role of these transcription factors in immunomodulation and neuroprotection open a new field of possible translational targets to improve myelin repair in MS.

Thyroid hormone receptor (TR): Thyroid hormone (TH) plays an important role in brain development (Koibuchi and Chin, 2000). Hypothyroidism results in hypomyelination (Walters and Morell, 1981) and there is increasing evidence that thyroid hormone affects oligodendrocyte development from its early stages until myelination (Koper et al., 1986). It is thought that TH favors the exit of progenitors from the cell cycle and promotes differentiation (Baas et al., 1997; Durand and Raff, 2000). While the evidence in support of a role of TH in oligodendrocyte development is undisputable, the exact molecular mechanisms remain uncertain. Different isoforms of thyroid hormone receptors (TR) $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$ are generated by alternative splicing of two thyroid hormone receptor genes (TR α and TR β) and among these, OPCs express mainly the α isoforms (TR α), whereas the expression of TR β is limited to mature oligodendrocytes (Carre et al., 1998). In EAE models, TH treatment enhanced oligodendrocyte differentiation and increased the levels of nestin and NGF (Calza et al., 2005). TH has also been shown to improve remyelination in cuprizone-induced demyelination in mice (Franco et al., 2008; Harsan et al., 2008). Even though the role of TH and thyroid hormones during remyelination default in MS remains to be elucidated, these experimental results further support the concept of nuclear receptors as valuable therapeutic targets.

Vitamin D receptor (VDR): Genetic polymorphisms of key enzymes in vitamin D metabolism and a low vitamin D status prior to disease onset have been associated with higher risk of developing (Pierrot-Deseilligny and Souberbielle, 2010). An inverse relation between Expanded Disability Status Scale (EDSS) progression and vitamin D levels has also been reported (Smolders et al., 2008) and co-treatment of X527, an analog of 1,25(OH) $_2$ D $_3$, with interferon (IFN)- β conferred disease protection in a preclinical model of MS (van Etten et al., 2007). Most effects of vitamin D are mediated by 1,25-dihydroxyvitamin D (1,25(OH) $_2$ D) binding to the intracellular vitamin D receptor (VDR), which regulates transcription of vitamin D responsive genes (Ramagopalan et al., 2012). Recent studies have suggested an immunomodulatory role of vitamin D (Adams and Hewison, 2008) and proposed that vitamin D metabolism in MS brain could exert anti-inflammatory effects, thereby preventing or limiting the development of MS lesions (Ascherio and Marrie, 2012; Smolders and Damoiseaux, 2011) and that altered levels of vitamin D metabolizing enzymes may affect disease course in MS. In chronic active MS lesions, nuclear staining for VDR was found in demyelinating microglia/macrophages and in reactive astrocytes and this suggested additional cell-specific functions of this receptor (Smolders et al., 2013). The safety profile of high doses of vitamin D and the potential synergic effect of IFN- β and vitamin D in a mouse model of MS, revealed the necessity of a double-blind placebo-controlled trial to determine the potential add-on effects of vitamin D $_3$ to IFN- β treatment (Smolders et al., 2010; van Etten et al., 2007). The SOLAR study (Supplementation of VigantOL® oil *versus* placebo as Add-on in patients with relapsing-remitting multiple sclerosis receiving Rebif® treatment) will be the first large, placebo-controlled international

study to assess vitamin D3 as add-on therapy to subcutaneous delivery of IFN β -1a in patients with RRMS, using clinical and MRI outcomes (NCT01285401). Given the difficulties to precisely determine the actual intake of vitamin D, given the variability of individual dietary habits, it will be important to evaluate outcomes to measurable plasma levels.

4. Cell replacement therapies

All the therapeutic strategies described above are aimed at stimulation of the endogenous regenerative potential of the adult brain. It is important to consider, however, that these strategies to restore function maybe severely compromised in a subset of patients and may therefore require the introduction of exogenous cells to promote repair and restore function. The concept of cell replacement therapy has been tested during the past 20 years and several cell types (Schwann cells, neural stem and OPCs, olfactory nerve ensheathing cells and bone marrow stromal cells) have been investigated for their ability to form new myelin. Extensive remyelination has been reported after transplantation in the brain of mice with genetic or acquired focal demyelination (Ben-Hur and Goldman, 2008; Yang et al., 2009). A very interesting cell type in this regard is the boundary cap cells, a population of highly migratory satellite DRG cells characterized by efficient differentiation when transplanted after spinal cord demyelination (Zujovic et al., 2010). However evidence of neuronal replacement, and establishment of connected remyelinated neural networks in demyelinating disorders, has not been clearly documented. Although cell therapy holds considerable promising features for treating demyelinating disorders, several significant challenges must be overcome when considering their clinical feasibility, including: the environment within the lesion, which has been described as not permissive for remyelination; the method of delivery; the potential development of secondary malignancies and the source of cells. A detailed and exhaustive review of current cell therapies in MS has been recently published and we refer the reader to it (Martino et al., 2010). Extensive research is ongoing in this field and we expect that important advances, especially in the field of induced pluripotent stem cells by reprogramming of skin fibroblasts will allow in the near future to overcome risks of allograft rejection and hopefully will allow cell-replacement therapy to become a reality in MS.

5. Concluding remarks

Besides the relative contribution of individual factors to axonal protection and myelin repair, it is important to highlight here the prominent role of environmental factors that have been described for MS pathogenesis and will likely also affect repair (Huynh and Casaccia, 2013; Ramagopalan et al., 2012). Environmental cues interact with gene expression by modulating the epigenome and inducing post-translational changes of nucleosomal histones and other chromatin components, regulating DNA methylation and microRNA expression that comprehensively modify cell-specific transcription profiles and therefore modulate the ability of cells to respond to treatment (Huynh and Casaccia, 2013). The concept of epigenetic alterations affecting repair in MS was suggested by studies in rodents (Shen et al., 2008) and in humans (Mastronardi et al., 2006; Pedre et al., 2011). Oligodendrocyte progenitor nuclei may not adequately respond to therapeutic intervention if their chromatin is folded in an unresponsive state or if genes that are critical for a beneficial therapeutic outcome are silenced by DNA methylation. Among the environmental factors, lifestyle is one of the main factors that may influence the epigenome. Smoking, for instance, has been reported to affect DNA methylation in humans (reviewed in Huynh and Casaccia 2013) while social interaction has profound impact on chromatin profiles in oligodendrocyte progenitors in the adult rodent brain (Liu et al., 2012). It is highly probable, although not proven, that dietary components such as saturated fats, vitamins or antioxidants, microbiome and

exercise might similarly affect the ability of brain parenchymal cells (*i.e.* glia and neurons) to respond to therapy.

Diet

From a strictly scientific perspective little is known about the nutritional status of MS patients and on the effect of diet on disease outcome. An increasing number of patients is self-administering nutritional supplements as a complement to their therapy (Yadav et al., 2010). The relation between various nutritional factors and MS has been considered in several epidemiological studies, including the evaluation of the impact of certain dietary regimens on MS outcomes (Farinotti et al., 2012). Vitamin supplementation, the ingestion of polyunsaturated fatty acids (PUFAs), allergen-free diets (milk and gluten-free) and several antioxidants have been proposed as dietary interventions that may have beneficial effects on the disease course although these claims demand a careful evaluation (Farinotti et al., 2012; von Geldern and Mowry, 2012). Recently, the beneficial effect of a ketogenic diet has been described in the EAE model and attributed to lower lesion load and decreased release of reactive oxygen species (Kim do et al., 2012). A potential pathway activated by the ketogenic diet is the activation of the transcription factor Nrf2, which has been shown to exert powerful antioxidant effects and therefore be protective against axonal damage caused by reactive oxygen and nitrogen species (Maalouf et al., 2007; Milder and Patel, 2012). Novel explanations are also beginning to emerge, as ketogenic diet results in the activation of additional pathways (Shimazu et al., 2013). Interestingly, the same pathway has also been proposed to be targeted by dimethylfumarate (BG12), a new oral therapy for MS, with the promise to be effective against the oxidative damage caused by inflammatory cells (Lin et al., 2011; Linker et al., 2011). On the other hand, the beneficial effect of dietary supplementation with PUFAs is likely to occur on oligodendrocyte differentiation via activation of the nuclear receptor PPAR and therefore promoting myelin formation (Vanden Heuvel, 2012). Unfortunately, despite the promising claims of dietary intervention, convincing and well controlled scientific evidence is still lacking. Small sample size and heterogeneity of the studied population, reduced validity of the endpoints and questioned the validity of the reported positive results (Farinotti et al., 2012). Future trials with proper designs, validated outcome measures and adequate sample size are needed to confirm the potential role of nutritional intervention in MS.

Besides diet, there is substantial evidence to favor the concept that oligodendrocytes respond well to neural signals. In children, for instance, enriched environment favors the development of motor skills, reading ability and cognitive function and this correlates with the development of white matter tracks (Paus et al., 1999; Schmithorst et al., 2005). Increased myelination of axons in corpus callosum and improved cognitive performance were also described in rodents raised in an enriched environment (Juraska and Kopcik, 1988; Sanchez et al., 1998). Conversely, defective CNS myelination has been described in response to lack of early social experiences in neonatal or juvenile animals (Makinodan et al., 2012). Also in adult mice social isolation resulted in decreased myelin levels (Liu et al., 2012) and ultrastructural changes of chromatin in oligodendrocytes in the prefrontal cortex (PFC), a region that is functionally relevant to the control of social behavior. These evidences extend beyond animal experiments. In 2005 Ullén et al. compared the structure of the white matter tracks in professional concert pianists compared to age-matched controls (Bengtsson et al., 2005). This study evidenced increased myelination with extensive piano playing. In MS, the remyelination of cortical lesions has been shown to be more extensive than that in white matter lesions (Albert et al., 2007). The molecular mechanism underlying this fact is not known; differences between OPCs from different anatomical regions could be a potential explanation, while increased neuronal activity promoting myelination (Ishibashi et al., 2006) could also be considered. Together these studies suggest the importance of

developing holistic strategies, which include traditional medicine and additional support modalities in order to promote endogenous CNS repair.

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Fig. 1.

Axonal damage in MS. Top panel indicates the normal appearance of a node of Ranvier between two internodal segments. Note the high density of Na^+ channels and mitochondria at the node. The lower panels depict current theories regarding the causes of axonal damage in MS. (A) Primary axonal damage independent of myelin loss. In this scenario, cytokines and toxic factors released by microglia have been proposed as key mediators of acute axonal damage. Accumulation of reactive oxygen and nitrogen species, increased energetic demand and ultimately Ca^{2+} overload promote structural injury. Cytosolic HDAC compromises axonal transport. (B) Axonal damage secondary to myelin loss. After myelin loss, Na^+ channels are diffusely distributed along demyelinated axolemma in an attempt to overcome the initial conduction block consequent to demyelination and allowing transmission of the electric impulse along the axon. This redistribution includes changes in channel subunit composition and increased and persistent Na^+ influx, leading to increased ATP demand. Increased intra-axonal Na^+ reverses the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, increasing the influx of Ca^{2+} . High levels of Ca^{2+} within the axon activate proteolytic enzymes and leading to mitochondrial damage. The lack of trophic support from the myelin sheath accompanied with the mitochondrial damage become a challenging situation for the axonal integrity. Over time, this situation results in irreversible degeneration of axons.

Fig. 2.

Regulation of remyelination in multiple sclerosis. Demyelination may result from an acute immune attack or secondary to oligodendroglialopathy or neuronal injury. Repair may either be successful and lead to remyelination (A) or fail (B). (A) The endogenous regenerative process occurs in subsequent phases. First, OPCs proliferate and migrate to the lesion site. Once recruited within the lesion, OPCs have to exit the cell cycle and differentiate into mature ensheathing oligodendrocytes. Several growth factors, extracellular molecules, transcriptional regulators and developmental pathways are involved in OPC maturation in response to injury. The integration of all the concurrent active pathways will determine the success the remyelination. (B) In some cases, remyelination fails and this leaves the axons exposed and vulnerable to damage and degeneration. This scenario is associated with a progressive neuronal dysfunction and accumulation of functional/cognitive disability. Several environmental factors such as social interactions, diets or smoking habits influence the epigenome of the OPCs, changing their responsiveness to factors that may regulate myelin formation and wrapping. These environmental factors may also affect remyelination by modulating key players involved in the regenerative process. Green: factors that favor remyelination; red: factors inhibiting remyelination.