Remyelination in Multiple Sclerosis – How Close are We?
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Abstract
Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with presumed autoimmune etiology. Within the last years an important success has been achieved in understanding the pathophysiology of the disease and in making available effective therapeutic agents able to change the natural course of the disorder, particularly of its relapsing-remitting form. More recently, the advances made in understanding the biology of remyelination in MS opened a wide window of opportunity to design innovative therapeutic strategies that could really have an impact in reducing progressive accumulation of disability in MS and actually function as neuroprotectors and neurorregenerators. Here we provide an overview of the key target pathways and mechanisms that were identified in this field and that can provide smart targets for future pharmacological intervention.

Keywords: Demyelination; Multiple sclerosis; Remyelination

Introduction
In 1961, Richard and Mary Bunge discovered and reported the phenomenon of spontaneous myelin repair using an animal model of demyelination [1]. Only four years later, the same possibility was observed in specimens from patients diagnosed with multiple sclerosis (MS), what would eventually be the starting point of a true scientific revolution – the demonstration that the human central nervous system (CNS) may be able of spontaneous self-repair [2]. Since then, over the past decades, some speculation has been produced about the possibility of developing new drugs that could enhance or improve spontaneous remyelination in MS. Although difficult, this goal seems to be getting closer and new therapeutic agents are being developed to fill this gap in MS care, accompanying an increasingly deep understanding of the biology of remyelination.

In this paper, we will review some basic aspects related to the mechanisms of remyelination as known so far, highlighting some molecules or signals that (at least theoretically) may have an important role to justify the design of new drugs that, depending on the context, could enhance or silence their effect (cellular therapy was considered outside the scope of this review). We will also reflect on the causes of intrinsic (or spontaneous) remyelination failure, exploring the challenges that must be overcome in order to bring this attractive field to the clinical practice.

Does it Make Sense to Think about Remyelination as a Therapeutic Strategy in Multiple Sclerosis?

Despite of the indisputable description of MS as a primary demyelinating disorder, the key phenomenon of axon loss helps to explain why there is good reason to believe MS might have some advantages over other CNS diseases in its eligibility for reparative therapies. This is mainly because axon connections remain predominantly intact in the very early stages of the disease. Therefore, repair therapies would only (although this “only” is not free of serious difficulties) need to recoat axons with myelin rather than re-establish connectivity in highly complex axonal nets, as it occurs in the majority of neurological diseases.

In the course of time, axonal/neuronal loss become evident and it is recognized as the major cause of chronic progression in MS, occurring as a consequence of demyelination in addition to damage induced by purely inflammatory mechanisms [3]. Evidence that myelin is required for axon survival is based on observations of genetically modified mouse models and studies of human pathology [4]; 1) using mice lacking some myelin proteins such as 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) and proteolipid protein (PLP), it was demonstrated that even in the presence of myelin sheaths (ultrastructurally normal or slightly abnormal) long-term axonal degeneration occurred [5,6]; 2) in the absence of PLP, a disturbance in axoplasmic transport was further identified and has led to the recognition of myelin-associated sirtuin 2 as a potential mediator of long-term axonal stability [7,8]; 3) in humans, myelin is also of critical importance for axon survival, since patients with Pelizaeus-Merzbacher disease (which is caused by mutations in PLP) have shown axon loss and studies of MS pathology (including autopsy tissue samples) have demonstrated preservation of axons in those areas where remyelination occurred [9,10]. More recently, axon degeneration has been observed as a consequence of genetically induced oligodendrocyte-specific ablation, even in rats with no functional lymphocytes [11]. This has provided the evidence that axon survival is dependent on intact oligodendrocytes and that axonal degeneration in chronically demyelinated lesions can occur independently of inflammation.

Replenishment of oligodendrocytes, renovation of the previously damaged myelin sheath and restoration of a normal glial environment should not only be useful as a reparative remyelination therapy, restoring salutary conduction in axons, but should represent a major boost to axon survival and a powerful protective intervention. If we can provide our MS patients with drugs promoting remyelination, we will be changing the natural history of the disease. That is why it makes sense to think about this, as a much needed therapeutic strategy.

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Remyelination in Multiple Sclerosis: Understanding the Mechanisms and Identifying Opportunities for Therapeutic Intervention

Spontaneous or intrinsic remyelination involves endogenous oligodendrocyte precursor cells (OPCs), which need to differentiate and generate mature oligodendrocytes, able to recoat damaged neurons with a new myelin sheath. These precursor cells are widespread throughout the CNS, occurring in both white matter and grey matter at a density similar to that of microglial cells (5-8% of the cell population) [12]. They can be isolated from the normal adult brain and are identified by the expression of transcription factors Olig2 and Nkx2-2 as well as the surface markers platelet-derived growth factor receptor (PDGFRα) and NG2, which are also expressed by OPCs in MS brain tissues [13-15]. Adult OPCs derive from their developmental forebears and the two cell types share many similarities, although the adult cell has a slower rate of migration and a longer basal cell cycle time [16].

Using transgenic mice subjected to experimental demyelination it was possible to show that OPCs originate the vast majority of remyelinating oligodendrocytes [17], which can also come from the precursor cells of the adult subventricular zone (SVZ) [18,19]. However, the contribution of these SVZ-derived cells may be small and their ability to repair away from white matter tracts that are close to the SVZ is probably negligible.

When an injury occurs, OPCs near the lesion undergo a switch from an essentially quiescent state to a phenotype with regenerative properties. This is the first step of the remyelination process – the activation phase – and involves not only morphological changes but also the up regulation of several genes and transcription factors [20]. For this activation, acute injury-induced changes in microglia and astrocytes play a crucial role. These two cell types seem to be the major source of mediators inducing a rapid proliferative response of OPCs, like the proteins Cdk2 and p27Kip-1 [21,22], the PDGF and the fibroblast growth factor (FGF) [23] and other factors demonstrated to have clear mitogenic effects in tissue cultures.

Following the activation, the migration or recruitment phase starts. Semaphorins are emerging as relevant regulators of OPCs migration. It has been shown that adult OPCs express class 3 semaphorin receptors and gain and loss of function experiments have demonstrated that semaphorin 3A impairs OPC migration towards demyelinated lesions, while semaphorin 3F overexpression contributes to accelerate OPCs recruitment and remyelination rate [24].

The recruited OPCs must next differentiate into remyelinating oligodendrocytes for remyelination to be complete. This is the differentiation phase and includes three different steps: 1) making contact with the previously demyelinated axon; 2) expressing myelin genes and producing a myelin membrane; 3) wrapping and compacting to form the myelin sheath, recoating damaged neurons. Although we are able to describe in theory all these steps, the truth is that we still have an incomplete understanding about all the mechanisms involved in the genesis of a new myelin sheath.

Some molecules have been shown to play a role in some of the intermediate steps of this complex repair process. FGF regulates the correct transition from the recruitment to the differentiation phase [25] and insulin-like growth factor-1 (IGF-1) seems also to play a role in both processes [26]. More recently, the ability of semaphorin 3A to inhibit OPCs differentiation was demonstrated, in addition to its role in the recruitment phase [27]. Therefore, the ability to manipulate semaphorin 3 receptors, neuropilins and plexines, as also the expression of semaphorins 3A and 3F around lesions emerge as a very attractive therapeutic strategy.

The leucine-rich repeat and Ig domain containing NOGO receptor interacting protein 1 (LINGO-1) has been found to have a negative effect on oligodendrocytes in differentiation and constitutes nowadays an interesting therapeutic target, considering the existence of a monoclonal antibody (BIIB033) that can block its effect and, thus, favors both neuroprotection and remyelination [28]. A phase II trial is ongoing and will give additional information regards to safety, tolerability and efficacy of this drug (NCT01864148). The human monoclonal IgM antibody 22 (rHlgM22) has been shown to have some activity promoting remyelination in a virus-mediated mouse model of demyelinating disease [29]. This effect probably involves the Src family kinase Lyn and PDGFβR signaling [30,31], but that needs to be clarified and a phase I clinical trial is now recruiting participants to evaluate safety, tolerability, pharmacokinetics and immunogenicity of a single dose of rHlgM22 (NCT01803867).

The canonical Wnt pathway has been recently implicated in a negative control of oligodendrocyte differentiation in both developmental myelination and remyelination processes [32]. Some data suggest that promoting the degradation of β-catenin and thus blocking the Wnt pathway in OPCs may be an effective approach to promoting remyelination. In this context, axin2 emerges as an attractive therapeutic target, once it negatively feeds back on the pathway and promotes β-catenin degradation [33]. But differences between the regulation of developmental myelination and remyelination must be emphasized. The transcription factor Olig1 is essential for the first of the mentioned processes, but has a permissive and less relevant role in OPCs differentiation during remyelination [34]. Depending on the ligand, Notch signaling pathway can exert a negative or a positive effect in developmental differentiation, but has a redundant function during remyelination, once the conditional knockout of the Notch1 gene in OPCs has little practical consequences [35-37]. The role of Notch signaling in the regulation of myelination is more complicated than first anticipated and needs to be deeply understood before considering it a viable therapeutic target. A further molecule critical in developmental myelination is sonic hedgehog (Shh), which is essential for oligodendrocyte specification. Shh seems to be relevant in maintaining some stem cell niches in the adult brain and its overexpression contributes for the increase in the production of precursor cells, which will ultimately differentiate along the oligodendroglial lineage [38].

The direct analysis of remyelinating tissue has been assigning to the nuclear retinoid X receptor-γ (RXRγ) a key role as a positive regulator of oligodendrocyte differentiation and the same has been demonstrated by gain/loss of function studies. Knockdown of RXRγ by interference RNA or RXR-specific antagonists severely inhibits oligodendrocyte differentiation in culture, while the RXR agonist 9-cis-retinoic acid promotes remyelination in some mice models [39]. These data provide a good intervention point for future drug targeting.

Other molecules that seem to be involved in these complex mechanisms are the chemokine CXCL12 and its receptor CXCR4 [40], the bone morphogenic proteins (specially 4, 6 and 7) [41] and the extracellular matrix protein hyaluronan (possibly through the Toll-like receptor 2) [42].

Despite not being developed specifically to promote remyelination, there are some drugs in advanced phases of research and other already licensed for clinical use that seem to have some effect in this area and therefore also have to be mentioned in this review.
Fingolimod is a sphingosine-1-phosphate receptor modulator, which acts as a selective immunosuppressive drug preventing T cells from exiting lymph nodes and it is currently approved for the treatment of relapsing-remitting MS. This drug demonstrated to promote rodent oligodendrocyte process extension and survival in vitro [43], but how it can really affect myelin regeneration remains unclear. In fact, using rodent slice multicellular culture preparations, it was possible to foster an environment favoring remyelination [44], but that was not confirmed in vivo in rodent studies [45]. An extension of the TRANSFORMS study, which included relapsing-remitting MS patients treated with oral fingolimod or intramuscular interferon beta-1a, reported no effect of fingolimod on disease progression [46]. However, there are still many questions that remain unanswered considering this drug's central effects and two other clinical trials continue (NCT00731692 and NCT01498887), trying to shed some light on several of these clinical issues.

Alemtuzumab is a monoclonal antibody directed against the surface antigen CD52, which is currently being developed for the treatment of patients diagnosed with relapsing-remitting MS. Two phase III clinical trials (CARE-MS I and CARE-MS II) were designed to demonstrate the benefits of this drug, comparing it with a first-line disease-modifying agent, interferon beta-1a [47,48]. In CARE-MS II (and only in this trial), patients treated with the monoclonal antibody showed a 42% reduction in sustained accumulation of disability and this observation raised the possibility of the antibody to be responsible for some degree of neuroprotection and remyelination. This hypothesis can be supported by data coming from the laboratory: when treated with alemtuzumab and stimulated with myelin basic protein, T cells (in particular) produce potentially useful neuronal growth factors that can promote OPCs survival and enhance oligodendrocyte differentiation and myelination abilities [49]. Future trials need to be planned to better characterize this potential remyelinating effect of alemtuzumab.

Dimethyl fumarate has recently been approved for MS treatment. Its precise mechanism of action is not currently known, but it seems to be mediated by an upregulation of the transcription factor Nr2 [50]. There is yet scarce evidence that this drug has effects on remyelination [51], but the related antipsychotic compound quetiapine (which is also a fumarate salt) seems to possess pro-remyelinating properties in animals [52]. Quetiapine promotes the differentiation of rodent OPCs into oligodendrocytes and myelination in cell cultures [53]. Using in vivo models, it was also possible to demonstrate reduced demyelination and loss of oligodendrocytes under quetiapine treatment, as well as faster production of myelin proteins [54,55]. More studies are needed to verify if dimethyl fumarate has the same effects on the biology of remyelination.

Alemtuzumab is an oral modified formulation of limonide, which has shown efficacy in different autoimmune disorders, including in MS. Its exact mechanism of action is not currently known, but there are some pathways through which this drug can possibly exert its immunomodulatory and neuroprotective effects. It may have some impact on several immune functions such as antigen presentation and dendritic cells kinetics [56], it may also inhibit leukocyte migration into the CNS [57], it seems to have a role increasing axonal integrity after an injury [58], it modulates cytokine production, promoting a shift from a pro-inflammatory Th1 to an anti-inflammatory Th2/Th3 phenotypes [59] and increases levels of brain-derived neurotrophic factor (BDNF), both in the periphery and within the CNS [60]. This neurotrophic factor secretion was tested in human patients undergoing laquinimod therapy demonstrated a significant and specific (up to 11-fold) elevation of serum BDNF levels compared to the placebo group after three months of treatment [61]. The impact of such an increase of BDNF levels in remyelination still needs to be clarified. In an animal model of spinal cord injury, it was possible to demonstrate that a matrix composed by BDNF-overexpressing cells and platelet-rich plasma increased both cellular migration towards demyelinated areas and differentiation of precursors [62]. But further studies are needed to better understand the true therapeutic potential of BDNF and of other neurotrophins.

It is clear now that remyelination is not regulated by one single molecule or mediator, but through a combination of signaling pathways acting on OPCs and oligodendrocytes (Figure 1), as well as on other cellular players like the microglia, astrocytes and even the blood vessels. The discovery of new molecular players and of pharmacological strategies to act on them is nowadays a priority, in order to provide, in this field, new therapeutic agents that can change the natural history of MS. Table 1 summarizes information about the drugs with a potential remyelinating effect already under investigation.

Why does Intrinsic Remyelination Fail?

The excitement of knowing some of the pathways implicated in the mechanisms of intrinsic remyelination in MS should be tempered by a hard fact: its effectiveness is low and rapidly exhaustible.

Like in other regenerative processes, the efficiency of intrinsic remyelination decreases with age and this probably has a strong implication in long-term outcomes, considering the chronicity of MS, a disease that evolves over many decades. Age can influence remyelination by decreasing both OPCs recruitment and differentiation [63]. This ageing effect is likely to be related with age-associated changes in the extrinsic environmental signals to which OPCs are exposed and also to intrinsic determinants of OPC behavior. An impaired
In MS, one of the first theoretical consequences of demyelination is the deletion of Notch in oligodendroglial cells resulting in a very limited remyelinating phenotype by OPCs, thus suggesting that Notch-jagged signaling is not a critical negative regulator of remyelination [74].

The accumulation of hyaluronan within demyelinated lesions may also contribute to an environment not conductive to remyelination, considering its potential inhibitor effect on OPCs via TLR2 signaling [42]. Demyelinated axons have been shown to express the adhesion molecule PSA-NCAM and may themselves act as remyelination inhibitors too, once that adhesion molecule has the ability to block myelination in cell culture [75].

But if it makes sense to think that demyelination failure may result from the presence of inhibitors of OPCs differentiation, it is also logical to think that the same effect may be due to the absence of differentiation stimulatory molecules. This hypothesis is difficult to prove, but it is compatible with a model in which the acute inflammatory events play a key role in activating precursor cells and creating an environment conductive to remyelination [76]. The two possibilities are not mutually exclusive and this integrative perspective is consistent with the more holistic view of the phenomenon: remyelination results from the interaction of multiple factors, both environmental and endogenous, that guide the various stages of myelin repair. As such, knowing more and more about these complex pathways will be the way to design smarter therapeutic interventions, with real clinical potential.

**Future Challenges**

The advances in knowledge about remyelination biology, in recent years, provide an optimistic view for the future and for bridging the gap from regenerative basic science to regenerative medicine. However, selection of a target with a strong scientific rationale is only the beginning, albeit an essential step in the long journey of drug development.

Any progress, in therapeutic terms, will have to be based on a very deep understanding about the human pathological hallmarks (because of the absence of direct translatability between preclinical animal models and human systems) and on the development of reliable biomarkers, which need to be really able to measure and quantify the remyelinating potential of any kind of investigational drug, in pivotal trials. Therefore, it seems logical that the demonstration of successful remyelination in MS patients cannot be achieved without significant advances in clinical radiology. Some innovative imaging techniques (such as magnetic transfer ratio and diffuse tensor imaging) were developed to measure myelin content and tissue organization using conventional magnetic resonance imagers. Together with measurements of cortical atrophy

### Table 1: Drugs with a potentially remyelinating effect under study, their mechanisms of action and development phases.

| Drug                        | Mechanism of action                                      | Development phase   | References                  |
|-----------------------------|----------------------------------------------------------|---------------------|-----------------------------|
| Fingolimod                  | S1P receptor modulator                                    | Licensed for clinical practice (remyelinating effect unclear) | Miron et al. [44] Hu et al. [45] |
| Dimethyl fumarate           | Unknown (probably involves upregulation of the transcription factor Notch) | Licensed for clinical practice (remyelinating effect unclear) | Fox et al. [51] |
| Quetiapine                  | Unknown (affinity for D2, 5-HT2A, H1 and 5-HT1A brain receptors) | Licensed as an antipsychotic drug for clinical practice (remyelinating effect unclear) | Mei et al. [53] Zhang et al. [54] |
| Alemtuzumab                 | Anti-CD52                                                 | Awaiting regulatory approval (remyelinating effect unclear) | Jones et al. [49] |
| Laquinimod                  | Unknown (probably involves BDNF secretion)                | Phase III (NCT01707992) | Aharoni et al. [59] Comi et al. [60] |
| BLiB033                     | Blockage of LINGO-1                                       | Phase II (NCT01864148) | Mi et al. [28] |
| rHlgM22                     | Unknown (probably involves the Src family kinase Lyn and PDGFRs signaling) | Phase I (NCT01803867) | Watzlawik et al. [30] Watzlawik et al. [31] |
| 9-cis-retinoic acid         | Retinoid X receptor agonist                               | Pre-clinical         | Huang et al. [39] |

### Notes

- Macrophage activity in ageing, associated with some delay in expressing inflammatory cytokines and chemokines can lead to a poor clearance of myelin debris and to a temporary accumulation of myelin-associated differentiation-inhibitory proteins in lesions [64]. The expression of remyelination-associated growth factors seems also to be decreased in older cells, contributing to the delay observed in OPCs activation, recruitment and differentiation [65]. For all this, a relevant question related with the success of developing remyelinating therapies is the extent to which age-associated changes could really be reversed. Some experiments based on skeletal muscle regeneration demonstrated that poor regenerative capacity in older animals can be renewed [66], but to what extent this can be replicated in the CNS remains unknown.

- Remyelination could also fail because of disease-specific aspects. In MS, one of the first theoretical consequences of demyelination could be a focal depletion of a CNS specific area in precursor cells, so further episodes of demyelination occurring at the same site (or in its vicinity) would fail to remyelinate due to a lack of OPCs. However, some experiments clearly indicate that these cells are very efficient in recolonizing areas that were injured by the disease [67], at least if the demyelinating insult is not sustained in time. So, although theoretically valid, this does not seem to be the main cause for a failure of intrinsic remyelination in MS patients.

- In this context, the failure of OPCs recruitment appears to be more relevant. It may arise due to disturbances in the expression of guidance cues (like semaphorins 3A and 3F) inside the lesion and this may be more or less important depending on the dimension of the demyelinated area [68]: larger lesions will require greater OPCs recruitment impetus (and it should not be forgotten that older OPCs are less responsive to recruitment signals). In some patients, antibodies recognizing OPC-expressed antigens (like NG2) were identified [69]. This could also be a mechanism of recruitment impairment.

- But despite all the previous considerations, around 70% of demyelinated MS lesions contain immature oligodendroglial cells that appear to be in an arrested state, unable to completely differentiate [70]. Several sets of observations corroborate that this stage of remyelination is the most vulnerable to failure in MS [14,70-72]. One possible explanation for this is that chronic lesions contain factors that can inhibit cellular precursors differentiation. One of the first candidates to be involved in this negative regulation was the Notch-jagged pathway, considering the detection of Notch and of its downstream activator Hes5 in OPCs and of jagged in astrocytes within chronic demyelinated MS lesions [73]. But further experiments detected the expression of the same mediators in cells undergoing remyelination and, more recently, the deletion of Notch in oligodendroglial cells resulted in a very limited remyelinating phenotype by OPCs, thus suggesting that Notch-jagged signaling is not a critical negative regulator of remyelination [74]. The accumulation of hyaluronan within demyelinated lesions may also contribute to an environment not conductive to remyelination, considering its potential inhibitor effect on OPCs via TLR2 signaling [42]. Demyelinated axons have been shown to express the adhesion molecule PSA-NCAM and may themselves act as remyelination inhibitors too, once that adhesion molecule has the ability to block myelination in cell culture [75].

- The advances in knowledge about remyelination biology, in recent years, provide an optimistic view for the future and for bridging the gap from regenerative basic science to regenerative medicine. However, selection of a target with a strong scientific rationale is only the beginning, albeit an essential step in the long journey of drug development.

- Any progress, in therapeutic terms, will have to be based on a very deep understanding about the human pathological hallmarks (because of the absence of direct translatability between preclinical animal models and human systems) and on the development of reliable biomarkers, which need to be really able to measure and quantify the remyelinating potential of any kind of investigational drug, in pivotal trials. Therefore, it seems logical that the demonstration of successful remyelination in MS patients cannot be achieved without significant advances in clinical radiology. Some innovative imaging techniques (such as magnetic transfer ratio and diffuse tensor imaging) were developed to measure myelin content and tissue organization using conventional magnetic resonance imagers. Together with measurements of cortical atrophy.
and retinal nerve fiber layer thickness, clinicians will soon be able to have a full array of imaging products that can allow the study and the assessment of the efficacy of a potential drug on myelination and neuroprotection in MS patients.

Conclusion

Specific remyelinating therapies for patients with MS are not yet a reality, but it seems appropriate at present to continue to hardly pursue a broad-based strategy for developing myelin repair therapies. Knowledge gained over the past few years about the biology of remyelination has pinpointed some therapeutic targets with clinical potential in the short and medium term. It will therefore be crucial to further our understanding of the pathways involved in MS lesions remyelination, as well as to develop strategies that, in clinical trials, allow us to clearly assess the impact of an experimental drug in this specific field. Any beneficial effect may actually be the key to change the therapeutic approach to patients diagnosed with MS and, thus, modify the natural history of the disease.

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