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Myelin Repair Strategies: A Cellular View

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Abstract

Purpose of review—The development of successful myelin repair strategies depends on the detailed knowledge of the cellular and molecular processes underlying demyelination and remyelination in the CNS of animal models and in patients with multiple sclerosis (MS). Based on the complexity of the demyelination and remyelination processes, it should be expected that effective therapeutic approaches will require a combination of strategies for immunomodulation, neuroprotection, and myelin replacement. This brief review highlights recent cellular and molecular findings and indicates that future therapeutic strategies to enhance remyelination may also require combinatorial treatment to accomplish.

Recent findings—The relapsing-remitting course of some forms of MS has typically fueled hope for effective repair of MS lesions if demyelinating activity could be attenuated. Recent findings support the potential of endogenous neural stem cells and progenitor cells to generate remyelinating oligodendrocytes. Importantly, interactions with viable axons and supportive astrocytic responses are required for endogenous immature cells to fulfill their potential remyelinating capacity.

Summary—The research described here will help in identifying the major obstacles to effective remyelination and potential therapeutic targets to guide development of comprehensive approaches for testing in animal models and eventual treatment of patients with MS.

Keywords

Neural progenitors; subventricular zone; oligodendrocytes; astrocytes; demyelination; multiple sclerosis

INTRODUCTION

White matter disorders involving myelin affect millions of individuals around the world and include a wide array of pathologies [1]. Among the most significant and extensively studied is the severe demyelination that occurs in multiple sclerosis (MS) patients. Myelin repair is a desired therapeutic approach for a variety of demyelinating or dysmyelinating disorders that can occur either during development of the CNS or in adulthood. A successful remyelination program would not only promote recovery of action potential propagation in affected axons, but also attenuate further axonal damage in white matter tracts of patients with demyelinating diseases. However, both the demyelination and remyelination processes are complex and involve a sequence of steps that correspond to loss and gain of specific physiological functions.

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Therefore, it is very likely that only combined interventional approaches that target the multiple rate-limiting steps that prevent successful remyelination will improve clinical outcomes.

Myelin repair therapies are not currently in use for clinical MS or other white matter disorders. However, recent research advances have singled out not only the major cellular players involved in the pathology associated with MS, but also some of the signaling pathways that mediate the cellular damage and the endogenous regenerative response of the CNS. Although two major cell types, oligodendrocytes and neurons, are directly engaged in remyelination, it is clear that astrocytes and microglia are also involved in the inflammatory damage to myelin and oligodendrocytes [2,3]. Last, but not least, it is now widely recognized that an endogenous pool of oligodendrocyte progenitor cells (OPCs) capable of remyelinating axons is present in the adult brain [4–8**]. Although in disseminated demyelinating diseases, such MS, a therapeutic approach involving OPC transplantation might present several difficulties and might not be effective, grafting of exogenous OPCs has been shown to promote remyelination (9). Therefore, these cells and the molecular mechanisms that either prevent or enhance their maturation to myelinating oligodendrocytes under pathological conditions represent major targets of future therapeutic strategies.

In this review, we will focus on remyelination in the adult CNS, particularly on recent experimental work performed in animal models and on MS tissue. We will discuss some of the major cellular issues currently being debated, in the context of developing effective interventional approaches. Because of space constraints, we will be unable to review in detail other important aspects of myelin repair strategies, including: i) exploiting intracellular pathways (such as transcription factors) for oligodendrocyte regeneration and remyelination; ii) integration of immunosuppressive strategies to shift the immune response toward myelin repair; iii) use of imaging and genetic analysis of MS to tailor myelin repair strategies; iv) developing interventions that may be effective in the context of a varied disease course; and v) analysis of MS in pediatric populations and their relevance for myelin repair strategies. These aspects have been at least in part discussed in other review articles in this issue or elsewhere [3,9–13].

Endogenous neural progenitors of the subventricular zone and in MS lesions: Cellular targets for myelin repair strategies?

It is now well established that the adult CNS contains an endogenous pool of OPCs that is capable of generating remyelinating oligodendrocytes. These OPCs are found within the subventricular zone (SVZ) at a relatively high concentration, distributed at low abundance throughout the CNS, and often persisting in demyelinated lesions [4–9,14–19**]. Multipotential progenitors capable of myelinating congenitally dysmyelinated brains have also been isolated from the human fetal (ventricular zone) and adult (subcortical white matter) brain [20]. Because of their regenerative potential, substantial effort is being focused on identifying the cellular and developmental properties (e.g. transcription factor “fingerprint”) of adult OPCs, and the molecular pathways that regulate their proliferation, migration and differentiation in response to a demyelinating stimulus. The SVZ has become a center of these studies, since: i) as one of the few neurogenic regions of the adult brain, it comprises a sizeable number of proliferating, undifferentiated OPCs [8**,19**,21–26**]; ii) these cells are able to migrate to various regions of the CNS and differentiate into mature glia, including oligodendrocytes [8**,25*,27]; and iii) the SVZ is “activated” after demyelination and its neural progenitor pool is expanded [8**,21]. SVZ activation also occurs in MS tissue, and involves an increase in the density and proliferation of progenitor cells expressing PSA-NCAM, Olig2 and Sox10 [19**]. Importantly, several reports have demonstrated that OPCs can migrate out of the SVZ into different brain regions after demyelination, or under different pathological conditions [8**,21,22,25*,28,29*]. Finally, neural progenitors isolated from the

SVZ can be successfully transplanted into the forebrain to replace lost oligodendrocytes and to remyelinate axons [9,30,31].

Based on the cellular and molecular characteristics of the lesion environment, cell-based regenerative therapies that involve SVZ OPCs will have to be optimized by manipulating the inherent properties of these neural progenitors, and/or modifying non-permissive aspects of the lesion environment, to improve OPC generation of remyelinating oligodendrocytes. In particular, exhaustion of the OPC pool [32] and attenuation of its proliferation and differentiation potential with age [18*,33–35], together with limited migration capacity [36, 37], represent significant impediments that could be overcome by engineering the OPC population [38,39]. However, the long-term stability of the cellular and developmental properties of the engineered OPCs represents a limitation to this approach, and in some cases short-term treatments with exogenous molecules prior to grafting might represent a safer alternative [40]. Finally, turning on the myelination program in OPCs in an unfavorable pathological environment might require mechanisms that are significantly different from reproducing the sequence of molecular and cellular events of normal white matter development. Targeting intrinsic regulators of OPC differentiation, such as Olig1 which plays a prominent functional role during remyelination [41], or by identifying new intrinsic factors [42*,43**], may allow OPCs to more effectively overcome signals in the lesion environment that can inhibit OPC differentiation into remyelinating oligodendrocytes.

The dynamic nature of the cellular changes occurring in the SVZ contrasts with the cellular pathology of the periventricular white matter (WM) as a crucial site of MS lesions and area of poor remyelination. In fact, although WM OPCs have been clearly identified in MS lesions, this population displays only limited proliferative and remyelinating capacity as progression of the disease occurs [5,32,44–46]. Furthermore, in WM, the density of PSA-NCAM+ progenitors is much higher in active and chronic active MS lesions than in chronic silent lesions [19**]. In active lesions, these undifferentiated progenitors were found most frequently in periventricular WM [19**]. In order to promote oligodendrogenesis and remyelination from progenitor cells present in the lesions, it will be important to define the role of intrinsic and extrinsic mechanisms that underlie the distinction between neural progenitor characteristics in active vs. silent lesions of the WM, as well as in the activated vs. normal SVZ. Furthermore, it will also have to be established whether intracellular transcription factor programs that promote progenitor maturation to myelinating oligodendrocytes are differentially activated in neural progenitors in distinct types of MS lesions.

How to integrate strategies to prevent axon damage or promote axon regeneration with strategies to repair myelin

Remyelination and functional recovery cannot occur without maintaining axonal integrity, including structural (e.g. nodes of Ranvier) and functional (e.g. clustering of Na+ and K+ channels for action potential propagation) properties of the axon that are essential for rapid propagation of action potentials [47]. In MS or other demyelinating disorders, axonal damage can either occur primarily in the acute inflammatory phase of the disease, or as a secondary result of chronic demyelination [48–50]. At least two sets of independent observations argue for a direct relationship between the extent of myelination and maintenance of axonal integrity and function. First, mutant mice carrying specific deletions of oligodendrocyte-specific genes display axonal degeneration [51,52], indicating that oligodendrocytes are necessary not only to maintain myelinated tracts, but also axonal integrity. Second, in animal models of demyelination/remyelination, grafting of stem cells [53], oligodendroglial lineage cells [54, 55**], Schwann cells [56], or olfactory ensheating cells [57,58] not only promotes remyelination, but also improves electrical conduction along corresponding fiber tracts.

In axons, the molecular structures of the nodes of Ranvier and the paranodes depend on selective interactions between several crucial proteins and the clustering of specific ionic channels [47]. Analysis of MS tissue demonstrated disruption of the clustering of nodal, paranodal and juxtaparanodal proteins, including sodium channels. Conversely, remyelinated lesions displayed normal aggregation of these proteins [59]. These results, together with the findings from animal models discussed above, suggest that promoting the formation of paranodal and juxtaparanodal structures after demyelination might not only enhance axonal recovery, but may also accelerate remyelination before irreversible axonal damage and loss of function have occurred. Among possible molecular targets, two isoforms of neurofascin might play a pivotal role, since these proteins are required for clustering of sodium channels at the node and for the proper assembly of paranodal structures [60]. Furthermore, neurofascin localization is altered in paranodal structures in MS lesions, which appears to occur before demyelination begins [61].

In order to integrate strategies to prevent axon damage - or promote axon regeneration - with strategies to repair myelin, inhibitors of remyelination expressed by axons and OPCs, such as PSA-NCAM [62,63] and LINGO-1 [64**,65*], will also have to be targeted. Regulation of expression of these inhibitors under pathological conditions is still undefined, but it is likely to represent a significant impediment to remyelination and recovery of axonal function. Future therapeutic approaches might be directed at modulating expression of these inhibitors through specific upstream regulatory pathways [65*].

Increased expression of neurotrophic factors in MS lesions may indicate a compensatory effect and a putative therapeutic target to enhance functional recovery. In MS tissue, the ciliary neurotrophic factor (CNTF) pathway is activated in cortical neurons, possibly as a neuroprotective response [66*]. Brain-derived neurotrophic factor (BDNF) can be secreted by both neurons and immune cells in MS brains. A complicated interaction between BDNF levels and MS pathology is suggested by correlations of immune cell BDNF secretion, which can be activity dependent, and imaging parameters of white and gray matter volume [67,68]. Finally, immunomodulatory treatments themselves can regulate neurotrophin expression and/or directly interact with neurotrophic signaling pathways [69], suggesting that immune cell-mediated delivery of neurotrophic factors should be taken into consideration in designing repair strategies in MS.

Targeting astrocytes as pivotal cellular elements of damage and repair processes in demyelinating disease

Astrocytes are a prominent feature of MS lesions. Importantly, different astrocytic characteristics have been implicated in processes that add to the ongoing damage and/or perturb repair, as well as in processes that delimit damaged tissue and promote repair [70,71]. This dichotomy of astrocytic effects has the potential to significantly influence the extent to which the lesion environment is supportive versus prohibitive to OPC recruitment and differentiation, oligodendrocyte survival, and remyelination. The pathological features of an MS lesion may evolve throughout the disease course from an early stage with active demyelination and hypertrophic or “reactive” astrocytes to a chronic inactive phase as a hypocellular plaque with fibrillary gliosis [72]. Inflammation associated with active demyelination corresponds with an environment that is conducive for remyelination [73,74]. Reactive astrocytes in active lesions may secrete growth factors, cytokines, and chemokines that contribute to the inflammatory response but also stimulate OPC proliferation and recruitment into lesion areas. In contrast, chronic plaques have a central region of demyelinated axons, usually with a reduced axonal density, and an environment with abnormal extracellular matrix composition and a dense network of astrocytic processes forming a glial scar.

Therapeutic approaches that modify the environment of chronic MS lesions may be able to optimize the repair capacity of endogenous cells (see section on SVZ progenitors above) as well as improve the potential of transplanted cells to remyelinate effectively. Astrocytes in non-remyelinating areas associated with the glial scar express: i) vimentin, nestin, PSA-NCAM, FGF2 and NGF [75]; ii) extracellular matrix molecules, such as tenascin family members, as well as Jagged-1 and high molecular weight hyaluronan that inhibit OPC migration and differentiation, respectively [76–78]; and a variety of chondroitin sulfate proteoglycans [79]. An attractive means to modify the lesion environment may be to exploit signaling pathways that regulate astrocytic transition from an early reactive state that supports repair processes to a glial scar phenotype that expresses signals that inhibit regeneration. Alternatively, modification of the lesion environment can be targeted to a specific non-permissive molecule of the glial scar. Both approaches have been addressed in similar studies of axonal regeneration, and to some extent remyelination, relative to glial scar formation as a consequence of traumatic spinal cord injury. To move forward in approaches to modify the lesion environment in demyelinating diseases, more complex analyses of the astrocytic response will be needed to consider the astrocytic characteristics relative to remyelination processes. For example, bone morphogenic protein (BMP) family members have increased expression in demyelinated lesions and induce astrogliosis while inhibiting OPC differentiation into oligodendrocytes [80–82]. BMP and other potential pathways that may regulate glial scar formation or specific non-permissive signals will be of interest as therapeutic targets if shown to impact the rate or extent of remyelination, especially in the context of chronic lesions.

CONCLUSION

The variability in the clinical symptoms observed in MS patients is matched by significant differences found in MS lesions at the pathological and cellular levels. In many instances, a remyelination program appears to be successfully activated, but in other cases it is severely impaired [83**,84*]. This striking inconsistency is most likely due to the complexity of the cellular interactions that occur during myelination and demyelination, and the fragile balance between cell damage and survival in a pathological milieu. Significant advances have been made in our understanding of some of the crucial cellular and molecular steps required for successful axonal myelination and remyelination. Oligodendrocyte regeneration, preservation of axonal functions and promoting changes in astrocytes to a “permissive” phenotype - together with modulation of the immune response – appear to be the most promising future approaches to enhance remyelination in demyelinating diseases.

Abbreviations

BDNF, brain-derived neurotrophic factor
BMP, bone morphogenic protein
CNS, central nervous system
CNTF, ciliary neurotrophic factor
EGF, epidermal growth factor
EGFR, epidermal growth factor receptor
FGF, fibroblast growth factor
MS, multiple sclerosis
NGF, nerve growth factor
OPC, oligodendrocyte progenitor cell
PSA-NCAM, polysialylated neural cell adhesion molecule
SVZ, subventricular zone
WM, white matter

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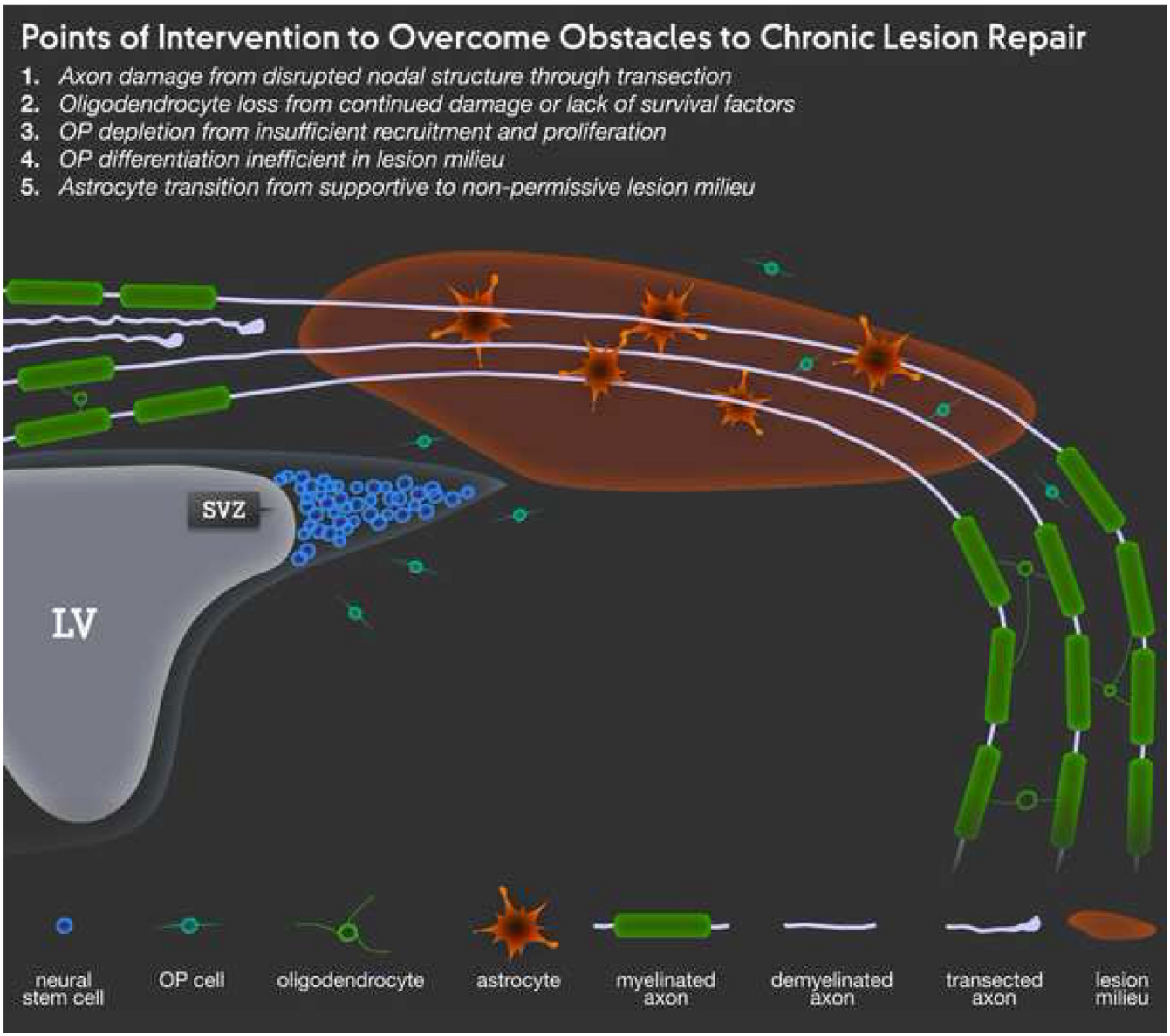

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The cellular and molecular components of chronically demyelinated lesions present obstacles to remyelination that may also serve as points of intervention to target therapeutically to enhance repair capacity. During early stages of demyelination, inflammatory processes can cause varying degrees of axonal damage. Axonal atrophy and loss can continue during chronic stages, which over time can accumulate and contribute to disability. Oligodendrocyte loss varies among different classes of MS pathology and may be worsened if newly generated oligodendrocytes have poor survival in the environment of chronic lesions. OP cells may be present in germinal zones, such as the subventricular zone (SVZ) adjacent to the lateral ventricles (LV), and distributed within normal tissues but appear to be depleted from areas of chronic demyelination. Astrocytes are activated in response to demyelination and contribute to the non-premissive environment of chonic plaques by scar formation that is expected to impair OP responses and axon outgrowth.