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COMMENTARY

Restoring the balance between disease and repair in multiple sclerosis: insights from mouse models

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Multiple sclerosis (MS) is considered an autoimmune-mediated demyelinating disease that targets the central nervous system (CNS). Despite considerable research efforts over multiple decades, our understanding of the basic biological processes that are targeted in the disease and the mechanisms of pathogenesis are poorly understood. Consequently, current therapies directed at controlling the progression of the disease are limited in their effectiveness. Historically, the primary focus of MS research has been to define the cellular and molecular basis of the immunological pathogenic mechanisms. Recently, however, it has become clear that long-term functional recovery in MS will require the development of strategies that facilitate myelin repair in lesion areas. The emerging evidence that the adult vertebrate CNS retains the capacity to regenerate neural cells that have been lost to disease or damage has provoked intensive research focused on defining the mechanisms of myelin repair. Unfortunately, the existing animal models of MS are poorly equipped to assess myelin repair, and new validated strategies to identify therapeutics targeted at promoting myelin repair are badly needed. This Commentary will review established murine models of MS, and discuss emerging technologies that promise to provide insights into the mechanisms of myelin repair.

Multiple sclerosis: current therapies

Multiple sclerosis (MS) is an autoimmune disease that disrupts brain and spinal cord function (Prineas, 1985; Raine, 1984). In many cases, the early stages of the disease are characterized by episodes of functional deficits that are followed by recovery periods with few residual symptoms (remissions). As the disease progresses, relapsing episodes ultimately lead to reduced recovery and increased functional deficits. In the majority of cases, later stages of the disease involve chronic loss of function and increasing disability. The underlying mechanisms generating functional deficits in MS appear to result from localized damage to myelin sheaths in the brain and spinal cord (Prineas, 1985; Raine, 1984) (Fig. 1).

In the vertebrate CNS, myelin is generated by oligodendrocytes. Myelin is a discontinuous fatty insulation around axons that helps lower the threshold for neuronal activation and increase the speed of action potential propagation along axons as a result of saltatory conduction. An individual oligodendrocyte can myelinate multiple segments along multiple axons and therefore damage to a relatively small number of oligodendrocytes can result in impaired axonal conduction, axonal loss (Trapp et al., 1998) and functional deficits (Bando et al., 2008).

Demyelination and oligodendrocyte loss in MS are largely a consequence of immunological attack on neural tissue. Thus, most current therapeutics are designed to suppress the immune system. Common therapeutics include immunosuppressive cytokines such as interferon β (Dhib-Jalbut and Marks, 2010), the immunomodulator glatiramer acetate (Racke et al., 2010), monoclonal antibodies such as natalizumab and alemtuzumab that inhibit immune cell entry to the CNS (Bielekova and Becker, 2010; Coles et al., 2008), and cytotoxic agents including mitoxantrone (Vollmer et al., 2010). Recent studies have shown that orally available immunomodulatory therapies such as cladribine might hold some promise for patients since it can lower the number of lesions and reduce annual relapse rates (Giovannoni et al., 2010; Rammohan and Shoemaker, 2010).

Although most of these approaches decrease the frequency of relapses, they have little effect on the progression of functional deficits in a large proportion of MS patients. Long-term improvement may require the stimulation of repair mechanisms to salvage damaged myelin and axons. Perhaps a combinatorial approach that targets immune-mediated insults and also enhances myelin repair will provide the most effective long-term benefits for patients.

Mouse models of myelination and demyelination

The fundamental mechanisms underlying oligodendrocyte development and myelination are closely conserved between mouse and human, making the mouse an invaluable model system for myelination and demyelination studies. In both organisms, oligodendrocytes arise from neural stem cells in distinct regions of the vertebrate CNS in response to specific inductive signals, such as sonic hedgehog (Miller, 2002; Orentas and Miller, 1996; Pringle et al., 1996). These oligodendrocyte precursor cells (OPCs) then disseminate throughout the CNS in response to specific dispersal cues (Tsai et al., 2003) before populating axon-rich developing white matter, where they undergo extensive proliferation and differentiation (Miller, 2002). Myelination of receptive axons follows

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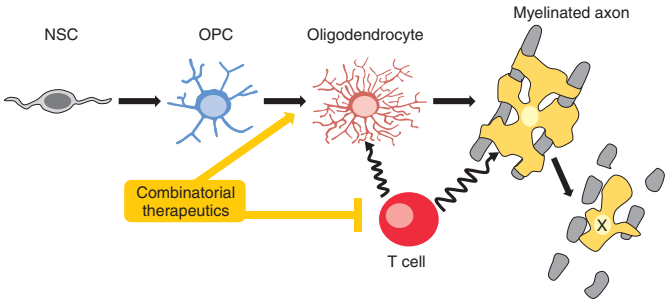

Fig. 1. Origin and function of oligodendrocytes, and immunological basis of MS. Myelin, the fatty insulation that wraps around axons in the vertebrate central nervous system, is produced by oligodendrocytes. During development oligodendrocytes are generated from neural stem cells (NSCs) that in specific locations commit to an oligodendrocyte lineage. Oligodendrocyte precursor cells (OPCs) then proliferate and migrate widely as they mature through a series of stages regulated by distinct signals before myelinating their target axons. Each oligodendrocyte can myelinate internodes on multiple axons; the precise number of axons myelinated by a single oligodendrocyte depends on axonal size and location. In autoimmune-mediated demyelinating diseases such as MS, T cells targeted against myelin proteins are stimulated to enter the CNS where they damage the myelin, resulting in demyelination, oligodendrocyte death and loss of axonal function. Ideal therapeutics should enhance the formation of oligodendrocytes from OPCs and inhibit the destructive functions of T cells.

a specific sequence that appears to be regulated by axon-glial interactions (Emery et al., 2009; Watkins et al., 2008). Proliferation of OPCs in both mouse and human is mediated largely through platelet-derived growth factor (PDGF) (Richardson et al., 1988), and the induction of myelination reflects the removal of inhibitory cues expressed on axons and OPCs such as LINGO-1 (Mi et al., 2007; Mi et al., 2005), PSA-NCAM and NOTCH (Wang et al., 1998). Developmental studies using chimeric animals have been instrumental in defining molecular cues shared between mouse and human (Windrem et al., 2008).

Understanding the adult pathology of MS using standard mouse models is challenging. In MS patients the onset of disease is difficult to determine, the disease progression varies, and the genetic linkage, while evident, is not easily defined (Oksenberg et al., 2008). Mouse models of MS have been developed that reproduce many of the immunological aspects of the disease, but the processes of demyelination and remyelination are less extensive and more acute than in the human condition. In order to facilitate the discovery of drugs to promote myelin repair, new mouse models are required. Current mouse models can be broadly classified into three major classes: (1) genetic models where genes important for CNS myelination have been manipulated; (2) induced pathogenic models where disease is generated in the adult through selective immunization; and (3) toxin-mediated (non-immune-mediated) demyelination models where toxins such as curpizone, lysolethicin, and ethidium bromide induce focal demyelination.

Genetic mouse models have identified major pathways involved in myelin formation

Mouse models with perturbed growth factor pathways combined with targeted ablation of receptors have provided detailed insight into the molecular regulation of induction, proliferation and differentiation of OPCs (Rowitch, 2004). For example, such studies revealed the pivotal role for PDGF-AA in OPC development (Richardson et al., 1988), and the influence of fibroblast growth factor (FGF) on multiple stages of OPC development dependent on selected receptor usage (Bansal et al., 1996; Fortin et al., 2005). Manipulation of specific transcription factors such as OLIG1, OLIG2, NKX2-2, SOX10 and myelin gene regulatory factor (MRF) (Bansal et al., 1996; Emery et al., 2009; Li and Richardson, 2008; Rowitch, 2004) has provided fundamental insights into cell specification and maturation. In general, these models are less useful in defining the underlying pathological mechanisms in MS, although in some instances a role for selected transcription factors in recovery from demyelinating insults has been described (Arnett et al., 2004).

Overall, the genetic approach has been less helpful in defining the detailed mechanisms of myelin sheath formation in the CNS. Studies of naturally occurring mutants of major myelin proteins have identified crucial components of CNS myelin such as proteolipid protein (PLP) and myelin basic protein (MBP) (Lunn et al., 1995), whereas targeted knockout of enzymes responsible for myelin lipid synthesis (Coetzee et al., 1996) has revealed a role for lipids in the stabilization of newly formed myelin (Kassmann and Nave, 2008). One area in which myelin mutants have proven useful is as hosts to assess the myelination capacities of isolated populations of neural cells. Transplantation of distinct populations of rodent and human cells into nonmyelinating hosts reveals the capacity of those cells to migrate long distances and generate substantial amounts of myelin – in some cases sufficient to reverse the host phenotype (Ben-Hur and Goldman, 2008; Low et al., 2009; Windrem et al., 2008).

Pathogenic mouse models have identified immune mediators of MS

The development of mouse models of the immunological aspects of MS has proven extremely valuable in identifying antigenic and cellular components important in demyelination (Furlan et al., 2009; Mix et al., 2008). The disease that develops in these models depends on the specific antigenic stimulation and the genetic background of the host animal (Baxter, 2007; Krishnamoorthy and Wekerle, 2009). For example, immunization of SJL mice with a peptide of PLP results in a relapsing-remitting disease course that closely mimics the early stages of MS. By contrast, immunization of C57/BL6 mice with a peptide of myelin oligodendrocyte glycoprotein (MOG) results in a chronic disease that closely mimics the later stages of MS. The reproducible disease that occurs in these models, along with genetic knockout/knock-in technology, has illuminated major pathways of immune-mediated demyelination, including the requirement for specific subsets of T cells.

Toxin-mediated (non-immune-mediated) models lead to localized demyelination, facilitating analyses of demyelination and remyelination

MS involves concurrent demyelination and remyelination. This is recapitulated in immune-mediated models, which necessarily demonstrate a complex phenotype (Fig. 2). To separate the distinct mechanisms involved in demyelination versus remyelination, several chemical demyelination models have been developed. The

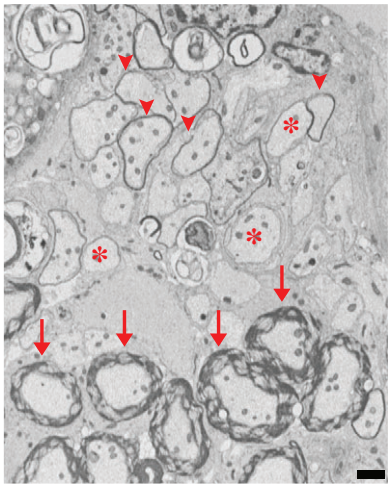

Fig. 2. In mouse models of MS, myelin repair can occur alongside demyelination. Axons surrounded by degenerating myelin (arrows) are frequently found adjacent to demyelinated axons (asterisks) and in close proximity to axons that are undergoing remyelination, as demonstrated by the presence of newly formed thin myelin sheaths (arrowheads), suggesting that functional deficits represent the balance between tissue damage and repair. Bar, 20 μm.

mouse strains C57/BL6 or SJL/SVJ exhibit localized demyelination when fed a chronic low dose of cuprizone, and removal of the toxin induces remyelination (Kipp et al., 2009; Lindner et al., 2009; Skripuletz et al., 2010). Alternatively, local injection of either lysolethicin (Wang et al., 2009) or ethidium bromide (Blakemore and Franklin, 2008; Talbott et al., 2007) results in focal demyelination followed by remyelination. Several complementary, but more limited, models of myelination and demyelination have recently emerged that allow for easier identification of potential molecular therapeutic targets compared with mouse models that experience changes throughout the immune and nervous systems.

Alternative approaches to mouse models of MS

In vitro models of myelination/demyelination facilitate mechanistic studies for MS therapies

The primary challenge for in vitro models is to retain sufficient relevance to the in vivo situation so that any insights are generally applicable. Myelinating slice cultures of rodent CNS have proven useful for removing the influences of the systemic immune system on myelination (Birgbauer et al., 2004; Mi et al., 2009; Notterpek et al., 1993). Unfortunately, these models are primarily derived from developing tissue and their ability to effectively mimic in vivo demyelination/remyelination is unclear (Birgbauer et al., 2004). In addition, slice preparations retain extensive cellular diversity, which complicates cellular and molecular interpretations.

In addition to slice cultures, oligodendrocyte-neuron co-cultures can be used to study the interactions between neurons and the cells that form myelin. Examples include the following co-cultures: dorsal root ganglion (DRG) neurons and Schwann cells (Paivalainen et al., 2008); DRG neurons and oligodendrocytes (Wang et al., 2007); CNS neurons and oligodendrocytes (Fex Svenningsen et al., 2003); and oligodendrocytes and spinal cord explants (Chen et al., 2010; Thomson et al., 2006). An ideal complement to the mouse models and rodent co-cultures may be the use of human cells or tissue in in vitro assays to identify potential therapeutics that might directly enhance myelin repair in MS patients. Viable human tissue for in vitro studies is limited, but human cell lines and cells derived from MS patients should become more available through new induced pluripotent stem (iPS) cell technologies (for a review, see Lako et al., 2010). Detailed myelination cell culture protocols are established for murine and rat cells (Chen et al., 2010; Emery et al., 2009; Watkins et al., 2008) and these will probably translate to human cells.

Conclusions and the future for models of MS

The notion that the adult vertebrate CNS is a relatively static structure with little plasticity is now essentially obsolete. New studies indicate the adult's capacity for extensive synaptic plasticity throughout the CNS (Holtmaat and Svoboda, 2009; McCoy et al., 2009). Furthermore, it is clear that the genesis of distinct populations of neurons is ongoing in the adult (Aguirre et al., 2004; Rivers et al., 2008). Even in the absence of disease or neural damage, new myelinating oligodendrocytes are generated throughout life (Rivers et al., 2008), and this capacity is enhanced following a range of pathologies. This newly recognized potential for adult CNS repair makes it an opportune time to revise the basic concepts guiding MS research.

Rather than considering the disease to be a reflection of unique disease-initiating events such as viral infection (Kriesel and Sibley,

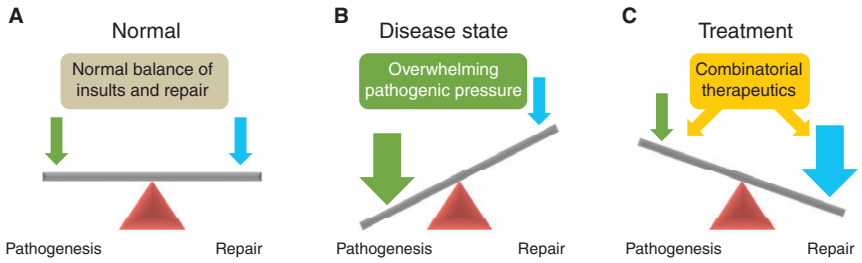

Fig. 3. The pivot point model for CNS-demyelinating diseases. In this model, normal conditions characterized by a lack of functional deficits (A) do not necessarily represent a total absence of pathogenic pressure but rather that the pressure resulting from injury or disease is effectively counteracted by the pressure of repair, resulting in a balance point and lack of detectable functional deficits. (B) Disease states occur when the pathogenic pressure overwhelms the pressure of repair, as a result of either elevated pathogenesis or reduced repair, resulting in functional deficits. (C) Effective treatments aim to re-establish the balance point by reducing pathogenic pressure or enhancing repair, or ideally both.

2005; Salvetti et al., 2009) or antigen mimicry (Blewett, 2010), it might be better to consider the disease in the setting of an imbalance between normal degradation and repair (Fig. 3). In this model the 'normal' CNS undergoes slow turnover, cell replacement and myelin repair in response to insults, which never manifest as functional deficits. Suppression of this repair process by additional insults, or by overwhelming natural repair as a result of pathogenic pressure, results in functional deficits and clinical manifestation of disease. If correct, this model expands the repertoire of potential therapeutic targets and suggests that combinatorial therapies that neutralize pathogenic pressure and enhance myelin repair will provide more effective long-term benefit. This endeavor requires the generation of new models of MS that allow the onset of demyelination and remyelination to be controlled and their extent accurately assessed.

What new mutant models are needed? There are two areas where development of new mouse models would be most valuable. First, models in which demyelination can be selectively induced in the adult through targeted death of oligodendrocytes would allow for a dissection of the neural responses accompanying demyelination and remyelination. One such genetic model has been developed, using *Cre-loxP* technology to induce the expression of diphtheria toxin A; this results in the selective ablation of specific cell types, such as oligodendrocytes (Brockschnieder et al., 2006). Unfortunately, this strategy is limited by the availability of specific Cre lines of mice and by the fact that inducible Cre lines are often capable of inducing only low levels of recombination, resulting in the incomplete expression of diphtheria toxin. Thus, some cells targeted for destruction by diphtheria toxin survive and complicate analysis. Second, the development of reporter animals in which adult myelin deposition can be accurately assessed would help define the rate-limiting steps in remyelination and allow the identification of novel therapeutic targets.

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COMPETING INTERESTS

The authors declare no competing financial interests.

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