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REVIEW

Stem cells, progenitors and myelin repair

Chao Zhao, Stephen P. J. Fancy, Laurent Magy, Joanna E. Urwin and Robin J. M. Franklin

Cambridge Centre for Brain Repair and The Neuroregeneration Laboratory, Department of Veterinary Medicine, University of Cambridge, UK

Abstract

Remyelination, the process by which new myelin sheaths are restored to demyelinated axons, represents one of the most compelling examples of adult multipotent progenitor cells contributing to regeneration of the injured central nervous system (CNS). This process can occur with remarkable efficiency in both clinical disease, such as multiple sclerosis, and in experimental models, revealing an impressive ability of the adult CNS to repair itself. However, the inconsistency of remyelination in multiple sclerosis, and the loss of axonal integrity that results from its failure, makes enhancement of remyelination an important therapeutic objective. Identifying potential targets will depend on a detailed understanding of the cellular and molecular mechanisms of remyelination. In this article we address two important issues. First, we consider the nature of the cell or cells that respond to demyelination and generate new oligodendrocytes, identifying current areas of uncertainty and addressing the role of adult CNS stem and progenitor cells. Second, we discuss the concept of adult progenitor activation following demyelination, focusing on the increased expression of (1) olig transcription factors, (2) bone morphogenetic proteins and (3) fyn, a member of the src-family of tyrosine kinases.

Key words stem cells; progenitors; remyelination; multiple sclerosis; demyelination; regeneration.

Introduction

Following demyelination in the central nervous system (CNS), a hallmark event in the disease multiple sclerosis (MS), there are two possible outcomes (Fig. 1). Either the axons remain demyelinated and are vulnerable to atrophy, an event that makes a significant contribution to the progressive phase of MS (De Stefano et al. 1998; Bjartmar et al. 2003), or new myelin sheaths can be restored to the demyelinated axons in a spontaneous regenerative process called remyelination (Prineas et al. 1993; Lassmann et al. 1997). It has been known for many years that remyelination restores saltatory conduction (Smith et al. 1979). More recently, however, it has become apparent that the presence of an intact myelin sheath has a profoundly beneficial effect on axonal integrity and that remyelination may therefore provide

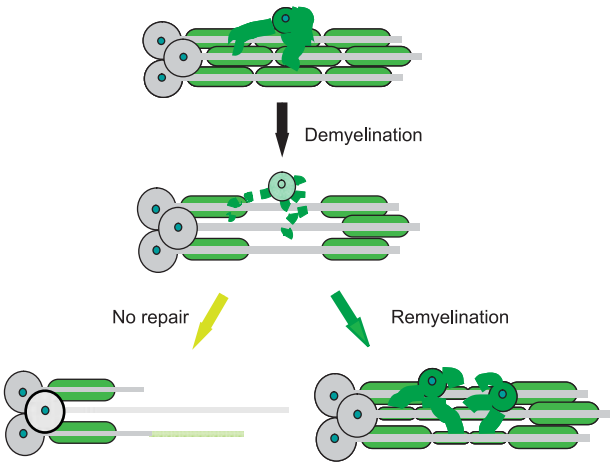

Fig. 1 Demyelination occurs when the oligodendrocyte or the myelin sheath its produces and maintains is the target of the disease process. Once axons have been demyelinated there are two possible outcomes: either the axon remains demyelinated, in which case it is vulnerable to axonal or even neuronal loss, or the axon can be remyelinated. This process involves the generation of new oligodendrocytes that reinvest the demyelinated axons with the thin, short myelin internodes characteristic of remyelination.

Correspondence
Dr Robin Franklin, Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES, UK. T: +44 (0)1223 337642; F: +44 (0)1223 337610; E: rjf1000@cam.ac.uk

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a highly effective means of preventing axonal loss in demyelinating disease (Griffiths et al. 1998; Kornek et al. 2000; Lappe-Siefke et al. 2003; Edgar et al. 2004; Xin et al. 2005). Thus, while strategies to prevent demyelination remain a major focus of MS therapy, approaches that promote remyelination and minimize axonal loss represent an important adjunct to the therapeutic armoury. Developing such therapies is likely to depend on a detailed understanding of the mechanism of remyelination, from which will emerge a better understanding of why this repair process often fails in MS patients (Franklin, 2002; Franklin & Goldman, 2004).

Several experimental models of CNS demyelination exist that have been used to study remyelination. Of these, the models that involve toxic death of oligodendrocytes have proved to be especially helpful because the demyelination is usually acute and focal and is followed by a defined and generally predictable regenerative response (Fig. 2A,B). From these models it has been possible to identify a sequence of events by which remyelination proceeds. The first event is the activation of a population of progenitor cells that then rapidly populate an area of demyelination by proliferating and migrating during the recruitment phase of remyelination. This phase then gives way to a second phase in which the recruited cells differentiate into oligodendrocytes, a highly specialized cell that generates new myelin sheaths around the demyelinated axons. This simple model of remyelination, which in its broad outline resembles many other regenerative processes in the body, raises a number of important questions. In this article we focus on two of these: what is the nature of the cell or cells that respond to demyelination and generate new oligodendrocytes, and how do these cells respond to injury in preparation for remyelination?

What cells give rise to remyelinating oligodendrocytes?

In most situations these cells are a distinctive phenotype widely referred to as adult oligodendrocyte progenitor cells (OPCs). These cells are the adult descendants of an extensively studied developmental progenitor, originally called the O-2A progenitor based on its ability *in vitro* to give rise to a distinctive type of astrocyte (the type 2 astrocyte) as well as oligodendrocytes (Raff et al. 1983; Wren et al. 1992). Because the type 2 astrocyte is thought to occur infrequently, if at all, during normal development, these cells are now generally referred to as simply oligodendrocyte progenitor cells (Fulton et al. 1992; Levison & Goldman, 1993). In adult tissue these cells have a characteristic multipolar morphology and express several markers, of which the proteoglycan NG2 and the growth factor receptor PDGFRα are the most commonly used (Nishiyama et al. 1996; Dawson et al. 2000, 2003). Whether OPCs express both markers in all

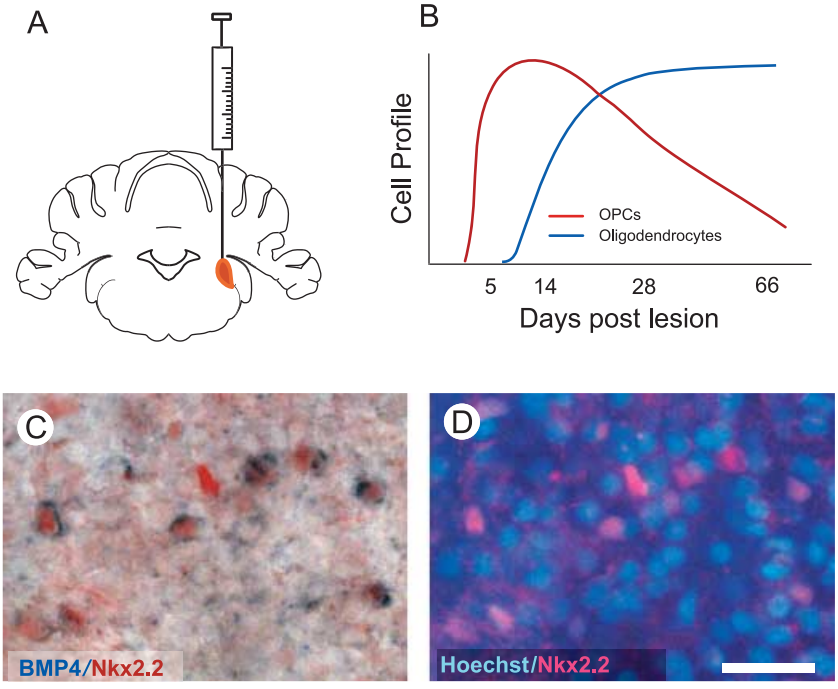

Fig. 2 (A) The EB-CCP lesion provides a useful model for studying the biology of CNS remyelination. A focal area of primary demyelination is created by stereotaxic injection of 4 μL of 0.01% EB into the large white matter tract of the caudal cerebellar peduncle (see Woodruff & Franklin, 1999). (B) In young adult rats (2–4 months of age), the demyelination induced by EB injection undergoes a stereotypic process of remyelination in which there is first an OPC response which is then followed by the appearance of new oligodendrocytes (derived from the recruited OPCs) that remyelinate the demyelinated axons. The process is complete at around 28 days (see Sim et al. 2002a,b). (C) Nkx2.2+ OPCs express high levels of BMP4 mRNA at 7 days after lesion induction. (D) Although there are many cell types within the lesion at this time point only a proportion are Nkx2.2+ OPCs, and the BMP4+ cells illustrated in C are all Nkx2.2+. Scale bar = 16 μm.

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circumstances and in all regions of the adult CNS is uncertain (Hampton et al. 2004); indeed, the extent to which this is a homogeneous population of cells throughout the adult neuraxis is also unresolved. There is now clear evidence that oligodendrocytes can be generated via several distinct lineage pathways and therefore from a developmental perspective progenitor phenotypes are diverse (Mallon et al. 2002; Liu & Rao, 2004; Cai et al. 2005; Vallstedt et al. 2005). For example, two distinct populations can be described on the basis of expression of PDGFRα or DM20, an alternatively spliced isoform of the proteolipid protein gene (Spassky et al. 1998, 2000). The extent to which OPCs in the adult CNS retain an imprint of their developmental origin remains to be unequivocally determined. One possibility is that adult OPCs are a homogeneous population of cells that have a similar phenotype and responsiveness to environmental signals despite their varied ontogeny. Alternatively, distinctive types of OPC may exist, either coexisting or being specific to a particular anatomical region. There is some evidence to suggest that this may be the case; in tissue culture the markers O4 and A2B5 appear to identify distinct populations of adult forebrain OPCs that respond differently to a range and combination of growth factors (Mason & Goldman, 2002). This is clearly an important issue to resolve, especially in adult human tissue, if growth-factor-based strategies are to be used therapeutically to enhance endogenous remyelination in clinical disease. The evidence that cells other than OPCs contribute to remyelination is scant. Two studies have demonstrated that when demyelinating lesions are induced in the corpus callosum close to the subventricular zone (SVZ), then neural progenitor cells can be deflected away from their normal path towards the olfactory bulb and towards the lesion where they can contribute to the generation of new oligodendrocytes during remyelination (Nait-Oumesmar et al. 1999; Picard-Riera et al. 2002). The component of the total remyelination attributable to SVZ-derived cells is uncertain but is likely to be small given the abundance and responsiveness of locally derived OPCs. A further uncertain issue is how close an area of demyelination must be in order for SVZ progenitors to respond. Although it is clear that lesions within the adjacent corpus callosum can induce this response, it is unlikely that white matter lesions remote from the SVZ in, for example, the spinal cord or brain stem white matter will do so given that most remyelinating cells are recruited from a narrow region surrounding a lesion (Franklin et al. 1997). In white matter regions remote from the SVZ there is no clear evidence at present that cells other than OPCs contribute to remyelination.

Do CNS stem cells contribute to remyelination?

If one applies strict criteria to the definition of a stem cell (a multipotent cell, generally attached to a basal lamina, that divides slowly and that is both self-renewing and able to give rise to rapidly proliferating progenitor cells by asymmetric division), then true stem cells within the adult mammalian CNS are rare, comprising the glial fibrillary acidic protein (GFAP)-expressing B cells of the SVZ and perhaps their hippocampal equivalents (Doetsch et al. 1999a,b; Sanai et al. 2004; Seri et al. 2004). There is currently no evidence that either of these cells directly contributes to remyelination (although one could argue that the SVZ B cells do so indirectly by giving rise to SVZ neural progenitors). Thus, adult CNS stem cells make a small and anatomically restricted contribution to endogenous remyelination in the adult. This is similar to other regenerating tissues where the proliferation of the stem cell population is scarcely affected by the sudden demand for new differentiated cells following injury. Instead, this demand is taken up by the transit-amplifying population of progenitors, which, unlike the stem cells from which they are generated, have the proliferative responsiveness rapidly to generate the new cells required to repair damaged tissue. Should one regard the OPCs of the adult brain as being stem cells or progenitor cells? OPCs certainly exhibit some stem cell properties: they exhibit multipotency, giving rise to oligodendrocytes, neurons and, at least *in vitro*, astrocytes (ffrench-Constant & Raff, 1986; Kondo & Raff, 2000; Belachew et al. 2003; Nunes et al. 2003), and have very high levels of telomerase activity allowing them to undergo many rounds of proliferation before undergoing senescence (Tang et al. 2001). However, their rapid proliferation, symmetrical division (the daughter cells of OPC proliferation are still OPCs regardless of whether they subsequently differentiate into oligodendrocytes or not) and absence of a distinct anatomical relationship with a basal lamina are more consistent with their being a transit-amplifying population and in our view are more accurately regarded as progenitors rather than stem cells. Indeed, a pertinent question to consider is how similar OPCs are to other multipotent neural progenitor cells within the adult CNS, and whether perhaps a generic term of neural

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progenitor should be more widely applied (Goldman, 2003)?

Because the cells responsible for generating new oligodendrocytes are transit-amplifying progenitor cells, can the capacity of these cells to proliferate in response to injury become exhausted if repeatedly tested? This question has important implications for understanding why remyelination often fails and how easy it will be to mobilize OPCs therapeutically. The ability of adult OPCs to repopulate areas from which they are deficient appears to be very robust (Chari & Blakemore, 2002). When the same area of CNS is exposed to several rounds of demyelination/remyelination, the OPC numbers are not reduced and the efficiency of remyelination is not impaired by previous rounds of remyelination (Penderis et al. 2003). This implies that a failure of remyelination is not due to an exhaustion of OPCs available to repopulate the demyelinated area and give rise to new oligodendrocytes. However, this appears only to be the case if sufficient time is left between demyelinating episodes to allow the OPC numbers to be replenished. If an area of demyelination is exposed to a continual demyelinating insult then OPC numbers do gradually diminish (Ludwin, 1980; Mason et al. 2004). The interpretation of these long-term experiments in rodents is confounded by ageing, as this process alone can significantly impair the responsiveness of OPCs to demyelination (Sim et al. 2002b), partly due to changes in the signalling environment with ageing (Hinks & Franklin, 2000) and possibly also due to intrinsic changes in the responsiveness of aged OPCs (Decker et al. 2002; Chari et al. 2003).

Reactive OPCs – a critical phenotypic switch for remyelination?

The reactive changes that occur in astrocytes and microglia in response to CNS injury are well documented and comprise a series of phenotypic changes that distinguish the reactive state from the resting state. Similar reactive changes occur in OPCs (Levine et al. 2001). This was first described as a change in morphology and more intense staining with the OPC marker NG2 (Levine & Reynolds, 1999). More recently it has become apparent that a number of distinct changes in gene expression occur that are associated with OPC activation. In this section we consider three of these, the Olig transcription factors, the bone morphogenetic proteins and the tyrosine kinase fyn.

Olig transcription factors

In the normal adult white matter PDGFRα+ OPCs also express mRNA of the bHLH transcription factor Olig1 at levels easily detectable by *in situ* hybridization. By contrast, the mRNA expression levels of the related transcription factor Olig2 and the homeodomain transcription factor Nkx2.2 are below the threshold for detection by this method. However, the expression of both Olig2 and Nkx2.2 mRNA within OPCs dramatically increases following induction of focal demyelination (Fancy et al. 2004; Watanabe et al. 2004; Talbott et al. 2005). The increase in Nkx2.2 expression occurs in the absence of detectable increases in sonic hedgehog mRNA expression (Fancy et al. 2004), which is responsible for its induction during development but appears not to be required for CNS remyelination (Briscoe et al. 1999; Lu et al. 2000). However, the increased expression of Olig2 mRNA could be accounted for by the rapid increase in expression of FGF-2 that occurs in toxin-induced demyelination (Hinks & Franklin, 1999). During development, the convergence of expression of Olig2 and Nkx2.2 within the same cell population is a necessary event for these precursor cells to differentiate into oligodendrocytes (Sun et al. 2001; Zhou et al. 2001). It seems possible therefore that the increased expression of these two genes in response to demyelination is a critical event required to convert quiescent OPCs into cells able to differentiate into remyelinating oligodendrocytes. Consistent with this hypothesis, the increases in Olig2 and Nkx2.2 expression are delayed in old animals where the rate of OPC differentiation is slower than in young animals (Sim et al. 2002b; Fancy et al. 2004).

Bone morphogenetic proteins (BMPs)

BMPs, members of the transforming growth factor superfamily of growth factors, play important roles in the development of many cell types including CNS glial cells (Mehler et al. 1997). They are also implicated in repair processes of several tissues, especially bone (Reddi, 1998). Their effects on OPCs include (1) promoting differentiation of OPCs into astrocytes while inhibiting oligodendrocyte differentiation (Mabie et al. 1997; Grinspan et al. 2000; Gomes et al. 2003), an effect mediated by their induction of the helix-loop-helix transcription inhibitors Id2 and Id4 and that can be overridden by the BMP antagonist noggin (Kondo & Raff, 2004; Samanta & Kessler, 2004), and (2) the inhibition

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of maturation of oligodendrocytes while promoting process formation in these cells (See et al. 2004). BMPs are expressed at high levels in developmental white matter. We carried out a study to investigate the expression of BMP2, BMP4 and BMP7, members of the family that most potently affect OPCs, and their antagonist noggin during the repair of focal toxin-induced demyelination in adult rat brain. The model employed involved stereotaxic injection of the DNA-intercalating agent ethidium bromide (EB) into the large white matter tract of the caudal cerebellar peduncle (CCP) of adult rats. Provided very dilute solutions of EB are used, this procedure creates a discrete focal area of primary demyelination in which few of the axons are damaged. This model, called the EB-CCP, has been used in many studies to examine the biology of CNS remyelination (Sim et al. 2002a; Arnett et al. 2004; Stidworthy et al. 2004) (Fig. 2). Using non-radioactive *in situ* hybridization, we found that neither BMP2 nor noggin were detectable in the demyelinated areas. Small numbers of weakly labelled BMP7 mRNA-expressing cells were seen at 14 days after lesion induction but not at earlier or later time points. However, many cells expressing readily detectable levels of BMP4 mRNA were detected within the lesion throughout the remyelination process. The distribution of BMP4-expressing cells resembled that of PDGFRα+ OPCs, but with a lower density and staining intensity. By combining BMP4 *in situ* hybridization with immunocytochemistry using antibodies to Nkx2.2 (Fancy et al. 2004), we were able to confirm that the majority of BMP4+ cells were OPCs (Fig. 2C). This co-labelling only occurred during the process of remyelination (Fig. 2B): when remyelination was complete at 28 days (Shields et al. 1999) the OPCs no longer expressed BMP4. Thus, the expression of BMP4 mRNA coincides with the stage at which OPCs are reactive and is a further indication of the complex changes in gene expression associated with this state. The functional significance of BMP4 mRNA expression by OPCs is not known at present. Based on developmental studies one would predict that high levels of BMP4 would contribute to an environment that favours astrocyte differentiation. Yet the majority of OPCs in toxin-induced demyelination appear to differentiate into oligodendrocytes. Is this because high levels of noggin counter this effect, as in the case in the myelinating optic nerve (Kondo & Raff, 2004)? The absence of detectable changes in noggin expression within the lesions does not support this hypothesis, although the expression of other BMP antagonists, such as chordin, follistatin or gremlin, has yet to be investigated. The functional role of BMP signalling during remyelination remains an intriguing and unresolved issue.

Fyn tyrosine kinase

Fyn, a member of the non-receptor-type Src family of tyrosine kinases, is a critical part of the signalling pathways by which oligodendrocytes undergo the morphological changes required for myelination. *In vitro*, interference with fyn prevents process extension and myelin sheath formation (Klein et al. 2002; Colognato et al. 2004), while *in vivo* the deletion of Fyn in oligodendrocytes results in hypo-myelination (Umemori et al. 1994; Biffiger et al. 2000; Sperber et al. 2001). One would therefore predict that Fyn expression would be increased within oligodendrocyte lineage cells responding to demyelination and maturing into remyelinating oligodendrocytes. To test this we used non-radioactive *in situ* hybridization with Fyn-specific cRNA probes. We initially confirmed the specificity of these probes by demonstrating Fyn mRNA expression during the myelination of white matter tracts in 2–3-day-old neonatal rats. In adult white matter, however, Fyn mRNA expression was barely at the level of detection. We then looked for Fyn mRNA-expressing cells after induction of demyelination in the adult rat using the EB-CCP model (Fig. 3). Fyn mRNA-expressing

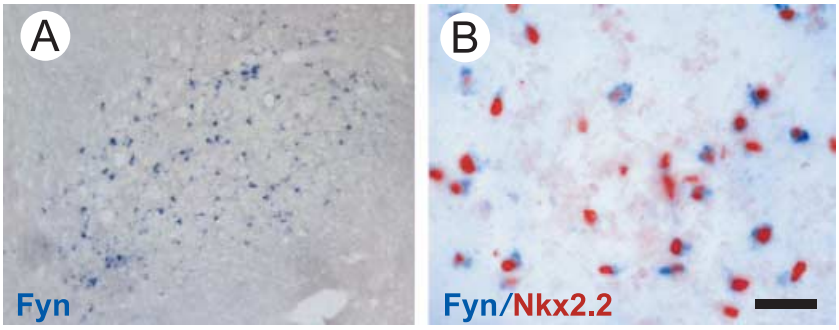

Fig. 3 (A) Fyn mRNA+ cells detected by *in situ* hybridization within an EB-CCP lesion 7 days after induction. (B) The Fyn mRNA+ cells also express the OPC marker Nkx2.2. Scale bar = 100 μm (A), 20 μm (B).

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cells were clearly detectable at 5 days after lesion induction and were most abundant after 7 days (Fig. 3A). Thereafter, the numbers gradually decreased. Double labelling studies revealed that a high proportion of Fyn mRNA-expressing cells also expressed Nkx2.2 (Fig. 3B), and that Fyn therefore had increased levels of message expression occurring in reactive OPCs present within the lesion at early stages of remyelination before myelin sheaths appear (Shields et al. 1999; Woodruff & Franklin, 1999; Sim et al. 2000). Fyn was exclusive to oligodendrocyte lineage cells because there was no colocalization with either astrocytes or macrophage/microglia.

Thus, in response to demyelination, OPCs switch on or increase the expression of multiple genes including Nkx2.2, Olig2, BMP4 and Fyn, converting them from the relatively quiescent state of the intact adult CNS to one where they are responsive to the complex environmental cues within demyelinating lesions and enabling them to differentiate into remyelinating oligodendrocytes. The identification of genes associated with the reactive state will be helpful not only in obtaining a clearer understanding of the molecular mechanisms of remyelination, from which therapeutic targets may emerge, but also in determining the functional status of OPCs present with MS lesions. For example, activation markers will make it possible to determine the likely receptiveness of these cells within areas of chronic demyelination to potential remyelination-enhancing therapies.

Although the prospects for devising pro-remyelination therapies are realistic and exciting there are many critical questions that need to be addressed. In this review we have raised several of these, including the diversity of progenitor cells types that can contribute to remyelination and the manner in which these cells become activated and are able to engage in the repair process. Resolving these questions will form a major part of the developing field of translational 'stem cell' regeneration therapies for demyelinating disease in the forthcoming years.

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