Myelin repair: the role of stem and precursor cells in multiple sclerosis

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Multiple sclerosis is the most common potential cause of neurological disability in young adults. The disease has two distinct clinical phases, each reflecting a dominant role for separate pathological processes: inflammation drives activity during the relapsing–remitting stage and axon degeneration represents the principal substrate of progressive disability. Recent advances in disease-modifying treatments target only the inflammatory process. They are ineffective in the progressive stage, leaving the science of disease progression unsolved. Here, the requirement is for strategies that promote remyelination and prevent axonal loss. Pathological and experimental studies suggest that these processes are tightly linked, and that remyelination or myelin repair will both restore structure and protect axons. This review considers the basic and clinical biology of remyelination and the potential contribution of stem and precursor cells to enhance and supplement spontaneous remyelination.

Keywords: multiple sclerosis; stem cells; precursor cells; neural repair; myelin; axonal injury

1. INTRODUCTION

Multiple sclerosis (MS) is the commonest cause of neurological disability in young adults with a prevalence of approximately 120 per 100 000 and a lifetime risk of 1 in 400 (Compston & Coles 2002). Although the cause of MS is unknown, it is well established that an interplay of genetic and environmental factors results in a multifocal and multiphasic disease defined histologically by inflammatory demyelination, axonal injury, astrocytosis and varying degrees of remyelination.

The clinical course in the majority of patients is initially characterized by episodes with complete recovery, followed by relapse with persistent deficits and finally secondary progression, a stage characterized by few, if any, discrete exacerbations. The natural history of MS reflects a dominant role for distinct but related pathological processes; thus, inflammation drives activity during the relapsing–remitting stage and axon degeneration becomes more prominent as disability accumulates and the disease starts slowly to progress. The occurrence of spontaneous remyelination has long been recognized, but is limited and seems ultimately to fail, resulting in progressive disability (Prineas & Connell 1979; Confavreux & Vukusic 2006a).

Comprehensive treatment strategies must therefore seek both to limit and repair the damage. At present, the modest achievements of disease-modifying treatments target only the inflammatory process and are ineffective in the progressive stage. While further advances in reducing relapse rates are expected, these will leave unsolved the clinical science of disease progression. Here, the requirement is for strategies that promote remyelination and prevent axonal loss. Pathological analyses and experimental studies suggest that these processes are tightly linked, and that remyelination or myelin repair will both restore structure and protect axons. This represents an oversimplification of processes that are not of them- selves mutually exclusive. In this review, which addresses the basic and clinical biology of remyelination, we argue that stem cell-based insights can also contribute to the development of strategies that will both supplement and enhance spontaneous remyelination.

2. AXONAL INJURY AND IRREVERSIBLE DISABILITY IN MULTIPLE SCLEROSIS

Over the last decade, the emergence of increasingly sophisticated imaging techniques allied to detailed histological studies has catalysed a resurgence of interest in the contribution of axonal injury to MS. In some ways, this is a revisiting of an old story, given the reports of axonal pathology in early pathological
descriptions of the disease (Compston 2006). The focus on inflammation and demyelination had obscured the importance of axonal pathology as a key determinant of disability (De Stefano et al. 1998; Bjartmar et al. 2000).

Most patients develop progressive irreversible disability within 10–15 years of disease onset. Clinical, radiological and pathological evidence suggests that irreversible impairment and progressive disability result from exhausting a finite axonal reserve (Davie et al. 1995; De Stefano et al. 1998; Stevenson et al. 1998). Ferguson et al. (1997) and, subsequently, Trapp et al. (1998) provided quantitative evidence for axonal injury in both acute and chronic lesions. Together, these studies strongly suggest that axonal loss is the pathological substrate of progressive disability (figure 1a).

The precise mechanism, however, of axonal injury remains largely unknown. Acute axonal injury correlates with active inflammation (Trapp et al. 1998; Kornek et al. 2000; Kuhlmann et al. 2002). These observations have been extended by the demonstration of axonal injury in both non-inflammatory chronic lesions and normal-appearing white matter (Ferguson et al. 1997; Trapp et al. 1998; Bjartmar et al. 2000; Evangelou et al. 2000; Kornek et al. 2000; Lovas et al. 2000). These (and other) observations suggest that mechanisms that account for chronic axonal loss in MS are independent of inflammation. In turn, this raises the question of what is the interplay between the cardinal clinical features of MS, namely relapses and progression, and their pathological correlates, inflammation and axonal loss. The question remains unanswered despite considerable basic and clinical research activities. The answer(s) will also need to reconcile the weight of epidemiological evidence that argues for redundancy of the phenotypic distinction between relapsing–remitting and secondary progressive MS on reaching the stage of fixed moderate disability (Coles et al. 1999; Kremenchutzky et al. 1999; Confavreux et al. 2000; Confavreux et al. 2003; Confavreux & Vukusic 2006a; Kremenchutzky et al. 2006). Further discussion on the aetiopathogenesis of axonal injury in MS is outside the scope of this review, and the reader is referred to Compston et al. (2006).

3. REMYELINATION MATTERS: OLIGODENDROCYTE SIGNALS MAINTAIN AXONAL INTEGRITY

Experimental and pathological evidence supports the idea that myelin, in addition to enabling saltatory conduction, has a dynamic and vital role in maintaining axonal homeostasis and integrity; thus, chronically demyelinated axons—devoid of myelin-derived support, consequent on inflammation perhaps—are vulnerable to degeneration (figure 1b; Griffiths et al. 1998; Scherer 1999; Kornek et al. 2000). The influence of oligodendrocytes on axonal calibre and function is well described; oligodendrocytes myelinate axons, increase axonal stability and induce local accumulation and phosphorylation of neurofilaments within the axon (Colello et al. 1994; Sanchez et al. 1996; Witt & Brady 2000). Neuronal
function is further influenced by oligodendrocyte-derived soluble factors that induce sodium channel clustering, necessary for saltatory conduction, along axons and maintain this clustering even in the absence of direct axon–glial contact (Kaplan et al. 1997, 2001; Waxman 2001). Defined factors produced by cultured cells of the oligodendrocyte lineage also support neuronal survival and modulate axonal length by distinct intracellular mechanisms (Wilkins & Compston 2005; Wilkins et al. 2001, 2003).

Recent studies on experimental myelin mutant animals have further suggested a role for structural myelin proteins in the maintenance of axonal integrity. Griffiths and co-workers demonstrated a late axonopathy in the absence of inflammation and demyelination in proteolipid (PLP) mutant mice associated with a progressive motor disability. These observations have been extended by the finding in 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) deficient mice of uncoupling between myelin assembly and axonal support compatible with the idea that oligodendrocyte dysfunction can result in a primary axonopathy (Lappe-Siefke et al. 2003). Along with the finding of axonal pathology in patients with a null mutation for PLP, these data suggest that myelin-derived signalling is necessary for the maintenance of axonal structure (Garbern et al. 2002). The function of such signals is unclear, although recent evidence implicates a role in enabling fast axonal transport (Pera et al. 2003; Edgar et al. 2004).

Recognition of the importance of oligodendrocyte signals in maintaining axonal health and the awareness that axonal degeneration occurs by regulated processes independent of apoptosis provide a compelling biological argument that remyelination is an essential part of any therapeutic strategy for MS (Raff et al. 2002).

4. WHAT CELLS GIVE RISE TO REMYELINATING OLIGODENDROCYTES?

It is now generally agreed that most, if not all, remyelinating oligodendrocytes arise from a population of adult precursor cells. This view is based on several lines of experimental evidence. First, proliferating cells that are likely to be NG2<sup>−</sup> precursors, can be labelled either by injecting a LacZ expressing retrovirus into normal white matter or by labelling with tritiated thymidine or BrdU, give rise to labelled remyelinating oligodendrocytes following induction of demyelination (Carroll & Jennings 1994; Gensert & Goldman 1997; Horner et al. 2000; Watanabe et al. 2002). Second, precursors isolated from adult central nervous system (CNS) can remyelinate areas of demyelination following transplantation (Zhang et al. 1999; Windrem et al. 2002). Third, oligodendrocyte precursors cells (OPCs) identified with a range of markers that include the growth factor receptor PDGFRα (Redwine & Armstrong 1998; Di Bello et al. 1999; Sim et al. 2002a; Fancy et al. 2004), the proteoglycan NG2 (Levine & Reynolds 1999; Mason et al. 2000a,b; Watanabe et al. 2002) and the transcription factors MyT1, Nkx2.2, Olig1 and Olig2 (Sim et al. 2002a,b; Fancy et al. 2004; Watanabe et al. 2004) have patterns of expression that are consistent with being the source of new oligodendrocytes, although for few of these markers is there unequivocal evidence that the cells they label become the remyelinating oligodendrocytes. In most situations, these cells are a distinctive phenotype widely referred to as adult OPCs. These cells are the adult descendants of an extensively studied developmental precursor. In adult tissue, these cells have a characteristic multipolar morphology and express several markers, of which NG2 and PDGFRα are the most commonly used (Nishiyama et al. 1996; Dawson et al. 2000, 2003). Apart from their ability to contribute to repair processes, it seems probable that they fulfil a range of normal physiological functions. Whether OPCs express both markers in all circumstances and in all regions of the adult CNS is uncertain (Hampton et al. 2004); indeed, the extent to which this is a homogenous 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, the 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 homogenous population of cells having 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 limited. 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 the lesion, where they can contribute to the generation of new oligodendrocytes during remyelination (Nait-Oumesmar et al. 1999; Picard-Riera et al. 2002; Menn et al. 2006). 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. While it is clear that lesions within the adjacent corpus callosum can induce this response, it is improbable 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.

5. DO ENDOGENOUS 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 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 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). Recent experimental evidence suggests that SVZ type B cells may contribute to remyelination (Menn et al. 2006). 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 proliferation of the stem cell population is scarcely affected by the sudden demand for new differentiated cells following injury. Instead, the transit-amplifying population of progenitors, which, unlike the stem cells from which they are generated, have the proliferative responsiveness to generate the new cells required to repair damaged tissue, takes up this demand. Should one regard the OPCs of the adult brain as being stem cells or progenitor cells? OPCs certainly exhibit some stem cell properties: they show multipotency, giving rise to oligodendrocytes, neurons and, at least in vitro, astrocytes (Ffrench-Constant & Raff 1986; Belachew et al. 2003; Kondo & Raff 2000; Nunes et al. 2003; Gaughwin et al. 2006), and have very high levels of telomerase activity allowing them to undergo many rounds of proliferation before becoming senescent (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, they are more accurately designated 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 progenitor should be more widely applied (Goldman 2003).

6. WHY DOES REMYELINATION FAIL?

Since the cells responsible for generating new oligodendrocytes are transit-amplifying progenitor cells, can their capacity 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 number of OPCs is not reduced and the efficiency of remyelination is unimpaired by previous rounds of remyelination (Penderis et al. 2003a). 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. OPC numbers do gradually diminish if an area of demyelination is exposed to a continuing demyelinating insult (Ludwin 1980; Mason et al. 2004). However, the interpretation of these long-term experiments in rodents is confounded by ageing, since this process alone can significantly impair the reponsiveness of OPCs to demyelination (Sim et al. 2002b), partly due to changes in the signalling environment with ageing and, possibly, also due to intrinsic changes in the responsiveness of aged OPCs (Hinks & Franklin 2000; Decker et al. 2002; Chari et al. 2003). For a more detailed description of the many environmental factors regulating remyelination and how disturbances in their patterns of expression might contribute to remyelination failure see Franklin (2002).

7. PROMOTING ENDOGENOUS REMYELINATION

Since endogenous remyelination spontaneously occurs in MS, sometimes partially but on occasions completely, an obvious therapeutic approach is to promote this naturally occurring repair process in situations where it is inefficient or has failed (Dubois-Dalcq et al. 2005; Lubetzki et al. 2005). Improved understanding of the mechanism of endogenous remyelination and why it fails will enable the development of strategies to promote spontaneous remyelination, as outlined in figure 2. In truth, while this approach is generally regarded as the preferred long-term means of promoting remyelination, it is currently further away from clinical implementation than the exogenous or transplantation approach and experimental proofs-of-principle are few. The reasons for this are many, including matching the information gained from experimental models to the clinical analyses. A commonly used inflammatory-mediated animal model of MS is experimental autoimmune encephalitic (EAE), created by immunization against specific oligodendrocyte/myelin components. Several studies have reported enhancement of remyelination in EAE models following administration (often systemic) of specific compounds (Komoly et al. 1992; Cannella et al. 1998; Fernandez et al. 2004). However, the significance of these studies and their interpretation is unclear for reasons including difficulty in separating effects on reduction of demyelination versus promotion of remyelination and relevance to chronically demyelinated MS lesions (which often contain abundant quiescent oligodendrocyte lineage cells that fail to fully differentiate into remyelinating oligodendrocytes) for which remyelination enhancing therapies are required (Scolding et al. 1998; Wolswijk 1998; Chang et al. 2002).

Some of these difficulties can be overcome by using toxin models of demyelination. However, using these models, interventions that either inhibit remyelination or have no effect have proven much easier to achieve than those that promote remyelination
mental differentiation of multipotent precursors into target transcription factor genes critical for the development of oligodendrocytes such as Olig1 (Arnett et al. 2004). Olig2 and Nkx2.2 are promising candidates since their expression increases in precursors responding to demyelination (Fancy et al. 2004).

8. REMYELINATION BY EXOGENOUS STEM/PRECURSOR CELLS

Considerable hope has been invested in the potential of stem cells as vehicles for neurological repair. In MS, expectation has been largely predicated on the potential of stem cells to yield unlimited numbers of defined myelinating cells. The emergence of methods to isolate and neutralize human embryonic stem cells in the last decade has fuelled that expectation. Successful remyelination has been achieved in a wide range of demyelinating models, using a variety of cell types. These have included embryonic- and adult-derived cells of the oligodendrocyte lineage, Schwann cells, olfactory ensheathing cells, and neural precursors (NPCs) and non-NPCs (figure 3; Blakemore & Crag 1988; Franklin & Blakemore 1997; Imaizumi et al. 1998a; Brustle et al. 1999; Keirstead et al. 1999; Zhang et al. 1999; Barnett et al. 2000; Kohama et al. 2001; Mitome et al. 2001; Akiyama et al. 2002).

Transplantation-mediated remyelination is effective. The question, however, is less ‘does it work?’ (it does), but rather ‘are experimental predominantly rodent-based observations relevant to a multiphasic, multifocal disease with a variable natural history?’ In order to address this question, it is helpful to consider the challenges and thus requirements of any putative pro-remyelinating cell. At a minimum, the cell must survive and navigate the pathological host environment to encounter and successfully reinvest demyelinated axons with new myelin. The ability to migrate between lesions would be a welcome addition to the curriculum vitae of such a cell given the multifocal nature of the disease. Other requirements such as sufficient numbers, resistance to endogenous disease and immune rejection are discussed later.

The pathological environment, however, is not a fixed target, but variable and determined in part by the clinical phenotype and natural history of the disease. Recognition of four different patterns of demyelination in MS suggests that subtly different reparative treatments tailored for the distinct pathologies may be necessary (Lassmann et al. 2001). For example, primary progressive MS, characterized in general by less inflammation and earlier and more sustained axonal loss, may require a different approach to the more common relapse–remitting (RR) phenotype (Lucchinetti & Bruck 2004). Furthermore, the three distinct stages in the evolution of tissue injury attributable to MS—RR, relapsing with persistent deficits and secondary progressive—require different treatment strategies. Traditionally, it has been considered that remyelination strategies are best focussed upon chronic plaques—which are pathologically similar regardless of disease onset—characterized by demyelination, variable amounts of inflammation and gliosis (Lassmann et al. 1998). However, insights from animal models and pathological studies of MS lesions suggest that either earlier, and hence more acute, lesions represent better targets for transplantation-mediated...
myelin repair, or those chronic ones in which the environment has been altered to more closely resemble that of an acute remyelinating lesion are to be preferred (Hammarberg et al. 2000; Foote & Blakemore 2005; Kotter et al. 2005, 2006; Setzu et al. 2006). These studies provide evidence that inflammation can be beneficial to remyelination.

9. CHOICE OF EXOGENOUS STEM/PRECURSOR CELL

Although it is highly improbable that xenografts will ever be contemplated in clinical practice, comparatively few studies have examined the remyelination potential of human-derived cells. Recognition of inter-species difference in the behaviour of NPCs with respect to their capacity to generate oligodendrocytes caution the extent to which extrapolation from other systems can reliably be made to human disease; this emphasizes the need for improved understanding of human precursor cell biology (Chandran et al. 2004).

Olfactory ensheathing cells and Schwann cells are presently the only readily accessible and potentially autologous adult human cell populations with well-characterized myelinating potential. Olfactory ensheathing cells are specialized glial cells that are entering phase I clinical studies in spinal cord injury on account of their ability to promote and augment axon growth (Feron et al. 2005). These cells may also have a role in myelin repair, given their ability to remyelinate central demyelinated axons with a Schwann cell–like phenotype (Franklin et al. 1996; Imaizumi et al. 1998a; Barnett et al. 2000; Sasaki et al. 2004). Moreover, unlike Schwann cells, olfactory ensheathing cells appear to be able to migrate and more readily integrate into an astrocytic environment (Lakatos et al. 2000; Lakatos et al. 2003). This is a distinct advantage, given that astrocytic gliosis is prevalent in both acute and chronic MS lesions.

In view of the need for scale, human NPCs represent the most plausible source of exogenous central myelinating cells. NPCs can be readily derived from embryonic stem cells and the foetal and adult CNS (figure 3). There are merits and disadvantages associated with selecting any human–derived material. NPCs and cells of more restricted glial and neuronal potential are found in the adult brain. Aside from the degree of phenotypic potential of adult glial progenitors, contingent on environment, it is clear that (viewed collectively) the adult human brain contains a range of NPCs (Kukekov et al. 1999; Arsenijevic et al. 2001; Palmer et al. 2001; Nunes et al. 2003; Sanai et al. 2004). Regardless of origin, the requirement to direct human precursors to the early oligodendrocyte lineage—necessary for remyelination—ex vivo presents a considerable challenge (Smith & Blakemore 2000). For example, foetal NPCs, although readily propagated, cannot be systematically directed to a myelinating phenotype (Murray et al. 1997; Quinn et al. 1999; Zhang et al. 2000; Chandran et al. 2004). Cell surface-based selection methods provide one approach directly to isolate human white matter precursor(s) that possesses remyelinating potential (Roy et al. 1999; Windrem et al. 2002, 2004). Although valuable as an experimental resource, limited availability of foetal and adult human material constrains any widespread clinical application. Furthermore, in...
addition to there being a limited supply stream, the inability to standardize and predict or define sample(s) in terms of age, region and co-morbidity (for adult biopsy-derived specimens) precludes ready comparison between samples and increases the ‘noise’ of any resulting data. By contrast, human embryonic stem cells offer an alternative means to generate potentially unlimited numbers of defined NPCs and enriched populations of functional oligodendrocytes (Carpenter et al. 2001; Reubinoff et al. 2001; Zhang et al. 2001; Keirstead et al. 2005; Nistor et al. 2005). Notwithstanding advances in isolation, propagation of human embryonic stem (hES) cells and neuralization protocols that bring closer the prospect of clinical grade hES-derived NPCs, much remains to be determined with respect to the long-term efficacy of hES-derived precursors (Klimanskaya et al. 2005; Joannides et al. 2006; Ludwig et al. 2006). To date, no long-term studies have demonstrated stable functional integration of hES-derived neural derivatives. Indeed, concerns regarding potential oncogenic complications of hES-derived material have catalysed the study of alternative sources of human NPCs.

10. NON-NEURAL STEM CELLS

Until recently, somatic stem cells were regarded as restricted to regeneration of their tissue of origin. Recent observations have raised the concept of more widespread phenotypic potential of adult somatic stem cells, despite additional explanations for some of the earlier experimental observations (Terada et al. 2002; Ying et al. 2002). Several lines of evidence focused largely around bone marrow and mesenchymal derivatives (figure 3) suggest that somatic stem cells derived from non-neural tissue may be capable of generating NPCs (Jiang et al. 2002, 2003; Clarke & Frisen 2001; Toma et al. 2001; Joannides et al. 2004). These studies find some support from opportunistic observations on the brains of females receiving bone marrow transplants from males indicating transdifferentiation rather than fusion as a potential explanation (Weimann et al. 2003; Cogle et al. 2004; Crain et al. 2005). The prospect of an ethically acceptable, readily accessible and potentially autologous source of NPCs is clearly very attractive. However, despite the evidence of remyelination by adult bone marrow-derived cells, there remains a large amount of basic characterization and improved understanding of the mechanism of ‘somatic stem cell plasticity’ to be gained before adult non-neural stem cells can be reasonably contemplated as a reliable source of myelinating cells (Akiyama et al. 2002; Takahashi & Yamanaka 2006). Additional properties of adult stem cells may, however, offer a more immediate and plausible role in remyelination and neuroprotective therapies.

11. CAN CELLULAR THERAPIES PROMOTE NEUROPROTECTION INDEPENDENT OF DIFFERENTIATION?

Cellular therapies for MS have until recently been viewed as a cell-replacement strategy to be targeted at site-specific repair. However, recognition of the potential utility of NPCs outside of directed differentiation offers additional therapeutic opportunities. The demonstration that intravenous administration of stem cells leads to delivery throughout the inflammatory neuraxis resulting in axonal protection and functional improvement is of considerable interest (Pluchino et al. 2003, 2005; Zappia et al. 2005). Specifically, increasing evidence suggests that stem cell-based therapies may be neuroprotective in models of multifocal inflammatory disease, independent of directed differentiation. These studies highlight the immune-modulatory effects of stem cells. Inflammation is not only central to disease pathogenesis, but is also likely to be necessary for optimum remyelination (see below), and the idea that cellular immune-modulation may blunt the former and promote the latter is intriguing. Two cell types have demonstrated efficacy: rodent NPCs (neonatal and adult) and adult mesenchymal stem cells (MSCs; Einstein et al. 2003; Pluchino et al. 2005; Zappia et al. 2005). Pluchino et al. (2003, 2005) have shown that systemically delivered undifferentiated adult NPCs into EAE mice can, contingent on the microenvironment, either differentiate into myelinating cells or, where inflammation predominates, exert a neuroprotective effect by inducing selective apoptotic death of Th1 cells. Expression of integrin and G-protein-coupled receptors permits circulating NPCs to be recruited to the CNS using adhesion and chemokine-mediated homing mechanisms analogous to those used by activated lymphocytes. In this regard, the expression of chemokine receptors by NPCs and MSCs is of interest (Tran et al. 2004; Dar et al. 2005; Honczarenko et al. 2005; Pluchino et al. 2005; Sordi et al. 2005). The mechanism of neuroprotection is uncertain, but evidence is provided suggesting that this is mediated, at least in part, by selective NPC-mediated T-cell death. Importantly, in the chronic recurrent EAE model, NPCs resulted in functional improvement and reduced axonal loss (Pluchino et al. 2005). A further study has demonstrated that peripheral delivery of human bone marrow-derived MSCs also promote functional recovery in EAE mice (Zhang et al. 2005). It remains to be determined whether MSCs also produce trophic factors that have previously been shown to promote axonal health, thus offering a further mechanism of neuroprotection (Wilkins et al. 2003).

The multifocal nature of MS has long been a conceptual barrier to stem cell-based therapies. However, the ability of precursors, delivered systemically or by the intrathecal route, to cross the blood–brain barrier and then exhibit migratory behaviour within the pathological brain suggests that the dilemma of how best to deliver and distribute a novel cellular therapy may not be problematic (Ben Hur et al. 2003; Pluchino et al. 2003). In addition to the idea of stem cells behaving as cellular immune-modulators, their demonstrated migratory and ‘homing’ effects additionally raise the prospect of using neural stem cells as cellular delivery vehicles. Proofs of concept studies in animal models have exploited the innate tropism of stem cells to target therapy to pathological lesions (Aboody et al. 2000; Benedetti et al. 2000). The molecular basis of homing is uncertain; however, inflammation appears to be a regulator of tropism through the action of various cytokines acting through receptors including CCR2,
CRR3, CCR5 and CXCR4 that are expressed in EAE and MS brains (Kennedy et al. 1998; Simpson et al. 2000; Tran et al. 2004; Honczarenko et al. 2005; Pluchino et al. 2005).

12. CONCLUSION

The Holy Grail in MS research is to deliver therapies that limit and repair damage. Despite significant advances in disease-modification treatments, strategies that enable repair remain elusive. This in part reflects the absence of consensus for the cause and mechanism of disease progression. At the heart of this question lies the role and interrelationship of inflammation and axonal loss. A parallel though ultimately convergent question is how can axonal loss, the pathological correlate of disability, be limited? The intuitive view that remyelination is protective of axons in MS is supported by considerable although largely indirect evidence. Remyelination as a neuroprotective therapy thus appears a reasonable hypothesis. Although therapeutic success will most probably require details of the pathological process that limit remyelination to be further understood, an increasing body of evidence provides grounds for cautious optimism that stem cell-based therapies offer realistic prospects for myelin repair over the next decade.

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