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Importance of oligodendrocyte protection, blood brain barrier breakdown and inflammation for remyelination

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). A better understanding why remyelination fails in MS is necessary to improve remyelination strategies. Remyelination is mediated by oligodendrocyte precursor cells (OPCs), which are widely distributed throughout the adult CNS. However, it is still unclear whether 1) OPCs detectable in MS lesions survived the inflammatory response and are unable to myelinate or 2) OPC and oligodendrocyte death is primarily responsible for remyelination failure and detectable OPCs entered demyelinated areas from adjacent tissue as the lesion evolves. Remyelination strategies should therefore focus on stimulation of differentiation or prevention of apoptosis as well as establishment of a supportive environment for OPC-mediated remyelination, which may be especially important in chronically demyelinated lesions.

Keywords

multiple sclerosis; remyelination strategies; demyelination; apoptosis; blood brain barrier; inflammation

1. Introduction

Demyelination in the central nervous system (CNS) is the pathological hallmark in multiple sclerosis (MS), which is a primary inflammatory process that leads to CNS damage and neurological deficits [1,2]. Demyelination disables saltatory conduction and leads to loss of neural functions. During demyelination ensheathed axons are unwrapped becoming more vulnerable to environmental stressors. The initial trigger(s) inducing demyelination are still unclear. Acute lesions are believed to begin with phagocytosis of normal myelin sheaths by macrophages in the presence of infiltrating T lymphocytes [3]. This concept is supported by studies of an animal model for MS, experimental allergic encephalomyelitis (EAE), where the myelin sheath is targeted by autoreactive $CD4^+$ T cells and lymphocyte infiltration is a primary event [4,5]. However, there is evidence that at least in some cases of MS oligodendrocyte death is the initial event in MS lesion formation with intact myelin sheaths. Apoptotic oligodendrocytes and activated microglia are found in the absence of inflammation with few or no myelin phagocytes or lymphocytes [6-9]. Death of oligodendrocytes and the formation

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of new MS lesions could be triggered by viral infection [10], followed by microglial activation and recruitment of virus-specific CD4+ and CD8+ T cells and macrophages into lesions.

2. Oligodendrocyte cell death in multiple sclerosis

In MS, demyelination is accompanied by extensive destruction and loss of oligodendrocytes [11]. Failure to remyelinate during the recovery phase after an acute attack occurs at least partially because of oligodendrocytes death and the inability of OPCs to differentiate into mature myelinating oligodendrocytes [12-15]. From the study of MS tissue we know that some active demyelinated lesions contain no OPCs [16] or only at the margins of the demyelinated area and very few or no OPCs in the center [16,17]. OPC numbers are also reduced in chronically demyelinated MS lesions often with a change in morphology [15,17]. Some chronically active demyelinated lesions have a similar OPC distribution compared to active demyelinated lesions with some OPCs at the margins and no or very few OPCs in the center [17].

In acute MS, apoptosis of oligodendrocytes has been documented [8,9,18] but has only rarely been seen in chronic MS lesions [19,20]. Apoptotic cell death of oligodendrocytes has been proposed to be the initial event in new lesion formation and the primary cause of inflammation in acute MS [8]. Barnett and co-workers examined a very early stage in lesion formation in a 14-year-old patient with relapsing-remitting MS within 17 hours of the onset of a new symptomatic and fatal brainstem lesion and concluded that oligodendrocyte death precedes the activation of complement and microglia. This was followed by demyelination and phagocytosis of complement-opsonized myelin sheets by macrophages [8]. In contrast, death of oligodendrocytes by apoptosis in chronic MS lesions and controls is an infrequent event, indicating that the major apoptotic loss of oligodendrocytes is an early event associated with acute lesion formation [21] and less prominent in chronic lesions [22]. Caspase 1 mRNA and protein levels are significantly elevated in OLs in acute and chronic MS, suggesting that caspase-1 may play a role in the inflammatory and apoptotic processes associated with MS pathogenesis [23]. In experimental demyelination models the number of apoptotic oligodendrocytes and severity of EAE are reduced in caspase-1- or caspase-11-deficient animals [24,25] or in transgenic animals over-expressing the caspase-inhibitory protein p35 [26].

These data clearly indicate the impact of oligodendrocyte apoptosis for the disease and therapeutic approaches in MS. Therefore rescuing mature myelinating oligodendrocytes from apoptosis is likely to be the major goal in preventing MS, and protecting OPCs against apoptotic triggers seems to be a major goal to increase remyelination.

2.1 Molecular triggers of oligodendrocyte death

A. Cellular effectors—Cytotoxic T lymphocytes (CTLs) with a $CD8^+$ phenotype are able to recognize and attack major histocompatibility complex (MHC) class I-expressing CNS cells. Most CNS cells can be stimulated to present peptides to $CD8^+$ CTLs by MHC class I molecules, and are susceptible to CTL-mediated cytotoxicity in culture [27]. In disease-affected CNS parenchyma, $CD8^+$ CTLs outnumber other T-cell subtypes and show clonal expansion in several inflammatory and degenerative CNS diseases, such as multiple sclerosis (MS). The extent of axonal damage in primary MS lesions is correlated to the number of activated microglia/macrophages and cytotoxic $CD8^+$ T lymphocytes [28]. MBP-reactive $CD8^+$ T cells induce MHC class I restricted cytotoxicity of OLs [29]. $CD8^+$ T cells have the potential to induce OL lysis in vivo as a likely consequence of direct antigen recognition [30].

Cultured OLs are not susceptible to MHC class II restricted cell lysis, but expression of CD56 in $CD4^+$ effector cells stimulates non-MHC-restricted cell lysis of human OLs [31]. $CD4^+$ T

cell mediated toxicity requires contact between OLs and T cells and is independent of the cytokine profile of the T cells and can be inhibited by pan-caspase inhibitors and Fas-targeting antibodies [32].

NK cells and γδ T cells are members of the innate immune system using non-MHC-restricted lytic mechanisms to mediate target cell injury and are detectable in MS lesions [33,34]. Interleukin-2 (IL-2)-mediated activation of NK cells may occur in the inflammatory environment of active MS lesions and could bypass protective effects of self-MHC class I molecules that may be expressed on OLs [35]. γδ T cells have been implicated in the pathogenesis of MS [36] and are cytotoxic toward OL via perforin [37]. γδ T and NK cells interact with OL via NKG2D receptor and a corresponding ligand expressed by OL and mediate cell death via cell lysis or by induction of apoptosis. The effector molecule perforin can induce cell lysis in OL [38] or apoptosis depending on the molecular environment [39].

B. Nitric oxide (NO)—Nitric oxide (NO) is a diffusible and reactive free radical involved in a variety of physiological functions, including control of the vascular tone, platelet aggregation, and the immune response [40,41] and a major factor contributing to the loss of neurons in ischemic stroke, demyelinating diseases, and other neurodegenerative disorders [42]. NO is involved in glutamate induced excitation with direct effects on BBB permeability, clearence of CNS inflammation, possibly via induction of encephalitogenic T cell apoptosis, and mediating demyelination, oligodendrocyte destruction and injury to axons [43]. NO is synthesized by three different types of NO synthases (NOS): the constitutively expressed nitric oxide synthase (cNOS), the inducible NO synthase (iNOS) and the mitochondrial NO synthase (mtNOS). Within the CNS cNOS is found in neurons and endothelial cells. cNOS is regulated in a calcium-dependent manner via calmodulin [44,45]. iNOS is expressed in various cell types in response to cytokines IL-1β, IFN-γ and TNF-α [46-49]. NO synthesis is increased during CNS inflammation in ependymal cells, macrophages and astrocytes to levels that are neurotoxic to the CNS environment. Detection of nitrotyrosine is indicative for oxidative cell membrane damage including NO-mediated changes. iNOS is abundantly expressed in astrocytes in MS lesions [50] and in brain biopsies of fulminant MS [51], but not detected in normal human CNS. Increased iNOS expression levels and nitrotyrosine were also detected in chronic active MS lesions in phagocytic macrophages and at the active lesion edge, in and around perivascular lesions, and in periventricular ependymal cells [52]. Labeling with iNOS decreases as lesion age and become less active [53]. In brain biopsies from two acute cases of MS iNOS was detected in both reactive astrocytes and macrophages, whereas no signal was detected in chronic inactive MS lesions [54].

High NO concentration induce apoptosis by activating mainly the mitochondrial apoptotic pathway including modulation of apoptosis-associated Bax and Bcl-2 expression [55,56], induction of DNA damage and activation of tumor suppressor p53 protein, which in turn induces regulatory gene expression, allowing DNA repair or programmed cell death [57,58]. NO can function as a direct neurotoxin or may react with superoxide (O_2^-) by a diffusion-controlled reaction to form peroxynitrite ($ONOO^-$), a species that also contributes to oxidative signaling and cellular apoptosis [42]. However, the mechanism by which $ONOO^-$ induces apoptosis remains unclear, although subsequent formation of reactive oxygen species (ROS) such as $O2^-$, H2O2, OH^-, and $ONOO^-$ has been suggested [42]. These observations support a potential role of iNOS in initiation of MS lesions.

C. Reactive oxygen species (ROS)—In the past few years more evidence has been emerged that reactive oxygen species (ROS) contribute to several mechanisms underlying the pathogenesis of MS lesions. ROS are produced upon interaction of monocytes with brain endothelium, leading to alterations of tight-junction [59], cytoskeleton rearrangement, enhancing the migration of monocytes into MS lesions by reduction of BBB integrity [60] and

subsequent leukocyte infiltration into the CNS. Infiltrated leukocytes produce high amounts of ROS leading to macrophage-mediated myelin degradation [61], hydrogen-peroxide- and NO-induced apoptotic cell death of oligodendrocytes [62,63] and neuronal and axonal damage [64,65]. Additionally, various antioxidants have beneficial effects in MS therapy, suggesting that ROS play an important role in MS pathogenisis [65,66]. Extensive oxidative damage occurs to proteins, lipids, and nucleotides in active demyelinating MS lesions, predominantly in reactive astrocytes and myelin-laden macrophages [67]. Counteracting the oxidative stress hypertrophic astrocytes and myelin-laden macrophages express antioxidant enzymes superoxide dismutase 1 and 2, catalase, and heme oxygenase 1, which are markedly up-regulated in active MS lesions compared to white matter from control brains [67]. Enhanced expression of antioxidant enzymes may reflect an adaptive defense mechanism against ROS-mediated cell damage in MS lesions.

D. TNFα—Tumor necrosis factor α (TNFα) is a cytokine involved in systemic inflammation stimulates acute phase reactions and is an important modulator of the immune response. TNF-α is produced by cells of the macrophage lineage, which includes microglia in the central nervous system [68]. TNFα is a well known trigger of apoptosis and necrosis of oligodendrocytes in experimental animal models [69,70] and in cell culture [71-73]. Inhibition of caspase-1 and caspase-3 protects oligodendrocytes against TNFα-induced apoptosis [71, 72,74,75]. More recently, non-caspase dependent mechanisms of TNF-induced cell apoptosis have been proposed. These mechanisms involve mitochondria-derived factors such as apoptosis inducing factor (AIF) [73,76] and endonuclease G [77,78]. Due to high TNFα concentrations in active MS lesions vs controls and the fact that TNFα induces apoptosis and necrosis of oligodendrocytes in experimental animal models [69,70] and in cell culture [71-73] it was suggested that TNFα is a major player to induce OL cell death also in active MS lesions [79]. Under cell culture conditions TNFα is associated with the activation of c-Jun NH2-terminal kinase (JNK) 3 [80,81] and activation of NFκB [79].

Microglia play a role in mediating the death of oligodendrocytes through the T-lymphocyte stimulated release of TNFα [82], which can be antagonized by interferon β-1b [68]. Since TNF-α neutralizing agents provoke inflammatory demyelination [83], TNF-α homoeostasis is a highly regulated process during inflammation and its maintenance may protect against demyelination.

Despite these results, attempts to treat MS with monoclonal antibodies targeting TNF- α showed worsening of the disease [83,84]. In addition treatment with monoclonal antibodies against TNF-α caused demyelinating lesions in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn disease [85].

E. Fas ligand—Fas ligand (FasL or CD95L) is a type II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. Fas ligand (FasL) is a homotrimeric protein and signals through trimerization of the Fas receptor (FasR), which spans the membrane of the "target" cell. This trimerization leads to apoptosis, or cell death [86]. The Fas death system has been proposed to contribute to plaque pathogenesis in chronic MS lesions [87,88]. Microglia and lymphocytes show intense staining for FasL in MS lesions [87,88]. FasR expression is increased in chronic MS lesions [88] and is restricted to oligodendrocytes [20,87]. However, Bonetti and co-workers showed in an EAE animal model, that the FasR-FasL system is used to eliminate infiltrating cells and microglia, but not oligodendrocytes in the CNS [20,89]. *In vitro* the FasL-FasR system induced caspase activation and cell death in human oligodendrocyte hybrid cells [90,91]. Supporting the role of caspases in Fas-signaling, mice over-expressing the caspase inhibitor p35 [26] or transgenic animals lacking caspase 11 [24] are resistant to Fas-mediated apoptosis. Overexpression of tumor protein 53 (p53), a transcription factor involved in several cellular processes like apoptosis and cell cycle arrest,

resulted in up-regulation of the death receptors FasR, death receptor 4 (DR4) and death receptor 5 (DR5) with subsequent caspase-mediated apoptosis of oligodendrocytes [92]. In addition to its complex functions as a nuclear transcription factor, p53 can act in the cytosol and mitochondria to promote apoptosis through transcription-independent mechanisms [93]. Oligodendrocytes were protected from p53-induced cell death by blocking signaling through FasR and/or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors [92].

F. TRAIL—TRAIL, also termed Apo2L, is a member of the TNF superfamily and expressed as a type II transmembrane protein (mTRAIL). TRAIL is released from the cell membrane after cleavage by metalloproteinases, yielding soluble TRAIL (sTRAIL). Active TRAIL forms a homotrimer and mTRAIL as well as an engineered soluble form induce apoptosis in several transformed cell lines [94]. The death receptors (DR), TNF-R1 (DR1), and Fas (DR2), are well-characterized members of the group and have been studied previously in MS [20,87,88]. DR3 is preferentially expressed by lymphocytes and is induced after T-cell activation [95]. DR4 and DR5 (TRAIL-R1 and TRAIL-R2), are two of five cloned receptors of the TNF-related apoptosis–inducing ligand, TRAIL [96-99]. Two other receptors of TRAIL, DcR1 and DcR2 (TRAIL-R3 and TRAIL-R4), are protective and act as decoy receptors (DcRs) [100,101]. RT-PCR data indicate that DR6 is abundant in normal human CNS [102]. Oligodendrocytes obtained from human fetal spinal cord expressed DR3, DR4, DR5, DR6, and DcR1 and DcR2 [102] and adult oligodendrocytes from human tissue expressed TRAIL-R1-4 [103]. More recently DR4 and DR6 was not detected in adult CNS tissue [21]. DR3 (TRAIL-R1) is one of the receptors inducing apoptosis in human oligodendrocytes in vitro [103,104] which is mediated by activation of JNK, but not p38 kinase or ERK1/2 kinases [104]. These data indicate that TRAIL and its receptors TRAIL-R1-4 are responsible in part for apoptosis or oligodendrocyte survival in MS tissue.

G. Interferon γ (IFNγ)—Interferon-gamma (IFN-γ) is a dimerized soluble cytokine that is the only member of the type II class of interferons. IFN-γ is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response, and by CD4 + and CD8+ cytotoxic T lymphocyte (CTL) effector T cells [105]. Production of IFN-γ by CD4+T cells results in activation of microglia, which causes these cells to function as antigen presenting cells (APCs) and to produce and secrete IFN-γ by themselves [106].

IFN-γ is a pro-inflammatory cytokine that plays an important role in many inflammatory processes, including demyelination. However, when IFN-γ is released in low levels, it supports the survival of neurons. More recently, IFNγ has been identified to activate the pancreatic endoplasmic reticulum kinase (PERK) thereby activating the ER stress response in OLs [107]. PERK coordinates an adaptive program known as the integrated stress response (ISR) by phosphorylating the α-subunit of eukaryotic translation initiation factor 2 (eIF2α). CNS delivery of IFN-γ before EAE onset ameliorated the disease course and prevented demyelination, axonal damage, and oligodendrocyte loss. However no IFN-γ-mediated beneficial effect could be observed in PERK-deficient animals [107]. Therefore, ISR activation may be considered as a potential therapeutic approach in MS.

Induction of EAE in mice lacking IFN-γ or the IFN-γ receptor as well as administration of anti–IFN-γ antibodies all resulted in more severe disease, suggesting that IFN-γ may limit disease [108-110].

In contrast, increased amounts of IFN-γ interfere with neuronal survival by activating microglia that damage CNS cells via the release of cytotoxic factors such as glutamate, nitric oxide, superoxide and pro-inflammatory cytokines [111]. Systemic administration of IFNγ causes exacerbations in MS patients associated with activation of the immune system [112,113].

IFNγ also modulates cellular responses in oligodendrocytes by increasing expression levels of FasR in vitro, thereby enhancing their susceptibility to FasL-induced apoptosis [87].

Additionally, TNFα increases the IFNγ-induced death of OPCs, which can be partially suppressed by caspase inhibitors [114]. Oligodendrocytes from caspase-11 knockout mice are less sensitive to IFNγ-induced cell death, supporting the requirement for caspase activation in oligodendrocyte cell death [24]. Moreover, the induction of IFN-expression after demyelinating insults significantly inhibits the remyelination process in EAE [115].

These data demonstrate that IFNγ has both the potential to ameliorate or exacerbate the severity of the disease, which indicates the complexity of different signaling pathways affected by the cytokine.

H. Excitotoxicity—Glutamate is the primary excitatory neurotransmitter in the CNS and is synthesized in all CNS cells as a key metabolite in the citric acid cycle. Glutamate is produced in high concentrations in neurons, packed into vesicles and stored in synapses, from where it can be released into the CNS. This glutamate release is the major extracellular source in the normal CNS. In gray matter astrocytes are major player in glutamate uptake, whereas glutamate homeostasis in white matter is primarily regulated by oligodendrocytes [116]. In MS lesions, microglia expresses increased levels of the glutamate-synthesizing enzyme glutaminase, whereas glutamate transporter expression in OLs is down-regulated [116,117]. Alterations in the glutamate homeostasis may contribute to OL death both through caspase-dependent and –independent mechanisms [118]. Excessive activation of the ionotropic glutamate receptors expressed by cultured rat oligodendrocytes may induce cell death thereby regulating the size of the cell population. Kainate induced toxicity suggested the involvement of both AMPA and kainite receptors [119]. In an EAE model, blocking of AMPA/kainite receptors improved time course of the disease and increased OL survival [117,120]. In addition, glutamate sensitizes OLs to complement attack and may contribute to OL death [121]. Excess glutamate may result in cytoskeletal degradation of axons and neurons via increased production of NOS, ROS, arachidonic acid, phospholipase A2, Ca^{2+} -influx and activation of calcium-dependent proteases such as calpain [122]. Thus, imbalanced glutamate homeostasis contributes to the OLGs cell death in MS.

3. What is remyelination?

Remyelination involves reinvesting demyelinated axons with new myelin sheaths resulting in recovery of axon function. Resulting myelin sheaths are often thinner and shorter on remyelinated compared to non-remyelinated axons [123,124]. The circumference of the axon divided by the circumference of the myelin sheath is called the g ratio. Unusually thin myelin sheaths with high g ratios are the most reliable factor for the identification of remyelination. Remyelination on large diameter axons with high g ratios is much easier to identify than for example remyelination in the corpus callosum, where remyelination on small diameter axons is almost indistinguishable to normally myelinated axons [125].

3.1 Extent of remyelination in MS and animal based MS models

Studies of experimental models of demyelination, induced either by immunological, viral or chemical stimuli, demonstrated rapid and efficient remyelination [123,126-129] with improved neurological functions [130,131].

The existences of shadow plaques, which represent fully remyelinated MS lesions, demonstrate that complete repair of MS lesions is possible [132]. However, it is more common to observe a rather limited repair at the edge of lesions [133]. Remyelination seems to be extensive weeks or month after the clinical onset of the disease as detected in biopsies and cases coming to

autopsy at these early time points [132,134-136]. With progression of the disease the extent of remyelination decreases [11], suggesting that chronically demyelinated lesions typically display limited remyelination restricted to the periphery of the MS plaque [133,137]. A more recent study investigated the extent of remyelination in cerebral tissue from two MS cases. From 168 white matter lesions they identified 22 % shadow plaques, 73 % partially remyelinated lesions and only 5 % completely demyelinated lesions with an average extent of lesion remyelination of 47 % for all white matter lesions [138], suggesting that the extent of remyelination may be more extensive than previously thought.

4. How does remyelination occur?

4.1 Which cells are primarily responsible for remyelination?

Based on data from experimentally induced demyelination in rodents adult oligodendrocyte progenitor cells (adult OPCs) but not surviving mature oligodendrocytes are the major source of remyelinating oligodendrocytes. This view is based on several lines of indirect experimental evidence. First, remyelinating oligodendrocytes in normal adult white matter originate from proliferating cells, which are identified by injecting LacZ expressing retrovirus into normal white matter or by labelling with tritiated thymidine or BrdU. These proliferating cells are likely adult OPCs which has not been proven yet [139-142]. Second, transplanted OPCs are efficiently able to remyelinate demyelinated brain areas [143,144]. In focal areas of demyelination, devoid of OPCs and oligodendrocytes, OPCs repopulate these areas before mature oligodendrocytes are detectable, indicating that OPCs may be the source of remyelinating cells [127,142]. In adult tissue OPCs have a characteristic multipolar morphology and express several markers, of which NG2 and PDGFRa are the most commonly used [145-147].

Mature oligodendrocytes outside areas of demyelination do not divide or migrate and therefore are unlikely to contribute to remyelination. Surviving mature oligodendrocytes have been detected in MS lesions and experimentally induced demyelination in rodents [9,148], some with shorn off processes and myelin sheaths, suggesting that these cells could recover and contribute to remyelination by growing out new processes and myelin sheaths. However, no remyelination could be detected after transplanting mature oligodendrocytes into experimentally demyelinated brain areas [149] or after triggering demyelination with the selective sparing of mature oligodendrocytes; anti-galactocerebroside antibodies and complement in combination with irradiation induced depletion of OPCs [148]. These studies indicate that the contribution of mature oligodendrocytes to remyelination is rather low compared to OPCs. However, anti-galactosylceramide antibody treatment together with irradiation of oligodendrocytes likely causes a very different damage in mature oligodendrocytes compared to conditions in MS lesions. Therefore it is unlikely that mature oligodendrocytes contribute to remyelination as well, but it can not be excluded.

4.2 Activation of adult OPCs

In response to injury, OPCs undergo a switch from an essentially quiescent state to a regenerative phenotype before they differentiate into oligodendrocytes and repair regions of demyelination. This activation step is disturbed in some chronically demyelinated MS lesions that contain quiescent OPCs [13]. Demyelinating lesions open the blood brain barrier (BBB), and recent findings suggest that this might be an important factor in activating the OPC population to induce remyelination [150].

A classical point of view is that microglia and astrocytes become reactive in case of CNS injury [150-153], proliferate [154] and become the major source of factors that stimulate OPC-mediated remyelination. However, the injury response of OPCs differs from that of other glia

[150]. In “closed” lesion models, where the blood brain barrier (BBB) is not disrupted, like facial nerve injury or sciatic nerve crush, microglia and astrocytes are rapidly activated [155-162], but no reactive NG2-positive OPCs are found around the lesioned neurons [150]. In contrast, after injury or infection of the CNS with BBB breakdown, OPCs show rapid responses [126,127,163-168], displaying an increased expression of chondroitin sulfate proteoglycans (CSPGs), including NG2 and transcription factors Olig2, NKX2.2, MYT1 and SoX2 [169-173] combined with a reactive morphology with hypertrophy of the cell body and processes at the site of tissue damage [152,167,174]. This may indicate that BBB disruption enhances OPC activation and therefore facilitates remyelination [150]. However, it is important to mentioned that remyelination is also efficient in cuprizone-induced demyelination models with a completely intact BBB [175], suggesting that OPCs activation occurs via different pathways or might be different in various animal based models.

In cuprizone-induced demyelination remyelination and OL density improved significantly in PDGF-A-overexpressing transgenic mice compared to wild-type mice [170]. OPC density and proliferation were increased in the corpus callosum during acute demyelination but not during chronic demyelination or the subsequent recovery period compared to controls [170]. Additionally, in cuprizone-induced demyelination the intracranially injection of growth factors PDGF-AA, FGF-2, NT3 and IGF-1 enhanced remyelination [239]. However, in GFAP-PDGF-A transgenic mice, where demyelination was induced by intraspinal injection of lysolecithin or dietary administration of cuprizone, morphological analysis of lysolecithin lesions did not reveal any difference in the time course or extent of remyelination between GFAP-PDGF-A and wild-type mice [176], whereas OPC density within lesions was significantly increased with both demyelinating triggers compared to wild-type mice. The extent of remyelination in both lysolecithin-induced and cuprizone-induced demyelination models was investigated because quantitative analysis during early stages of remyelination in the corpus callosum after cuprizone-induced demyelination have been shown to be unreliable [125,176]. Additionally, factors that have been shown to be mitogenic and chemotactic for OPCs under cell culture conditions (PDGF, FGF-2, EGF, TGF) were unable to activate OPCs in experimental animal models, whereas various injury response-related cytokines (TNFα, TGFβ1, IL-1α, IFNγ), which may come from platelets or macrophages provoked the OPC injury response and increased expression of CSPGs (particularly NG2) [150].

Reactive NG2-positive OPCs undergo rapid cell division within 1–2 mm of the lesion site and accumulate in number for at least 7 days post-lesion [152,165,167,177]. The agent that initiates reactive changes in OPCs is not a component of serum, since freshly extracted serum injected into the CNS did not enhance OPC reactivity [150]. However, whole blood, macrophages and platelets were all shown individually to cause reactive changes in OPCs [150]. The association between reactive behavior of OPCs, BBB breakdown and inflammation, and the surveillance-like functions of OPCs previously proposed [147,164,178-181] imply a crucial mechanism linking OPCs with platelet-mediated healing and the inflammatory response to CNS injury.

In general, dysfunction of the BBB is a major hallmark of MS [182,183] and BBB damage has been shown in acute MS plaques [184] and chronic-progressive MS [185,186]. A key factor in MS progression appears to be BBB alteration in genetically predisposed individuals, leading to increased vascular permeability and leukocyte infiltration into the brain [187,188]. Deposition of the serum protein fibrinogen in MS lesions is one of the earliest events in the formation of MS lesions [189-192]. Extravascular fibrinogen that is deposited in tissues upon vascular rupture is not merely a marker, but a mediator of diseases like MS with an inflammatory component and has been shown to activate microglia even in the absence of T cells [193,194]. Additionally, the extracellular matrix (ECM) proteins vitronectin and fibronectin are detected in MS lesions [195-197]. Similar to fibrinogen, fibronectin and vitronectin bind to integrins and induce microglial activation and expression of matrix

metalloproteinase-9 (MMP-9) ([198], which facilitates remyelination in part by processing the inhibitory NG2 proteoglycan [199].

Although the role of NG2 in remyelination has not been investigated and this proteoglycan has previously been found to have an inhibitory effect on axon elongation [200,201], NG2-positive cells in the developing and adult brain are part of the oligodendrocyte lineage and capable of giving rise to new oligodendrocytes under both normal and demyelinating conditions [202].

4.3. Recruitment, proliferation and differentiation of adult OPCs

Once OPCs are activated, reactive microglia and astrocytes support the proliferative response of OPCs to demyelinating injury by stimulating the production of growth factors platelet derived growth factor-AA (PDGF-AA) and basic fibroblast growth factor (FGF-2) [139,153, 154,163,203], which are up-regulated during remyelination [204,205]. The number of oligodendrocyte progenitors recruited to the lesions is modulated by the levels of the cell cycle regulatory protein p27Kip-1 [206]. OPC proliferation and migration into demyelinated lesions is regulated in a similar manner to what has been identified by *in vitro* studies. Neonatal OPCs proliferate *in vitro* in response to PDGF-AA [207], FGF-2 [208], or insulin-like growth factor-1 (IGF-1) [209]. They migrate in response to PDGF-AA and, to a lesser extent, with FGF-2 treatment [210-212]. PDGF-AA also acts as a survival factor for neonatal oligodendrocyte progenitors and oligodendrocytes [213]. PDGF-AA and FGF-2 also stimulates proliferation of OPCs from adult spinal cord or optic nerve, but cells are less motile and respond at a slower rate than neonatal progenitors [214,215]. The combination of PDGF-AA and FGF-2 has a striking effect on adult OPCs. OPCs from adult spinal cord or optic nerve migrate and proliferate to the same extent as neonatal progenitor cells [214,215].

To have an impact on remyelination activated OPCs have to differentiate into oligodendrocytes. Within this differentiation phase the oligodendrocytes have to establish contact with the axon that is to be remyelinated, myelin gene expression has to be induced to generate a myelin membrane and this membrane has to wrap around the axon and compact to form the sheath. The understanding of how axo–glial contact is established and how this interaction regulates myelination is still uncomplete. There are many similarities between developmental myelination and remyelination and some common molecules have been shown to contribute to the regulation of both. FGF-2 seems to play a major role in the inhibition of differentiation and therefore regulates the transition from the proliferating and migrating OPCs into differentiating oligodendrocytes [216-218]. Signaling through the insulin-like growth factor receptor1 (IGF1R) plays a critical role in remyelination via effects on oligodendrocyte progenitors [219]. IGF-1 is a survival factor for oligodendrocytes [220-222] and a differentiation factor for neonatal [209,223] and adult [224] oligodendrocyte progenitors *in vitro*. Its levels are elevated within demyelinating and remyelinating lesions in the adult CNS [225-227].

Remyelination is often associated with a prominent inflammatory response in experimental demyelination models and MS lesions [136,228,229]. These studies demonstrate an impairment of remyelination in the absence of lymphocytes, MHC Class II antigens, inflammatory cytokines, macrophages, and inhibition of microglial activation [230-237]. From the study of MS tissue we know that remyelination occurs in lesions that contain macrophages [238].

Conversely, in a cuprizone-induced demyelination model which has a minimal inflammatory response the intracranially injection of growth factors PDGF-AA, FGF-2, NT3 and IGF-1 enhanced remyelination [239] and increased the expression of proinflammatory cytokines [240]. Specifically TNFα [237,240], IL-1β [231,240], the lymphotoxin β receptor (LTβR) [241] and the major histocompatibility complex class II (MHCII) were elevated [236]. The

increased cytokine levels correlate with increased remyelination, but it is very unlikely that they directly stimulate OPC-mediated remyelination (**see chapter 2.1**).

5. Failure of remyelination

It has been difficult to clarify why remyelination fails due to a lack of suitable experimental model. However, by using novel experimental models, including OPC transplantation, the significance of the relationship between inflammation and remyelination becomes clear. As discussed earlier remyelination is often associated with an inflammatory response in experimental demyelination models and MS lesions, however remyelination is impaired in the absence of lymphocytes, MHC Class II antigens, inflammatory cytokines, macrophages, and inhibition of microglial activation (**see chapter 4.3**). Additionally, dysfunction of the BBB is an inflammatory response and a major hallmark of MS [182,183]. In some MS lesions the BBB maybe restored before remyelination is complete, which might prevent further OPC responses and remyelination [150]. Supporting the importance of BBB breakdown for remyelination it has been shown that myelin debris, which is removed by phagocytic macrophages, inhibits OPC differentiation both *in vitro* and during remyelination [242-244].

In a chronic demyelination model the induction of inflammation is sufficient to induce remyelination [150,245]. In the absence of inflammation OPCs survive poorly and do not migrate after transplantation into the normal adult CNS [246]. However, in x-irradiated spinal cord, implanted OPCs survive and migrate into both grey and white matter, which demonstrates that the failure of OPC survival and migration in normal adult white matter is due to a nonpermissive environment and not a property of the transplanted cells [246].

In the absence of transplanted OPCs demyelinated areas become repopulated with OPCs from adjacent non-damaged tissue at a rate that depends on the animal's age [247,248]. Neonatal OPCs were 3-5 times more efficient than adult OPCs to colonize OPC-depleted tissue [249], indicating that the recipients age as well as the OPCs donor age are important factors for effective remyelination [247]. In cases where the demyelinated areas are large and OPCs must migrate over 1-2 months to reach the center of the lesion, Blakemore and co-workers documented a decrease in the remyelination potential of transplanted OPCs over time. Resolution of the inflammatory response limits the remyelination capacity of OPCs [249]. It is possible to increase the remyelination potential of OPCs by adding important inflammatory cytokines. When OPCs are injected into the demyelinated retina together with zymosan, a drug that induces proinflammatory cytokine secretion in immune cells e.g. TNFα-secretion in macrophages [250], remyelination is improved [251].

Chronically demyelinated lesions usually contain nonreactive, scarring astrocytes, which are unable to produce OPC supporting growth factors [163,205,252-254]. In a chronic demyelination model, transplanted OPCs did not repopulate areas of chronic demyelination, but they did repopulate chronically demyelinated astrocytosed tissue without remyelination [245], which is similar to the situation found in some chronically demyelinated MS lesions. Induction of acute inflammation in these demyelinated, but OPC repopulated areas resulted in remyelination [245], suggesting that it might be possible to induce remyelination in chronically demyelinated MS lesions. These results together with data from MS lesions [8] (**see chapter 2**) suggest that at least in some cases OPC death due to a hostile, non-supporting environment is the primary reason why MS lesions fail to remyelinate. If OPCs in acute MS lesions were protected against cell death their activation, proliferation and differentiation would be supported by the inflammatory process, thereby improving remyelination. As an alternative OPCs in chronically demyelinated lesions are the result of cells that have entered the area after the inflammatory burst. They remain inactivated and unable to remyelinate [255]. They are not

OPCs that survived the primary demyelination insult and are unable to differentiate into myelinating oligodendrocytes [256].

6. Promotion of remyelination

So far no clinical therapy is available that promotes remyelination. There are at least two major approaches in animal models of demyelination to stimulate remyelination. One strategy is based on cell replacement by transplanting OPCs into areas of demyelination (exogenous therapies) while the others aim to stimulate resident precursor cell populations to repair demyelinated lesions (endogenous therapies).

A. Exogenous therapies

Concerning cell transplantation there are many different sources of cells available that can be potentially differentiated into myelinating cells including primary OPCs [143,257,258], Schwann cells [259-261], neural stem cell lines [262] and embryonic stem cell derived glial precursors [263]. These studies provided evidence that transplanted cells can contribute to remyelination. However, as mentioned earlier (**chapter 2**), at least some MS lesions already contain a considerable amount of OPCs that due to their non-supportive environment are unable to myelinate. Therefore, there may be very little benefit to transplant OPCs into these MS lesions. Especially in case of chronically demyelinated lesions it seems to be inevitable to re-establish a supportive environment for remyelination before cell transplantation is considered as a choice to repair demyelinated areas. Additionally, all potential sources of cells for transplantation have technical or ethical problems. Peripheral stem cells from bone marrow that generate peripheral glia are attractive candidates for cell transplantations into the brain, as autografting would be possible, but the incompatibility of Schwann cells with astrocyte-containing tissue limits the feasibility of using these cells in MS [264]. Multipotent neural progenitor cells with features of somatic stem cells can differentiate into neurons, astrocytes and oligodendrocytes and are found in the adult brain [265]. They support neurogenesis, can be expanded extensively *in vitro*, survive in the CSF and have been tested to induce recovery in EAE [266], which makes them a potential source for cell transplantation in various human CNS diseases [141,267]. Intraventricular and intravenous delivery techniques of stem and precursor cells have been developed that allows these cells to enter the CNS and to repair demyelinated areas [266,268]. However, this beneficial impact on remyelination in EAE seems to be an indirect immunomodulatory effect of neural stem cells on T cell populations in the CNS and peripheral lymph nodes rather than a direct contribution of these cells to remyelination [269,270]. Sourcing and ethical problems are a major concern in the use of fetal or adult brain grafts, which contain large numbers of neural precursor cells. Pluripotent embryonic stem cells can be differentiated into oligodendrocytes via neural precursor cells [271]. In addition, oligodendrocytes from embryonic stem cells require at least a month in cell culture under strictly controlled conditions and transformed stem cell lines carry a risk of tumour formation [272].

B. Endogenous therapies

Enhancing endogenous remyelination is conceptually a very attractive approach with abundant cells throughout the adult brain that are capable to myelinate. Stimulating physiological repair mechanisms is an important therapeutic goal in MS and other demyelinating diseases. Several promising approaches are currently being explored including antibodies to LINGO-1, remyelination promoting IgM antibodies and hormone treatments.

LINGO-1 is a cell surface protein and a component of the Nogo-66 receptor/p75 signaling complex only expressed in neuronal tissue that has been implicated in the inhibition of myelination [273,274] and regulated by NGF [275]. The inhibitory action is achieved through

RhoA-GTP upregulation in response to the presence of MOG, MAG or Nogo-66 in the CNS [274]. LINGO-1 antagonists promote OPC differentiation and myelination *in vitro* and accelerate remyelination after lysophosphatidylcholine- or cuprizone-induced demyelination [276] as well as in a rat EAE model [277]. This remyelination is associated with functional recovery of conduction velocities in demyelinated axons. It is suggested that LINGO-1 functions as an inhibitor of OPC differentiation. Blocking LINGO-1 is a very encouraging approach to promote remyelination.

Several human and mouse monoclonal IgM antibodies have been identified, that promote substantial remyelination in several animal models of MS [278-283] A common feature of these antibodies is their ability to bind to the surface of oligodendrocytes and myelin, which is necessary, but not sufficient, for induction of remyelination *in vivo*. Although the precise molecular mechanisms for this effect remain unclear [284], a human remyelination promoting IgM prevents apoptosis in CG4 cells [81]. These autoantibodies may constitute a component of the endogenous remyelination process [279]. A recombinant form of a human IgM (rHIgM22) identified from a patient with Waldenström macroglobulinemia is under GMP development and will soon enter Phase I clinical trials.

The observation that women with MS are protected against relapses during pregnancy [285] initiated two studies showing that the lactation associated hormone prolactin enhances remyelination in toxin induced demyelination models [286]. Due to increased prolactin levels during pregnancy, the numbers of OPCs in the CNS are increased during pregnancy. Prolactin receptors are present on OPCs and their activation by prolactin stimulates the maturation of these cells into myelin-competent oligodendrocytes [286]. Another class of hormones, the thyroid hormones, has been shown to promote differentiation of OPCs and to induce remyelination after cuprizone-induced demyelination [287,288]. Overexpression of growth factor PDGF in toxin induced demyelination models induced a strong recruitment of OPCs into demyelinated areas, but without improved remyelination [176]. Overexpressing PDGF in a chronic demyelination model resulted in reduced apoptosis in the corpus callosum during the recovery period. Therefore, PDGF may support oligodendrocyte generation and survival to promote remyelination of chronic, but not acute, lesions [170]. Antagonizing the inhibitory effect of FGF-2 on OPC differentiation might be a future therapeutic approach to enhance endogenously remyelination, because *FGF2*-/- mice created a sufficiently permissive lesion environment that led to effective remyelination after cuprizone-induced remyelination in mice [289].

7. Expert commentary and Five-year view

Future prospects over the coming years for repair of MS lesions are encouraging, especially with respect to remyelination. Several promising therapeutic approaches are close to clinical trials, including cell transplantation, remyelination promoting antibodies and hormone therapy. However, promoting remyelination in the adult CNS and especially in chronically demyelinated lesions with its hostile, non-permissive conditions is a very difficult task. Stimulating repair in MS lesions is challenging and the choice of animal model in which the therapy is designed will influence the choice of clinical trials in humans. Protecting OPCs and oligodendrocytes from inflammatory mediated cell death in acute MS lesions may be a powerful approach to enhance remyelination. There clearly is a need to identify additional inhibitory or missing factors responsible for the failure of remyelination. This will likely lead to combination therapies for remyelination e.g. cell transplantation along with cytokines or immune modulation. The significant advances made in remyelination biology in recent years provide reasons for optimism.

Key issues

- Apoptotic cell death of oligodendrocytes appears to be the initial event in new MS lesion formation and the initiator of inflammation in acute MS.
- Failure of remyelination after an acute attack occurs because of oligodendrocyte and OPC death, and the inability of OPCs to differentiate into myelinating oligodendrocytes.
- OPCs in chronically demyelinated lesions are the result of cells that have entered the area after the demyelinating process is complete. They remain dormant and unable to remyelinate until activated by the inflammatory milieu.
- Transplantation of OPCs into chronically demyelinated lesions may not be necessary to induce remyelination because they are already present in the lesion.
- OPCs must be activated before they differentiate into myelinating oligodendrocytes.
- Demyelinating lesions open the blood brain barrier (BBB), which may activate the OPCs to induce remyelination.
- Invasion of macrophages or platelets into demyelinated lesions causes NG2 expression of OPCs by secretion of proinflammatory cytokines.
- Resolution of the inflammatory response limits the remyelination capacity of OPCs.

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Literature

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359(9313):1221–31. [PubMed: 11955556]
2. Noseworthy JH, et al. Multiple sclerosis. N Engl J Med 2000;343(13):938–52. [PubMed: 11006371]
3. Raine CS, Scheinberg LC. On the immunopathology of plaque development and repair in multiple sclerosis. J Neuroimmunol 1988;20(23):189–201. [PubMed: 3198745]
4. Paterson PY. Transfer of allergic encephalomyelitis in rats by means of lymph node cells. J Exp Med 1960;111:119–36. [PubMed: 14430853]
5. Ben-Nun A, Wekerle H, Cohen IR. The rapid isolation of clonable antigen-specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis. Eur J Immunol 1981;11(3):195–9. [PubMed: 6165588]
6. Rodriguez M, et al. Oligodendrocyte injury is an early event in lesions of multiple sclerosis. Mayo Clin Proc 1993;68(7):627–36. [PubMed: 8350635]
7. Rodriguez M, Scheithauer B. Ultrastructure of multiple sclerosis. Ultrastruct Pathol 1994;18(12):3–13. [PubMed: 8191643]
8. Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol 2004;55(4):458–68. [PubMed: 15048884] Apoptosis of oligodendrocytes is supposed to be one of the earliest events in the formation of new MS lesions and the primary cause of inflammation in acute MS
9. Lucchinetti C, et al. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000;47(6):707–17. [PubMed: 10852536]

10. Lipton HL, et al. A specific viral cause of multiple sclerosis: one virus, one disease. Ann Neurol 2007;61(6):514–23. [PubMed: 17455291]
11. Ozawa K, et al. Patterns of oligodendroglia pathology in multiple sclerosis. Brain 1994;117(Pt 6): 1311–22. [PubMed: 7820568]
12. Wolswijk G. Oligodendrocyte survival, loss and birth in lesions of chronic-stage multiple sclerosis. Brain 2000;123(Pt 1):105–15. [PubMed: 10611125]
13. Wolswijk G. Chronic stage multiple sclerosis lesions contain a relatively quiescent population of oligodendrocyte precursor cells. J Neurosci 1998;18(2):601–9. [PubMed: 9425002]
14. Kuhlmann T, et al. Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. Brain 2008;131(Pt 7):1749–58. [PubMed: 18515322]
15. Chang A, et al. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. N Engl J Med 2002;346(3):165–73. [PubMed: 11796850]
16. Chang A, et al. NG2-positive oligodendrocyte progenitor cells in adult human brain and multiple sclerosis lesions. J Neurosci 2000;20(17):6404–12. [PubMed: 10964946]
17. Peterson JW, et al. VCAM-1-positive microglia target oligodendrocytes at the border of multiple sclerosis lesions. J Neuropathol Exp Neurol 2002;61(6):539–46. [PubMed: 12071637]
18. Dowling P, et al. Cell death and birth in multiple sclerosis brain. J Neurol Sci 1997;149(1):1–11. [PubMed: 9168159]
19. Breij EC, et al. Homogeneity of active demyelinating lesions in established multiple sclerosis. Ann Neurol 2008;63(1):16–25. [PubMed: 18232012]
20. Bonetti B, Raine CS. Multiple sclerosis: oligodendrocytes display cell death-related molecules in situ but do not undergo apoptosis. Ann Neurol 1997;42(1):74–84. [PubMed: 9225688]
21. Cannella B, et al. Multiple sclerosis: death receptor expression and oligodendrocyte apoptosis in established lesions. J Neuroimmunol 2007;188(12):128–37. [PubMed: 17610960]
22. Raine CS. Multiple sclerosis: classification revisited reveals homogeneity and recapitulation. Ann Neurol 2008;63(1):1–3. [PubMed: 18232014]
23. Ming X, et al. Caspase-1 expression in multiple sclerosis plaques and cultured glial cells. J Neurol Sci 2002;197(12):9–18. [PubMed: 11997061]
24. Hisahara S, et al. Caspase-11 mediates oligodendrocyte cell death and pathogenesis of autoimmune-mediated demyelination. J Exp Med 2001;193(1):111–22. [PubMed: 11136825]
25. Furlan R, et al. Caspase-1 regulates the inflammatory process leading to autoimmune demyelination. J Immunol 1999;163(5):2403–9. [PubMed: 10452974]
26. Hisahara S, et al. Targeted expression of baculovirus p35 caspase inhibitor in oligodendrocytes protects mice against autoimmune-mediated demyelination. Embo J 2000;19(3):341–8. [PubMed: 10654933]
27. Neumann H, et al. Cytotoxic T lymphocytes in autoimmune and degenerative CNS diseases. Trends Neurosci 2002;25(6):313–9. [PubMed: 12086750]
28. Neumann H. Molecular mechanisms of axonal damage in inflammatory central nervous system diseases. Curr Opin Neurol 2003;16(3):267–73. [PubMed: 12858061]
29. Jurewicz A, Biddison WE, Antel JP. MHC class I-restricted lysis of human oligodendrocytes by myelin basic protein peptide-specific CD8 T lymphocytes. J Immunol 1998;160(6):3056–9. [PubMed: 9510211]
30. Saxena A, et al. Cutting edge: Multiple sclerosis-like lesions induced by effector CD8 T cells recognizing a sequestered antigen on oligodendrocytes. J Immunol 2008;181(3):1617–21. [PubMed: 18641296]
31. Antel JP, et al. Non-MHC-restricted cell-mediated lysis of human oligodendrocytes in vitro: relation with CD56 expression. J Immunol 1998;160(4):1606–11. [PubMed: 9469416]
32. Hestvik AL, et al. Idiotope-specific CD4(+) T cells induce apoptosis of human oligodendrocytes. J Autoimmun 2009;32(2):125–32. [PubMed: 19250800]
33. Traugott U, Raine CS. Further lymphocyte characterization in the central nervous system in multiple sclerosis. Ann N Y Acad Sci 1984;436:163–80. [PubMed: 6398015]

34. Wucherpfennig KW, et al. Gamma delta T-cell receptor repertoire in acute multiple sclerosis lesions. Proc Natl Acad Sci U S A 1992;89(10):4588–92. [PubMed: 1374907]
35. Morse RH, et al. NK cell-mediated lysis of autologous human oligodendrocytes. J Neuroimmunol 2001;116(1):107–15. [PubMed: 11311336]
36. Selmaj K, Brosnan CF, Raine CS. Colocalization of lymphocytes bearing gamma delta T-cell receptor and heat shock protein hsp65+ oligodendrocytes in multiple sclerosis. Proc Natl Acad Sci U S A 1991;88(15):6452–6. [PubMed: 1830662]
37. Zeine R, et al. Mechanism of gammadelta T cell-induced human oligodendrocyte cytotoxicity: relevance to multiple sclerosis. J Neuroimmunol 1998;87(12):49–61. [PubMed: 9670845]
38. Zeine R, et al. Structural dynamics of oligodendrocyte lysis by perforin in culture: relevance to multiple sclerosis. J Neurosci Res 2001;64(4):380–91. [PubMed: 11340645]
39. Chavez-Galan L, et al. Cell death mechanisms induced by cytotoxic lymphocytes. Cell Mol Immunol 2009;6(1):15–25. [PubMed: 19254476]
40. Mannick JB. Immunoregulatory and antimicrobial effects of nitrogen oxides. Proc Am Thorac Soc 2006;3(2):161–5. [PubMed: 16565425]
41. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43(2):109–42. [PubMed: 1852778]
42. Lim W, et al. Inhibition of mitochondria-dependent apoptosis by 635-nm irradiation in sodium nitroprusside-treated SH-SY5Y cells. Free Radic Biol Med 2009;47(6):850–7. [PubMed: 19545621]
43. Smith KJ, Lassmann H. The role of nitric oxide in multiple sclerosis. Lancet Neurol 2002;1(4):232–41. [PubMed: 12849456]
44. Brown GC, Borutaite V. Nitric oxide inhibition of mitochondrial respiration and its role in cell death. Free Radic Biol Med 2002;33(11):1440–50. [PubMed: 12446201]
45. Brown GC, Borutaite V. Interactions between nitric oxide, oxygen, reactive oxygen species and reactive nitrogen species. Biochem Soc Trans 2006;34(Pt 5):953–6. [PubMed: 17052235]
46. Bo L, et al. Induction of nitric oxide synthase in demyelinating regions of multiple sclerosis brains. Ann Neurol 1994;36(5):778–86. [PubMed: 7526776]
47. Forstermann U, et al. Isoforms of nitric oxide synthase. Properties, cellular distribution and expressional control. Biochem Pharmacol 1995;50(9):1321–32. [PubMed: 7503779]
48. Forstermann U, Kleinert H. Nitric oxide synthase: expression and expressional control of the three isoforms. Naunyn Schmiedebergs Arch Pharmacol 1995;352(4):351–64. [PubMed: 8532063]
49. Forstermann U, et al. Expression and expressional control of nitric oxide synthases in various cell types. Adv Pharmacol 1995;34:171–86. [PubMed: 8562433]
50. Giovannoni G, et al. The potential role of nitric oxide in multiple sclerosis. Mult Scler 1998;4(3): 212–6. [PubMed: 9762676]
51. Bitsch A, et al. Lesion development in Marburg's type of acute multiple sclerosis: from inflammation to demyelination. Mult Scler 1999;5(3):138–46. [PubMed: 10408713]
52. Hill KE, et al. Inducible nitric oxide synthase in chronic active multiple sclerosis plaques: distribution, cellular expression and association with myelin damage. J Neuroimmunol 2004;151(12):171–9. [PubMed: 15145615]
53. Liu JS, et al. Expression of inducible nitric oxide synthase and nitrotyrosine in multiple sclerosis lesions. Am J Pathol 2001;158(6):2057–66. [PubMed: 11395383]
54. Oleszak EL, et al. Inducible nitric oxide synthase and nitrotyrosine are found in monocytes/ macrophages and/or astrocytes in acute, but not in chronic, multiple sclerosis. Clin Diagn Lab Immunol 1998;5(4):438–45. [PubMed: 9665945]
55. Brune B. The intimate relation between nitric oxide and superoxide in apoptosis and cell survival. Antioxid Redox Signal 2005;7(34):497–507. [PubMed: 15706097]
56. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol Rev 2007;87(1):315–424. [PubMed: 17237348]
57. Brune B, Schneiderhan N. Nitric oxide evoked p53-accumulation and apoptosis. Toxicol Lett 2003;139(23):119–23. [PubMed: 12628747]
58. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol 2007;8(4):275–83. [PubMed: 17380161]

59. Lee HS, et al. Hydrogen peroxide-induced alterations of tight junction proteins in bovine brain microvascular endothelial cells. Microvasc Res 2004;68(3):231–8. [PubMed: 15501242]
60. Van der Goes A, et al. Reactive oxygen species enhance the migration of monocytes across the blood-brain barrier in vitro. Faseb J 2001;15(10):1852–4. [PubMed: 11481252]
61. van der Goes A, et al. Reactive oxygen species are required for the phagocytosis of myelin by macrophages. J Neuroimmunol 1998;92(12):67–75. [PubMed: 9916881]
62. Mronga T, et al. Mitochondrial pathway is involved in hydrogen-peroxide-induced apoptotic cell death of oligodendrocytes. Glia 2004;46(4):446–55. [PubMed: 15095374]
63. van Meeteren ME, et al. Dietary compounds prevent oxidative damage and nitric oxide production by cells involved in demyelinating disease. Biochem Pharmacol 2004;67(5):967–75. [PubMed: 15104250]
64. Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J Neurol 2004;251(3):261–8. [PubMed: 15015004]
65. Hendriks JJ, et al. Macrophages and neurodegeneration. Brain Res Brain Res Rev 2005;48(2):185–95. [PubMed: 15850657]
66. Mirshafiey A, Mohsenzadegan M. Antioxidant therapy in multiple sclerosis. Immunopharmacol Immunotoxicol 2009;31(1):13–29. [PubMed: 18763202]
67. van Horssen J, et al. Severe oxidative damage in multiple sclerosis lesions coincides with enhanced antioxidant enzyme expression. Free Radic Biol Med 2008;45(12):1729–37. [PubMed: 18930811]
68. Chabot S, Williams G, Yong VW. Microglial production of TNF-alpha is induced by activated T lymphocytes. Involvement of VLA-4 and inhibition by interferonbeta-1b. J Clin Invest 1997;100(3):604–12. [PubMed: 9239408]
69. Heppner FL, et al. Experimental autoimmune encephalomyelitis repressed by microglial paralysis. Nat Med 2005;11(2):146–52. [PubMed: 15665833]
70. Akassoglou K, et al. Oligodendrocyte apoptosis and primary demyelination induced by local TNF/p55TNF receptor signaling in the central nervous system of transgenic mice: models for multiple sclerosis with primary oligodendrogliopathy. Am J Pathol 1998;153(3):801–13. [PubMed: 9736029]
71. Selmaj KW, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. Ann Neurol 1988;23(4):339–46. [PubMed: 3132891]
72. Robbins DS, et al. Production of cytotoxic factor for oligodendrocytes by stimulated astrocytes. J Immunol 1987;139(8):2593–7. [PubMed: 3116087]
73. Jurewicz A, et al. Tumour necrosis factor-induced death of adult human oligodendrocytes is mediated by apoptosis inducing factor. Brain 2005;128(Pt 11):2675–88. [PubMed: 16219674]
74. Louis JC, et al. CNTF protection of oligodendrocytes against natural and tumor necrosis factor-induced death. Science 1993;259(5095):689–92. [PubMed: 8430320]
75. Hisahara S, et al. ICE/CED-3 family executes oligodendrocyte apoptosis by tumor necrosis factor. J Neurochem 1997;69(1):10–20. [PubMed: 9202289]
76. Daugas E, et al. Mitochondrio-nuclear translocation of AIF in apoptosis and necrosis. Faseb J 2000;14(5):729–39. [PubMed: 10744629]
77. Parrish J, et al. Mitochondrial endonuclease G is important for apoptosis in C. elegans. Nature 2001;412(6842):90–4. [PubMed: 11452313]
78. Li LY, Luo X, Wang X. Endonuclease G is an apoptotic DNase when released from mitochondria. Nature 2001;412(6842):95–9. [PubMed: 11452314]
79. Bonetti B, et al. Activation of NF-kappaB and c-jun transcription factors in multiple sclerosis lesions. Implications for oligodendrocyte pathology. Am J Pathol 1999;155(5):1433–8. [PubMed: 10550297]
80. Jurewicz A, et al. TNF-induced death of adult human oligodendrocytes is mediated by c-jun NH2-terminal kinase-3. Brain 2003;126(Pt 6):1358–70. [PubMed: 12764057]
81. Howe CL, et al. Antiapoptotic signaling by a remyelination-promoting human antimyelin antibody. Neurobiol Dis 2004;15(1):120–31. [PubMed: 14751777]
82. Merrill JE, et al. Microglial cell cytotoxicity of oligodendrocytes is mediated through nitric oxide. J Immunol 1993;151(4):2132–41. [PubMed: 8102159]

83. Mohan N, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001;44(12):2862–9. [PubMed: 11762947]
84. Tanno M, et al. New-onset demyelination induced by infliximab therapy in two rheumatoid arthritis patients. Clin Rheumatol 2006;25(6):929–33. [PubMed: 16328088]
85. Lozeron P, et al. Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-alpha-blocker therapy. Arch Neurol 2009;66(4):490–7. [PubMed: 19364934]
86. Sharma K, et al. Death the Fas way: regulation and pathophysiology of CD95 and its ligand. Pharmacol Ther 2000;88(3):333–47. [PubMed: 11337030]
87. D'Souza SD, et al. Multiple sclerosis: Fas signaling in oligodendrocyte cell death. J Exp Med 1996;184 (6):2361–70. [PubMed: 8976190]
88. Dowling P, et al. Involvement of the CD95 (APO-1/Fas) receptor/ligand system in multiple sclerosis brain. J Exp Med 1996;184(4):1513–8. [PubMed: 8879222]
89. Bonetti B, et al. Cell death during autoimmune demyelination: effector but not target cells are eliminated by apoptosis. J Immunol 1997;159(11):5733–41. [PubMed: 9548518]
90. Pouly S, et al. Interferon-gamma modulates human oligodendrocyte susceptibility to Fas-mediated apoptosis. J Neuropathol Exp Neurol 2000;59(4):280–6. [PubMed: 10759183]
91. Li W, et al. Apoptotic death following Fas activation in human oligodendrocyte hybrid cultures. J Neurosci Res 2002;69(2):189–96. [PubMed: 12111800]
92. Wosik K, et al. Oligodendrocyte injury in multiple sclerosis: a role for p53. J Neurochem 2003;85 (3):635–44. [PubMed: 12694389]
93. Speidel D. Transcription-independent p53 apoptosis: an alternative route to death. Trends Cell Biol. 2009
94. Hoffmann O, Zipp F, Weber JR. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) in central nervous system inflammation. J Mol Med 2009;87(8):753–63. [PubMed: 19449143]
95. Bodmer JL, et al. TRAMP, a novel apoptosis-mediating receptor with sequence homology to tumor necrosis factor receptor 1 and Fas(Apo-1/CD95). Immunity 1997;6(1):79–88. [PubMed: 9052839]
96. Wiley SR, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity 1995;3(6):673–82. [PubMed: 8777713]
97. Walczak H, et al. TRAIL-R2: a novel apoptosis-mediating receptor for TRAIL. Embo J 1997;16(17): 5386–97. [PubMed: 9311998]
98. Sheridan JP, et al. Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. Science 1997;277(5327):818–21. [PubMed: 9242611]
99. Pan G, et al. The receptor for the cytotoxic ligand TRAIL. Science 1997;276(5309):111–3. [PubMed: 9082980]
100. Degli-Esposti MA, et al. Cloning and characterization of TRAIL-R3, a novel member of the emerging TRAIL receptor family. J Exp Med 1997;186(7):1165–70. [PubMed: 9314565]
101. Degli-Esposti MA, et al. The novel receptor TRAIL-R4 induces NF-kappaB and protects against TRAIL-mediated apoptosis, yet retains an incomplete death domain. Immunity 1997;7(6):813–20. [PubMed: 9430226]
102. Harrison DC, et al. TR3 death receptor expression in the normal and ischaemic brain. Neuroscience 2000;96(1):147–60. [PubMed: 10777386]
103. Matysiak M, et al. TRAIL induces death of human oligodendrocytes isolated from adult brain. Brain 2002;125(Pt 11):2469–80. [PubMed: 12390973]
104. Jurewicz A, et al. TRAIL-induced death of human adult oligodendrocytes is mediated by JNK pathway. Glia 2006;53(2):158–66. [PubMed: 16206163]
105. Schoenborn JR, Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol 2007;96:41–101. [PubMed: 17981204]
106. Sanders P, De Keyser J. Janus faces of microglia in multiple sclerosis. Brain Res Rev 2007;54(2): 274–85. [PubMed: 17383006]
107. Lin W, et al. The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage. J Clin Invest 2007;117(2):448–56. [PubMed: 17273557]

108. Furlan R, et al. Intrathecal delivery of IFN-gamma protects C57BL/6 mice from chronic-progressive experimental autoimmune encephalomyelitis by increasing apoptosis of central nervous system-infiltrating lymphocytes. J Immunol 2001;167(3):1821–9. [PubMed: 11466408]

109. Willenborg DO, et al. IFN-gamma plays a critical down-regulatory role in the induction and effector phase of myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. J Immunol 1996;157(8):3223–7. [PubMed: 8871615]

110. Willenborg DO, et al. IFN-gamma is critical to the control of murine autoimmune encephalomyelitis and regulates both in the periphery and in the target tissue: a possible role for nitric oxide. J Immunol 1999;163(10):5278–86. [PubMed: 10553050]

111. Butovsky O, et al. Activation of microglia by aggregated beta-amyloid or lipopolysaccharide impairs MHC-II expression and renders them cytotoxic whereas IFN-gamma and IL-4 render them protective. Mol Cell Neurosci 2005;29(3):381–93. [PubMed: 15890528]

112. Panitch HS, et al. Treatment of multiple sclerosis with gamma interferon: exacerbations associated with activation of the immune system. Neurology 1987;37(7):1097–102. [PubMed: 3110648]

113. Panitch HS, et al. Exacerbations of multiple sclerosis in patients treated with gamma interferon. Lancet 1987;1(8538):893–5. [PubMed: 2882294]

114. Andrews T, Zhang P, Bhat NR. TNFalpha potentiates IFNgamma-induced cell death in oligodendrocyte progenitors. J Neurosci Res 1998;54(5):574–83. [PubMed: 9843148]

115. Lin W, et al. Interferon-gamma inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress. Brain 2006;129(Pt 5):1306–18. [PubMed: 16504972]

116. Werner P, Pitt D, Raine CS. Multiple sclerosis: altered glutamate homeostasis in lesions correlates with oligodendrocyte and axonal damage. Ann Neurol 2001;50(2):169–80. [PubMed: 11506399]

117. Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. Nat Med 2000;6(1):67–70. [PubMed: 10613826]

118. Sanchez-Gomez MV, et al. Caspase-dependent and caspase-independent oligodendrocyte death mediated by AMPA and kainate receptors. J Neurosci 2003;23(29):9519–28. [PubMed: 14573531]

119. Matute C, et al. Glutamate receptor-mediated toxicity in optic nerve oligodendrocytes. Proc Natl Acad Sci U S A 1997;94(16):8830–5. [PubMed: 9238063]

120. Smith T, et al. Autoimmune encephalomyelitis ameliorated by AMPA antagonists. Nat Med 2000;6(1):62–6. [PubMed: 10613825]

121. Alberdi E, et al. Activation of kainate receptors sensitizes oligodendrocytes to complement attack. J Neurosci 2006;26(12):3220–8. [PubMed: 16554473]

122. Matute C, et al. The link between excitotoxic oligodendroglial death and demyelinating diseases. Trends Neurosci 2001;24(4):224–30. [PubMed: 11250007]

123. Blakemore WF. Pattern of remyelination in the CNS. Nature 1974;249(457):577–8. [PubMed: 4834082]

124. Ludwin SK, Maitland M. Long-term remyelination fails to reconstitute normal thickness of central myelin sheaths. J Neurol Sci 1984;64(2):193–8. [PubMed: 6747666]

125. Stidworthy MF, et al. Quantifying the early stages of remyelination following cuprizone-induced demyelination. Brain Pathol 2003;13(3):329–39. [PubMed: 12946022]

126. Di Bello IC, et al. Generation of oligodendroglial progenitors in acute inflammatory demyelinating lesions of the rat brain stem is associated with demyelination rather than inflammation. J Neurocytol 1999;28(45):365–81. [PubMed: 10739577]

127. Levine JM, Reynolds R. Activation and proliferation of endogenous oligodendrocyte precursor cells during ethidium bromide-induced demyelination. Exp Neurol 1999;160(2):333–47. [PubMed: 10619551]

128. Miller DJ, Rodriguez M. Spontaneous central nervous system remyelination in strain A mice after infection with the Daniel's (DA) strain of Theiler's virus. Acta Neuropathol 1996;91(6):559–65. [PubMed: 8781653]

129. Reynolds R, Wilkin GP. Cellular reaction to an acute demyelinating/remyelinating lesion of the rat brain stem: localisation of GD3 ganglioside immunoreactivity. J Neurosci Res 1993;36(4):405–22. [PubMed: 8271315]

130. Jeffery ND, Blakemore WF. Locomotor deficits induced by experimental spinal cord demyelination are abolished by spontaneous remyelination. Brain 1997;120(Pt 1):27–37. [PubMed: 9055795]

131. Murray PD, et al. Spontaneous remyelination following extensive demyelination is associated with improved neurological function in a viral model of multiple sclerosis. Brain 2001;124(Pt 7):1403–16. [PubMed: 11408335]

132. Prineas JW, et al. Continual breakdown and regeneration of myelin in progressive multiple sclerosis plaques. Ann N Y Acad Sci 1984;436:11–32. [PubMed: 6598010]

133. Prineas JW, Connell F. Remyelination in multiple sclerosis. Ann Neurol 1979;5(1):22–31. [PubMed: 426466]

134. Lucchinetti CF, et al. Distinct patterns of multiple sclerosis pathology indicates heterogeneity on pathogenesis. Brain Pathol 1996;6(3):259–74. [PubMed: 8864283]

135. Prineas JW, et al. Multiple sclerosis: remyelination of nascent lesions. Ann Neurol 1993;33(2):137–51. [PubMed: 8434875]

136. Raine CS, Wu E. Multiple sclerosis: remyelination in acute lesions. J Neuropathol Exp Neurol 1993;52(3):199–204. [PubMed: 7684075]

137. Perier O, Gregoire A. Electron microscopic features of multiple sclerosis lesions. Brain 1965;88(5): 937–52. [PubMed: 5864468]

138. Patani R, et al. Remyelination can be extensive in multiple sclerosis despite a long disease course. Neuropathol Appl Neurobiol 2007;33(3):277–87. [PubMed: 17442065]

139. Carroll WM, Jennings AR. Early recruitment of oligodendrocyte precursors in CNS demyelination. Brain 1994;117(Pt 3):563–78. [PubMed: 8032866]

140. Gensert JM, Goldman JE. Endogenous progenitors remyelinate demyelinated axons in the adult CNS. Neuron 1997;19(1):197–203. [PubMed: 9247275]

141. Horner PJ, et al. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. J Neurosci 2000;20(6):2218–28. [PubMed: 10704497]

142. Watanabe M, Toyama Y, Nishiyama A. Differentiation of proliferated NG2-positive glial progenitor cells in a remyelinating lesion. J Neurosci Res 2002;69(6):826–36. [PubMed: 12205676]

143. Zhang SC, Ge B, Duncan ID. Adult brain retains the potential to generate oligodendroglial progenitors with extensive myelination capacity. Proc Natl Acad Sci U S A 1999;96(7):4089–94. [PubMed: 10097168]

144. Windrem MS, et al. Progenitor cells derived from the adult human subcortical white matter disperse and differentiate as oligodendrocytes within demyelinated lesions of the rat brain. J Neurosci Res 2002;69(6):966–75. [PubMed: 12205690]

145. Nishiyama A, et al. Co-localization of NG2 proteoglycan and PDGF alpha-receptor on O2A progenitor cells in the developing rat brain. J Neurosci Res 1996;43(3):299–314. [PubMed: 8714519]

146. Dawson MR, Levine JM, Reynolds R. NG2-expressing cells in the central nervous system: are they oligodendroglial progenitors? J Neurosci Res 2000;61(5):471–9. [PubMed: 10956416]

147. Dawson MR, et al. NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol Cell Neurosci 2003;24(2):476–88. [PubMed: 14572468]

148. Keirstead HS, Blakemore WF. Identification of post-mitotic oligodendrocytes incapable of remyelination within the demyelinated adult spinal cord. J Neuropathol Exp Neurol 1997;56(11): 1191–201. [PubMed: 9370229]

149. Targett MP, et al. Failure to achieve remyelination of demyelinated rat axons following transplantation of glial cells obtained from the adult human brain. Neuropathol Appl Neurobiol 1996;22(3):199–206. [PubMed: 8804021]

150. Rhodes KE, Raivich G, Fawcett JW. The injury response of oligodendrocyte precursor cells is induced by platelets, macrophages and inflammation-associated cytokines. Neuroscience 2006;140 (1):87–100. [PubMed: 16631314] Blood brain barrier breakdown is necessary to induce macrophage- or platelet-mediated activation of OPCs.

151. Fitch MT, Silver J. Activated macrophages and the blood-brain barrier: inflammation after CNS injury leads to increases in putative inhibitory molecules. Exp Neurol 1997;148(2):587–603. [PubMed: 9417835]

152. Hampton DW, et al. The responses of oligodendrocyte precursor cells, astrocytes and microglia to a cortical stab injury, in the brain. Neuroscience 2004;127(4):813–20. [PubMed: 15312894]
153. Wilson HC, Scolding NJ, Raine CS. Co-expression of PDGF alpha receptor and NG2 by oligodendrocyte precursors in human CNS and multiple sclerosis lesions. J Neuroimmunol 2006;176(12):162–73. [PubMed: 16753227]
154. Schonrock LM, et al. Identification of glial cell proliferation in early multiple sclerosis lesions. Neuropathol Appl Neurobiol 1998;24(4):320–30. [PubMed: 9775398]
155. Dumoulin FL, et al. Differential Regulation of Calcitonin Gene-related Peptide (CGRP) in Regenerating Rat Facial Nucleus and Dorsal Root Ganglion. Eur J Neurosci 1991;3(4):338–342. [PubMed: 12106191]
156. Raivich G, et al. Inhibition of posttraumatic microglial proliferation in a genetic model of macrophage colony-stimulating factor deficiency in the mouse. Eur J Neurosci 1994;6(10):1615–8. [PubMed: 7850025]
157. Raivich G, et al. Immune surveillance in the injured nervous system: T-lymphocytes invade the axotomized mouse facial motor nucleus and aggregate around sites of neuronal degeneration. J Neurosci 1998;18(15):5804–16. [PubMed: 9671668]
158. Raivich G, Gehrmann J, Kreutzberg GW. Increase of macrophage colony-stimulating factor and granulocyte-macrophage colony-stimulating factor receptors in the regenerating rat facial nucleus. J Neurosci Res 1991;30(4):682–6. [PubMed: 1664863]
159. Werner A, et al. Intercellular adhesion molecule-1 (ICAM-1) in the mouse facial motor nucleus after axonal injury and during regeneration. J Neurocytol 1998;27(4):219–32. [PubMed: 10640181]
160. Morioka T, Streit WJ. Expression of immunomolecules on microglial cells following neonatal sciatic nerve axotomy. J Neuroimmunol 1991;35(13):21–30. [PubMed: 1720134]
161. Kloss CU, et al. Integrin family of cell adhesion molecules in the injured brain: regulation and cellular localization in the normal and regenerating mouse facial motor nucleus. J Comp Neurol 1999;411(1):162–78. [PubMed: 10404114]
162. Jones LL, et al. Regulation of the cell adhesion molecule CD44 after nerve transection and direct trauma to the mouse brain. J Comp Neurol 2000;426(3):468–92. [PubMed: 10992250]
163. Redwine JM, Armstrong RC. In vivo proliferation of oligodendrocyte progenitors expressing PDGFalphaR during early remyelination. J Neurobiol 1998;37(3):413–28. [PubMed: 9828047]
164. Ong WY, Levine JM. A light and electron microscopic study of NG2 chondroitin sulfate proteoglycan-positive oligodendrocyte precursor cells in the normal and kainate-lesioned rat hippocampus. Neuroscience 1999;92(1):83–95. [PubMed: 10392832]
165. McTigue DM, Wei P, Stokes BT. Proliferation of NG2-positive cells and altered oligodendrocyte numbers in the contused rat spinal cord. J Neurosci 2001;21(10):3392–400. [PubMed: 11331369]
166. Levine JM, Enquist LW, Card JP. Reactions of oligodendrocyte precursor cells to alpha herpesvirus infection of the central nervous system. Glia 1998;23(4):316–28. [PubMed: 9671962]
167. Levine JM. Increased expression of the NG2 chondroitin-sulfate proteoglycan after brain injury. J Neurosci 1994;14(8):4716–30. [PubMed: 8046446]
168. Keirstead HS, Levine JM, Blakemore WF. Response of the oligodendrocyte progenitor cell population (defined by NG2 labelling) to demyelination of the adult spinal cord. Glia 1998;22(2):161–70. [PubMed: 9537836]
169. Watanabe M, Hadzic T, Nishiyama A. Transient upregulation of Nkx2.2 expression in oligodendrocyte lineage cells during remyelination. Glia 2004;46(3):311–22. [PubMed: 15048854]
170. Vana AC, et al. Platelet-derived growth factor promotes repair of chronically demyelinated white matter. J Neuropathol Exp Neurol 2007;66(11):975–88. [PubMed: 17984680]
171. Talbott JF, et al. Endogenous Nkx2.2+/Olig2+ oligodendrocyte precursor cells fail to remyelinate the demyelinated adult rat spinal cord in the absence of astrocytes. Exp Neurol 2005;192(1):11–24. [PubMed: 15698615]
172. Shen S, et al. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci 2008;11(9):1024–34. [PubMed: 19160500]
173. Fancy SP, Zhao C, Franklin RJ. Increased expression of Nkx2.2 and Olig2 identifies reactive oligodendrocyte progenitor cells responding to demyelination in the adult CNS. Mol Cell Neurosci 2004;27(3):247–54. [PubMed: 15519240]

174. Jones LL, et al. NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and is expressed by macrophages and oligodendrocyte progenitors. J Neurosci 2002;22(7):2792–803. [PubMed: 11923444]

175. Bakker DA, Ludwin SK. Blood-brain barrier permeability during Cuprizone-induced demyelination. Implications for the pathogenesis of immune-mediated demyelinating diseases. J Neurol Sci 1987;78(2):125–37. [PubMed: 3553434]

176. Woodruff RH, et al. Platelet-derived growth factor regulates oligodendrocyte progenitor numbers in adult CNS and their response following CNS demyelination. Mol Cell Neurosci 2004;25(2):252–62. [PubMed: 15019942]

177. Rhodes KE, Moon LD, Fawcett JW. Inhibiting cell proliferation during formation of the glial scar: effects on axon regeneration in the CNS. Neuroscience 2003;120(1):41–56. [PubMed: 12849739]

178. Ong WY, Garey LJ. A light and electron microscopic study of GluR4-positive cells in human cerebral cortex. Neurosci Lett 1996;210(2):107–10. [PubMed: 8783284]

179. Butt AM, et al. Synantocytes: new functions for novel NG2 expressing glia. J Neurocytol 2002;31 (67):551–65. [PubMed: 14501223]

180. Butt AM, et al. Cells expressing the NG2 antigen contact nodes of Ranvier in adult CNS white matter. Glia 1999;26(1):84–91. [PubMed: 10088675]

181. Bergles DE, et al. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. Nature 2000;405(6783):187–91. [PubMed: 10821275]

182. McQuaid S, et al. The effects of blood-brain barrier disruption on glial cell function in multiple sclerosis. Biochem Soc Trans 2009;37(Pt 1):329–31. [PubMed: 19143657]

183. Broman T. Blood-Brain Barrier Damage in Multiple Sclerosis Supravital Test-Observations. Acta Neurol Scand Suppl 1964;40:21–4. [PubMed: 14196025]

184. Gay D, Esiri M. Blood-brain barrier damage in acute multiple sclerosis plaques. An immunocytological study. Brain 1991;114(Pt 1B):557–72. [PubMed: 2004256]

185. Kwon EE, Prineas JW. Blood-brain barrier abnormalities in longstanding multiple sclerosis lesions. An immunohistochemical study. J Neuropathol Exp Neurol 1994;53(6):625–36. [PubMed: 7964903]

186. Claudio L, Raine CS, Brosnan CF. Evidence of persistent blood-brain barrier abnormalities in chronic-progressive multiple sclerosis. Acta Neuropathol 1995;90(3):228–38. [PubMed: 8525795]

187. Lassmann H, et al. Pathogenetic aspects of demyelinating lesions in chronic relapsing experimental allergic encephalomyelitis: possible interaction of cellular and humoral immune mechanisms. Prog Brain Res 1983;59:305–15. [PubMed: 6198681]

188. Engelhardt B, et al. E- and P-selectin are not involved in the recruitment of inflammatory cells across the blood-brain barrier in experimental autoimmune encephalomyelitis. Blood 1997;90(11):4459–72. [PubMed: 9373256]

189. Vos CM, et al. Blood-brain barrier alterations in both focal and diffuse abnormalities on postmortem MRI in multiple sclerosis. Neurobiol Dis 2005;20(3):953–60. [PubMed: 16039866]

190. Marik C, et al. Lesion genesis in a subset of patients with multiple sclerosis: a role for innate immunity? Brain 2007;130(Pt 11):2800–15. [PubMed: 17956913]

191. Kermode AG, et al. Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis. Pathogenetic and clinical implications. Brain 1990;113(Pt 5): 1477–89. [PubMed: 2245307]

192. Filippi M, et al. Magnetization transfer changes in the normal appearing white matter precede the appearance of enhancing lesions in patients with multiple sclerosis. Ann Neurol 1998;43(6):809–14. [PubMed: 9629851]

193. Furtado GC, et al. A novel model of demyelinating encephalomyelitis induced by monocytes and dendritic cells. J Immunol 2006;177(10):6871–9. [PubMed: 17082601]

194. Adams RA, et al. The fibrin-derived gamma377-395 peptide inhibits microglia activation and suppresses relapsing paralysis in central nervous system autoimmune disease. J Exp Med 2007;204 (3):571–82. [PubMed: 17339406]

195. Sobel RA, Mitchell ME. Fibronectin in multiple sclerosis lesions. Am J Pathol 1989;135(1):161–8. [PubMed: 2528301]

196. Sobel RA, et al. Vitronectin and integrin vitronectin receptor localization in multiple sclerosis lesions. J Neuropathol Exp Neurol 1995;54(2):202–13. [PubMed: 7533209]

197. Sobel RA. The extracellular matrix in multiple sclerosis lesions. J Neuropathol Exp Neurol 1998;57 (3):205–17. [PubMed: 9600212]

198. Milner R, et al. Fibronectin- and vitronectin-induced microglial activation and matrix metalloproteinase-9 expression is mediated by integrins alpha5beta1 and alphavbeta5. J Immunol 2007;178(12):8158–67. [PubMed: 17548654]

199. Larsen PH, et al. Matrix metalloproteinase-9 facilitates remyelination in part by processing the inhibitory NG2 proteoglycan. J Neurosci 2003;23(35):11127–35. [PubMed: 14657171]

200. Fidler PS, et al. Comparing astrocytic cell lines that are inhibitory or permissive for axon growth: the major axon-inhibitory proteoglycan is NG2. J Neurosci 1999;19(20):8778–88. [PubMed: 10516297]

201. Dou CL, Levine JM. Inhibition of neurite growth by the NG2 chondroitin sulfate proteoglycan. J Neurosci 1994;14(12):7616–28. [PubMed: 7996200]

202. Polito A, Reynolds R. NG2-expressing cells as oligodendrocyte progenitors in the normal and demyelinated adult central nervous system. J Anat 2005;207(6):707–16. [PubMed: 16367798]

203. Prineas JW, et al. Multiple sclerosis. Oligodendrocyte proliferation and differentiation in fresh lesions. Lab Invest 1989;61(5):489–503. [PubMed: 2811298]

204. Messersmith DJ, et al. Fibroblast growth factor 2 (FGF2) and FGF receptor expression in an experimental demyelinating disease with extensive remyelination. J Neurosci Res 2000;62(2):241–56. [PubMed: 11020217]

205. Hinks GL, Franklin RJ. Distinctive patterns of PDGF-A, FGF-2, IGF-I, and TGF-beta1 gene expression during remyelination of experimentally-induced spinal cord demyelination. Mol Cell Neurosci 1999;14(2):153–68. [PubMed: 10532806]

206. Crockett DP, et al. Number of oligodendrocyte progenitors recruited to the lesioned spinal cord is modulated by the levels of the cell cycle regulatory protein p27Kip-1. Glia 2005;49(2):301–8. [PubMed: 15472992]

207. Richardson WD, et al. A role for platelet-derived growth factor in normal gliogenesis in the central nervous system. Cell 1988;53(2):309–19. [PubMed: 2834067]

208. McKinnon RD, et al. FGF modulates the PDGF-driven pathway of oligodendrocyte development. Neuron 1990;5(5):603–14. [PubMed: 2171589]

209. McMorris FA, Dubois-Dalcq M. Insulin-like growth factor I promotes cell proliferation and oligodendroglial commitment in rat glial progenitor cells developing in vitro. J Neurosci Res 1988;21(24):199–209. [PubMed: 3216421]

210. Milner R, et al. Contrasting effects of mitogenic growth factors on oligodendrocyte precursor cell migration. Glia 1997;19(1):85–90. [PubMed: 8989571]

211. Milner R. Understanding the molecular basis of cell migration; implications for clinical therapy in multiple sclerosis. Clin Sci (Lond) 1997;92(2):113–22. [PubMed: 9059311]

212. Armstrong RC, Harvath L, Dubois-Dalcq ME. Type 1 astrocytes and oligodendrocyte-type 2 astrocyte glial progenitors migrate toward distinct molecules. J Neurosci Res 1990;27(3):400–7. [PubMed: 2097382]

213. Barres BA, et al. Cell death and control of cell survival in the oligodendrocyte lineage. Cell 1992;70 (1):31–46. [PubMed: 1623522]

214. Wolswijk G, Noble M. Cooperation between PDGF and FGF converts slowly dividing O-2Aadult progenitor cells to rapidly dividing cells with characteristics of O-2Aperinatal progenitor cells. J Cell Biol 1992;118(4):889–900. [PubMed: 1323567]

215. Engel U, Wolswijk G. Oligodendrocyte-type-2 astrocyte (O-2A) progenitor cells derived from adult rat spinal cord: in vitro characteristics and response to PDGF, bFGF and NT-3. Glia 1996;16(1): 16–26. [PubMed: 8787770]

216. Zhou YX, et al. Retroviral lineage analysis of fibroblast growth factor receptor signaling in FGF2 inhibition of oligodendrocyte progenitor differentiation. Glia 2006;54(6):578–90. [PubMed: 16921523]

217. Murtie JC, et al. PDGF and FGF2 pathways regulate distinct oligodendrocyte lineage responses in experimental demyelination with spontaneous remyelination. Neurobiol Dis 2005;19(12):171–82. [PubMed: 15837572]

218. Armstrong RC, et al. Absence of fibroblast growth factor 2 promotes oligodendroglial repopulation of demyelinated white matter. J Neurosci 2002;22(19):8574–85. [PubMed: 12351731]

219. Mason JL, et al. Insulin-like growth factor (IGF) signaling through type 1 IGF receptor plays an important role in remyelination. J Neurosci 2003;23(20):7710–8. [PubMed: 12930811]

220. Ye P, D'Ercole AJ. Insulin-like growth factor I protects oligodendrocytes from tumor necrosis factor-alpha-induced injury. Endocrinology 1999;140(7):3063–72. [PubMed: 10385398]

221. Mason JL, et al. Insulin-like growth factor-1 inhibits mature oligodendrocyte apoptosis during primary demyelination. J Neurosci 2000;20(15):5703–8. [PubMed: 10908609]

222. Barres BA, et al. Multiple extracellular signals are required for long-term oligodendrocyte survival. Development 1993;118(1):283–95. [PubMed: 8375338]

223. Mozell RL, McMorris FA. Insulin-like growth factor I stimulates oligodendrocyte development and myelination in rat brain aggregate cultures. J Neurosci Res 1991;30(2):382–90. [PubMed: 1665869]

224. Mason JL, Goldman JE. A2B5+ and O4+ Cycling progenitors in the adult forebrain white matter respond differentially to PDGF-AA, FGF-2, and IGF-1. Mol Cell Neurosci 2002;20(1):30–42. [PubMed: 12056838]

225. Yao DL, et al. Cryogenic spinal cord injury induces astrocytic gene expression of insulin-like growth factor I and insulin-like growth factor binding protein 2 during myelin regeneration. J Neurosci Res 1995;40(5):647–59. [PubMed: 7541476]

226. Mason JL, et al. Mature oligodendrocyte apoptosis precedes IGF-1 production and oligodendrocyte progenitor accumulation and differentiation during demyelination/remyelination. J Neurosci Res 2000;61(3):251–62. [PubMed: 10900072]

227. Liu X, et al. Astrocytes express insulin-like growth factor-I (IGF-I) and its binding protein, IGFBP-2, during demyelination induced by experimental autoimmune encephalomyelitis. Mol Cell Neurosci 1994;5(5):418–30. [PubMed: 7529631]

228. Ludwin SK. Chronic demyelination inhibits remyelination in the central nervous system. An analysis of contributing factors. Lab Invest 1980;43(4):382–7. [PubMed: 7442125]

229. Graca DL, Blakemore WF. Delayed remyelination in rat spinal cord following ethidium bromide injection. Neuropathol Appl Neurobiol 1986;12(6):593–605. [PubMed: 3561693]

230. Njenga MK, et al. Absence of spontaneous central nervous system remyelination in class II-deficient mice infected with Theiler's virus. J Neuropathol Exp Neurol 1999;58(1):78–91. [PubMed: 10068316]

231. Mason JL, et al. Interleukin-1beta promotes repair of the CNS. J Neurosci 2001;21(18):7046–52. [PubMed: 11549714]

232. Li WW, et al. Minocycline-mediated inhibition of microglia activation impairs oligodendrocyte progenitor cell responses and remyelination in a non-immune model of demyelination. J Neuroimmunol 2005;158(12):58–66. [PubMed: 15589038]

233. Kotter MR, et al. Macrophage-depletion induced impairment of experimental CNS remyelination is associated with a reduced oligodendrocyte progenitor cell response and altered growth factor expression. Neurobiol Dis 2005;18(1):166–75. [PubMed: 15649707]

234. Kotter MR, et al. Macrophage depletion impairs oligodendrocyte remyelination following lysolecithin-induced demyelination. Glia 2001;35(3):204–12. [PubMed: 11494411]

235. Bieber AJ, Kerr S, Rodriguez M. Efficient central nervous system remyelination requires T cells. Ann Neurol 2003;53(5):680–4. [PubMed: 12731006]

236. Arnett HA, et al. Functional genomic analysis of remyelination reveals importance of inflammation in oligodendrocyte regeneration. J Neurosci 2003;23(30):9824–32. [PubMed: 14586011]

237. Arnett HA, et al. TNF alpha promotes proliferation of oligodendrocyte progenitors and remyelination. Nat Neurosci 2001;4(11):1116–22. [PubMed: 11600888]

238. Lucchinetti C, et al. A quantitative analysis of oligodendrocytes in multiple sclerosis lesions. A study of 113 cases. Brain 1999;122(Pt 12):2279–95. [PubMed: 10581222]

239. Kumar S, et al. Combination of growth factors enhances remyelination in a cuprizone-induced demyelination mouse model. Neurochem Res 2007;32(45):783–97. [PubMed: 17186374]

240. Biancotti JC, Kumar S, de Vellis J. Activation of inflammatory response by a combination of growth factors in cuprizone-induced demyelinated brain leads to myelin repair. Neurochem Res 2008;33 (12):2615–28. [PubMed: 18661234]

241. Plant SR, et al. Lymphotoxin beta receptor (Lt betaR): dual roles in demyelination and remyelination and successful therapeutic intervention using Lt betaR-Ig protein. J Neurosci 2007;27(28):7429–37. [PubMed: 17626203]

242. Syed YA, et al. Inhibition of oligodendrocyte precursor cell differentiation by myelin-associated proteins. Neurosurg Focus 2008;24(34):E5. [PubMed: 18341408]

243. Miller RH. Contact with central nervous system myelin inhibits oligodendrocyte progenitor maturation. Dev Biol 1999;216(1):359–68. [PubMed: 10588885]

244. Kotter MR, et al. Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation. J Neurosci 2006;26(1):328–32. [PubMed: 16399703] Myelin debris inhibits remyelination by preventing OPCs from differentiating into myelinating oligodendrocytes. The role of phagocytic macrophages in removing myelin debris following demyelination is therefore critical to successful remyelination

245. Foote AK, Blakemore WF. Inflammation stimulates remyelination in areas of chronic demyelination. Brain 2005;128(Pt 3):528–39. [PubMed: 15699059] Induction of acute inflammation in demyelinated, but OPC repopulated areas resulted in remyelination.

246. O'Leary MT, Blakemore WF. Oligodendrocyte precursors survive poorly and do not migrate following transplantation into the normal adult central nervous system. J Neurosci Res 1997;48(2): 159–67. [PubMed: 9130144]

247. Chari DM, Crang AJ, Blakemore WF. Decline in rate of colonization of oligodendrocyte progenitor cell (OPC)-depleted tissue by adult OPCs with age. J Neuropathol Exp Neurol 2003;62(9):908–16. [PubMed: 14533780]

248. Chari DM, Blakemore WF. Efficient recolonisation of progenitor-depleted areas of the CNS by adult oligodendrocyte progenitor cells. Glia 2002;37(4):307–13. [PubMed: 11870870]

249. Blakemore WF, et al. Modelling large areas of demyelination in the rat reveals the potential and possible limitations of transplanted glial cells for remyelination in the CNS. Glia 2002;38(2):155–68. [PubMed: 11948809] Delaying the time of interaction between OPCs and demyelinated axons limits the remyelination potential of transplanted OPCs.

250. Sato M, et al. Direct binding of Toll-like receptor 2 to zymosan, and zymosan-induced NF-kappa B activation and TNF-alpha secretion are down-regulated by lung collectin surfactant protein A. J Immunol 2003;171(1):417–25. [PubMed: 12817025]

251. Setzu A, et al. Inflammation stimulates myelination by transplanted oligodendrocyte precursor cells. Glia 2006;54(4):297–303. [PubMed: 16856149]

252. Williams A, et al. Semaphorin 3A and 3F: key players in myelin repair in multiple sclerosis? Brain 2007;130(Pt 10):2554–65. [PubMed: 17855378]

253. Franklin RJ, Crang AJ, Blakemore WF. Transplanted type-1 astrocytes facilitate repair of demyelinating lesions by host oligodendrocytes in adult rat spinal cord. J Neurocytol 1991;20(5): 420–30. [PubMed: 1869880]

254. Albrecht PJ, et al. Astrocytes produce CNTF during the remyelination phase of viral-induced spinal cord demyelination to stimulate FGF-2 production. Neurobiol Dis 2003;13(2):89–101. [PubMed: 12828933]

255. Blakemore WF. Regeneration and repair in multiple sclerosis: the view of experimental pathology. J Neurol Sci 2008;265(12):1–4. [PubMed: 17459413]

256. Franklin RJ, Ffrench-Constant C. Remyelination in the CNS: from biology to therapy. Nat Rev Neurosci 2008;9(11):839–55. [PubMed: 18931697]

257. Windrem MS, et al. Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. Nat Med 2004;10(1):93–7. [PubMed: 14702638]

258. Groves AK, et al. Repair of demyelinated lesions by transplantation of purified O-2A progenitor cells. Nature 1993;362(6419):453–5. [PubMed: 8464477]

259. Honmou O, et al. Restoration of normal conduction properties in demyelinated spinal cord axons in the adult rat by transplantation of exogenous Schwann cells. J Neurosci 1996;16(10):3199–208. [PubMed: 8627358]

260. Blakemore WF, Crang AJ. The use of cultured autologous Schwann cells to remyelinate areas of persistent demyelination in the central nervous system. J Neurol Sci 1985;70(2):207–23. [PubMed: 4056820]

261. Blakemore WF. Limited remyelination of CNS axons by Schwann cells transplanted into the sub-arachnoid space. J Neurol Sci 1984;64(3):265–76. [PubMed: 6470739]

262. Hammang JP, Archer DR, Duncan ID. Myelination following transplantation of EGF-responsive neural stem cells into a myelin-deficient environment. Exp Neurol 1997;147(1):84–95. [PubMed: 9294405]

263. Brustle O, et al. Embryonic stem cell-derived glial precursors: a source of myelinating transplants. Science 1999;285(5428):754–6. [PubMed: 10427001]

264. Baron-Van Evercooren, A.; B, W. Remyelination through engraftment in Myelin biology and disorders. Lazzarini, R., editor. Elsevier Science; 2004. p. 143-72.

265. Clarke D, Frisen J. Differentiation potential of adult stem cells. Curr Opin Genet Dev 2001;11(5): 575–80. [PubMed: 11532401]

266. Pluchino S, et al. Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. Nature 2003;422(6933):688–94. [PubMed: 12700753]

267. Teng YD, et al. Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proc Natl Acad Sci U S A 2002;99(5):3024–9. [PubMed: 11867737]

268. Ben-Hur T, et al. Transplanted multipotential neural precursor cells migrate into the inflamed white matter in response to experimental autoimmune encephalomyelitis. Glia 2003;41(1):73–80. [PubMed: 12465047]

269. Pluchino S, et al. Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. Nature 2005;436(7048):266–71. [PubMed: 16015332]

270. Einstein O, et al. Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression. Ann Neurol 2007;61(3):209–18. [PubMed: 17187374]

271. Chandran S, et al. Differential generation of oligodendrocytes from human and rodent embryonic spinal cord neural precursors. Glia 2004;47(4):314–24. [PubMed: 15293229]

272. Nistor GI, et al. Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. Glia 2005;49(3):385–96. [PubMed: 15538751]

273. Mi S, et al. LINGO-1 negatively regulates myelination by oligodendrocytes. Nat Neurosci 2005;8 (6):745–51. [PubMed: 15895088]

274. Mi S, et al. LINGO-1 is a component of the Nogo-66 receptor/p75 signaling complex. Nat Neurosci 2004;7(3):221–8. [PubMed: 14966521]

275. Lee X, et al. NGF regulates the expression of axonal LINGO-1 to inhibit oligodendrocyte differentiation and myelination. J Neurosci 2007;27(1):220–5. [PubMed: 17202489]

276. Mi S, et al. Promotion of central nervous system remyelination by induced differentiation of oligodendrocyte precursor cells. Ann Neurol 2009;65(3):304–15. [PubMed: 19334062] LINGO-1 antagonists promote OPC differentiation and myelination in vitro and accelerate remyelination after lysophosphatidylcholine- or cuprizone-induced demyelination.

277. Mi S, et al. LINGO-1 antagonist promotes spinal cord remyelination and axonal integrity in MOG-induced experimental autoimmune encephalomyelitis. Nat Med 2007;13(10):1228–33. [PubMed: 17906634]

278. Warrington AE, et al. A recombinant human IgM promotes myelin repair after a single, very low dose. J Neurosci Res 2007;85(5):967–76. [PubMed: 17304578]

279. Warrington AE, et al. Human monoclonal antibodies reactive to oligodendrocytes promote remyelination in a model of multiple sclerosis. Proc Natl Acad Sci U S A 2000;97(12):6820–5. [PubMed: 10841576]

280. Pavelko KD, van Engelen BG, Rodriguez M. Acceleration in the rate of CNS remyelination in lysolecithin-induced demyelination. J Neurosci 1998;18(7):2498–505. [PubMed: 9502810]

281. Miller DJ, et al. Monoclonal autoantibodies promote central nervous system repair in an animal model of multiple sclerosis. J Neurosci 1994;14(10):6230–8. [PubMed: 7931575]

282. Asakura K, et al. A monoclonal autoantibody which promotes central nervous system remyelination is highly polyreactive to multiple known and novel antigens. J Neuroimmunol 1996;65(1):11–9. [PubMed: 8642059]

283. Asakura K, et al. Monoclonal autoantibody SCH94.03, which promotes central nervous system remyelination, recognizes an antigen on the surface of oligodendrocytes. J Neurosci Res 1996;43 (3):273–281. [PubMed: 8714516]

284. Paz Soldan MM. Remyelination-promoting antibodies activate distinct Ca2+ influx pathways in astrocytes and oligodendrocytes: relationship to the mechanism of myelin repair. Mol Cell Neurosci 2003;22(1):14–24. [PubMed: 12595235]

285. Confavreux C, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med 1998;339(5):285–91. [PubMed: 9682040]

286. Gregg C, et al. White matter plasticity and enhanced remyelination in the maternal CNS. J Neurosci 2007;27(8):1812–23. [PubMed: 17314279]

287. Franco PG, et al. Thyroid hormones promote differentiation of oligodendrocyte progenitor cells and improve remyelination after cuprizone-induced demyelination. Exp Neurol 2008;212(2):458–67. [PubMed: 18572165]

288. Fernandez M, et al. Thyroid hormone administration enhances remyelination in chronic demyelinating inflammatory disease. Proc Natl Acad Sci U S A 2004;101(46):16363–8. [PubMed: 15534218]

289. Armstrong RC, et al. Endogenous cell repair of chronic demyelination. J Neuropathol Exp Neurol 2006;65(3):245–56. [PubMed: 16651886]