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Review

Multiple sclerosis - remyelination failure as a cause of disease progression

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Summary. Multiple sclerosis (MS) is the most frequent demyelinating disease of the central nervous system (CNS) that affects worldwide about 2.5 million people. The morphological correlates of the disease are multiple lesions in brain and spinal cord which are characterized by demyelination, inflammation, gliosis and axonal damage. The underlying cause for the permanent neurological deficits in MS patients is axonal loss. Demyelinated axons are prone to damage due to the lack of trophic support by myelin sheaths and oligodendrocytes, as well as the increased vulnerability to immune mediated attacks. Remyelination occurs, but especially in chronic lesions is frequently limited to a small rim at the lesion border. Current treatment strategies are based on anti-inflammatory or immunomodulatory drugs and have the potential to reduce the numbers of newly evolving lesions, although as yet no treatment strategy exists to influence or prevent the progressive disease phase. Therefore, the development of neuroprotective treatment options, such as the promotion of endogenous remyelination is an attractive strategy. A prerequisite for the development of such new treatments is the understanding of the mechanisms leading to remyelination and the reasons for insufficient endogenous repair in chronic MS. This review will therefore provide an overview of the current concepts regarding remyelination in the rodent and human CNS. We will also summarize a selected number of inhibitory pathways and non-disease related factors which may contribute to remyelination failure in chronic MS.

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Multiple sclerosis

Multiple sclerosis (MS), defined as an inflammatory demyelinating disease of the central nervous system (CNS) is the most frequent demyelinating disease in young adults, usually starting between 20-40 years of age (Weinshenker, 1998). MS is characterized by inflammation, progressive immune mediated demyelination and gliosis, as well as axonal injury and loss. In physiological conditions myelin, the insulating material ensheating CNS axons, conducts action potentials, enabling the communication between neurons (Baumann and Pham-Dinh, 2001). In MS demyelination and cell death of mature oligodendrocytes, the myelin maintaining cells of the CNS affect the ability of axons to conduct electrical signals, which results in the reduction or complete loss of action potential transmission. Although these demyelinated lesions, also called plaques, can develop everywhere in the CNS, they have a preference for brain stem, spinal cord, optic nerve and periventricular areas (Noseworthy et al., 2000). Demyelinated lesions undergo either remyelination or end up in chronic scar formation accompanied by fibrillar astrogliosis. The disease in the majority of patients with MS starts with a relapsing (demyelinating and inflammatory episodes) and remitting disease course resulting in permanent neurological deficits in the secondary progressive disease phase, whereas a primary progressive disease course is only observed in a small proportion of patients (Debouverie et al., 2008). Remission of disease symptoms in the initial disease stages most likely represents a combination of resolution of inflammation, axonal plasticity and remyelination,

whereas the permanent neurological deficits in the progressive disease phase are caused by axonal loss rather than by demyelination. MS is considered as a T cell mediated autoimmune disease; however the pathogenesis of the disease is only partly understood. Animal models, especially experimental autoimmune encephalomyelitis (EAE) which shares some similarities with the human disease, as well as genetic evidence, point to a central role for the immune system in MS (Zamvil and Steinman, 1990; Ffrench-Constant, 1994). Autoreactive T cells are considered as major players in the early stages of lesion formation. Most likely, other factors (e.g. cells of the myeloid lineage, antibodies/ complement, CNS intrinsic processes) contribute to tissue pathology (McFarland and Martin, 2007). Current treatment strategies are based on anti-inflammatory and immunomodulatory agents modulating the formation of new inflammatory lesions. However, none of these therapies can significantly influence the progressive disease phase. Therefore, the development of neuroprotective agents promoting tissue repair and remyelination represent an attractive new treatment strategy.

Oligodendrocyte development and CNS myelination

Although the stages of oligodendrocyte development are well characterized, the factors contributing to oligodendrocyte differentiation and subsequent myelination are still not fully understood. Mature oligodendrocytes are glial cells with highly ramified processes that form membrane sheets following the generation of oligodendrocyte-axon contact. The compaction of these primary membrane wraps results in the generation of the multilamellar insulating myelin sheath (Bauer et al., 2009). The myelin sheaths form so called internodes which are separated by Nodes of Ranvier where action potentials are generated (Bauer et al., 2009). The internodes are flanked by paranodes, the region next to the Nodes of Ranvier. A small region beside the paranode where the potassium channels cluster is called the juxtaparanode (Girault and Peles, 2002). During development axons are ensheathed by oligodendroglial precursor cells. OPCs are generated in different CNS regions during embryogenesis. In the spinal cord oligodendrocyte precursor cells (OPCs) originate in the subventricular zone of the neural tube in late embryonic development (Fu et al., 2002; Cai et al., 2005; Vallstedt et al., 2005; Kessaris et al., 2006). This takes place in response to signal cascades induced by the ventral midline signal Sonic hedgehog (Shh) (Noll and Miller, 1993; Pringle et al., 1998). The floor plate signal Shh controls the specification of precursors in the ventral spinal cord by inducing expression of transcription factors such as Nkx6.6 and Olig2 required for oligodendrocyte development (Zhou et al., 2000; Lu et al., 2002; Zhou and Anderson, 2002). OPCs start to migrate from the subventricular zone outwards along the periphery of the tube and then along its length in order to populate the spinal cord. A second, potentially Shh-independent oligodendrocyte population is generated from the dorsoventral midline late during embryogenesis; this oligodendroglial population accounts for approximately 5 % of the oligodendrocytes (Cai et al., 2005; Fogarty et al., 2005; Vallstedt et al., 2005). In the rodent brain OPCs are generated in three waves. The first OPCs originate from the medial ganglionic eminence and anterior entopeduncular area of the ventral forebrain and populate telencephalon and cortex. The second wave arises from the lateral and caudal ganglionic eminences, whereas the third wave is generated in postnatal cortex (Kessaris et al., 2006). Although these different OPC populations in principle can compensate and replace each other, the first wave is almost completely eliminated in the adult CNS. The newly generated OPCs start to spread and actively initiate axon contact in order to start differentiation and myelination of axons (Miller, 2002). Migration of OPCs is tightly controlled by secreted molecules such as growth factors (e.g. FGF, PDGF), guidance molecules (netrins, semaphorins) and chemokines (e.g. CXCL1), as well as by contact mediated mechanisms such as extracellular matrix molecules. The tight control of these extrinsic and intrinsic factors is a prerequisite for successful differentiation of oligodendroglial lineage cells and myelination.

Remyelination in demyelinating animal models and MS

Remyelination is histologically characterized by shortened internodes and decreased myelin thickness resulting in an increased g ratio (= axon diameter/axon diameter + myelin sheath diameter). A prerequisite for remyelination is the presence of axons, OPCs and the correct interaction of extrinsic signalling pathways, resulting in activation of a complex intrinsic differentiation program. The majority of OPCs generated during development differentiate into mature myelinating and myelin maintaining oligodendrocytes. However, a small population of immature OPCs remains as progenitors that respond to demyelination by proliferation, migration and differentiation and formation of new myelin sheaths (Horner et al., 2000; Franklin, 2002; Dawson et al., 2003). Antibodies used to identify cells at this progenitor stage usually include NKX2.2, PDGFRα, Olig1 and 2, as well as NG2 and A2B5, whereas mature myelinating oligodendrocytes can be visualized using MBP, PLP, CNPase, MOG or NogoA antibodies (Wolswijk, 2000; Kuhlmann et al., 2007). In rodent animal models remyelination is an efficient and fast endogenous repair process which occurs independently of the mechanism by which demyelination is achieved (toxic demyelination by ethidium bromide, lysolecithin or cuprizone, virally, autoimmune or traumatically induced demyelination) (Woodruff and Franklin, 1999; Matsushima and Morell, 2001; Smith and Jeffery, 2006; Blakemore and Franklin,

2008; Lasiene et al., 2008) (for review see (Franklin, 2002)). Remyelination enhances axonal survival and restores neurological functions at least in animal models (Irvine and Blakemore, 2006; Duncan et al., 2009). In MS lesions the situation is more complex. Whereas remyelination is a frequent phenomenon in early MS lesions, the majority of chronic MS lesions is characterized by limited remyelination confined to a small rim at the lesion borders (Goldschmidt et al., 2009). In progressive MS only about 20% of the lesions display a significant remyelination (Patrikios et al., 2006; Patani et al., 2007; Goldschmidt et al., 2009). The extent of remyelination may be influenced by the anatomical localization, size of the lesions, disease course or patient dependent factors (Patrikios et al., 2006; Patani et al., 2007; Goldschmidt et al., 2009; Bramow et al., 2010). Periventricular and cerebellar lesions for example display less remyelination than subcortical lesions (Patrikios et al., 2006; Goldschmidt et al., 2009). In cortical MS lesions, remyelination is more extensive compared to white matter lesions (Albert et al., 2007), a phenomenon that has been confirmed in animal studies in which focal cortical lesions displayed faster resolution of inflammation, as well as remyelination, compared to white matter lesions (Merkler et al., 2006). The molecular mechanisms responsible for the varying extent of remyelination in different CNS regions are unknown, but potential explanations include intrinsic differences between OPCs from distinct anatomical localizations or differences in the surrounding microenvironment. Furthermore, neuronal activity which promotes myelination (Ishibashi et al., 2006) may be more likely to be intact close to the neuronal cell body e.g. in subcortical lesions.

Proliferation, migration and differentiation of OPCs in demyelinating animal models and MS

Proliferation, migration and differentiation of OPCs are required for successful remyelination. In demyelinating animal models, and even in the healthy rodent CNS, relatively high numbers of proliferating oligodendroglial progenitor cells can be identified by BrdU labelling or immunohistochemistry (Sim et al., 2002; Dimou et al., 2008). This is in contrast to MS lesions where the vast majority of proliferating cells are astrocytes or microglia/macrophages and only few proliferating Olig2-positive oligodendroglial lineage cells are observed (Kuhlmann et al., 2008; Schonrock et al., 1998). However, this does not exclude that earlier lineage cells, e.g. neural stem cells in the subventricular zone have the potential to proliferate and migrate (Nait-Oumesmar et al., 2007). In MS lesions an accumulation of OPCs in the periplaque white matter is observed, suggesting that demyelination promotes the migration of OPCs towards the lesion (Kuhlmann et al., 2008). During development the migration of OPCs is regulated by a broad variety of signals that can be divided into short and long range migration cues. Short range cues are for example extracellular matrix molecules (ECM) such as laminin, fibronectin or vitronectin which promote OPCs motility, in contrast to tenascin-C that acts as a migration inhibitor (for review see (Jarjour and Kennedy, 2004)). In MS lesions changes of the ECM have been reported; tenascin-C expression for example is reduced in acute lesions whereas chronic MS lesions display tenascin-C levels comparable to the normal appearing white matter (Gutowski et al., 1999). In active demyelinating lesions an upregulation of the migration promoting factors fibronectin and vitronectin within the parenchyma has been reported (Sobel and Mitchell, 1989; Esiri and Morris, 1991; Sobel et al., 1995). The most important long range cues are netrins and semaphorins. Netrin-1 is expressed during development in the CNS, whereas its receptors (DCC, Unc5H1) are located on OPCs (Sugimoto et al., 2001; Spassky et al., 2002; Jarjour et al., 2003). The lack of either netrin-1 or DCC results in an impaired OPC migration during development in vivo (Jarjour et al., 2003). Semaphorins are a family of secreted transmembrane proteins. Class 3 semaphorins have mostly a repellent function and act via a receptor complex consisting of plexins and neuropillins, and the latter have been detected on oligodendrocytes (Sugimoto et al., 2001). The repulsive factor semaphorin 3A, as well as the attractive family member semaphorin 3F, are expressed by astrocytes and microglial cells in active demyelinating but not in chronic MS lesions whereas neuropillin 1 and 2 mRNAs are found in a subset of oligodendroglial lineage cells in the periplaque white matter by in situ hybridization (Williams et al., 2007). These data indicate a dynamic regulation of short and long range guidance molecules in MS plaques with a migration-promoting environment in active demyelinating lesions that shifts to a less favourable environment with lesion chronicity.

Chronically demyelinated MS lesions are almost completely depleted of mature oligodendrocytes, whereas OPCs can - although in somewhat reduced numbers - be detected, suggesting that a differentiation block of OPCs contributes to remyelination failure in chronic MS lesions (Wolswijk, 1998, 2002; Chang et al., 2002; Kuhlmann et al., 2008). The mechanisms responsible for impaired differentiation of oligodendrocytes are only incompletely understood. In recent years a number of inhibitory signaling cascades (Notch-Jagged-pathway, BMPs, Wnt, Lingo1, myelin debris, PSA-NCAM) as well as non-disease related factors (sex, age and epigenetic modifications) have been described, which may contribute in a non-exclusive way to limited remyelination in MS. A selected number of these inhibitory signalling cascades and non-disease related factors reflecting different aspects of the complex network regulating remyelination are discussed below.

Inhibitory signaling cascades

Notch - Jagged signaling

Notch1 belongs to a family of transmembrane receptors that interact with membrane bound ligands

such as Delta, Jagged or contactin. Binding of Noch1 to its ligand Jagged1 results in the activation of Hes5, a transcription factor that inhibits oligodendroglial differentiation (Fig. 1) (Artavanis-Tsakonas et al., 1999; Pierfelice et al., 2011). Within and around MS lesions lacking remyelination an upregulation of Jagged1 was observed, whereas oligodendrocytes expressed Notch1 and Hes5. In contrast, no Jagged1 expression was found in remyelinated lesions, suggesting that the Jagged-Notch1-pathway may contribute to remyelination failure in MS (John et al., 2002). A similar expression pattern of Notch1 and its ligand was observed in demyelinating animal models, but targeted deletion of Notch1 in PLP expressing oligodendroglial lineage cells had no effect on remyelination (Stidworthy et al., 2004). However, Notch1 inactivation in earlier stages of oligodendrocyte differentiation indicated by Olig1 expression resulted in accelerated remyelination (Zhang et al., 2009). *In vitro* experiments confirmed this remyelination promoting effect of Notch inhibition, demonstrating that inclusion of early oligodendrocytes as targets for Notch1 inactivation is a prerequisite for affecting remyelination. Interestingly, Notch1 signaling not only has an inhibitory effect on oligodendroglial differentiation, but binding of Notch1 to axonal contactin also promotes oligodendroglial differentiation and myelination via transduction of signals through the NICD/Deltex complex (Fig. 1) (Hu et al., 2003; D'Souza et al., 2008). In chronic MS lesions the translocation of NCID to the nucleus is impaired in OPCs; potentially by interaction with TIP30, a known inhibitor of NICD transport to the nucleus (Nakahara et al., 2009). These combined data gained from studies of human MS tissues and transgenic animal approaches suggest that maybe not only the reactivation of the differentiation inhibiting canonical Notch-Jagged pathway but also blocking of the differentiation promoting non-canonical Notch signaling contributes to remyelination failure in MS lesions.

PSA-NCAM: A negative regulator of oligodendrocyte-axon contact

Myelination depends on precise interaction of axonal and oligodendroglial signals. One signalling molecule contributing to this process is the neural cell adhesion molecule (NCAM), a member of the immunoglobulin superfamily that plays a role in a number of developmental processes, such as axonal pathfinding and fasciculation, nerve branching and cell migration as well as synaptic plasticity (Doherty et al., 1990; Zhang et al., 1992; Wang et al., 1994, 1996). Splicing leads to several isoforms which are all capable of bearing polysialic acid (PSA) moieties. PSA-NCAM is an extensively glycosylated molecule thereby preventing cell-cell interactions (Doherty et al., 1990; Kiss et al., 1994; Fannon and Colman, 1996). In the adult CNS PSA-NCAM is absent with the exception of brain areas that undergo neurogenesis e.g. the dentate gyrus, olfactory bulb and the hypothalamus-pituitary system (Seki and Arai, 1991, 1993; Rougon, 1993; Theodosis et al., 1999). *In vitro* and during development, disappearance of PSA-NCAM precedes initiation of myelination (Charles et al., 2000). Masking or removal of PSA-NCAM from axonal surfaces by antibodies or enzymatic cleavage promotes myelination *in vitro* and *in vivo* (Charles et al., 2000, 2002). In demyelinated MS lesions PSA-NCAM is re-expressed on axons in contrast to shadow plaques, periplaque white matter or white matter from patients

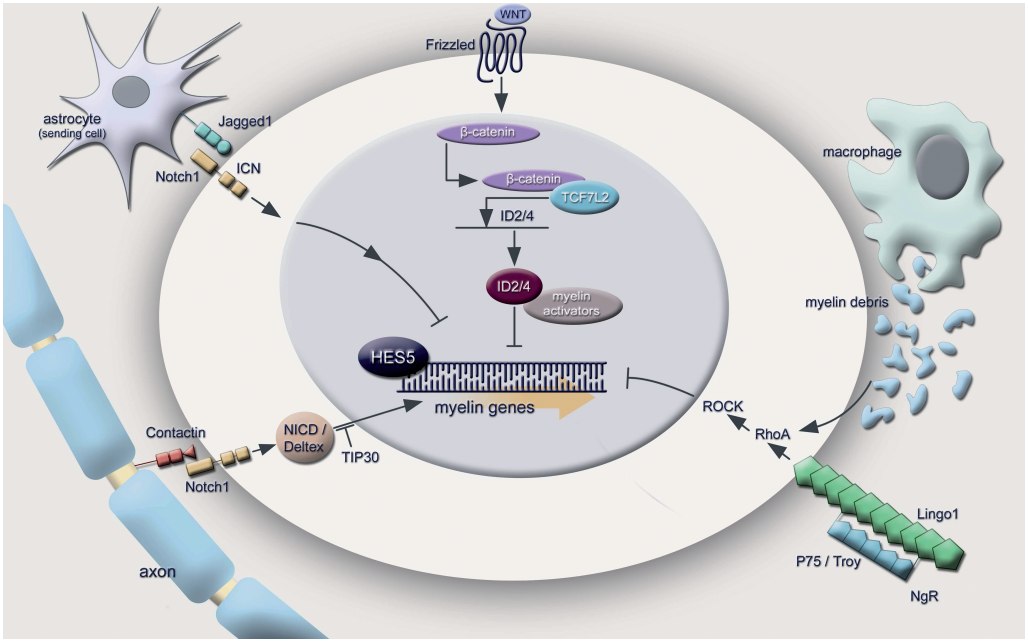

Fig. 1. Potential inhibitory pathways in MS. Myelin debris as well as astrocytes may contribute to remyelination failure by activation of inhibitory pathways. Astrocytes express Jagged1 that binds its receptor Notch1 resulting in the activation of myelin inhibitors such as Hes5. Myelin debris activates similar as Lingo1 the RhoA-ROCK cascade. ß-cateinin is stabilized after binding of Wnt to its receptor and transported into the nucleus. Binding of ß-catenin to TCF7L2 promotes the expression of myelin gene inhibitors such as Id2 and 4. Paranodal contactin binds Notch1 as well and promotes oligodendroglial differentiation via the translocation of the NICD/Deltex complex into the nucleus. However, in MS lesions the expression of TIP30 has been observed, a known inhibitor of this transport.

without neurological diseases, suggesting that it thereby contributes to remyelination failure (Charles et al., 2002). However, PSA-NCAM is not only expressed on axons but also for example on oligodendroglial lineage cells and neural progenitors. After demyelination PSA-NCAM expressing progenitor cells located either in the rodent subventricular zone or transplanted into demyelinating lesions proliferate, migrate and remyelinate demyelinated axons (Keirstead et al., 1999; Nait-Oumesmar et al., 1999); and *in vitro* experiments confirm that expression of PSA-NCAM in OPCs promotes migration (Wang et al., 1996). Comparable to the findings in rodents, PSA-NCAM-positive progenitors are also detected in the human SVZ (Nait-Oumesmar et al., 2007). Interestingly, increased expression of PSA-NCAM in Schwann cells transplanted into demyelinated lesions even enhances their migration and remyelination capabilities (Franceschini et al., 2004; Lavdas et al., 2006; Bachelin et al., 2010). These data suggest that PSA-NCAM might have a dual function in MS lesions depending on the cellular localization. Axonal PSA-NCAM may contribute to remyelination failure by preventing the interaction of axons and OPCs; on the other hand PSA-NCAM on neural progenitors and oligodendroglial cells may promote migration and even remyelination. Further studies are required to understand the exact function of PSA-NCAM in MS lesions.

Myelin debris

A fundamental difference between myelination during development and remyelination is the presence of cellular or tissue components associated with demyelination, such as inflammatory cells or myelin debris. Myelin debris is abundant in MS lesions, especially in early lesion stages where it is phagocytosed by macrophages/microglia. Macrophages/microglia recognize myelin debris via receptors. Receptors that may contribute to myelin phagocytosis is the triggering receptor expressed on myeloid cells (TREM), the Fc or complement receptors (Kuhlmann et al., 2002; Takahashi et al., 2007). *In vitro* myelin debris inhibits oligodendroglial differentiation (Miller, 1999). Depletion of macrophages impairs remyelination due to reduced OPC recruitment (Kotter et al., 2005) and slower remyelination in old adult rodents correlates with impaired clearance of myelin debris (Zhao et al., 2006). Similarly, depletion of adult oligodendrocytes in a genetic mouse model in which oligodendroglial cell death is induced using a Cre-dependent diphtheria toxin fragment A (DT-A) is associated with slow myelin debris clearance and incomplete remyelination (Pohl et al., 2011). The fact that injection of myelin debris into demyelinating lesions reduces remyelination capacity further supports the hypothesis that the clearance of myelin itself, and not a certain activation status of macrophages/microglia induced by myelin phagocytosis, is beneficial for remyelination (Kotter et al., 2006). Interestingly, this study demonstrated also that indeed oligodendroglial differentiation and not OPC recruitment is disturbed by myelin. This impaired differentiation can be improved by modulation of the Fyn-RhoA and protein kinase C signalling pathway (Fig. 1) (Baer et al., 2009). These findings show that myelin debris in demyelinating lesions represent a potent inhibitory factor of OPC differentiation. Thus, efficient phagocytic clearance of myelin debris is a prerequisite for remyelination (Miller, 2002; Kotter et al., 2006).

LINGO-1

The leucine-rich-repeat and Ig domain containing NOGO receptor interacting protein 1 or simply LINGO-1 is a CNS specific highly evolutionary conserved transmembrane protein that plays a role in neurogenesis, axon guidance and myelination in development. LINGO-1 expression in rat brains reaches its peak at postnatal day 1; it can be detected in neurons and oligodendroglial lineage cells with highest levels in OPCs (Mi et al., 2008). In neurons LINGO-1 is a component of the Nogo-66 receptor (NgR1)/p75 and NgR1/Troy signaling complexes and axonal LINGO-1 inhibits oligodendroglial differentiation and myelination (Mi et al., 2004; Shao et al., 2005; Lee et al., 2007). In OPCs downregulation of LINGO-1 leads to reduced RhoA activity associated with oligodendroglial differentiation and increased myelination (Fig. 1) (Mi et al., 2005; Lee et al., 2007; Zhao et al., 2007). Oligodendrocytes cultured from LINGO-1 KO mice do not only differentiate more rapidly than WT cells but also show a premature myelination *in vitro* (Mi et al., 2008). Similarly, co-cultures consisting of oligodendrocytes and dorsal root ganglion (DRG) neurons treated with LINGO-1 antagonists show significantly increased numbers of myelinated axons as well as an increased expression of different myelin genes (Mi et al., 2005; Lee et al., 2007). LINGO-1 deficient mice exhibit less severe EAE symptoms, which is accompanied by increased numbers of myelinated axons, whereas adoptive EAE experiments reveal no effect of Lingo-1 deficiency on the immune response (Mi et al., 2007). Blocking anti-Lingo-1 antibodies promotes remyelination in toxic demyelination, such as cuprizone and lysolecithin induced demyelination, as well as in inflammatory demyelination, e.g. MOG induced optic neuritis or EAE (Mi et al., 2007, 2009). In MS lesions LINGO-1 is identified in subpopulations of astrocytes, macrophages/microglia and neurons but not in oligodendrocytes. LINGO-1 protein levels are reduced in MS brains compared to controls (Satoh et al., 2007), further questioning whether LINGO-1 expression contributes significantly to remyelination failure in chronic MS lesions. However, the findings from *in vitro* and animal studies indicate that anti-Lingo-1 is a promising agent to promote regenerative processes in demyelinating lesions and phase1 studies are currently under way.

Wnt signaling

Transcription factors (TFs) are key components of all regulatory pathways. Recent studies focused on the role of TFs in oligodendrocyte differentiation and subsequent myelination (Rowitch, 2004; He et al., 2007; Emery et al., 2009). A genome wide screen of TFs expressed in cells of the oligodendrocyte lineage identified T cell factor 4 (tcf4, aka TCF7L2), as being highly expressed during remyelination in rodents (Fancy et al., 2009). TCF7L2 is an important mediator of the canonical Wnt signaling pathway that is activated by binding of Wnt to its receptors Frizzeled and LRP5/6 (van de Wetering et al., 2002; Nelson and Nusse, 2004; Fancy et al., 2009). In the absence of Wnt, ß-catenin is phosphorylated and degraded, binding of Wnt to Fz and LRP5/6 prevents the phosphorylation of ß-catenin which accumulates in the nucleus where it, together with transcriptional co-activators e.g. TCF7L2 induces the transcription of target genes (for review see (Moon et al., 2002)). Wnt signaling is also involved in the regulation of oligodendroglial differentiation. During myelination, but not in the adult rodent CNS, TCF7L2 is expressed in OPCs, although it is re-expressed in injured white matter e.g. during remyelination (Fancy et al., 2009). Wnt signaling prevents oligodendroglial differentiation from progenitors to immature cells. In contrast, blocking of Wnt promotes oligodendroglial differentiation *in vitro* and *in vivo* (Shimizu et al., 2005; Langseth et al., 2010). Furthermore, mice expressing only one functional copy of the Wnt pathway inhibitor APC, resulting in activation of the Wnt pathway, show delayed remyelination (Fancy et al., 2009). Taken together, prolonged Wnt pathway activation in OPCs is considered to be a negative regulator of oligodendrocyte differentiation preventing OPCs from exiting the cell cycle, thus remaining unresponsive to differentiation inducers (Shimizu et al., 2005; Fancy et al., 2009). Interestingly, mice lacking TCF7L2 suffer as well from impaired differentiation of oligodendrocytes, similar to mice deficient for certain histone deacetylases. Lack of histone deacetylases is associated with stabilization and translocation of ß-catenin to the nucleus (Ye et al., 2009). Therefore, the hypothesis evolved that TCF7L2 either interacts with histone deacetylases, resulting in the differentiation of oligodendrocytes by preventing binding of TCF7L2 to ß-catenin, or that it forms a transcriptional complex with ß-catenin, thereby inhibiting the differentiation of oligodendroglial lineage cells (Fig. 1) (Ye et al., 2009).

Non-disease related factors

Sex and age

In rodent animal models it is well established that non-disease associated factors such as age and sex influence remyelination capacity. Female rodents for example display a higher number of dying and proliferating oligodendroglial lineage cells compared to males. Furthermore female sex hormones, such as progesterone and estradiol, stimulate oligodendroglial process branching, myelin sheath formation and remyelination (Ibanez et al., 2004; Marin-Husstege et al., 2004; Cerghet et al., 2006; Gerstner et al., 2007). A similar effect has been observed with other hormones, such as thyroid hormone and prolactine, which both promote remyelination in toxic demyelination (Gregg et al., 2007; Harsan et al., 2008). Testosterone, however, has on the one hand protective influence on EAE animals; on the other hand it has excitotoxic effects on oligodendrocytes *in vitro* (Dalal et al., 1997; Bebo et al., 1998; Caruso et al., 2004). In summary these data suggest that female sex is a beneficial factor for remyelination, in contrast to age, which has a negative impact on remyelination. Remyelination in rodents of higher age fails or is delayed (Gilson and Blakemore, 1993; Shields et al., 2000); this is associated with a delayed recruitment of progenitor cells, impaired oligodendrocyte differentiation and disturbed myelin phagocytosis (Gilson and Blakemore, 1993; Sim et al., 2001; Woodruff et al., 2004; Zhao et al., 2006). Furthermore, growth factor treatment promotes the mobilization of subventricular progenitor cells in young but not aged animals in response to demyelination (Decker et al., 2002). This can at least partly be explained by age-associated epigenetic changes (see below). Since so far no imaging technique is available that specifically measures remyelination *in vivo* little is known about the effects of age and sex on remyelination in MS patients. We observed more extensive remyelination in lesion samples from women with MS compared to male patients; however the difference was not significant (Kuhlmann et al., 2009). While remyelination appears to be a frequent phenomenon in early stages of MS lesions it is limited in chronic MS lesions and confined to the lesion borders (Raine and Wu, 1993; Goldschmidt et al., 2009) although no histological study exists that demonstrates a negative correlation between age and remyelination; instead marked remyelination was found to be associated with longer survival (Patrikios et al., 2006).

Epigenetics

Epigenetics, changes in gene activity without altering the underlying primary DNA sequence, play an essential role in many cellular processes, like proliferation and differentiation. Epigenetic modifications include, for example, post-translational modifications of nucleosomal histones, DNA methylation and microRNAs. One of the best characterized chromatin remodelling mechanisms is histone acetylation which is modulated by the interplay of histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Shen et al., 2005, 2008a). Acetylation of specific lysine residues in the N-terminal tail regions of histones by HATs reduces their overall

charge, evoking the de-compaction of chromatin structure, thus increasing the accessibility of DNA (Nan et al., 1998; Shen et al., 2008a). In order to reverse this action, HDACs can remove the acetyl groups, thereby rendering the DNA less accessible (Nan et al., 1998). HDACs were shown not only to be involved in oligodendrocyte maturation during development, but also in remyelination (Shen et al., 2005, 2008a; Fukuda et al., 2006; Popko, 2008; Haberland et al., 2009). Histone deacetylation is required for oligodendroglial differentiation and myelination (Marin-Husstege et al., 2002; Shen et al., 2005). In rodents aging is associated with decreased histone deacetylase activity, re-expression of myelin gene inhibitors, such as Hes5 and Id4, and impaired remyelination (Shen et al., 2008a,b). These aging associated changes can be recapitulated by treatment with histone deacetylase inhibitors *in vitro* and *in vivo* (Shen et al., 2008a,b). In the aged human CNS, as well as in the normal appearing white matter in MS, a shift to increased histone acetylation is observed that is also associated with an upregulation of myelin gene inhibitors (Pedre et al., 2011). In contrast, in early MS lesions a marked reduction of histone acetylation in oligodendroglial lineage cells was observed, suggesting that histone acetylation may modulate the remyelination capacity in MS (Pedre et al., 2011). A second epigenetic mechanism contributing to oligodendroglial differentiation are microRNAs, which are involved in mRNA translational regulation by binding to specific target mRNAs, resulting in degradation or translational repression of target mRNAs. MicroRNAs are differentially regulated in differentiating oligodendrocytes (Lau et al., 2008). Ablation of oligodendroglial Dicer, an enzyme required for the generation of "mature" microRNAs, during embryonic development leads to severe hypomyelination, whereas postnatal (P14) deletion of Dicer results in a milder phenotype (Shin et al., 2009; Zhao et al., 2010). The microRNAs miR-219 and miR-338 were identified as important regulators of oligodendroglial differentiation. Overexpression of both siRNAs promotes myelination, whereas downregulation impairs oligodendroglial differentiation by modulation of negative regulators of oligodendroglial differentiation (e.g. Hes5, Sox6) (Zhao et al., 2010). In summary, these data illustrate that epigenetic mechanisms are important regulators of oligodendroglial differentiation, aging and/or remyelination and may represent new therapeutical targets for neuroprotective treatment strategies in MS.

Conclusion

Considerable progress has been made in elucidating the mechanisms underlying oligodendroglial differentiation, myelination and remyelination and this review was only able to summarize some of the findings. It has become obvious that remyelination is the result of a complex interaction between extrinsic signals, intrinsic pathways, transcription factors and non-disease related factors that requires correct timing to result in successful remyelination. Most likely not only the presence of remyelination promoting factors, as well as the absence of inhibitory factors are a prerequisite for successful remyelination, but also the precise timing of events (Franklin, 2002). The question why remyelination is successful in rodents but fails in the majority of patients with chronic MS is still not resolved despite the identification of a broad range of potentially inhibitory signalling cascades. This might be either due to intrinsic differences between the rodent and the human CNS or the lack of an appropriate rodent animal model for this aspect of the human disease. Hopefully, further insights will come from combined animal and human studies. The successful development of remyelination promoting treatment strategies may contribute to the prevention of axonal loss and would represent a valuable treatment option for the progressive disease phase.

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