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INVITED REVIEW

The contribution of oligodendrocytes and oligodendrocyte progenitor cells to central nervous system repair in multiple sclerosis: perspectives for remyelination therapeutic strategies

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Abstract

Oligodencrocytes (OLs) are the main glial cells of the central nervous system involved in myelination of axons. In multiple sclerosis (MS), there is an imbalance between demyelination and remyelination processes, the last one performed by oligodendrocyte progenitor cells (OPCs) and OLs, resulting into a permanent demyelination, axonal damage and neuronal loss. In MS lesions, astrocytes and microglias play an important part in permeabilization of blood-brain barrier and initiation of OPCs proliferation. Migration and differentiation of OPCs are influenced by various factors and the process is finalized by insufficient acummulation of OLs into the MS lesion. In relation to all these processes, the author will discuss the potential targets for remyelination strategies.

Key Words: *multiple sclerosis; oligodencrocytes; oligodendrocyte progenitor cells; demyelination; remyelination; semaphorin; basic helix-loop-helix transcription factor oligodendrocyte transcription factor 2; leucin-rich repeat and immunoglobulin-like-domain-containing nogo receptor-interacting protein 1; canonical Notch signaling; endocrine receptors*

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The Role of Oligodencrocytes and Oligodendrocyte Progenitor Cells in Myelination

Oligodencrocytes (OLs) are the main glial cells of the central nervous system (CNS) involved in myelination of axons. Myelination allows saltatory conduction between nodes of Ranvier which increases both speed and energy efficiency of nerve conduction. OLs also provide trophic support to axons, lactate as energy source and have a critical role in maintenance of axonal integrity (Fünfschilling et al., 2012). However, the role of OLs in myelin sheath maintenance was uncoupled from their role in supporting axonal integrity. These results imply that OLs dysfunction alone is sufficient to cause secondary axonal degeneration and raises the possibility that OLs may be a primary cellular target in neurodegenerative disease (Tognatta and Miller, 2016).

Oligodendrocyte progenitor cells (OPCs) constitute the largest dividing population among neural cells making up on average 5% of total CNS cells and they are uniformly distributed throughout CNS (Dawson et al., 2003). They belong to the same population of progenitors that give rise to OLs during CNS development. However, a large number of OPCs do not differentiate and remain in a cyclic state during adulthood (Fernandez-Castaneda and Gaultier, 2016) until a local CNS injury occurs and triggers differentiation to OLs. During development, OPCs are generated in sequential waves from specific germinal sites; the first wave starts in the ventral midline of caudal regions of the neural tube as a result of inductive cues from adjacent tissues. Later in development, a second source of OPCs arises in dorsal spinal cord that generates a second wave of myelinating OLs (Cai et al., 2005) and a third wave that occurs after birth from the progenitor cells around central canal (Rowitch and Kriegstein, 2010). In more rostral regions of the CNS, cre-lox fate mapping experiments showed multiple waves of OPC generation with a ventral to dorsal progression begining at embryonic stage (Kessaris et al., 2006).

The generation of OPCs from neural progenitor cells (NPCs) continues throughout adulthood. Two primary sources of NPCs have been defined: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus. In these regions, anatomically different populations of stem cells retain the capacity to generate neurons, astrocytes and OLs (Tognatta and Miller, 2016).

In humans, most of CNS myelination occurs during the first two decades of life (Yakovlev and Lecours, 1967; Mitew et al., 2014) although there is evidence that myelination continues throughout life either to remyelinate following demyelination or brain injury or to myelinate previously unmyelinating axon (Bartzokis et al., 2012; Young et al., 2013).

Demyelination and Remyelination in Multiple Sclerosis (MS)

Persistent demyelination in MS is the result of an imbalance between dysfunction and loss of OLs that produces demyelination and the impaired/reduced generation of OLs that leads to an insufficient remyelination, evolving in parallel with axonal damage and neuronal loss.

Two patterns of OLs dysfunction can be distingushed histopatologically in MS: an immune mediated OLs dysfunction and

a primary olidendrogliopathy. Studies using *in vitro* models and animal models of MS provided evidence for a direct attack to myelin and OLs of antigen specific cytotoxic T lymphocytes (Na et al., 2008; Lassmann, 2014) and specific auto-antibodies (Linington et al., 1988), T-cell mediated cytotoxicity independent from antigen recognition (Nitsch et al., 2004) as well as activation of microglia and macrophages by pro-inflammatory molecules (Felts et al., 2005). Another important player in MS lesions is the astrocyte involved in inflammation and blood-brain barrier (BBB) integrity and function. Astrocytes contribute to T cell recruitment, activation and differentiation through pro-inflammatory cytokines and chemokines production (Sørensen et al., 1999; Choi et al., 2014; Xie and Yang, 2015). They also exert, through a cell to cell contact mechanism, a direct TNF toxicity towards OPCs (Kim et al., 2011). Astrocytes secrete matrix metalloproteinases (MMPs) that increase the permeability and produce the remodeling of BBB (Williams et al., 2007). In addition, they limit the remyelination processes through interaction of NOGO with LINGO in MS plaques (Karnezis et al., 2004; Satoh et al., 2007).

Remyelination in MS occurs as a spontaneous regenerative process following demyelination (Franklin and Ffrench-Constant, 2008; Crawford et al., 2013; Aharoni, 2015) and presents greater efficiency in MS lesions appearing early in the disease course (Patrikios et al., 2006; Patani et al., 2007). In MS, the capacity of remyelination declines with age and disease progression. Remyelination in MS lesions is variable and often incomplete leading to persistent demyelination and axon degeneration (Patrikios et al., 2006; Compston and Coles, 2008; Franklin and Ffrench-Constant, 2008; Piaton et al., 2009). In general, the extent of remyelination varies from patient to patient and from a lesion to another (Zhang et al., 2016b). The remyelination is mostly restricted to the periphery of lesions, starts early in the lesion formation and is present in active lesions (Bø et al., 2013). About 10–20% of chronic lesions are completely remyelinated forming the so called shadow plaques (Patani et al., 2007). However, remyelinated regions may be more vulnerable to repeated demyelination in comparison to normally appearing white matter (NAWM) (Bramow et al., 2010) and entirely demyelinated areas are the result of repeated episodes of demyelination and incomplete remyelination (Brown et al., 2014).

Remyelination in MS was extensively studied on animal models and appears to occur in several steps. Following demyelination, factors produced by microglial cells and astrocytes activate OPCs that shift from quiescent to a regenerative fenotype that presents a different morphology and an up-regulation of several genes such as transcription factors oligodendrocyte transcription factor 2 (Olig 2), Sex determining region Y-box 2 (Sox2) and Nkx2.2 (Levine et al., 2001; Fancy et al., 2004; Talbott et al., 2005). The OPCs activation is proportional to the inflammatory reaction that succeeds demyelination and is required for succesful remyelination (Miron et al., 2011). The activated OPCs migrate to white matter lesions in response to mitogens and pro-migratory factors released by microglia and astrocytes. The migration of OPCs appears to be regulated by chemo-attractant factors such as platelet derived growth factor (PDGF) and semaphorin 3F (Sema 3F), chemo-reppelents netrin-1, semaphorin 3A (Sema 3A), ephrins and stop-signals chemokine (CXCL)1 and tenascin C (Dubois-Dalcq and Murray, 2000; Kakinuma et al., 2004; Sobel, 2005; Williams et al., 2007; Kerstetter et al., 2009; Miron et al., 2011; Bin et al., 2013; Boyd et al., 2013).

To populate demyelinated areas, the recruited OPCs start to differentiate into remyelinating OLs (Franklin and Ffrench-Constant, 2008; Bradl and Lassmann, 2010). The differentiation of OPCs is promoted by insulin-like growth factor (IGF-1), ciliary neurotrophic factor (CNTF) and thyroid hormone (Zhang et al., 2015, 2016a) and requires the function of Olig1, Olig2, Nkx2.6, Myt1 and sex determining region Y box (SOX)-10 (Nunes et al., 2003; Fancy et al., 2004; Nicolay et al., 2007). Then OLs need to establish a contact with the axon to be remyelinated, before generating the myelin protein membrane. Axon-glia interaction and myelin membrane trafficking are essential for remyelination. Src-family kinase Fyn plays a central role in axonal signal integration by OLs (White and Krämer-Albers, 2014). The development of myelin sheath in remyelination follows a similar pattern with developmental myelination, although the rate of OPCs migration is slower and the myelin sheaths in remyelinated areas are thinner and shorter but sufficient to ensure full functional recovery of the axons (Bradl and Lassmann, 2010; Fancy et al., 2010; Crawford et al., 2013).

Recent animal models studies, using genetic fate mapping techniques, implicate OPCs as the cells responsible for remyelination and not the mature previously myelinating OLs (Tripathi et al., 2010; Zawadzka et al., 2010).

Causes of Remyelination Failure in MS

The causes of remyelination failure in MS appear to be related to the depletion of OPCs as well as the impaired migration and differentiation of OPCs (**Figure 1**).

Thus, OPCs were identified within active MS lesions but their number and capacity to differentiate decreases with disease duration and OPCs were more vulnerable to injury mediators than OLs (Chang et al., 2002). However, depletion of OPCs is not the only cause of remyelination failure since studies of autopsy from MS patients showed the presence of OPCs and immature OLs contacting the axons but failing to myelinate (Câmara and ffrench-Constant, 2007). Also, analysis of focal demyelinated lesions showed that areas of succesive demyelination-remyelination as well as first time remyelinated areas presented no evidence of OPCs depletion and, in chronic MS lesions, OPCs are present but fail to remyelinate (Kuhlmann et al., 2008; Hartley et al., 2014). In chronic lesions remyelination impairment is due to deficient OPCs recruitment phase which involves proliferation, migration and repopulation of lesions (**Figure 2**). Activated microglia and astrocytes in the setting of demyelination are the source of mitogens/growth factors such as fibroblast growth factor 2 (FGF-2) and PDGF-2A that induce rapid proliferative responses in OPCs (Armstrong et al., 2002; Woodruff et al., 2004). This OPCs response is regulated by p27Kip1 (Crockett et al., 2005) and Cdk (Caillava and Baron-Van Evercooren, 2012; Tognatta and Miller, 2016). In chronic MS lesions the changes in the extracellular matrix and the formation of the astroglial scar (Franklin and Ffrench-Constant, 2008) contribute to reduction of proliferation, migration and accumulation of OPCs in the lesion (Franklin, 2002).

Several studies identified inhibitors of OPCs migration during remyelination but their action is not well understood (Piaton et al., 2011). One of the factors that modulate OPCs migration are group 3 semaphorins, Sema 3A is an inhibitory in contrast

to Sema 3F which is an attractive migratory signal for OPCs. Active MS lesions contain higher mRNA expression of chemoattractant Sema 3F than chemoreppelent Sema 3A (Williams et al., 2007). Another study analyzed a series of MS lesions in post-mortem tissue and found a correlation between a lower number of OPCs, chronic active lesion type and a higher expression of chemoreppelent Sema 3A (Boyd et al., 2013). In contrast, a low expression of Sema 3A and a higher expression of chemoattractant Sema 3F correlated with active lesions and more variable, but generally higher numbers of OPCs.

Another factor that influences OPCs migration and remyelination is chemoreppelent netrin-1. The role of netrin-1 as a repellent for migrating OPCs during development (Sugimoto et al., 2001; Jarjour et al., 2003; Bin et al., 2013; Tepavčević et al., 2014) and its expression by neurons and glia in the mature CNS (Manitt et al., 2001) suggest that it might also influence OPCs migration and remyelination in MS. Full length and fragmented netrin-1 were found in adult human white matter as well as in demyelinated MS lesions, where they exert inhibitory influences on OPCs migration (Manitt et al., 2006; Löw et al., 2008; Bin et al., 2013).

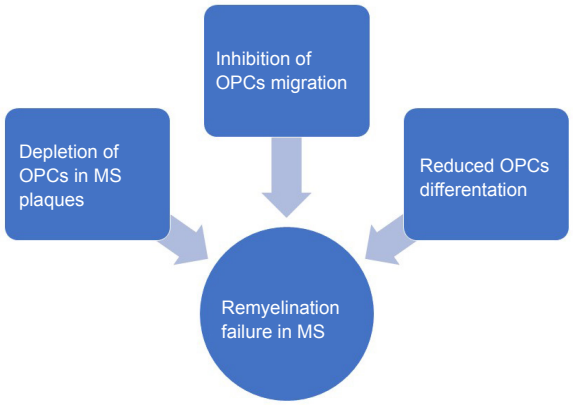

Figure 1 Causes of remyelination failure in MS.
MS: Mltiple sclerosis; OPCs: oligodendrocyte progenitor cells.

Chemokines exert various effects on migration of OPCs and OLs and differentiation of OPCs throughout the process of remyelination. OLs express at least four chemokine receptors: CXCR1, CXCR2, CXCR3 and CXCR4 (Nguyen and Stangel, 2001; Omari et al., 2005). Histological studies suggest that chemokine CXCL1 is upregulated around the peripheral areas of demyelination. Also, localized inhibition of CXCR2 signaling reduces lesion size and enhances remyelination (Kerstetter et al., 2009). CXCL12 was significantly upregulated within activated astrocytes and microglia during demyelination, as were numbers of $CXCR4^{+}NG2^{+}$ OPCs. Loss of CXCR4 signaling *via* either pharmacological blockade or *in vivo* RNA silencing led to decreased OPCs maturation and failure to remyelinate (Patel et al., 2010).

The differentiation of OPCs is regulated by a complex interplay of intrinsic, extrinsic and epigenetic factors during development (Rowitch and Kriegstein, 2010), some of them being also involved in remyelination in MS.

Among intrinsic factors, the basic helix-loop-helix (bHLH) transcription factor Olig2 has a critical role in OLs determination (Rowitch, 2004). Wegener et al. (2015) demonstrate that Olig2 displays a differential expression pattern in MS lesions that correlates to lesion activity. Olig2 was predominantly detected in $NOGO\text{-}A^{+}$ (now known as RTN4-A) maturing OLs, which prevale in active lesion borders, rather than chronic silent and shadow plaques.

Leucin-rich repeat and immunoglobulin-like-domain-containing nogo receptor-interacting protein 1 (LINGO-1) is a potent negative regulator of neuron and OL survival, neurite extension, axon regeneration, OL differentiation, axonal myelination and functional recovery (Yin and Hu, 2014). In experimental autoimmune encephalomyelitis (EAE) models of MS, LINGO-1 knockout mice exhibit enhanced myelin sheath formation and

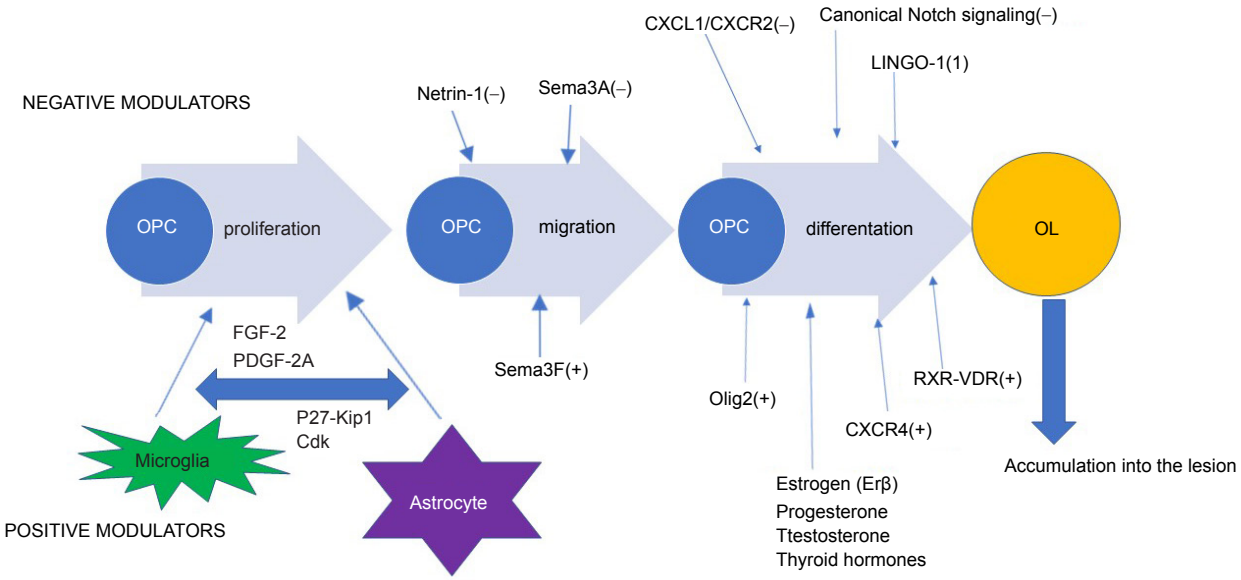

Figure 2 Factors influencing remyelination in MS lesions.
MS: Mltiple sclerosis; OPC: oligodendrocyte progenitor cell; OL: oligodencrocyte; Sema3A: semaphorin 3A; Sema3F: semaphorin 3F; CXCL: chemokine; Olig2: helix-loop-helix transcription factor Olig2; LINGO-1: Leucin-rich repeat and immunoglobulin-like-domain-containing nogo receptor-interacting protein 1; RXR-VDR: nuclear retinoid X receptor-vitamin D receptor; FGF-2: fibroblast growth factor 2; PDGF-2A: platelet derived growth factor-2A.

recovery (Mi et al., 2007) and treatment with LINGO-1 antagonist result in increased OPCs differentiation and remyelination (Zhang et al., 2015, 2016a) suggesting that blocking LINGO-1 may be a useful therapeutic approach (Rudick et al., 2008). In a phase I clinical trial, anti-LINGO-1 monoclonal antibody (BIIB033) showed safety and tolerability in MS patients (Tran et al., 2014). Further more, two phase two clinical studies have been started. A phase II placebo-controlled clinical trial (RENEW) in 82 patients with optic neuritis who received six intravenous infusions of opicimumab or placebo every four weeks, followed up for 32 weeks, showed that opicimumab was no better than placebo for improving visual function but statistically significant improved the visual evoked potentials (Cadavid et al., 2017). The second phase II clinical trial (SYNERGY) including 418 relapsing remitting or secondary progressive MS patients showed that opicimumab had satisfactory tolerability, however did not lead to an improvement in disability or a slow down in disability progression but there were indications of a clinical effect that will be further studied (McCroskery et al., 2017).

Canonical Notch signaling, which occurs through ligands such as Jagged, inhibits OPCs differentiation during development (Genoud et al., 2002), however its role in CNS remyelination is still debated. Hammond et al. (2014) recently demonstrated that OPC differentiation following lysolecithin demyelination is inhibited by Jagged1-expressing astrocytes, which directly bind to Notch1 on OPCs. Reactive astrocytes express Jagged1 in MS plaques (John et al., 2002) and this expression appears to be regulated by the secreted protein endothelin-1 (ET-1) (Hammond et al., 2014), which inhibits OL differentiation during development (Chamberlain et al., 2016).

Wnt proteins are secreted ligands that play numerous roles in regulating development, including OLs genesis (Ortega et al., 2013). However the contribution of Wnt pathway in remyelination process is controversial and targeting Wnt pathway as potential remyelinating therapy must be approached with caution (Xie et al., 2014; Guo et al., 2015).

Nuclear retinoid X receptor (RXR) pathway plays an important role in cell proliferation and development (Mark et al., 2009). RXR couple with retinoic acid receptor, vitamin D receptor (VDR), thyroid receptor and peroxisome proliferator-activated receptor to induce gene transcription (Rastinejad, 2001). RXR-VDR signaling induces OPCs differentiation and VDR agonist vitamin D enhances OPCs differentiation (de la Fuente et al., 2015). Several studies showed expression of VDR in oligodendroglial lineage cells in MS, revealing a potential role of vitamin D in remyelination (Ballanger et al., 2010; de la Fuente et al., 2015).

Other potential remyelination targets are endocrine receptors. MS shows a female-to-male gender prevalence and disturbances in sex steroid production (Kipp et al., 2012). Estrogen and progesterone operate in reducing central and brain-intrinsic immune responses and regulating local growth factors supply, OL and astrocyte function (Kipp et al., 2012). Several studies showed that low estrogen states favor exacerbations of MS in women (Christianson et al., 2015; Triantafyllou et al., 2016) and levels of progesterone and testosterone metabolites are decreased in cerebrospinal fluid of MS patients (Caruso et al., 2014). Endocrine targets have been investigated in preclinical models of MS as potential modulators of myelination. Numerous preclinical studies demonstrated that 17-β estradiol, estriol and other estrogen receptor (ER) ligand treatments have protective effects on susceptibility to EAE (Crawford et al., 2010), thyroid hormones promote myelin repair (Harsan et al., 2008; Calza et al., 2010; D'Intino et al., 2011), progesterone decreases demyelination, disease severity and neurological deficits (Schumacher et al., 2012) and testosterone enhances remyelination through neural androgen receptor (Hussain et al., 2013). However, clinical trials using estrogen therapy in MS patients showed an increased risk of breast and uterine cancer, heart disease and stroke (Prentice et al., 2009), the majority of these effects being mediated through ER α (Caringella et al., 2011). As a result, ERβ became interesting as a target for neuroprotective therapy (Planey et al., 2014). Other clinical trials showed that testosterone treatment in MS patients was correlated to reduced inflammation and improved cognition (Sicotte et al., 2007; Gold et al., 2008).

Conclusion

OLs and OPCs are essential cells for myelination of the CNS. The process of myelination starts during development and continues throughout life under the control of a complex genetic mechanism. In MS, the immune process induces a pathological cascade that injures OLs and OPCs generating demyelination and impaired remyelination. The identification of key molecules and pathways controlling the migration and differentiation of OPCs and myelination has provided clues for potential targets of drug candidates in order to develop efficient remyelination strategies for MS.

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