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Immunology of oligodendrocyte precursor cells *in vivo* and *in vitro*

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ABSTRACT

Remyelination following myelin/oligodendrocyte injury in the central nervous system (CNS) is dependent on oligodendrocyte progenitor cells (OPCs) migrating into lesion sites, differentiating into myelinating oligodendrocytes (OLs), and ensheathing axons. Experimental models indicate that robust OPC-dependent remyelination can occur in the CNS; in contrast, histologic and imaging studies of lesions in the human disease multiple sclerosis (MS) indicate the variable extent of this response, which is particularly limited in more chronic MS lesions. Immune-mediated mechanisms can contribute either positively or negatively to the presence and functional responses of OPCs. This review addresses i) the molecular signature and functional properties of OPCs in the adult human brain; ii) the status (presence and function) of OPCs in MS lesions; iii) experimental models and *in vitro* data highlighting the contribution of adaptive and innate immune constituents to OPC injury and remyelination; and iv) effects of MS-directed immunotherapies on OPCs, either directly or indirectly via effects on specific immune constituents.

1. Introduction

Oligodendrocyte (OL)/myelin support for axons is essential not only to maintain efficient electrical conduction in the CNS but also to maintain axonal integrity by serving as a source of energy for neurons. Selective destruction of myelin is a pathologic hallmark of multiple sclerosis (MS), although concurrent axonal injury is also well described. Such selective destruction is also found at the penumbra of ischemic and traumatic CNS injury in neonates and adults. Remyelination in the human CNS is well documented by histologic and imaging criteria in MS. In toxin-induced demyelination animal models, complete remyelination can be observed following the lethal injury of existent OLs. This observed remyelination is attributed to the recruitment of new progenitor cells rather than the action of previously-myelinating cells that survived the injury process. Histologic criteria used to document remyelination as compared to primary myelination include altered ratios of myelin thickness:axon diameter (g-Ratio) and shortening of internode distances. In models that transplant oligodendrocyte progenitor cells (OPCs) into the CNS of myelin-deficient animals, resultant myelination exhibits properties of primary myelination rather than remyelination. “Shadow plaques” in the MS CNS are characterized by reduced myelin content. These plaques are usually considered a reflection of partial remyelination, but could also reflect partial injury. In this regard, *in vivo* imaging documents reduced myelin signals after metabolic injury (e.g. chemotherapies); subsequent increase in myelin signals may be due to recovery of function of sub-lethally-injured OLs or new myelin formation. Furthermore, expression of myelin-associated genes and proteins are shown to be modulated in response to environmental events such as social stress in the absence of myelin destruction (Lehmann et al., 2017).

This chapter will emphasize the interactions of OPCs and the immune system as related to injury and repair in the human MS brain (summarized in Figs. 1–3). As such, we will consider: i) the molecular signature and functional properties of OPCs in the adult human brain; ii) the status (presence and function) of OPCs in MS lesions; iii) experimental models and *in vitro* data highlighting the contribution of adaptive and innate immune constituents to OPC injury and remyelination responses; and iv) effects of MS-directed immunotherapies on OPCs, either directly or indirectly via effects on specific immune constituents.

The OPCs maturation-differentiation process is tightly orchestrated by cell-cell interactions in the central nervous system. The cell environment plays a crucial role and could exert either a positive or a negative modulation of this remyelination intervention.

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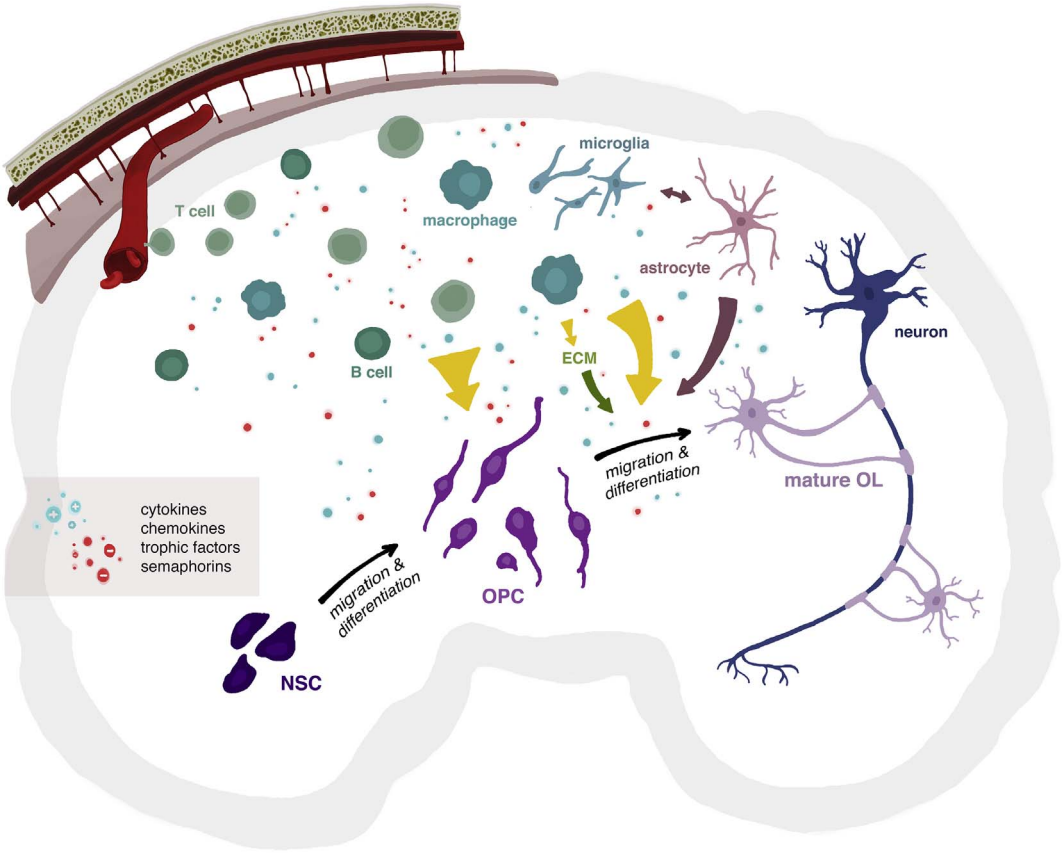

Fig. 1. Schmatic detailing how cells of the adaptive and innate immune systems as well as endogenous neural cells can have direct or indirect effects on OPC-mediated remyelination.

2. Molecular signature and functional properties of OPCs in the adult human brain

Extensive information exists regarding the identity and functional regulation of OPCs during initial myelination in the developing central nervous system (CNS). The regulation of OPCs in development occurs in a carefully-regulated time- and region-dependent manner, proceeding from the spinal cord to the cerebrum, with significant species differences. In humans, myelination begins late in the second trimester and continues into young adulthood. Regulation of myelination is complex, involving both intrinsic sequential expression of lineage markers and transcription factors and dynamic responses to environmental cues. A central issue is the relationship between these intrinsic and extrinsic signals that guide the primary myelination process and those involved in remyelination following disease or injury in the CNS. Carbon-14 dating studies in humans suggest there is little turnover of oligodendrocytes under physiologic conditions (Yeung et al., 2014), raising the issue of the role of OPCs in the adult brain – that is, if the cells are present in case of a need to repair, or if the cells perform additional physiologic functions, as will be discussed later.

2.1. Identity of adult human OPCs

These cells were initially identified in the adult brain using an array of putative lineage markers corresponding to those found in the developing brain. Early studies used O4 immunoreactivity, with absence of galactocereboside (galC), as an identifier of pre-oligodendrocytes in the normal adult brain (Armstrong et al., 1992; Scolding et al., 1999; Wolswijk, 2002). More recent genetic lineage tracing studies have provided new insights into the properties of adult human brain OPCs.

2.2. A2B5

An early marker used to identify progenitors in the adult brain was the ganglioside-recognizing antibody, A2B5 (Ruffini et al., 2004). In the adult human brain, A2B5-immunoreactive cells are estimated to account for up to 5% of total cells in white matter. Such cells will ensheath axons when transplanted into the CNS of the immunosuppressed, genetically myelin-deficient *shiverer* mice (Nunes et al., 2003). In the developing rodent and human brain, A2B5 positivity marks a heterogeneous, pluripotent group of cells not yet committed to the OL lineage. At this early stage, such cells have the potential to evolve into neurons, astrocytes, or OLs. In the late second trimester in the human fetal brain, a significant percent of $A2B5^+$ cells begin to express more lineage restricted markers, such as platelet derived growth factor receptor α (PDGFRα). PDGFRα expressing cells are referred to as OPCs, although as shown in the rodent system, they maintain pleurpotential capability as they can be driven along astrocyte or oligodendrocyte lineage pathways (Franklin and Ffrench-Constant, 2017). A summary of human OL lineage development is provided in Fig. 2.

The inability to use the A2B5 antibody *in situ* has limited direct comparisons of cells in tissue with those *in vitro*. Transcriptional analyses of $A2B5^+$ cells isolated from the adult human brain by cell sorting indicate that these cells express low levels of PDGFRα and chondroitin sulfate proteoglycan-4 (CSPG4) neuron/glial antigen-2 (NG2) (Leong et al., 2014). This observation is consistent with genetic tracing studies that have found marked age-associated downregulation of PDGFRα in murine OPCs (Moyon et al., 2015), identified as being $O4^+MBP^-$. The majority of the human adult $A2B5^+$ cells express the OL-restricted lineage marker O4, consistent with the profile of “pre-oligodendrocytes” described by Armstrong et al. (1992). Our microRNA (miRNA) analyses indicated more similarities between the gene

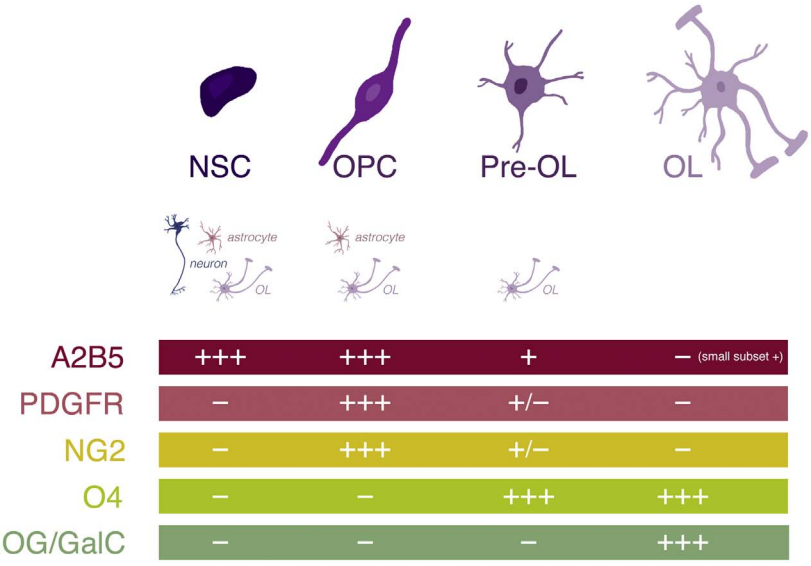

Fig. 2. Synopsis of cell surface markers associated with human OL cell lineage development. The sequential differentiation of oligodendrocyte lineage is labelled with several characteristic cell surface markers. Expressions of A2B5, PDGFRα, NG2, O4, MOG/GalC define the transformation from brain progenitor cells to mature OLs.

expression profiles of the adult A2B5$^+$ cells and mature human OLs than fetal human brain-derived A2B5$^+$ cells. Comparison between transcriptional profiles of human adult derived A2B5$^+$ cells (Sim et al., 2006) and OPCs derived from the adult rodent brain (Dugas et al., 2006) indicate marked species differences in the expression of genes related to the OL lineage.

2.3. NG2/PDGFRα

During OL development there is significant overlap between NG2 and PDGFRα populations (Eugenin-von Bernhardi and Dimou, 2016, Kang et al., 2010). Of specific relevance to this presentation is the expression of these markers on cell types other than OLs. *In situ* hybridization analysis of adult human brain sections (Allen Brain Atlas, *www.brain-map.org*) reveals a large number of NG2 and PDGFRα-expressing cells, but these studies have not identified the specific cell type expressing these markers. To date, transfer experiments into the *shiverer* mouse brain have been performed with PDGFRα-expressing cells derived from late second trimester fetal but not from adult human brain (Sim et al., 2006). Such xenotransplants have also been accomplished using OL lineage cells derived from human inducible pluripotent stem (iPS) cell sources; such cells express high levels of PDGFRα compared to primary adult human OLs and A2B5$^+$ cells (Ehrlich et al., 2017).

In rat tissue, the NG2 antibody labels an evenly-distributed cell population present in both white and grey matter, distinct from HLA-DR$^+$ myeloid cells (Reynolds et al., 2002). Putative OPCs express both NG2 and PDGFRα within normal-appearing white matter in the adult human brain and within areas of active demyelination in MS, but not in chronic lesions (Wilson et al., 2006). Such cells were also seen in association with remyelination in MS tissue and with developmental myelination in the human spinal cord. The same study also reported NG2$^+$ cells that did not express PDGFRα. As these cells did not express microglial or astrocyte markers, they were considered to be representative of more mature OPCs that have lost PDGFRα expression. Numerous NG2$^+$/PDGFRα$^+$ cells with extensive arborization of cell processes have also been detected in the adult human brain (Chang et al., 2000, Nishiyama et al., 1999). Such cells did not express antigens specific to mature OLs, astrocytes, microglia, or neurons. Their frequency was estimated to be ~50% relative to that of the microglia population. NG2 positivity was also noted on endothelial cells.

A number of studies implicate NG2-expressing cells in immune-related responses. Kucharova and Stallcup found that selective genetic deletion of NG2 in mice OLs resulted in reduced generation of OPCs following demyelination in the lysolecithin model. However, they also showed that selective NG2 knock-out in myeloid cells diminished demyelination due to a reduction (of ~70%) in myeloid cell recruitment to lesions (Kucharova and Stallcup, 2015). The reduced macrophage/microglia numbers also resulted in decreased myelin repair due to diminished clearance of myelin debris and reduced stimulatory effects on OPCs. More recently, NG2 has been referred to as an early marker of pericyte activation in pathological conditions, and it was also found that NG2 was expressed by immune cells, including T cells, macrophages, and dendritic cells (DCs), in addition to OL lineage cells (Ferrara et al., 2016). Ferrara et al. further showed that experimental autoimmune encephalomyelitis (EAE) was less severe in NG2 knock-out animals without concurrent changes in OPC number. The study concluded that absence of NG2 impacted DC function.

3. OPCs in remyelinating MS lesions

Current consensus is that the putative OPCs that contribute to remyelination in the adult human brain are derived from the parenchymal cell pool and not from specialized progenitor niches. The precise molecular signature of these cells remains to be defined. Attempts have involved use of lineage-associated surface markers as outlined above (Wolswijk, 2002) and intracellular markers such as transcription factors. The consensus from surface marker studies (O4$^+$galC$^-$ and NG2$^+$PDGFRα$^+$) is that OPCs increase in number around acute lesions and are reduced in number in chronic MS lesions (Chang et al., 2000).

A combination of immunostaining with antibodies recognizing the transcription factor olig2 and the mature cell marker NOGO-A has been used to assess OPC numbers and function in MS lesions (Kuhlmann et al., 2008). In early lesions, double stained cells (olig2$^+$NOGO-A$^+$) were found to accumulate at the rim of lesions consistent with OPC recruitment and differentiation. In chronic lesions, olig2$^+$ cells were still present but in significantly reduced numbers compared to the early lesions. In addition, there was little evidence of ongoing OPC differentiation in the chronic lesions, an occurrence Kuhlmann et al. referred to as a "differentiation block". The above studies raise the questions of what the basis for the reduction in OPC numbers over time in MS lesions is, and why the accumulation of OPCs is not accompanied by remyelination (Reynolds et al., 2002).

4. Immune-mediated injury and destruction of OPCs

The reduction in OPC number over time in MS lesions could reflect the vulnerability of OPCs to the same mechanisms that injure mature OLs in the same micro-environment. In our analysis of early MS lesions, we compared the relative reductions in numbers of OPCs (olig2$^+$) with the relative reduction of mature OLs within the same lesions, using OPCs and OL number in the normal-appearing white matter as a reference (Cui et al., 2013). We found a relatively greater loss of OPCs, suggesting such cells have an increased susceptibility to the common insults encountered within the MS lesional environment. In elucidating mechanisms of tissue injury in the inflammatory milieu of active MS lesions, we consider both direct effects of classic immune mediators derived from the systemic compartment (also referred to as "outside-in"-mediated injury) and the impact of changes in the overall lesion microenvironment. We refer to the latter as metabolic stress (also referred to as "inside-out" injury). In this regard, histologic analyses of acute MS lesions indicate pathologic heterogeneity that implicates multiple potential injury mechanisms that are not necessarily mutually exclusive (Lassmann et al., 2007; Lassmann et al., 2012).

This illustration gives a non-exhaustive overview with many other signaling molecules likely to be involved. Brain cells, adaptive and innate immune cells can either promote or impair the OLs differentiation through a range of cytokines, chemokines and trophic factors.

4.1. Adaptive immune cells

Injury could be mediated directly via cell-cell contact or through the release of soluble mediators. OL lineage cells express MHC class I molecules, making them susceptible to potential recognition by myelin-reactive CD8 T-cells (Jurewicz et al., 1998). Although OL lineage cells lack MHC class II expression, CD4 T-cells can acquire promiscuous or NK-like cytotoxic properties involving the NKG2 family of molecules (Saikali et al., 2007). Supernatants from human pro-inflammatory T-cells (Th1/Th17) have been observed to have a direct cytotoxic effect on human A2B5$^+$ neural progenitor cells, resulting in decreased generation of O4$^+$galC$^+$ OL lineage cells (Moore et al., 2015). The study further showed that the same pro-inflammatory supernatants induced astrocytes to secrete soluble mediators – specifically, CXCL10 – that resulted in decreased OPC differentiation without an apparent increase in cell death. Supernatants from Th2-polarized T cells had neither a direct nor an indirect impact on OPCs. Moreover, supernatants derived from MS patient B-cells were found to be cytotoxic to OPCs contained within neonatal rat glial cells cultures (Lisak et al., 2012). The effect, however, was not linked to immunoglogulin, tumor necrosis factor alpha (TNF-α), lymphotoxin alpha (LT-α), interleukin 6 (IL-6), interleukin-10 (IL-10), or transforming growth factor beta 1 (TGF-β1). Lisak et al. concluded that the effect could be direct and/or indirect involving either microglia and/or astrocytes. Another study has found that remyelination was enhanced in Beta 2 microglobulin-deficient animals in the chronic Theiler encephalomyelitis virus mouse (TMEV) model, concluding that the immune response inhibits myelin regeneration (Miller et al., 1995). Conversely, naturally-occurring IgM antibodies can promote remyelination as shown in the same model (Watzlawik et al., 2013).

4.2. Innate immune cells

Myeloid lineage cells have been studied with regard to how their state of polarization impacts OPC injury and repair processes. *In vitro* studies show that human microglia polarized to the M1 phenotype but not M2 are toxic to human OPCs with TNF-α implicated as the soluble mediator (Moore et al., 2015). The effects of TNF-α-mediated injury involve TNFR1, whereas activation of TNFR2 can mediate protection (Finsen et al., 2002; Plant et al., 2007). Activated microglia have been shown to induce a neurotoxic astrocyte phenotype that may be detrimental to OPC survival and differentiation (Liddelow et al., 2017) Fig. 4

4.3. Metabolic injury

We have modeled the susceptibility of OLs to metabolic stresses mimicking those encountered in MS lesions by exposing human adult brain-derived OLs to culture conditions deficient in nutrients such as glucose (Rone et al., 2016). To directly examine the relative susceptibility of immature *versus* mature OLs to such insults, we compared the vulnerability of newborn rat-derived OPCs, *in vitro* OPC-matured OLs, and OLs derived from the mature rat brain (Rao et al., 2017). We observed that the least mature cells (newborn OPCs) were most vulnerable to injury. Resistance to metabolic insult increased with cell differentiation but was still decreased compared to OLs derived from the adult brain. Lethal injury in the newborn cells involved activation of the caspase cascade and could be partially protected by the pan-caspase inhibitor *Z*-VAD. In contrast, the reduced levels of cell death found for cells derived from mature animal was not protected by using the pan-caspase inhibitor. Metabolic studies conducted using a Seahorse bioanalyzer revealed increased dependence of the OPCs on oxidative phosphorylation to produce ATP compared to the preferential use of glycolysis by adult rat OLs. The increased vulnerability of immature as compared to the mature OL lineage cells was also seen in studies that induced injury with NMDA receptor agonists (Wosik et al., 2004) and with TNF-α as illustrated in Fig. 4. Our experimental studies of injury susceptibility also indicate a need to consider species variability (rodent vs. human).

4.4. Modulation of OPCs migration and differentiation by immune-related molecules

In addition to their participation in OPC injury and survival as described above, immune cells and their products can also positively or negatively impact the remyelination process via actions on OPC migration, differentiation into myelinating OLs, and survival (summarized in Fig. 3). These immune-mediated effects could act directly on the OPCs, or through interactions with intermediaries including other glia (astrocytes), blood brain barrier (BBB), and the extracellular matrix (ECM). A large number of cytokines can modulate the myelination process by indirectly inducing responses in astrocytes. Specific cytokines that directly act on OPCs include IL-11 and IL-17A, both found to enhance OPC survival and maturation (Maheshwari et al., 2013; Rodgers et al., 2015; Wang et al., 2017; Zhang et al., 2006), while IL-9 has been reported to decrease OPC proliferation and differentiation (Ding et al., 2015). Neurotrophic factors such as brain derived growth factor (BDNF) and leukemia inhibitory factor (LIF) can promote survival and/or differentiation of OPCs. Although the neurotrophic factors are usually considered to be produced by CNS-resident cells, the molecules can also be produced by infiltrating lymphocytes and myeloid cells (Rittchen et al., 2015; Tsiperson et al., 2015; Vanderlocht et al., 2006). OPCs express an array of chemokine receptors that respond to chemokines secreted by the immune compartment in the CNS, resulting in various effects. A number of chemokines including CXCL1 and CXCL12 are significant contributors to OPC migration and maturation (Chu T et al., 2017, Kremer et al., 2016, Patel et al., 2010, Patel et al., 2012, Zilkha-Falb et al., 2016). CXCL1 and CXCL2 acting via CXCR2 may also protect OPCs from apoptosis (Hosking et al., 2010). Treatment of OPCs with CXCL10 results in cell death (Zilkha-Falb et al., 2016). OL lineage cells may themselves be a source of chemokines (Zeis et al., 2016). Systemic immune cells can also be sources of semaphorins that inhibit OPC migration (Costa et al., 2015; Kremer et al., 2015; Piaton et al., 2011).

With respect to myeloid cells in the experimental lysolecithin toxin demyelination model, it has been shown that M2 microglia supported remyelination (Miron et al., 2013). Our microarray analyses of human

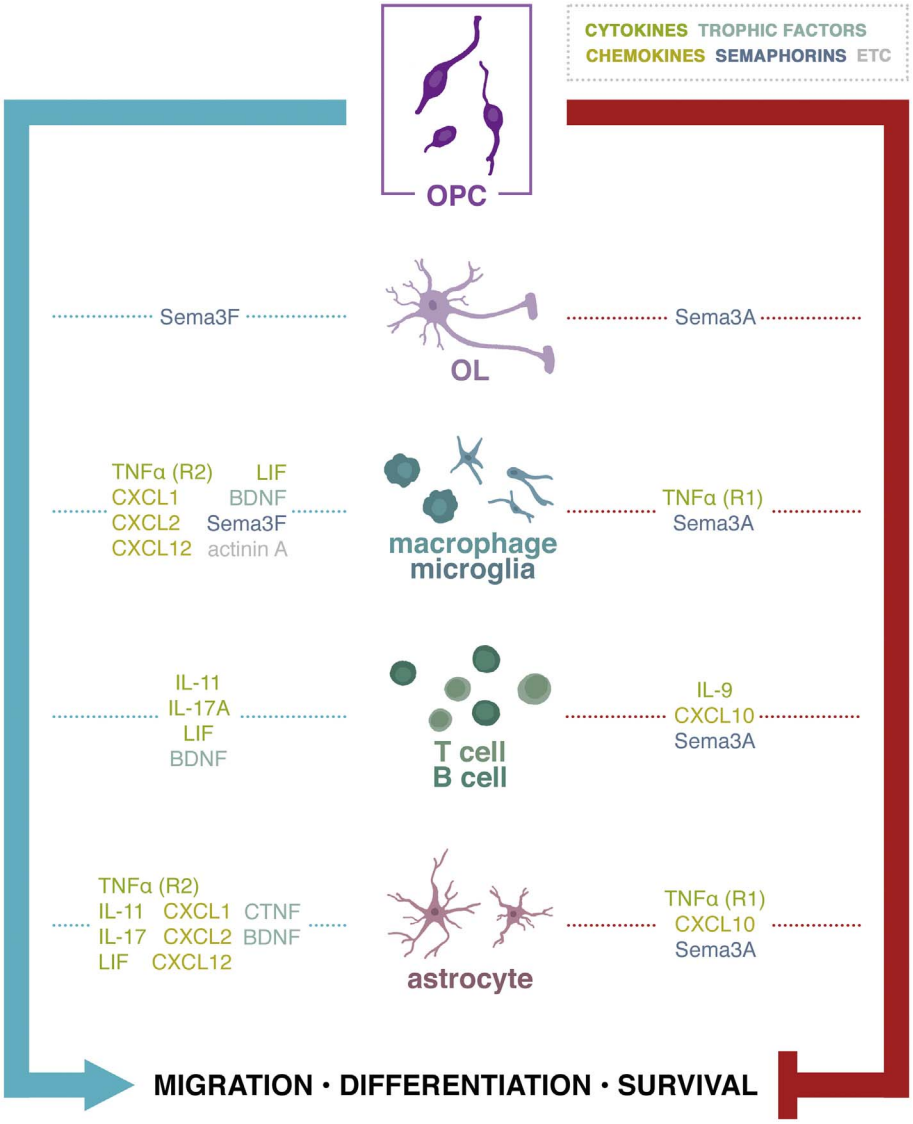

Fig. 3. Summary of molecular factors involved in OPC migration, differentiation, and survival.

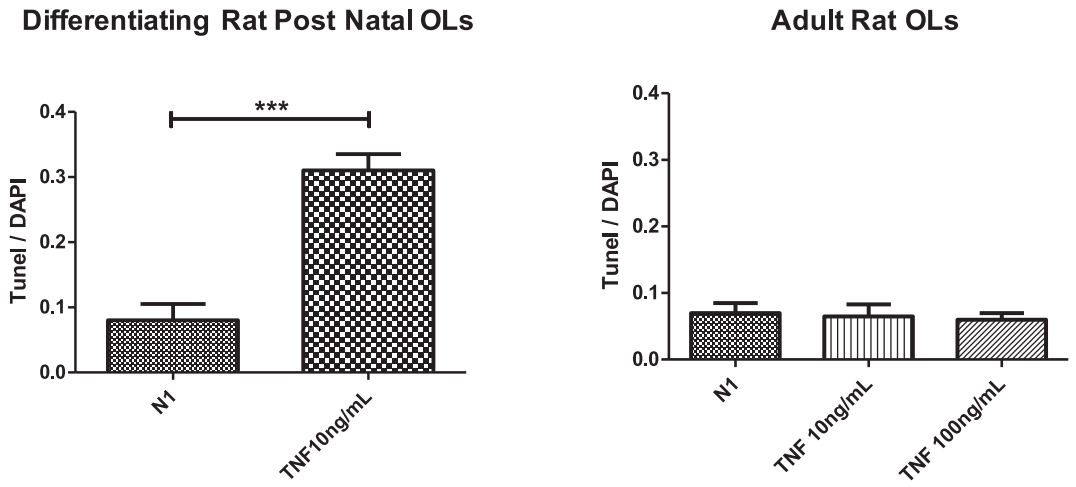

Fig. 4. Rat post-natal OLs show increased *in vitro* susceptibility to TNF-α mediated injury compared to that of adult rat brain-derived OLs, as measured by % TUNEL+ cells after 24-h exposure to TNF-α.

microglia and monocyte-derived-macrophages confirmed that M1-polarized cells favor inflammation-mediated injury, while M2-favored potential protective/repair molecules (Healy et al., 2016b). Under all such conditions, microglia were more biased to the repair than injury-mediating phenotype when compared to monocyte-derived-macrophages. In neuroinflammatory disease as suggested by studies in the EAE model, another important consideration is how injury of neural progenitors in the sub-ventricular niches by myeloid cells may influence the overall repair process (Rasmussen et al., 2011; Xing et al., 2014; Kazanis et al., 2017).

One can extend the effects of the immune system on OPCs to their role in modulating the overall CNS microenvironment. A specific example is the presence of inhibitors of OPC migration, such as myelin debris, in MS lesions (Boyd et al., 2013; Plemel et al., 2013). The extent and nature of myelin breakdown products present in phagocytosing myeloid cells is used as an index of lesion activity in MS (Kuhlmann et al., 2017), with clearance of myelin being dependent on myeloid cells. We have found that the process of myelin clearance is at least in part due to the actions of the tyrosine kinase receptor, MerTK, a member of the TAM family of receptors (Healy et al., 2016a). Microglia are more effective phagocytosers than monocytes-derived-macrophages, and the activity of phagocytosis is dependent on the polarization state of these myeloid cells. Monocyte-derived-macrophage-mediated myelin phagocytosis is defective in MS patient-derived cells (Healy et al., 2017; Natrajan et al., 2015). This process may be amenable to therapeutic intervention. Additional considerations would be the presence in the microenvironment of inhibitory molecules such as netrin and proteoglycans (Bin et al., 2013; Sloane et al., 2010).

5. Effects of immunotherapies

Systemic immune-directed therapies are the foundation of current MS therapy. To be considered are the effects of agents on OPCs, including those that can directly access the CNS and/or those that indirectly affect immune cells (or their products) that in turn gain access to the CNS. The initial platform therapies in MS – namely, subcutaneously injected type 1 interferons (IFN) and glatiramer acetate (GA) – do not reach the CNS. GA polarizes the immune response in a Th2 direction and induces BDNF production by cells in MS lesions (Aharoni et al., 2008; Rosato Siri et al., 2013; Stadelmann et al., 2002). We found that supernatants from human GA-reactive T-lymphocytes potentiated OL numbers in rodent and human OPC cultures (Zhang et al., 2010). The effects of Th2-polarized lines were stronger than Th1-polarized cells. Microarray and protein analyses revealed increased expression of IGF-2 and BMP-7 neurotrophic factors in Th2 and Th1-polarized GA-reactive cell lines. Functional studies confirmed IGF-2 as trophic for OPCs (Zhang et al., 2010). Type-1 IFNs have also been claimed to induce a Th2 shift. B-cell depleting therapies exert their immediate effect by reducing the production of immunoregulatory soluble molecules that are immunoglobulin-independent. As mentioned, B-cell products can be toxic to OPCs (Lisak et al., 2012).

Sphingosine-1-phosphate receptor (S1PR) modulators can access the CNS and are shown to have direct effects on OPCs *in vitro*. We found that *in vitro* addition of FTY720p to human fetal brain-derived progenitors induced an initial cell process retraction that was reversed by uncoupling S1PR3 and 5 from their respective G-proteins. Continued FTY720p exposure resulted in process extension that could be reproduced by an S1PR1 agonist (Miron et al., 2008). Quantitative real-time polymerase chain reaction showed that FTY720p induced reciprocal and cyclic modulation of S1PR1 and S1PR5 messenger RNA levels. siRNA studies in rat OPCs revealed that S1PR1 participates in PDGF-induced OPC mitogenesis (Jung et al., 2007). Miron et al. found that FTY720p enhanced remyelination following lysolecithin exposure in rat brain organotypic cultures. This enhancement was associated with increased microglia numbers and increased immunoreactivity for the astrocytic marker glial fibrillary acidic protein (GFAP) (Miron et al., 2010). Our additional studies with human fetal progenitors in dissociated culture indicated that FTY720p acted directly on OPCs to impact differentiation, and also indirectly via neurons and astrocytes by activating ERK1/2 and p38 MAPK (Cui et al., 2014; De Paula et al., 2014). *In vivo* studies using toxin models have not consistently been able to demonstrate significant remyelination with FTY720p, although some studies indicate an initial protective effect (Alme et al., 2015; Blanc et al., 2015; Hu et al., 2011; Kim et al., 2011; Slowik et al., 2015; Yazdi et al., 2015). FTY720p induces protective and anti-inflammatory responses in astrocytes, including type-1 IFNs (Hoffmann et al., 2015; Rothhammer et al., 2017). However, it has been found through using IFNR1-null mice that type-1 IFNs were redundant for the remyelination process (Schmidt et al., 2009; Zhang et al., 2015). FTY720p treatment promoted proliferation and differentiation of OPCs in mice with EAE (Zhang et al., 2015). FTY720p can also promote cell response in the neurogenic niches (Cipriani et al., 2017). To date, clinical studies with the agent, while showing reduced lesion formation in MS, have not documented enhanced remyelination. With regards to additional agents that access the CNS, there was found to be no detectable effect of fumarates in the cuprizone model (Moharregh-Khiabani et al., 2010).

6. Conclusion

Experimental studies described above indicate the potential for components of the adaptive and innate immune systems to directly and indirectly impact the capacity of OPCs to remyelinate. Potential therapeutic approaches to enhance the remyelination process would be to promote the positive and/or reduce the negative actions of the immune system in order to affect OPC survival, migration, and differentiation capacity. While focusing on immune-OPC interactions, it is critical to consider the status of the axons, the ultimate target of the remyelination process. In the current era of immunotherapy in MS, we await definitive observations on the effects of any current therapies on neuroprotection and repair and the development of agents that will positively impact immune-OPC interactions as described in this review.

Conflict of interest

No conflicts of interest to disclose.

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