Immunology & Cell Biology 2022; 1–11
www.wileyonlinelibrary.com/journal/icb

REVIEW

OPEN

Immune–stem cell crosstalk in the central nervous system: how oligodendrocyte progenitor cells interact with immune cells

Sonia Cabeza-Fernández[1,2], Jessica A White[3], Christopher E McMurran[4,5], José A Gómez-Sánchez[1,2] & Alerie G de la Fuente[1,2,3]

1 Instituto Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain
2 Instituto de Neurosciencias CSIC-UMH, San Juan de Alicante, Spain
3 Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
4 Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
5 Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

Keywords
Immunomodulation, macrophages, microglia, OPCs, remyelination, T cells

Correspondence
Alerie G de la Fuente, Instituto Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain.
E-mail: guzman_ale@isabial.es

Received 30 September 2022;
Revised 23 November 2022;
Accepted 24 November 2022

doi: 10.1111/imcb.12610

Immunology & Cell Biology 2022; 1–11

Abstract

The interaction between immune and stem cells has proven essential for homeostasis and regeneration in a wide range of tissues. However, because the central nervous system was long considered an immune-privileged organ, its immune–stem cell axis was not deeply investigated until recently. Research has shown that oligodendrocyte progenitor cells (OPCs), a highly abundant population of adult brain stem cells, establish bidirectional interactions with the immune system. Here, we provide an overview of the interactions that OPCs have with tissue-resident and recruited immune cells, paying particular attention to the role they play in myelin regeneration and neuroinflammation. We highlight the described role of OPCs as key active players in neuroinflammation, overriding the previous concept that OPCs are mere recipients of immune signals. Understanding the mechanisms behind this bidirectional interaction holds great potential for the development of novel therapeutic approaches limiting neuroinflammation and promoting myelin repair. A better understanding of the central nervous system's immune–stem cell axis will also be key for tackling two important features shared across neurodegenerative diseases, neuroinflammation and myelin loss.

INTRODUCTION

Despite having been initially studied in the context of immunity and protection from pathogens, the immune system has since proven to be essential for tissue function in homeostasis and repair. In homeostasis, the immune system is key for the local immune surveillance and maintenance of the stem cell niche.[1,2] Following tissue injury, an early inflammatory response and clearance of damage-associated debris are essential for stem cell activation. In addition, immune cells have recently emerged as key regulators of stem cell differentiation in several tissue regenerative processes including muscle[3] and intestine.[2] Besides receiving signals from the immune system, stem cells are known to be active players in immune–stem cell crosstalk. It is well established that intestinal or neural stem cells can modulate the immune system by secreting anti-inflammatory factors.[2,4] Furthermore, it has been shown that stem cells can regulate their immune-privileged status by altering the surface expression of major histocompatibility complex (MHC)-I based on their level of activity, and thus, can modulate their clearance by $CD8^+$ cytotoxic T cells.[5] Therefore, the bidirectional crosstalk between the immune system and tissue-resident stem cells is essential for maintaining tissue integrity and driving regeneration.[1] This crosstalk, however, has only more recently been explored in the central nervous system (CNS). Unlike

other tissues, the CNS is anatomically protected by the blood–brain barrier, supporting the idea of the CNS being an immune-privileged organ.[6] Thus, investigations into the immune–stem cell crosstalk have focused on pathological situations where this barrier was breached. The concept of an immune-privileged CNS has now been challenged by the presence of peripheral immune cells in the healthy parenchyma during development and adulthood,[7–9] as well as the discovery of meningeal lymphatics.[10,11] In addition, adaptive immune cells have been identified in the healthy CNS, where they can alter CNS stem cell behavior.[12,13] These reports have highlighted novel roles for CNS stem cell and immune system crosstalk beyond pathological situations, opening the door to address this crosstalk in CNS development, homeostasis and repair. In this review, we will focus our attention on the role of the CNS immune–stem cell axis in the context of neuroinflammation and myelin regeneration.

While the neuronal compartment of the CNS has a poor regenerative capacity, this is not the case for myelin —the protective lipid-rich layer surrounding axons. Myelin can be lost as a result of immune-mediated mechanisms [as occurs in multiple sclerosis (MS)], because of the presence of specific mutations (e.g. leukodystrophies) or it can be altered with aging[14] and neurodegenerative diseases, such as Alzheimer's disease.[15,16] Lost myelin can be efficiently restored by a tightly controlled regenerative process driven by a highly abundant (5–8% of total CNS cells) population of adult brain stem cells, known as oligodendrocyte progenitor cells (OPCs). In the brain and spinal cord, OPCs arise in sequential waves from discrete regions of the ventral and then dorsal neuroepithelium during embryonic development.[17,18] These OPCs give rise to oligodendrocytes, the cells that form myelin for axonal ensheathment during developmental myelination and myelin regeneration (remyelination), physically protecting the axon, providing trophic support and preventing axonal loss.[19] OPCs can be identified by the expression of oligodendrocyte lineage transcription factors, including Olig2 and Sox10, along with nerve/glial antigen 2 or platelet-derived growth factor receptor alpha (PDGFRα).[20] OPCs comprise a heterogenous population of diverse developmental origin,[17,18] regional specification[21] and transcriptional expression.[22,23] The traditional function of OPCs has been their capacity to differentiate into myelin-forming oligodendrocytes. However, OPC heterogeneity and the presence of quiescent OPCs throughout adulthood[24] suggest they may have a more complex role in the CNS than first thought. In fact, recent discoveries have shown that OPCs are multifaceted regulators of the CNS in health and disease,[25] regulating neuronal activity,[26] modulating neural circuits *via* synapse engulfment[27] and regulating the growth and remodeling of axon arbors.[28] Furthermore, OPCs are known to regulate angiogenesis and blood–brain barrier permeability. In development, OPCs contact endothelial cells and regulate neonatal angiogenesis and vascular remodeling through OPC-encoded Wnt activity.[29] Upon white matter injury, OPCs also alter blood–brain barrier permeability by increasing matrix metalloprotease 9 secretion in the proximity of endothelial cells,[30] and can cluster on top of vasculature, interfering with astrocyte endfeet and endothelial tight junction integrity.[31] Furthermore, novel research has shown that OPCs can adopt behaviors that are usually attributed to cells from the immune system, such as immune surveillance, expressing cytokines and adhesion molecules associated with immune cell infiltration and presenting antigens to T cells in the CNS.[32–34]

Recent discoveries have also shown that, like other regenerative processes, successful remyelination is associated with inflammation and an adequate immune–stem cell crosstalk. Immune cells are therefore not only associated with myelin damage but are also required for adequate myelin regeneration, to maintain CNS homeostasis and to prevent axonal loss.[35–37] Therefore, there is increasing evidence supporting the concept of bidirectional immune–stem cell crosstalk in the CNS. OPC–immune cell crosstalk during myelin regeneration has been mainly studied using toxin-induced demyelination models, which allow for the study of immune cells in remyelination independent of their pathogenic role.[38] Research using gain- and loss-of-function studies has demonstrated that the immune system is required for successful remyelination. An investigation by Setzu *et al.*[39] using OPCs transplanted in retinal ganglion cell explants has shown that promoting inflammation by zymosan, a Toll-like receptor-2 agonist, enhances myelination. Furthermore, loss-of-function studies based on depleting either the innate[35] or the adaptive immune system[36] have shown impaired myelin regeneration. Both the innate and adaptive immune cells and their secreted factors alter OPC survival, proliferation and differentiation capacity, thus affecting the remyelination process.

The role of OPCs in neuropathological conditions goes further than their regenerative function during remyelination. Recent data have shown that OPCs also appear to be actively involved in shaping immune responses, through immunomodulatory properties, similar to what has been described for other stem cells.[1] Cumulative evidence has shown that OPCs can modulate innate and adaptive immune cell CNS recruitment, infiltration and activation through the expression of

cytokines, chemokines and cell adhesion molecules. For example, it is now well established that in an inflammatory environment, like that observed in demyelination,[32,34] exposure to MS patient–derived cerebrospinal fluid[40] or cytokines such as interleukin (IL)-1β, tumor necrosis factor-α or interferon-gamma (IFNγ)[41] enhances the OPC secretion of proinflammatory cytokines and chemokines, such as C–X–C motif chemokine ligand 10, chemokine (C–C motif) ligand (CCL) 2, CCL5 or IL-1β.[42] Furthermore, the expression of immune-associated genes linked to antigen processing and presentation by OPCs was described by Suzumura *et al.* in 1986.[43] More recently, single-cell RNA sequencing revealed the presence of a specific disease–associated OPC cluster characterized by the upregulation of genes involved in several immune processes,[32,44] rekindling interest in the immunomodulatory properties of OPCs.

Here, we review the CNS immune–stem cell crosstalk, focusing on immune–OPC interactions. We discuss the evidence that immune cells are not only associated with myelin damage but are also key drivers of OPC differentiation and remyelination. In addition, we summarize the mounting evidence suggesting an active immune modulatory role of OPCs in this bidirectional crosstalk, which places OPCs as important players in neuroinflammation. A better understanding of the immune–OPC axis will be key to investigating novel pathways and developing potential therapeutic targets for limiting CNS inflammation and boosting myelin regeneration in neurological disorders.

OPC–T-CELL INTERACTIONS

The interaction between the immune system and oligodendrocyte lineage cells in pathological conditions, such as MS, in which myelin-reactive T cells attack oligodendrocytes and destroy myelin, is well established and has already been extensively reviewed.[16,45] Here we focus on the immune–OPC crosstalk during regeneration and how OPCs can modulate the immune response through interactions with T cells.

In 2003, Bieber *et al.* reported that T cells (both $CD4^+$ and $CD8^+$ T cells) are necessary for remyelination, as mice lacking these cells have impaired remyelination after lysolecithin-induced demyelination in the spinal cord.[36] These results support the idea of a neuroprotective and proregenerative role for T cells after damage in the CNS, an idea that was previously proposed for myelin-reactive T cells, which enhance the recruitment of microglia, macrophages and B cells expressing neurotrophic factors.[46] Myelin-reactive T cells were also shown to promote OPC differentiation and increase oligodendrocyte numbers when administered prior to a brain lesion.[47] T cells are not a homogenous population and even within $CD4^+$ or $CD8^+$ T cells, we find different subsets with defined immune functions. Within an inflammatory and demyelinating context, for example, T helper (Th) 1 and Th17 $CD4^+$ T cells and $CD8^+$ T cells are proinflammatory, while Th2 and regulatory T cells (Tregs) have anti-inflammatory properties.[48] However, the specific roles of the different effector T-cell subsets in OPC biology, and subsequently in remyelination, are not yet fully defined.

Lymphocytes derived from peripheral mononuclear blood of patients with MS have been shown to impair remyelination when grafted in a lysolecithin-induced demyelination mouse model. While there was an increase in OPC proliferation, there was also an associated impairment in OPC differentiation and remyelination mediated by the microglial/macrophage secretion of CCL19.[49] Similarly, activated $CD4^+$ and $CD8^+$ T-cell supernatants enhance OPC proliferation in OPCs derived from human hematopoietic stem cells or from human fetal brains. This enhanced proliferative effect seems to be mediated by the liberation of vascular endothelial growth factor A, which interacts with the vascular endothelial growth factor receptor 2 expressed on the OPC membrane.[50] However, different T-cell subsets can also directly influence OPC biology.

Using a model of cuprizone-induced demyelination combined with the adoptive transfer of myelin-reactive $CD4^+$ T cells, it has been shown that both Th1 and Th17 $CD4^+$ T cells infiltrate the CNS and that Th17 infiltration is associated with impaired remyelination and increased axonal stress.[51] This impaired remyelination is likely mediated by the secretion of IL-17, which alters OPC proliferation and impairs differentiation by increasing the expression of potassium channel Kv1.3 and Notch1 activation in OPCs.[52,53] Alternatively, impaired remyelination may result from the direct contact between Th17 cells and new myelinating oligodendrocytes, which increases oligodendrocyte cell death through glutamate release.[54]

$CD4^+$ Th1 cells also impact OPC biology *in vitro*, with contradictory results in human and murine OPCs. On the one hand, activated Th1 cell supernatant impairs human $A2B5^+$ OPC differentiation into O4- and GalC-expressing oligodendrocytes.[55] On the other hand, murine Th1 cell supernatants and OPC–Th1 cell cocultures alter OPC morphology, leading to a significant extension of processes, which suggests increased differentiation.[56,57] IFNγ, a key cytokine secreted by $CD4^+$ Th1 cells, does not explain these contradictory results, as exposure of OPCs to T-cell–derived IFNγ enhances OPC proliferation while inhibiting OPC

differentiation and increasing oligodendrocyte apoptosis.[58] Therefore, the effect of Th1 cells on OPC biology remains to be elucidated.

As with Th1 and Th17, Th9 cells may also influence OPC biology through the secretion of IL-9, as the IL-9 receptor is highly expressed by OPCs.[59] IL-9 in combination with other proinflammatory cytokines, such as IL-17, tumor necrosis factor-α and IL-1β (but not by itself), can impair OPC proliferation and differentiation. On the contrary, when combined with IFNγ, IL-9 promotes OPC proliferation and differentiation. These data suggest that Th9 cells may also influence OPC biology, but only in combination with an inflammatory microenvironment.[59]

Unlike Th1, Th17 and Th9 cells, Tregs have been shown to have proregenerative functions in the CNS, similar to what is seen in other tissues such as muscle.[3] Diphtheria toxin–mediated depletion of Tregs has revealed that Tregs are essential for adequate myelin regeneration in lysolecithin-induced demyelination[60] and a stroke model.[61] These two models have shown that Tregs enhance OPC differentiation and remyelination by acting directly on OPCs but also indirectly through microglia modulation. The Treg secretome also directly enhances OPC differentiation in pure OPC cultures *in vitro* and increases myelination in cerebellar brain slices. This direct prodifferentiation effect on OPCs is, at least *in vitro*, partially mediated by Treg-derived cellular communication networ factor 3 (CCN3),[60] even though CCN3 deletion does not affect OPC differentiation or remyelination upon lysolecithin-induced demyelination.[62] In an ischemic stroke model, by contrast, Treg-dependent white matter repair was mediated by osteopontin secretion, which promotes tissue-reparative microglia and a subsequent increase in OPC differentiation and remyelination.[61] Together, we can conclude that different types of T cells have different effects on OPC biology during inflammation which can help or impair myelin regeneration. Identifying the mechanisms by which these cells enhance remyelination could lead to new therapeutic targets in neurological diseases.

However, OPC–T-cell interactions are not unidirectional, and it is now accepted that OPCs are not only recipients of immune signals but are also active agents with both proinflammatory and anti-inflammatory roles depending on the context. To address how OPCs can modulate T-cell–mediated inflammatory responses, we review the current literature regarding OPC–T-cell interactions, including antigen presentation by oligodendrocyte lineage cells and the capacity of OPCs to modulate T cells through other mechanisms.

Although antigen presentation by oligodendrocyte lineage cells has been described for several years, how this expression is linked to OPC–T-cell interplay was not properly described until recently. The most compelling evidence for OPC–T-cell interactions has emerged from several studies addressing this crosstalk in the context of MS. In 2018, Falcão *et al.*[32] described a disease-specific OPC population through single-cell transcriptomics of oligodendrocyte lineage cells in mice undergoing experimental autoimmune encephalomyelitis (EAE)—a mouse model of T-cell–mediated demyelination. In this study, they revealed that a cluster of OPCs can express genes linked to the MHC-II antigen-presenting pathway and that this gene expression pattern can be recapitulated *in vitro* by stimulating OPCs with IFNγ. In response to IFNγ, MHC-II–expressing OPCs can phagocytose myelin and act as antigen-presenting cells, activating memory and effector $CD4^+$ T cells.[32] Additional evidence supporting this idea was published shortly after, when a gene expression analysis was performed in an *in vivo* experiment on the genetic fate tracing of OPCs into mature oligodendrocytes in the cuprizone model. This study reported that IFNγ not only promotes the expression of genes involved in MHC-II antigen processing and cross-presentation, but also immunoproteasomes and MHC-I antigen processing and presentation in both demyelinating mouse models and samples from patients with MS. Therefore, OPCs could activate not only $CD4^+$ T cells as previously reported, but also $CD8^+$ T cells, leading to OPC death.[33] Beyond classic MHC-I and MHC-II pathways, antigen presentation by OPCs also seems to be mediated by low-density lipoprotein receptor–related protein 1, which is highly expressed by several cells in the CNS, including OPCs.[63] An oligodendroglia-specific knockout of low-density lipoprotein receptor–related protein 1 was developed using both *Olig1*$^{Cre/Cre}$ and *Pdgfra*^{CreERT2} mice to better understand its role in OPC biology. Deletion of this gene resulted in enhanced OPC differentiation and remyelination, reduced expression of inflammatory genes in the cuprizone model, reduced inflammation, lower clinical scores and reduced spinal cord T-cell infiltration in mice undergoing EAE.[63] OPCs lacking low-density lipoprotein receptor–related protein 1 expression also showed a reduced MHC-I, MHC-II and immunoproteasome expression. This reduced expression led to the disruption of OPC antigen cross-presentation to $CD8^+$ T lymphocytes, decreasing $CD8^+$ T-cell proliferation and overall inflammation.[63] Moreover, OPCs can express CD81, CD82 and CD9, which are associated with MHC-I and MHC-II clustering, and thus, further contributing to OPC-mediated T-cell activation.[32,64]

Besides molecules associated with the antigen processing and presentation pathways, OPCs can

exacerbate T-cell–mediated inflammation *via* the expression of the nuclear factor-kappa β activator Act1. OPC-specific deletion of Act1 was found to attenuate IL-17–induced EAE pathogenesis.[65] Conversely, OPCs can also decrease T-cell–mediated inflammation by expressing programmed death 1 ligands CD273 and CD274, and FasL *in vitro* upon exposure to cerebrospinal fluid from patients with MS. This is known to reduce T-cell activation and subsequent inflammation.[40,66]

As mentioned previously, OPCs can also modulate immune cell responses through cell adhesion molecules. It has been shown that OPCs isolated from mice undergoing T-cell–mediated demyelination (i.e. EAE) upregulate cell adhesion molecules intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. This upregulation has also been described *in vitro*, when OPCs are exposed to an inflammatory environment, such as the secretome of Th1 cells. This increased intercellular adhesion molecule-1 and vascular cell adhesion molecule 1 expression in OPCs augments the formation of stable contacts between Th1 cells and OPCs, increasing OPC–T-cell interactions.[57]

In summary, OPCs can bidirectionally modulate T-cell–mediated inflammation depending on the CNS environment, through either cell–cell contact *via* the expression of antigen-presenting molecules, adhesion molecules and other receptors, or through the secretion of cytokines and chemokines (Figure 1).

OPC–B-CELL INTERACTIONS

Like T cells, B cells have also been considered pathogenic in the CNS, with special attention being played to their role in cortical pathology, MS pathogenesis and progression. In fact, several successful therapies for MS treatment, and especially those focused on the progressive phase of the disease, include agents that selectively deplete B cells, such as ocrelizumab.[67] Fewer studies have been performed to understand the interaction between B cells and OPCs in remyelination. Existing evidence points toward some positive effects of B-cell infiltration in the brain not only in pathogenesis but also during homeostasis, with B-1a cells being present in neonatal brain samples. B-1a cells induce OPC proliferation by immunoglobulin M–FCα/μR signaling, and, if depleted, can lead to a decrease in OPCs and mature oligodendrocyte numbers,[9] suggesting a key role in OPC differentiation. Moreover, a recent study demonstrated that regulatory B-cell adoptive transfer in mice undergoing EAE reverses the clinical phenotype, decreases CNS myeloid cell content and increases OPC numbers and differentiation, thus promoting myelin repair.[68]

There is little to no literature at present describing OPC signaling to B cells, thus we could not include it here, but we consider it an interesting interaction to be further explored and that will likely be described in the near future.

OPC–MICROGLIA/MACROPHAGE INTERACTIONS

Like other tissues, the CNS has its own population of resident macrophages known as microglia. In addition to microglia, in the context of injury, there is an influx of monocyte-derived macrophages from the periphery into the CNS, which can also interact with OPCs. Despite the clear differences between microglia and macrophages in terms of origin, transcriptomic profile, proliferation and temporal dynamics, because of experimental limitations, many studies in the context of remyelination have grouped these two populations as a single microglia/macrophage pool.[69,70] Thus, we will continue to use the term microglia/macrophages, unless these are distinguished in a relevant study.

Microglia/macrophages have been shown to influence OPC biology and myelination in development through mechanisms that may also be relevant during myelin repair. Using an *ex vivo* model of perinatal injury and cerebral slices from the human infant CNS, microglial activation was found to be linked to NLR family pyrin domain containing 3 inflammasome activation and subsequent IL-1β release, which increased follistatin levels and inhibited activin-A to limit OPC differentiation and myelination. In addition, during myelination, as a homeostatic mechanism, ameboid microglia can invade the myelinating corpus callosum and engulf nerve/glial antigen 2^+ OPCs that express markers of premyelinating oligodendrocytes in a fractalkine receptor–dependent manner. This result suggests that microglia phagocytose OPCs to ensure adequate developmental myelination.[71] It is yet to be determined whether a similar phagocytosis process occurs during remyelination and if so, how it contributes to successful repair.

Besides their roles in maintaining developmental myelination, microglia/macrophages are also important for adequate myelin regeneration after injury. Initial experiments using clodronate liposomes, which are toxic to cells that phagocytose them, made clear that microglia/macrophages are essential for successful remyelination in mouse models of lysolecithin-induced demyelination.[35] Microglia/macrophages can interact with OPCs and facilitate OPC differentiation and remyelination through (a) the clearance of myelin debris, which is inhibitory for OPC differentiation and

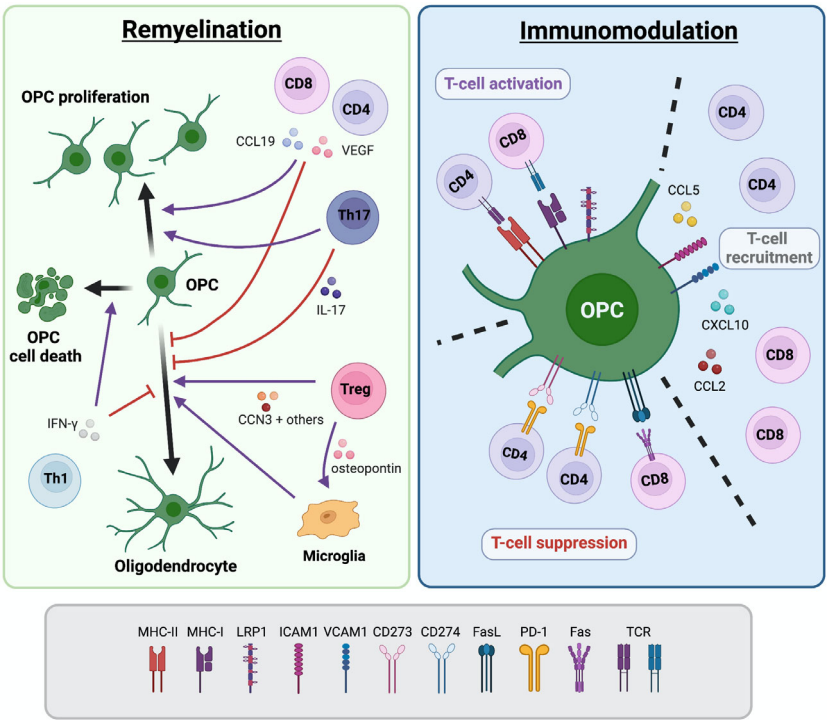


Figure 1. Summary of the interactions between oligodendrocyte progenitor cells (OPCs) and T cells. Factors secreted by different T cells mediating OPC differentiation and proliferation. OPC-mediated activation, recruitment or suppression of T cells by the expression of different ligands and molecules. The figure was created with BioRender.com. CCL, chemokine (C–C motif) ligand; CCN3, cellular communication factor 3; CXCL, C–X–C motif chemokine ligand; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; LRP1, low-density lipoprotein receptor–related protein 1; MHC, major histocompatibility complex; PD-1, programmed cell death-1; TCR, T-cell receptor; Th, T helper cell; Treg, regulatory T cell; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

remyelination; and (b) the secretion of growth signals, cytokines and other proregenerative factors. As the interaction of microglia/macrophages with OPCs and their role in remyelination have already been reviewed extensively,[37,72] we will briefly highlight key aspects of OPC–microglia/macrophage interactions focusing on the effect of secreted factors.

It is now well accepted that microglia/macrophages interact differently with OPCs depending on their proinflammatory state, as they undergo a switch from a proinflammatory to proregenerative phenotype during remyelination. This transition is mediated by microglia necroptosis and repopulation.[73] Anti-inflammatory and proregenerative macrophages secrete activin-A, which enhances OPC differentiation *in vitro*, an effect that is abrogated when activin-A is blocked in a microglia/macrophage secretome.[74] Proinflammatory and activated microglia, however, can also express neuropilin-1 in the white matter in an age- and activity-dependent manner. This is associated with adequate OPC proliferation and subsequent myelin repair through PDGFRα transactivation.[75] In addition, microglia and macrophages secrete insulin-like growth factor 1, which is important for OPC survival, proliferation and adequate myelination.[76]

It is clear that microglia and macrophages can interact with OPCs indirectly by the phagocytosis of myelin debris but can also secrete proregenerative factors such as activin A, neuropilin-1 and insulin-like growth factor 1, which promote OPC differentiation and remyelination. Exploring the pathways associated with this interaction may therefore provide us with novel approaches to boost remyelination through the manipulation of the innate immune system.

As it is now well established that OPCs can express immunomodulatory cytokines, it is not surprising that OPCs can also modulate microglia/macrophage-mediated inflammation in the CNS. Several studies have now shown that OPCs have a key role in maintaining the microglial homeostatic signature in the CNS and that OPC depletion leads to microglial activation and enhanced neuroinflammation. Nakano *et al.*[77] used the expression of herpes simplex virus tyrosine kinase under the nerve/glial antigen 2 promoter to deplete OPCs upon ganciclovir injections in the healthy CNS. OPC depletion was found to be associated with increased neuronal cell

death as a result of exacerbated microglia activation, indicating that OPCs are key to maintaining microglial homeostatic states. These results were also observed when depleting OPCs in both brain slices and *in vivo*, through the administration of either PDGFRα inhibitors or diphtheria toxin–mediated PDGFRα$^+$ cell depletion in PDGFRα-iDTR mice.[78] Loss of PDGFRα$^+$ OPCs led to a decrease in the expression of genes associated with a homeostatic signature in microglia (e.g. *Tmem110, P2ry12, Oflfml3*). These results indicate that OPCs are essential to maintaining homeostatic microglia and can prevent undesired microglial activation in the healthy CNS. However, we need to exercise caution on the interpretation of these results. Dying OPCs resulting from diphtheria toxin injection or pharmacological approaches could indirectly be phagocytosed by microglia, which are responsible for eliminating CNS cell debris. The presence of death cell debris and its phagocytosis could lead to an indirect activation of microglia *per se*, independent of OPC immunomodulation. Thus, it is essential to identify the mechanisms that may mediate this OPC immunomodulatory effect to prove that the observed microglial activation is genuinely a result of the absence of OPCs and not a consequence of excessive cell death in the CNS.

Considering the highly inflammatory environment observed in different neuropathological conditions, it is highly plausible that OPCs help to maintain microglial homeostasis not only in the healthy CNS but also during neuroinflammation. Using three different models of diphtheria toxin–mediated depletion, based on the expression of the diphtheria toxin receptor under the promoters of Olig1, nerve/glial antigen 2 and PLP, Zhang *et al.*[79] found that OPCs but not oligodendrocytes are required for limiting lipopolysaccharide-mediated CNS inflammation. OPC depletion in this model also caused an exacerbation of lipopolysaccharide-mediated proinflammatory cytokine expression in the CNS (IL-1β, IL-6, tumor necrosis factor-α, IL-12) because of an increase in the number of microglia and changes in microglial morphology that reflect a hyperresponsive state. This hyperresponsive microglial phenotype was rescued through lentiviral overexpression of CX3CR1 in OPC-depleted mice. OPC-mediated modulation of microglial activation in this context was shown to be driven by the maintenance of CX3CR1 expression in microglia through the secretion of transforming growth factor-beta 2 by OPCs, which bound to microglial transforming growth factor-beta receptor 2.[79] Therefore, these data suggest that microglial activation was triggered by the absence of OPCs and not by diphtheria toxin–mediated general cell death, as mentioned previously. In addition to transforming growth factor-beta 2, OPCs can modulate microglial activation and microglial-mediated inflammation through the expression of tumor necrosis factor receptor-2. A lack of oligodendroglial tumor necrosis factor receptor-2 expression was found to worsen disease progression and inflammation in mice with EAE.[80] This could be explained, at least in part, as a result of the increased expression of proinflammatory cytokines, such as CCL2, CCL11, C–X–C motif chemokine ligand 10 or C–X–C motif chemokine ligand 12, which was observed in tumor necrosis factor receptor-2 knockout OPCs *in vitro* when exposed to an inflammatory milieu.[41]

Consequently, OPCs can act as gatekeepers for inflammation in the CNS in health and disease by maintaining a homeostatic microglial signature and by preventing neurodegeneration associated with exacerbated microglial inflammation (Figure 2).

CONCLUSIONS AND FUTURE REMARKS

The interplay between the immune system and stem cells has proven to be essential for the maintenance of tissue homeostasis by limiting inflammation and promoting regeneration. These two features are both important for preventing axonal loss and the accumulation of symptoms linked to neurological disease progression. The research summarized here shows that a complex bidirectional crosstalk between the immune system and OPCs is fundamental for maintaining CNS health. Understanding how the immune system drives myelin repair provides an exciting avenue of research for developing proremyelinating therapies, as the peripheral immune system is more accessible for therapeutic interventions than the CNS. However, the complexity of immune–stem cell crosstalk is important to consider in the direct systemic manipulation of the immune system for CNS therapeutic gain. Therefore, future efforts should aim for a better understanding of the specific molecular mechanisms behind the proremyelinating capacities of the immune system, which are essential for developing more specific and local approaches to targeting the CNS immune–stem cell axis. This would also allow us to enhance CNS remyelination and benefit from the immune system's proregenerative functions while minimizing its other deleterious effects.

While OPCs have previously been thought to play a limited role in neurodegenerative disorders, the discovery of OPCs' immune-modulatory functions provides a new path for targeting CNS inflammation, a hallmark of diverse neurological disorders. Nevertheless, our understanding of OPC immune modulatory properties and their crosstalk with the immune system remains in its infancy. Current research has proven that instead of

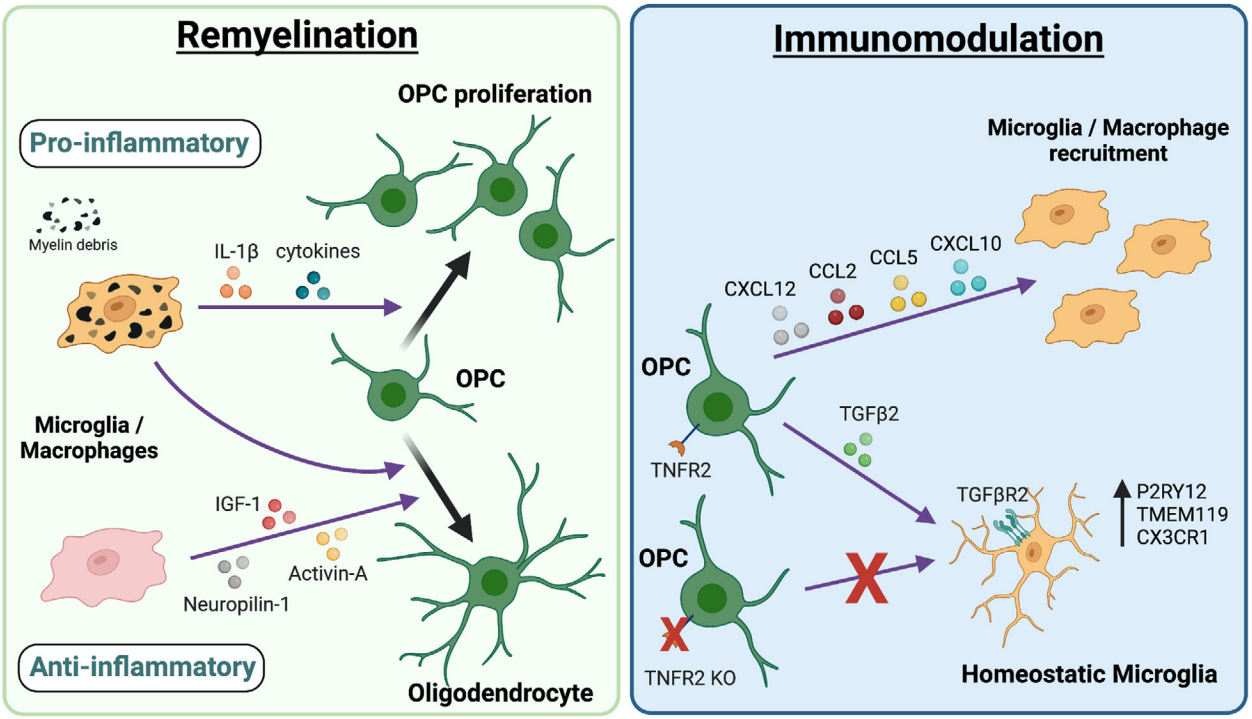


Figure 2. Summary of the interactions between oligodendrocyte progenitor cells (OPCs) and microglia/macrophages. Phagocytosis of myelin debris and secreted factors promoting regeneration. OPC microglial recruitment and phenotype regulation through secreted factors. The figure was created with BioRender.com. CCL, chemokine (C–C motif) ligand; CXCL, C–X–C motif chemokine ligand; IGF-1, insulin-like growth factor 1; IL, interleukin; KO, knock out; TGFβ2, transforming growth factor-beta 2; TGFβR2, transforming growth factor-beta receptor 2; TNFR2, tumor necrosis factor receptor-2.

being mere bystanders in neuroinflammation, OPCs are active players in orchestrating the CNS immune response. OPCs are also key gatekeepers of CNS homeostasis, limiting inflammation in the healthy CNS while being highly sensitive to inflammatory environments, like those observed in neurodegenerative diseases. Novel evidence has also shown that in an inflammatory milieu, OPCs may switch to become active contributors to pathology, the significance of which is yet to be determined. Therefore, joint efforts must be made to acquire a wider and deeper understanding of the different immune processes that OPCs can modulate, as well as the molecular mechanisms behind them. Increasing our understanding of how OPCs limit or enhance inflammation will allow us to manipulate OPC plasticity for developing novel approaches that target CNS inflammation locally. This will help counteract the detrimental effects of CNS inflammation in multiple neurodegenerative diseases.

CNS inflammation, myelin alteration and loss are widespread and persistent phenomena across CNS disorders. These phenomena are further aggravated with aging, a major risk factor for most neurodegenerative diseases, which further complicates the immune–OPC interactions described here. Thus, further investigations are required to expand our current knowledge on the immune–OPC axis, especially in the context of aging, to develop therapies that could utilize the immune modulatory properties of OPCs to limit CNS inflammation while promoting myelin regeneration.

ACKNOWLEDGMENTS

This work was supported by the Miguel Servet Fellowship (CP21/00032) from the Instituto Carlos III to Alerie G de la Fuente, Plan Nacional 2021 from the Agencia Estatal de Investigación to Alerie G de la Fuente (PID2021-124465OA-I00), a grant from the Conselleria de Educació Generalitat Valenciana (PROMOTEO CIPROM/2021/048), which funds José A Gómez-Sánchez's postdoctoral position, a grant from the Northern Ireland Department of Economy and a grant from the Wellcome which funds Jessica A White's position.

AUTHOR CONTRIBUTIONS

Sonia Cabeza-Fernandez: Conceptualization; resources; writing – original draft; writing – review and editing. **Jessica Aimee White:** Conceptualization; resources; writing – review and editing. **Christopher E McMurran:** Conceptualization;

resources; writing – review and editing. **Jose Antonio Gomez-Sanchez:** Conceptualization; resources; writing – review and editing. **Alerie Guzman de la Fuente:** Conceptualization; resources; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

REFERENCES

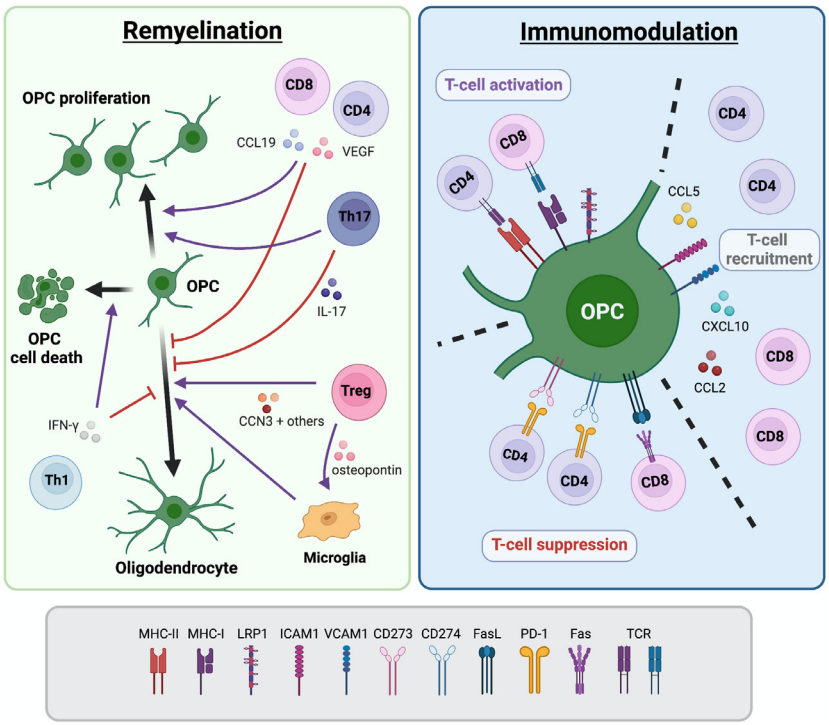
1. Naik S, Larsen SB, Cowley CJ, Fuchs E. Two to tango: dialog between immunity and stem cells in health and disease. *Cell* 2018; **175**: 908–920.
2. Biton M, Haber AL, Rogel N, *et al*. T helper cell cytokines modulate intestinal stem cell renewal and differentiation. *Cell* 2018; **175**: 1307–1320.
3. Burzyn D, Kuswanto W, Kolodin D, *et al*. A special population of regulatory T cells potentiates muscle repair. *Cell* 2013; **155**: 1282–1295.
4. Pluchino S, Cossetti C. How stem cells speak with host immune cells in inflammatory brain diseases. *Glia* 2013; **61**: 1379–1401.
5. Agudo J, Park ES, Rose SA, *et al*. Quiescent Tissue Stem Cells Evade Immune Surveillance. *Immunity* 2018; **48**: 271–285.
6. Louveau A, Harris TH, Kipnis J. Revisiting the concept of CNS immune privilege. *Trends Immunol* 2015; **36**: 569.
7. Smolders J, Heutinck KM, Fransen NL, *et al*. Tissue-resident memory T cells populate the human brain. *Nat Commun* 2018; **9**: 4593.
8. Pasciuto E, Burton OT, Roca CP, *et al*. Microglia require CD4 T cells to complete the Fetal-to-adult transition. *Cell* 2020; **182**: 625–640.
9. Tanabe S, Yamashita T. B-1a lymphocytes promote oligodendrogenesis during brain development. *Nat Neurosci* 2018; **21**: 506–516.
10. Louveau A, Smirnov I, Keyes TJ, *et al*. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015; **523**: 337–341.
11. Louveau A, Herz J, Alme MN, *et al*. CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat Neurosci* 2018; **21**: 1380–1391.
12. Kaya T, Mattugini N, Liu L, *et al*. $CD8^+$ T cells induce interferon-responsive oligodendrocytes and microglia in white matter aging. *Nat Neurosci* 2022; **25**: 1446–1457.
13. Dulken BW, Buckley MT, Navarro Negredo P, *et al*. Single-cell analysis reveals T cell infiltration in old neurogenic niches. *Nature* 2019; **571**: 205–210.
14. Wang F, Ren SY, Chen JF, *et al*. Myelin degeneration and diminished myelin renewal contribute to age-related deficits in memory. *Nat Neurosci* 2020; **23**: 481–486.
15. Chen JF, Liu K, Hu B, *et al*. Enhancing myelin renewal reverses cognitive dysfunction in a murine model of Alzheimer's disease. *Neuron* 2021; **109**: 2292–2307.
16. Stinissen P, Medaer R, Raus J. Myelin reactive T cells in the autoimmune pathogenesis of multiple sclerosis. *Mult Scler* 1998; **4**: 203–211.
17. Pringle NP, Richardson WD. A singularity of PDGF alpha-receptor expression in the dorsoventral axis of the neural tube may define the origin of the oligodendrocyte lineage. *Development* 1993; **117**: 525–533.
18. Kessaris N, Fogarty M, Iannarelli P, Grist M, Wegner M, Richardson WD. Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. *Nat Neurosci* 2006; **9**: 173–179.
19. Franklin RJM, Ffrench-Constant C. Regenerating CNS myelin - from mechanisms to experimental medicines. *Nat Rev Neurosci* 2017; **18**: 753–769.
20. Bergles DE, Richardson WD. Oligodendrocyte development and plasticity. *Cold Spring Harb Perspect Biol* 2015; **8**: a020453.
21. Viganò F, Möbius W, Götz M, Dimou L. Transplantation reveals regional differences in oligodendrocyte differentiation in the adult brain. *Nat Neurosci* 2013; **16**: 1370–1372.
22. Marisca R, Hoche T, Agirre E, *et al*. Functionally distinct subgroups of oligodendrocyte precursor cells integrate neural activity and execute myelin formation. *Nat Neurosci* 2020; **23**: 363–374.
23. Marques S, van Bruggen D, Vanichkina DP, *et al*. Transcriptional convergence of oligodendrocyte lineage progenitors during development. *Dev Cell* 2018; **46**: 504–517.
24. Psachoulia K, Jamen F, Young KM, Richardson WD. Cell cycle dynamics of NG2 cells in the postnatal and ageing brain. *Neuron Glia Biol* 2009; **5**: 57–67.
25. Fernandez-Castaneda A, Gaultier A. Adult oligodendrocyte progenitor cells – multifaceted regulators of the CNS in health and disease. *Brain Behav Immun* 2016; **57**: 1–7.
26. Orduz D, Maldonado PP, Balia M, *et al*. Interneurons and oligodendrocyte progenitors form a structured synaptic network in the developing neocortex. *Elife* 2015; **2015**: 1–53.
27. Auguste YSS, Ferro A, Kahng JA, *et al*. Oligodendrocyte precursor cells engulf synapses during circuit remodeling in mice. *Nat Neurosci* 2022; **25**: 1273–1278.
28. Xiao Y, Petrucco L, Hoodless LJ, Portugues R, Czopka T. Oligodendrocyte precursor cells sculpt the visual system by regulating axonal remodeling. *Nat Neurosci* 2022; **25**: 280–284.
29. Chavali M, Ulloa-Navas MJ, Pérez-Borredá P, *et al*. Wnt-dependent Oligodendroglial-endothelial interactions regulate White matter vascularization and attenuate injury. *Neuron* 2020; **108**: 1130–1145.
30. Seo JH, Miyamoto N, Hayakawa K, *et al*. Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury. *J Clin Invest* 2013; **123**: 782–786.
31. Niu J, Tsai HH, Hoi KK, *et al*. Aberrant oligodendroglial–vascular interactions disrupt the blood–brain barrier, triggering CNS inflammation. *Nat Neurosci* 2019; **22**: 709–718.

32. Falcão AM, van Bruggen D, Marques S, *et al*. Disease-specific oligodendrocyte lineage cells arise in multiple sclerosis. *Nat Med* 2018; **24**: 1837–1844.
33. Kirby L, Jin J, Cardona JG, *et al*. Oligodendrocyte precursor cells present antigen and are cytotoxic targets in inflammatory demyelination. *Nat Commun* 2019; **10**: 1–20.
34. Moyon S, Dubessy AL, Aigrot MS, *et al*. Demyelination causes adult CNS progenitors to revert to an immature state and express immune cues that support their migration. *J Neurosci* 2015; **35**: 4–20.
35. Kotter MR, Setzu A, Sim FJ, van Rooijen N, Franklin RJM. Macrophage depletion impairs oligodendrocyte remyelination following lysolecithin-induced demyelination. *Glia* 2001; **35**: 204–212.
36. Bieber AJ, Kerr S, Rodriguez M. Efficient central nervous system remyelination requires T cells. *Ann Neuro* 2003; **53**: 680–684.
37. Rawji KS, Yong VW. The benefits and detriments of macrophages/microglia in models of multiple sclerosis. *Clin Dev Immunol* 2013; **2013**: 948976.
38. McMurran CE, Zhao C, Franklin RJM. Toxin-based models to investigate demyelination and remyelination. *Methods Mol Biol* 1936; **2019**: 377–396.
39. Setzu A, Lathia JD, Zhao C, *et al*. Inflammation stimulates myelination by transplanted oligodendrocyte precursor cells. *Glia* 2006; **54**: 297–303.
40. Zveik O, Fainstein N, Rechtman A, *et al*. Cerebrospinal fluid of progressive multiple sclerosis patients reduces differentiation and immune functions of oligodendrocyte progenitor cells. *Glia* 2022; **70**: 1191–1209.
41. Desu HL, Illiano P, Choi JS, *et al*. TNFR2 Signaling regulates the immunomodulatory function of oligodendrocyte precursor cells. *Cell* 2021; **10**: 1785.
42. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. *Nat Rev Clin Oncol* 2022; **19**: 237–253.
43. Suzumura A, Silberberg DH, Lisak RP. The expression of MHC antigens on oligodendrocytes: induction of polymorphic H-2 expression by lymphokines. *J Neuroimmunol* 1986; **11**: 179–190.
44. Kenigsbuch M, Bost P, Halevi S, *et al*. A shared disease-associated oligodendrocyte signature among multiple CNS pathologies. *Nat Neurosci* 2022; **25**: 876–886.
45. Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple sclerosis: mechanisms and immunotherapy. *Neuron* 2018; **97**: 742–768.
46. Barouch R, Schwartz M. Autoreactive T cells induce neurotrophin production by immune and neural cells in injured rat optic nerve: implications for protective autoimmunity. *FASEB J* 2002; **16**: 1304–1306.
47. Hvilsted Nielsen H, Toft-Hansen H, Lambertsen KL, Owens T, Finsen B. Stimulation of adult oligodendrogenesis by myelin-specific T cells. *Am J Pathol* 2011; **179**: 2028–2041.
48. Zhou L, Chong MMW, Littman DR. Plasticity of $CD4^+$ T cell lineage differentiation. *Immunity* 2009; **30**: 646–655.
49. el Behi M, Sanson C, Bachelin C, *et al*. Adaptive human immunity drives remyelination in a mouse model of demyelination. *Brain* 2017; **140**: 967–980.
50. Choi EH, Xu Y, Medynets M, *et al*. Activated T cells induce proliferation of oligodendrocyte progenitor cells via release of vascular endothelial cell growth factor-a. *Glia* 2018; **66**: 2503–2513.
51. Baxi EG, DeBruin J, Tosi DM, *et al*. Transfer of myelin-reactive Th17 cells impairs endogenous remyelination in the central nervous system of cuprizone-fed mice. *J Neurosci* 2015; **35**: 8626–8639.
52. Liu H, Yang X, Yang J, *et al*. IL-17 inhibits oligodendrocyte progenitor cell proliferation and differentiation by increasing K^+ channel Kv1.3. *Front Cell Neurosci* 2021; **15**: 222.
53. Wang C, Zhang CJ, Martin BN, *et al*. IL-17 induced NOTCH1 activation in oligodendrocyte progenitor cells enhances proliferation and inflammatory gene expression. *Nat Commun* 2017; **8**: 1–16.
54. Larochelle C, Wasser B, Jamann H, *et al*. Pro-inflammatory T helper 17 directly harms oligodendrocytes in neuroinflammation. *Proc Natl Acad Sci USA* 2021; **118**: e2025813118.
55. Moore CS, Cui QL, Warsi NM, *et al*. Direct and indirect effects of immune and central nervous system–resident cells on human oligodendrocyte progenitor cell differentiation. *J Immunol* 2015; **194**: 761–772.
56. Lisak RP, Benjamins JA, Bealmear B, *et al*. Differential effects of Th1, monocyte/macrophage and Th2 cytokine mixtures on early gene expression for glial and neural-related molecules in central nervous system mixed glial cell cultures: Neurotrophins, growth factors and structural proteins. *J Neuroinflammation* 2007; **4**: 1–20.
57. González-Alvarado MN, Aprato J, Baumeister M, *et al*. Oligodendrocytes regulate the adhesion molecule ICAM-1 in neuroinflammation. *Glia* 2022; **70**: 522–535.
58. Agresti C, D'Urso D, Levi G. Reversible inhibitory effects of interferon-γ and tumour necrosis factor-α on Oligodendroglial lineage cell proliferation and differentiation *In vitro*. *Eur J Neurosci* 1996; **8**: 1106–1116.
59. Ding X, Cao F, Cui L, Ciric B, Zhang GX, Rostami A. IL-9 signaling affects central nervous system resident cells during inflammatory stimuli. *Exp Mol Pathol* 2015; **99**: 570–574.
60. Dombrowski Y, O'Hagan T, Dittmer M, *et al*. Regulatory T cells promote myelin regeneration in the central nervous system. *Nat Neurosci* 2017; **20**: 674–680.
61. Shi L, Sun Z, Su W, *et al*. Treg cell-derived osteopontin promotes microglia-mediated white matter repair after ischemic stroke. *Immunity* 2021; **54**: 1527–1542.
62. de la Vega GN, Penalva R, Dittmer M, *et al*. Dynamic CCN3 expression in the murine CNS does not confer essential roles in myelination or remyelination. *Proc Natl Acad Sci USA* 2020; **117**: 18018–18028.
63. Fernández-Castañeda A, Chappell MS, Rosen DA, *et al*. The active contribution of OPCs to neuroinflammation is mediated by LRP1. *Acta Neuropathol* 2020; **139**: 365–382.
64. Mela A, Goldman JE. The tetraspanin KAI1/CD82 is expressed by late-lineage oligodendrocyte precursors and may function to restrict precursor migration and promote oligodendrocyte differentiation and myelination. *J Neurosci* 2009; **29**: 11172–11181.

65. Kang Z, Wang C, Zepp J, *et al.* Act1 mediates IL-17–induced EAE pathogenesis selectively in $NG2^{+}$ glial cells. *Nat Neurosci* 2013; **16**: 1401–1408.
66. Choi C, Benveniste EN. Fas ligand/Fas system in the brain: regulator of immune and apoptotic responses. *Brain Res Rev* 2004; **44**: 65–81.
67. Cencioni MT, Mattoscio M, Magliozzi R, Bar-Or A, Muraro PA. B cells in multiple sclerosis — from targeted depletion to immune reconstitution therapies. *Nat Rev Neurol* 2021; **17**: 399–414.
68. Pennati A, Nylen EA, Duncan ID, Galipeau J. Regulatory B cells normalize CNS myeloid cell content in a mouse model of multiple sclerosis and promote Oligodendrogenesis and remyelination. *J Neurosci* 2020; **40**: 5105–5115.
69. Hickman SE, Kingery ND, Ohsumi TK, *et al.* The microglial sensome revealed by direct RNA sequencing. *Nat Neurosci* 2013; **16**: 1896–1905.
70. Plemel JR, Stratton JA, Michaels NJ, *et al.* Microglia response following acute demyelination is heterogeneous and limits infiltrating macrophage dispersion. *Sci Adv* 2020; **6**: eaay6324.
71. Nemes-Baran AD, White DR, DeSilva TM. Fractalkine-dependent microglial pruning of viable oligodendrocyte progenitor cells regulates myelination. *Cell Rep* 2020; **32**: 108047.
72. Lloyd AF, Davies CL, Holloway RK, *et al.* Central nervous system regeneration is driven by microglia necroptosis and repopulation. *Nat Neurosci* 2019; **22**: 1046–1052.
73. Lloyd AF, Miron VE. The pro-remyelination properties of microglia in the central nervous system. *Nat Rev Neurol* 2019; **15**: 447–458.
74. Miron VE, Boyd A, Zhao JW, *et al.* M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. *Nat Neurosci* 2013; **16**: 1211–1218.
75. Sherafat A, Pfeiffer F, Reiss AM, Wood WM, Nishiyama A. Microglial neuropilin-1 promotes oligodendrocyte expansion during development and remyelination by trans-activating platelet-derived growth factor receptor. *Nat Commun* 2021; **12**: 1–17.
76. Wlodarczyk A, Holtman IR, Krueger M, *et al.* A novel microglial subset plays a key role in myelinogenesis in developing brain. *EMBO J* 2017; **36**: 3292–3308.
77. Nakano M, Tamura Y, Yamato M, *et al.* NG2 glial cells regulate neuroimmunological responses to maintain neuronal function and survival. *Sci Rep* 2017; **7**: 1–15.
78. Liu Y, Aguzzi A. NG2 glia are required for maintaining microglia homeostatic state. *Glia* 2020; **68**: 345–355.
79. Zhang SZ, Wang QQ, Yang QQ, *et al.* NG2 glia regulate brain innate immunity via TGF-β2/TGFBR2 axis. *BMC Med* 2019; **17**: 204.
80. Madsen PM, Desu HL, de Rivero Vaccari JP, *et al.* Oligodendrocytes modulate the immune-inflammatory response in EAE via TNFR2 signaling. *Brain Behav Immun* 2020; **84**: 132–146.

Graphical Abstract

The contents of this page will be used as part of the graphical abstract of html only. It will not be published as part of main.



In this review, we discuss the bidirectional interaction between oligodendrocyte progenitor cells (OPCs) and the immune system in central nervous system health and disease. We focus on describing two main aspects: (a) how immune cells regulate OPC biology and their regenerative capacity, and (b) describe the novel immune regulatory roles of OPCs. Understanding the crosstalk between OPCs and the immune system will open new avenues for tackling neuroinflammatory diseases.