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Abstract

Microglia are the resident macrophages of the central nervous system (CNS), implicated in developmental processes, homeostasis, and responses to injury. Derived from the yolk sac during development, microglia self-renew, self-regulate their numbers during homeostatic conditions, and show a robust proliferative capacity even in adulthood. Together with monocyte-derived macrophages (MDM), microglia coordinate the regeneration of CNS myelin around axons, termed remyelination. Gene expression analyses and experimental modelling have identified pro-remyelination roles for microglia/MDM in clearance of myelin debris, secretion of growth factors, and remodelling of the extracellular matrix. Further investigations into the molecular mechanisms controlling these regenerative functions will reveal novel therapeutic strategies to enhance remyelination, via harnessing the beneficial effects of the innate immune response to injury.

Keywords	microglia; macrophage; remyelination; regeneration; repair; myelin; oligodendrocyte
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Suggested reviewers	Wee Yong, Robin Franklin

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Dear Prof. Stevens,

Herein is our revised version of the review article CONEUR_2017_101 'Microglia: origins, homeostasis, and roles in myelin repair'. We appreciate the reviewer's comment that the review is well written, concise, and timely, and have addressed all the suggestions which have been highlighted in yellow in the text, and described below:

At least some mention could be made of the potential "dark side" of microglia/MDMs in demyelinating disease, even if only to put the current focus on their beneficial roles into a historical perspective (e.g., contribution to oxidative stress, inflammatory cytokine production...)

We have added the following to the introduction: 'As such, microglia are early responders to CNS damage or abnormality and are thus placed to quickly coordinate subsequent responses. These can be damaging, for instance in contributing to neurodegeneration³, dysregulated synaptic pruning⁴, and associated with dementia⁵, reviewed in detail elsewhere⁶.' We chose not to elaborate on the damaging aspects of microglia reactions further due to existing review articles on this topic, and our focus on the regenerative properties. The damaging effects of MDMs are outlined in main text, as described in answer to the reviewer's second comment, below.

The discussion of the differing transcriptional profiles of resident microglia and MDMs during demyelination is interesting but would be complemented by greater focus on the few studies that have shown functional differences between the two populations. The description of the recent TNFR2 ablation study by Gao et al. (2017) is a good start but could be complemented by Yamasaki et al. (2014)'s findings that MDMs appear to show greater association with nodes of Ranvier in EAE, actively removing myelin segments. Ajami et al., 2011 (Nature Neuroscience 14, 1142-1149) could also be used as evidence for functionally distinct roles between the two.

In addition to the description of distinct microglia and MDM functions in EAE from Yamasaki and Lewis papers, we have now added the following to the main text: 'Other studies have demonstrated the requirement for MDM in initiating EAE disease and progression⁵¹ via CCR2 signalling^{52,53}; accordingly, Yamasaki et al. showed that MDMs in close association with axoglial units have myelin inclusions⁴⁹, suggesting that these cells may directly induce demyelination', referencing the above studies and some additional ones we found were relevant.

Figure: Consider including OPCs/OLs in the diagram and indicate where some of the microglia functions are thought to act on the lineage.

We have updated the figure to include the oligodendroglial lineage cell responses.

"Microglia are the resident tissue macrophages in the central nervous system (CNS), comprising up to 12-16 % of total neural cells in mouse and human". These figures seem to be the upper estimates, with figures for most CNS regions being somewhat below these percentages. The sentence could be revised to reflect more typical estimates

We have updated the sentence to read: 'Microglia are the resident tissue macrophages in the central nervous system (CNS), comprising 5-12 % of total neural cells in mouse brain and 0.5-16% in human brain^{1,2}'

Best regards

Veronique Miron

Current Opinion in Neurobiology

Invited review special issue: Glial Biology

Title: Microglia: origins, homeostasis, and roles in myelin repair

Authors: Amy F. Lloyd*¹, Claire L. Davies*¹, Veronique E. Miron¹

Highlights:

- Microglia origins differ in development versus during postnatal homeostasis
- Microglia gene expression profiles during remyelination reveal roles in tissue homeostasis and regulation of oligodendroglial lineage cell recruitment/differentiation
- Microglia and monocyte-derived macrophages coordinate remyelination via phagocytosis of myelin debris, remodelling of the extracellular matrix, and secretion of growth factors that drive oligodendrocyte lineage cell responses.

Current Opinion in Neurobiology

Invited review special issue: Glial Biology

Title: Microglia: origins, homeostasis, and roles in myelin repair

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Abstract

Microglia are the resident macrophages of the central nervous system (CNS), implicated in developmental processes, homeostasis, and responses to injury. Derived from the yolk sac during development, microglia self-renew, self-regulate their numbers during homeostatic conditions, and show a robust proliferative capacity even in adulthood. Together with monocyte-derived macrophages (MDM), microglia coordinate the regeneration of CNS myelin around axons, termed remyelination. Gene expression analyses and experimental modelling have identified pro-remyelination roles for microglia/ MDM in clearance of myelin debris, secretion of growth factors, and remodelling of the extracellular matrix. Further investigations into the molecular mechanisms controlling these regenerative functions will reveal novel therapeutic strategies to enhance remyelination, by harnessing the beneficial effects of the innate immune response to injury.

Introduction

Microglia are the resident tissue macrophages in the central nervous system (CNS), comprising 5-12 % of total neural cells in mouse brain and 0.5-16% in human brain^{1,2}. As members of the innate immune system, a major function of microglia is to survey the microenvironment for signs of injury, such as damage-associated molecular patterns (DAMPs) released from dying or stressed cells. As such, microglia are early responders to CNS damage or abnormality and are thus placed to quickly coordinate subsequent responses. These can be damaging, for instance in contributing to neurodegeneration³, dysregulated synaptic pruning⁴, and associated with dementia⁵, reviewed in detail elsewhere⁶. However, although less studied, microglial post-injury responses can also be regenerative; indeed, studies over the past 16 years have revealed the supportive role of macrophages (i.e. microglia and monocyte-derived macrophages (MDMs)) in the regeneration of myelin, termed remyelination⁷⁻¹⁵.

Remyelination reinstates and preserves axonal function and health¹⁶⁻²⁰. This involves recruitment and proliferation of oligodendrocyte progenitor cells (OPCs), their differentiation into mature oligodendrocytes, and ensheathment of axons with new myelin. The failure of remyelination in various neurological contexts, such as with ageing and in progressive multiple sclerosis (MS), is considered to contribute to the axonal loss which correlates to decline in motor, sensory, and cognitive functions. Failed remyelination with ageing has been associated with dysregulated macrophage responses in experimental models^{10,11,21}, highlighting a key pro-regenerative therapeutic target. Although clinical trials aimed at enhancing remyelination by directly stimulating oligodendrocyte lineage cells are currently ongoing for the first time, whether these drugs will be successful, and whether they will work efficiently in all patients, remains to be seen. Given the plethora of evidence

implicating macrophages in remyelination in both rodent and human pathological studies, further investigations into microglia biology will reveal novel therapeutic strategies based on manipulating the innate immune response. Here, we summarize current knowledge on microglia development, homeostasis, and gene expression/ functions during remyelination.

Origins, maintenance, & repopulation of microglia during homeostasis

Microglia regulate developmental processes, including but not limited to oligodendrocyte differentiation²², neural precursor migration²³, and synaptic pruning²⁴. Accordingly, microglia arise early on in development, populating the murine neuroepithelium by embryonic day 9.5 (E9.5)²⁵, and subsequently being closed off from the periphery by the formation of the blood brain barrier by E13.5. Between E10.5 and birth, microglia rapidly proliferate to colonise the CNS, maturing into ramified microglia²⁶. This early CNS colonisation of microglia is conserved across vertebrates²⁷. Indeed, in humans, Iba-1⁺ CD68⁺ CD45⁺ MHCII⁺ amoeboid microglia penetrate the cerebral cortex by gestational week (gw) 4.5^{28,29} and migrate to the immature white matter via the ventricular lumen and leptomeninges²⁸. A second wave of infiltration of microglia at 12-13 gw then seeds the embryonic brain via the vasculature²⁹. By 22 gw, microglia take on a ramified morphology, becoming fully mature by 35 gw.

Microglia originate from erythromyeloid progenitors (EMPs) in the yolk sac²⁵, elegantly shown using fate mapping where progenitor cells expressing runt-related transcription factor 1 (Runx1) express yellow fluorescent protein (YFP) after tamoxifen-induced Cre recombination. Specific labelling of yolk sac EMPs in embryos, achieved by injection of 4-hydroxytamoxifen (4-OHT) into pregnant females prior to foetal liver haematopoiesis (at E7.5), allowed tracing of YFP⁺ cells to the rudimental brain²⁵. This migratory process is

circulation-dependant, as *Ncx-1*^{-/-} mice devoid of a functioning blood circulation lack microglia³⁰ despite undergoing normal haematopoiesis²⁵. Although yolk sac EMP-derived primitive macrophages can colonise the whole embryo by E9.5, these cells are committed to a microglia fate by downregulation of *Timd4* and *Cd206* and upregulation of *Sall1* and *Sall3*³¹. In addition, interferon regulatory factor 8 (*Irf8*), working in a heterodimeric partnership with *Pu1*, is a critical survival factor expressed during early microgliogenesis, essential for microglia development and specification²⁶. Furthermore, RNAseq analysis revealed that the precise coordination of gene expression directs differentiation of early progenitors (expressing *Mcm5*, *Dab2*, *Lyz2* and *Pf4*) into post-natal microglia (upregulating *Csf1R* and *Cxcr2*) and finally into mature microglia (expressing *Cd14* and *Mafb*)³². Yolk sac-derived microglia can persist until adulthood^{25,33,34}, yet it cannot be dismissed that a small proportion of microglia may be replaced by haematopoietic stem cells (HSCs) since in zebrafish, adult microglia originate from the ventral wall of the dorsal aorta, a source of definitive haematopoiesis³³.

After birth, microglial numbers initially increase in the first two weeks of life, followed by a decrease to a steady homeostatic level via apoptosis and reduced proliferation^{35,36}. Under homeostatic conditions, yolk-sac derived microglia were historically considered to be long-lived cells with low turnover. However, recent evidence has shown that the microglia population in the mouse brain is dynamically regulated at the individual cell level via coupling of apoptosis and proliferation, with a minimum of 1.38% of microglia estimated to be proliferating (as shown by BrdU incorporation) at any given time and 1.23% of microglia dying every 24 hours³⁷. Altogether, it is therefore estimated that a whole microglial population in the murine CNS can turn over in 96 days. In human brain, slightly higher rates

of proliferation were observed (Ki67⁺ Iba-1⁺ cells)³⁷, but rates of death are unknown. Dynamic regulation of the microglia population in the adult mouse brain has also been observed by repopulation from CNS-endogenous cells following global depletion of microglia³⁸⁻⁴¹. These studies involved adult mice, thereby revealing that repopulation of microglia occurs in a mode distinct from the original seeding in development. There are currently 2 proposed models of microglia repopulation. The first study, using a *Cx3cr1-CreERT2*;iDTR mouse model, ablated a minimum of 80% of microglia in the cortex, cerebellum, and spinal cord by 3 days post-diphtheria toxin⁴⁰. A subsequent rapid repopulation was observed at 7 days post-diphtheria toxin, mediated by self-renewing proliferating microglia (expressing Nestin), with numbers returning back to control levels 1 week later⁴⁰. The second model, where >90% of microglia were depleted using a CSF1R inhibitor, observed repopulation from a CX3CR1-negative CNS-resident cell³⁹. BrdU labelling showed that 70% of labelled cells were positive for Nestin but negative for microglia markers such as Iba-1. When repopulation was complete, almost all BrdU labelled cells were positive for microglial markers, leading to the conclusion that the Nestin⁺ cells differentiated into microglia³⁹. These repopulating cells heterogeneously expressed a range of markers for hematopoietic stem cells or neural stem cells including Nestin, CD34, and c-kit, as well as lectin-IB4, CD45, and Ki67³⁹. Further investigations showed that the repopulated microglia have similar inflammatory gene expression and functional responses to lipopolysaccharide compared to pre-depletion microglia³⁹, however the identity and origin of these cells remains unclear and is hotly debated. Definitive lineage tracing and RNA-sequencing of Nestin⁺ cells should ultimately uncover their identity and role in the CNS. Differences in between these two studies may reflect different levels of depletion (>99%³⁹ compared to 80%⁴⁰), and only the DTR-driven depletion leading to a robust pro-

inflammatory response and astrogliosis⁴⁰. Although there is uncertainty as to the role of Nestin in microglia repopulation, be it re-expression by residual microglia⁴⁰ or cells potentially capable of differentiating into microglia³⁹, it is clear that cells expressing Nestin are nonetheless integral to the rapid repopulation of microglia following depletion. Determining whether the dynamic regulation of microglial turnover/ repopulation is dysregulated in the context of failed remyelination may be critical in understanding how to therapeutically target microglia.

Transcriptional profiles of microglia and monocyte-derived macrophages during central nervous system remyelination

The importance of inflammation and microglia/ MDM in remyelination was initially suggested by transcriptomic studies of whole remyelinating lesions. For example, a microarray gene expression analysis of whole mouse brain tissue following cuprizone toxin-induced demyelination revealed regulation of genes associated with inflammation and/or the recruitment/stimulation of macrophages. For instance, lysozyme M (*LyzM*) and leukocyte common antigen/CD45 (*Ptprc*), and genes associated with recruitment/ activation of macrophages (*Ccl2* (MCP-1), *Ccl9* (MIP γ), *Ccr5*, *Mmp12*), were upregulated at the time of concomitant demyelination and initiation of remyelination (6 weeks after initiation of cuprizone treatment) and subsequently downregulated during the later stages of remyelination (6 weeks recovery on normal diet)⁴². Downregulation of these genes during late remyelination coincided with the upregulation of myelin-associated genes (such as proteolipid protein 1 (*Plp*), myelin associated glycoprotein (*Mag*), myelin oligodendrocyte glycoprotein (*Mog*)), as well as synectin (*Gipc1*), BCL tumour suppressor 7C (*Bcl7c*), lysophosphatidic acid receptor 1 (*Lpar1*; important for Schwann cell myelination⁴³), kinesin

family member 5A (*Kif5a*; required for transport of neurofilament), and NK6 transcription factor related (*Gtx*; expressed during myelination and remyelination⁴⁴). To further identify genes involved in remyelination, Arnett, et al. ⁴⁵ analysed whole brains isolated from *Tnfa*^{-/-} mice, which do not remyelinate efficiently after cuprizone-induced demyelination. In comparison to wildtype mice, microarray analysis identified differential expression of genes during remyelination (6 weeks recovery on normal diet after 6 weeks of cuprizone diet) associated with the immune response (downregulation of *Mhc-II*, *Ccr6*, *Cd19*, *Cd105*; upregulation of *Ifn*), as well as the cell cycle (upregulation of *Cyclin-e*, *Polg*, *Cdk5r2*), development (downregulation of *Crygd*, *Crybb2*, *Igf1/2*; upregulation of *Fzd*, *Sema5b*) and regulation of transcription (upregulation of *Myt1*)⁴⁵.

Importantly, these studies support that the immune response is a critical component of remyelination; however, these results do not reflect transcriptional profiles of individual cell populations. Indeed, Srinivasan, et al. ⁴⁶ showed that the expression profiles of cells extracted from tissues affected by neurodegenerative disease are influenced by cell composition, and whole tissue RNA analysis may obscure significant gene changes in microglia and, thus, could be misleading. Similarly, some studies have combined microglia and MDM together for analysis, as a result of the challenges of distinguishing and isolating microglia from MDM⁴⁷. To overcome this, Lewis, et al. ⁴⁸ isolated microglia from MDM by fluorescence-activated cell sorting (FACS) using differential expression of the surface marker CD44, and investigated the transcriptomes of these cell populations in the pathogenesis of experimental autoimmune encephalomyelitis (EAE). Microglia and MDM were isolated from naive mouse brains when clinical symptoms were absent (at 7 days post immunisation; disease score of 0) and when partial hind-limb paralysis was observed (at 14 days post

immunisation; disease score of 3), and transcriptomes were determined using RNA sequencing. Principal component analysis revealed that the two cell populations remained distinct at the transcriptome level during the course of EAE. The distinct microglia and MDM expression profiles during EAE were confirmed in a separate study⁴⁹, which identified that MDM were more likely than microglia to express genes related to effector functions, including secreted factors and surface molecules. Furthermore, it was recently shown that differential expression of genes by microglia and MDM can lead to differing functions in EAE pathogenesis. For instance, microglial expression of tumour necrosis factor receptor 2 (*Tnfr2*) is protective against EAE, whilst MDM expression of *Tnfr2* drives immune cell activation and initiation of EAE⁵⁰. Other studies demonstrated the requirement for MDM in initiating EAE disease and progression⁵¹ via CCR2 signalling^{52,53}; accordingly, Yamasaki et al. showed that MDMs in close association with axoglial units have myelin inclusions⁴⁹, suggesting that these cells may directly induce demyelination. These studies highlight the differential functions of microglia and macrophages during myelin injury, and point to the requirement to analyse these populations separately to accurately assess their roles during remyelination.

Using this approach, Olah et al. performed microarray analysis of microglia isolated from cuprizone-treated mice and identified 6200 genes expressed during homeostasis, demyelination and remyelination¹³. The major patterns observed were i) downregulation of metabolic processes and acute inflammatory responses during demyelination and remyelination; ii) upregulation of cell cycle during demyelination only; and iii) upregulation of immune response, phagocytosis and antigen processing/presentation during demyelination and remyelination¹³. However, the microglial transcriptome was largely

similar between demyelination/ early remyelination (5 weeks cuprizone treatment) and late remyelination (5 weeks cuprizone treatment then 2 weeks recovery). At both these time points, microglia upregulated expression of toll-like receptor 4 (*Tlr4*), lysozyme 1 and 2 (*Lyz1*, *Lyz2*), tumour necrosis factor (*Tnf*), interleukin 1 β (*Il1b*), interleukin receptor 4 α (*Il4ra*), genes associated with MHC-II (*Cd74*, *H2Aa*), whilst common microglial markers such as Iba1 (*Aif1*), F4/80 (*Emr1*), and Pu.1 (*Spi1*) were stably expressed. The authors proposed numerous microglial effector functions during demyelination and remyelination, including phagocytosis of debris/ apoptotic cells, salvage of myelin constituents, recruitment of OPCs and trophic support, and tissue remodelling. Overall, this study highlighted that the overarching role of microglia is to maintain tissue homeostasis and to provide an environment supportive of regeneration, which was even evident during demyelination.

A significant function associated with microglia is the clearance of myelin debris, which is required for remyelination to occur. Impaired removal of myelin debris is one factor contributing to poor remyelination following cuprizone treatment of *Trem2*^{-/-} mice⁵⁴. This is underpinned by impaired upregulation of genes associated with phagocytosis of myelin debris (*Axl*) and molecules central to lipid transport and metabolism (apolipoprotein-E (*ApoE*), apolipoprotein C1 (*Apoc1*), lipoprotein lipase (*Lpl*), cholesterol 25-hydroxylase (*Ch25h*)) during demyelination and remyelination. Furthermore, microglia provide trophic support to newly recruited OPCs, and a growth factor critical for OPC differentiation (insulin-like growth factor 1; *Igf1*) was found to be downregulated in *Trem2*^{-/-} mice after cuprizone-induced demyelination. Together, these results suggest that a central role of microglia in responding to demyelination is to carry out myelin clearance and promote OPC maturation for remyelination to occur efficiently. These studies have elucidated microglia gene

expression profiles during demyelination and remyelination, however subsequent unbiased investigations into expression profiles of microglia versus MDM during remyelination may reveal cell-specific functions during regeneration.

Functional contributions of microglia and monocyte-derived macrophages to central nervous system remyelination

Activated macrophages are a component of remyelinating lesions in both experimental models and human disease (e.g. multiple sclerosis, spinal cord injury, Alzheimer's disease)⁵⁵. For instance, the density of macrophages (HLA-DR+) at the border of MS lesions coincides with areas of robust remyelination⁵⁶. In contrast to experimental models with concurrent demyelination and remyelination (such as EAE and the cuprizone model), focal toxin-induced lesion models with temporally distinct damage and regeneration are the most appropriate to specifically associate cellular responses/ gene expression profiles/ molecules with the regenerative response to damage. Indeed, a recent study identified that remyelination is limited in EAE and occurs only at very late stages²⁰. Conversely, focal models show robust remyelination (in young animals) following injection of demyelinating agents (such as lysolecithin, ethidium bromide, or lysophosphatidylserine (LPS)) into white matter tracts such as the spinal cord, corpus callosum, or caudal cerebellar peduncles. These models have been imperative in linking the beneficial effects of the immune response to the regulation of OPC responses during remyelination^{7-11,57}. More specifically, this allowed for the discovery that macrophages are required for efficient remyelination, given that blocking the macrophage response soon after demyelination, either via depletion using clodronate-liposomes^{7,10} or by administration of minocycline⁵⁸, inhibits remyelination. Furthermore, inducing macrophage activation is sufficient to enhance myelination or remyelination, for

example via stimulation with the Toll-like receptor (TLR)-4 agonist LPS⁵⁹, TLR-2 agonist zymosan⁶⁰, or a combination of the anti-fungal agent amphotericin B with macrophage colony stimulating factor (M-CSF)¹⁴.

Our recent work has identified that efficient remyelination requires the dynamic regulation of functional macrophage phenotypes¹⁰. More specifically, soon after demyelination macrophages adopt expression of inducible nitric oxide synthase (iNOS), CD16/32, and tumor necrosis alpha (TNF- α), and support the proliferation of OPCs, yet these pro-inflammatory macrophages are not required for remyelination to proceed¹⁰. Importantly, the rate limiting step in remyelination efficiency is the transition to a pro-regenerative macrophage phenotype expressing arginase-1, mannose receptor (CD206), and insulin-like growth factor-1 (IGF-1) which drives oligodendrocyte differentiation to initiate remyelination¹⁰. Lineage tracing identified that both microglia and MDM contributed to both phenotypes¹⁰. Additionally, using *Ccr2* knockout mice in which monocytes cannot extravasate from bone marrow and are thus excluded from lesions, we observed that microglia could undergo this transition in activation even in the absence of MDM¹⁰. Although the molecular mechanisms underpinning this critical transition in macrophage activation are unknown, microglia and MDM gene expression/ activation can be manipulated by electrical nerve stimulation⁶¹, antipsychotic drug/ calcium suppression⁶², inhibition of Rho Kinase⁶³, modulation of signalling through NF κ B (reviewed by Lloyd and Miron⁶⁴), and histone deacetylase (HDAC) inhibition⁶⁵.

The aforementioned phagocytosis of myelin debris by macrophages is required for remyelination to proceed, as this debris is otherwise inhibitory for the recruitment/ differentiation of oligodendrocyte lineage cells⁹ and potentially for new myelin sheath

extension⁶⁶. Indeed, in MS lesions, the density of oligodendrocyte precursor cells (O4⁺) is proportional to the density of macrophages which have phagocytosed debris⁶⁷. Microglia and MDM may have differential phagocytic potential for engulfment of myelin debris depending on the context, being greater *in vitro* in human primary microglia versus MDM^{68,69} yet relatively repressed in microglia at onset of EAE⁴⁹. Nonetheless, several receptors have been implicated in regulating the phagocytosis of myelin debris: MerTK⁶⁸, TLR4⁶⁶, CX3CR1¹⁵, TREM2⁵⁴, and RXR α ²¹. For instance, myelin debris clearance is impaired following spinal cord injury in TLR4 knockout mice⁷⁰ and accelerated following TLR4 stimulation after peripheral nerve injury⁶⁶. Additionally, stimulation of MS patient-derived monocytes with the RXR α agonist bexarotene enhances their phagocytic capacity²¹. Healy *et al.* found that TGF- β treatment of primary human brain-derived microglia, which renders *in vitro* microglia more like *in vivo* microglia⁷¹, increased myelin ingestion via upregulation of MerTK, whilst blocking MerTK decreased phagocytic potential⁶⁸. Stimulation of human microglia and MDMs also influences uptake of myelin *in vitro*, with highest efficiency seen following treatment with M-CSF, interleukin (IL)-13 and IL-4⁶⁹. An additional beneficial role of microglia and MDM during remyelination is the release of factors that support oligodendrocyte lineage cell responses. These include activin-A, endothelin-2, IGF-1, TNF α , IL-1 β , platelet-derived growth factor (PDGF)-AA, fibroblast growth factor (FGF)-2, galectin-3, osteopontin-M, CXCL12, semaphorin-3F, and iron (reviewed in ⁷²). Thus, it is conceivable that these factors synergistically induce coordinated and temporally controlled signalling in OPCs which drives their responses during remyelination. Furthermore, macrophages play important roles in remodelling the extracellular matrix to support remyelination, for instance by degrading chondroitin sulfate proteoglycans⁷³⁻⁷⁵. Microglia and MDMs may also coordinate a pro-remyelination environment via interaction with other cell types. For

instance, a recent study identified that regulatory T cells drive remyelination⁵⁷, and one may speculate that macrophages and regulatory T cells may cooperate to support regeneration. Indeed, a recent study found that a secreted phenylalanine oxidase termed interleukin-4-induced-1 (IL4I1), which is highly enriched in microglia and upregulated during remyelination, regulates both macrophage activation during remyelination and reduces T cell expansion in EAE, leading to less dystrophic axons⁷⁶. Using cultures of primary human neural cells, another study found that microglia release cytokines which modulate astrocytes, which in turn influence OPC responses⁷⁷.

Importantly, the failure of remyelination seen with ageing is associated with a reduced recruitment of macrophages, reduced activation to a pro-regenerative macrophage phenotype^{10,78}, and impaired phagocytic potential^{11,21,78}. Altogether, these findings point towards the importance of regulating macrophages following demyelination for efficient remyelination to take place, and the need for macrophage-specific targeting in developing effective therapeutic strategies for the enhancement of remyelination.

Conclusions

As sensors of damage in the central nervous system, microglia are early responders to injury, such as demyelination, and have roles in supporting the regenerative process of remyelination. Transcriptomics and functional assays have identified these to include the phagocytosis of myelin debris, remodelling of the extracellular matrix, and secretion of factors influencing oligodendrocyte lineage cell responses (such as differentiation into myelinating oligodendrocytes). Although microglia are likely supported by MDMs in many of these functions, whether there are distinct roles of the endogenous and exogenously-derived macrophages during remyelination, as observed during myelin injury, is unknown. It

also remains to be determined whether the dynamic turnover of microglia observed during homeostasis is altered during injury and remyelination. Nonetheless, the numerous studies implicating macrophages in supporting remyelination highlight that these cells are important therapeutic targets for promoting remyelination in various neurological disorders characterized by poor myelin integrity.

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Figure legend

In development, erythromyeloid progenitors (EMPs) derived from the yolk sac colonize the embryonic brain (at embryonic day 9.5 in mice, and gestational week (gw) 4.5 and 12-13 in human). Mouse studies showed these cells will express *Runx1*, *Pu.1*, *Irf8*, *Sall1*, and *Sall3*. These cells reach full maturation between E10.5 and birth in the mouse, and gw 22-35 in the human. In mouse, this involves expression of *Csfr1*, *Cxcr2*, *Cd14*, and *Mafb*. In adulthood, the microglia population turns over regularly by coupled apoptosis (via *Bad*) and proliferation (expression of *Mad211*, *Mdm2*, *Cdca3*, *Cdk1*, *Cdc20*, *Cdc20b*). In the cuprizone model of demyelination, injury is associated with microglial expression of *LyzM*, *Ccl2*, *Ccl19*, *Ccr5*, and *Mmp12*. The regeneration of myelin that ensues (remyelination) is coordinated by microglia and monocyte-derived macrophages (MDM) which phagocytose myelin debris, remodel tissue, and secrete regenerative factors that altogether affect the recruitment of oligodendrocyte progenitor cells (OPCs) via chemoattraction, their proliferation, and differentiation into mature myelin-forming oligodendrocytes. Gene expression profiling of microglia identified pathways associated with decreased metabolic processing, increased immune response, antigen presentation and processing, and expression of *Tlr4*, *Lyz1*, *Lyz2*, *Tnf*, *Il1b*, *Il4ra*, *Cd74*, *H2Aa*, *Axl*, *Apoe*, *Apoc1*, *Lpl*, and *Ch25h*. The remyelination-associated gene expression profile in MDM is currently unknown.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as * of special interest and ** of outstanding interest.

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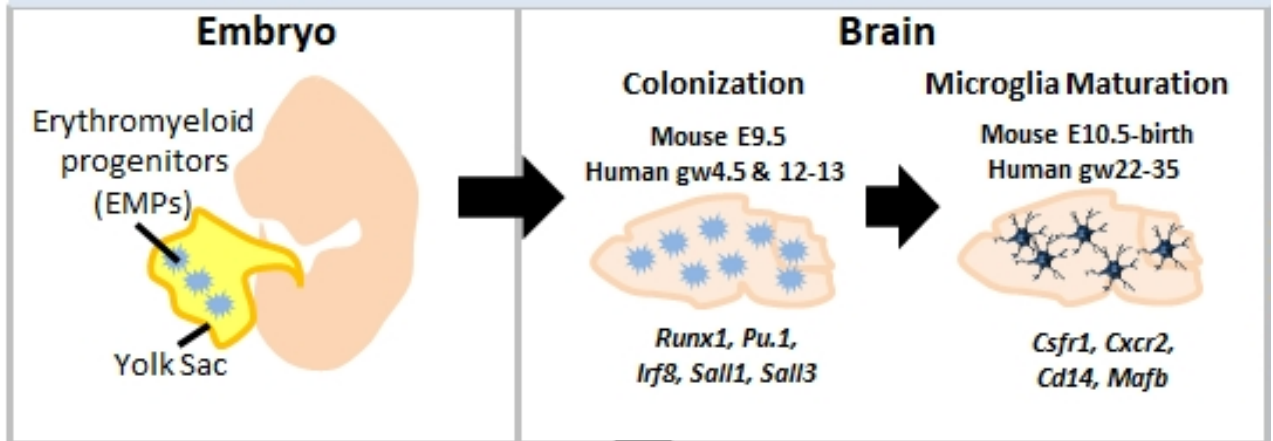
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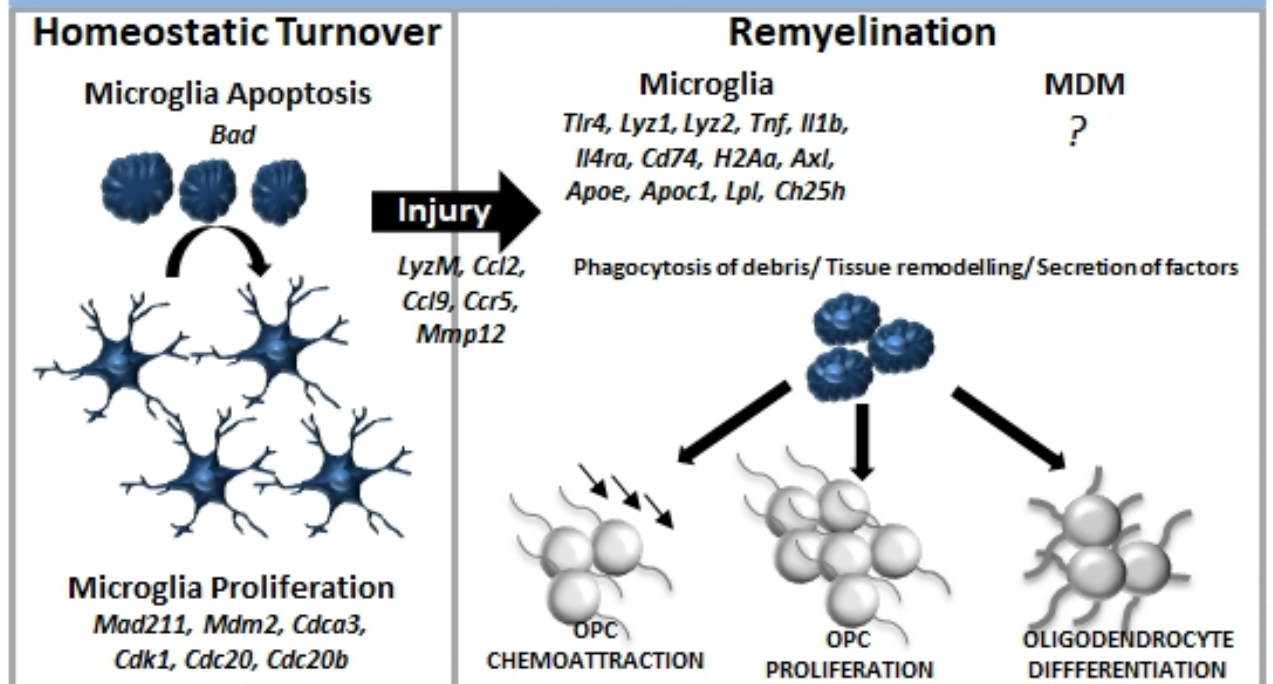
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Development



Adulthood



Current Opinion in Neurobiology

Invited review special issue: Glial Biology

Title: Microglia: origins, homeostasis, and roles in myelin repair

Authors: Amy F. Lloyd*¹, Claire L. Davies*¹, Veronique E. Miron¹

Conflict of interest

V.E.M. has received grant funding from Biogen Idec, GlaxoSmithKline, and Clene Nanomedicine related to the role of microglia and macrophages in remyelination. A.F.L. and C.L.D. have nothing to declare.