The good, the bad and the ugly. Macrophages/microglia with a focus on myelin repair

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1. ABSTRACT

A feature of most neurological disorders is demyelination, whereby myelin is lost from axons partly through stripping by macrophages/microglia. Spontaneous remyelination by oligodendrocytes that mature from oligodendrocyte precursor cells occurs following demyelination, even in the chronic inflammatory disorder of the central nervous system, multiple sclerosis. If remyelination does not occur or is prevented, then one consequence besides the loss of saltatory nerve conduction is the degeneration of axons. Thus, promoting remyelination is a desired result. In this article, we review the data that despite a reputation as "bad" factors for CNS wellbeing, including the promotion of neuroinflammation and demyelination, some aspects of macrophages/microglia activity are indeed "good", and can engender repair from the "ugly" phenomenon of demyelination. We discuss factors that help promote the benefits of macrophages/microglia activity for remyelination.

2. INTRODUCTION

In neurodegenerative diseases of the central nervous system (CNS) such as multiple sclerosis (MS) and Alzheimer's disease, or in acute traumatic insults such as spinal cord injury, the demyelination that accompanies axonal/neuronal loss contributes to the devastating outcomes for afflicted patients. Repair of myelin, i.e. remyelination, occurs in these conditions but its extent is often insufficient in many patients. The extent of remyelination is influenced by factors such as the age of the subject, gender, disease duration, area of injury, as well as the genetic background (1-5). If the extent is optimal, remyelination can lead to functional recovery (6).

Currently, the available medications for patients with demyelinating diseases such as MS affect principally the immune cells in the periphery and do not directly enhance remyelination; moreover, they are not focussed on promoting the endogenous cells that are a prerequisite for
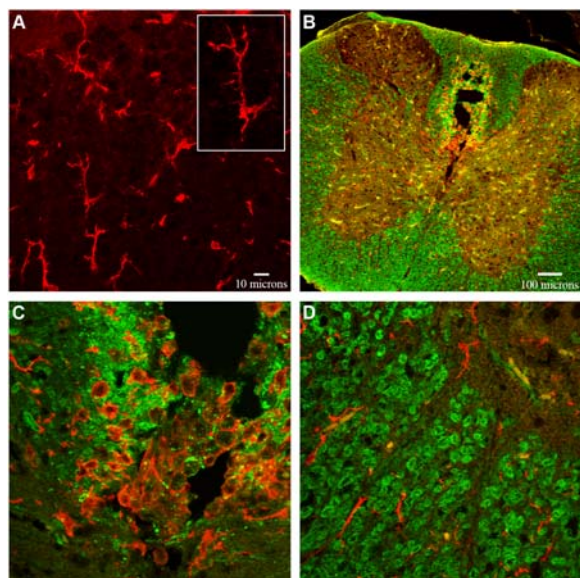
Figure 1. Immunofluorescence staining of paraformaldehyde-fixed mouse spinal cord tissue at three days post-demyelination by lysolecithin applied to the dorsal column. Macrophages/microglia cells are stained with Iba-1 (red) and myelin is stained for myelin basic protein in green. A) Healthy ramified macrophages/microglia cells remote from the lesion. Higher magnification insert shows a ramified microglia cell. B) Low magnification view of the spinal cord three days after lysolecithin injection into the dorsal column. Note the sizeable lesion confined to the dorsal column. C) Higher magnification of lesion border depicted in B. Activated macrophages/microglia with a typical amoeboid morphology can be observed; myelin-debris staining is more intense than intact myelin in the lesion border, presumably due to the exposure of more myelin basic protein epitopes due to myelin degradation. D) Healthy area opposite from the side of insult depicted in B; only ramified macrophages/microglia morphology can be observed. A centric ring of intact myelin can be detected around healthy axons.

remyelination in the CNS, the oligodendrocyte precursor cells (OPCs) that mature into myelin-forming oligodendrocytes (7). In recent years, however, an increasing body of research has been directed towards stimulating remyelination through endogenous OPCs. These studies have applied trophic factors for OPCs, or medications that augment the activity of transcription factors that promote the generation of oligodendrocyte lineage cells, or they have employed agents aimed at neutralizing the inhibitory microenvironment for remyelination (8-10). Another approach to stimulate remyelination may involve harnessing the body's intrinsic mechanism to repair damage to areas such as the skin: that of using inflammatory cells. Pioneering this direction of harnessing "beneficial inflammation" has been the group of Michal Schwartz (11, 12), who developed the idea that certain components of inflammation in the CNS (neuroinflammation) have beneficial outcomes; this initial idea has now been supported by the work of other researchers (13-16).

This review focuses on a subset of innate immune cells that have the potential to stimulate repair, namely macrophages and microglia. A pertinent question in the field has been: Do macrophages/microglia serve good or bad roles in the process of repair of the ugly phenomenon also known as demyelination?

3. REPRESENTATION OF MACROPHAGES/MICROGLIA IN THE CNS IN HEALTH AND INJURY

The origin of adult ramified microglia in the brain is thought to be amoeboid microglial cells; the latter are present ubiquitously in the brain during fetal and early postnatal development before they transform into ramified microglia in adulthood (17). Studies from Ling and others support the contention that microglia cells are monocytic rather than mesodermal or neuroectodermal in origin; they have shown that monocytes invade the brain during embryonic and early postnatal life and transform into amoeboid microglial cells with similar properties to macrophages in other tissues (18).

In adulthood, ramified microglial cells (Figure 1A) serve as CNS resident immune cells with the capacity of antigen presentation and phagocytosis (19-21). The microglial population in the adult CNS has a very slow turnover rate and is maintained throughout life via division of cells *in situ* (22) as well as through replenishment by the immigration of blood-borne monocytes (23). Others have described that microglia can be divided into 3 subclasses based partly on their location: radially branched (gray matter), longitudinal branched (white matter) and compact microglia (restricted to blood brain barrier lacking areas) (24), but so far no functional differences have been reported.

In the normal uninjured state, the ramified microglia is highly dynamic (25, 26), as their processes undergo continuous cycles of de novo formation and withdrawal and it is thought that this motility may enable microglia cells to observe and control the microenvironment. Upon trauma inflicted by a laser beam, there was targeted movement of microglia processes towards the site of injury, and the number of responding cells was proportional to the severity of insult (25, 27).

In conditions such as MS and spinal cord injury, the activated microglia undergo morphological transformation from a cell with ramified processes to one with few and thicker processes (28); indeed morphological transformation to an amoeboid morphology occurs with severe and chronic insult (e.g. in an toxin-induced demyelinating animal model, Figure 1B-D). There is also cellular movement of microglia, where cells migrate towards the insult; it is thought that this migration is required to clear debris, but the activated microglia also release a wide range of cytotoxins, free radicals, neurotrophic factors and immunomodulatory molecules (20, 21, 29, 30) and may thus serve other functions such as an attempt to contain the damage.

Besides the activation of CNS-intrinsic microglia, blood-borne monocytes also enter the CNS upon an injury to mature into macrophages. Indeed, it becomes difficult to distinguish macrophages from microglia in the injured CNS following injury, since both take on amoeboid morphology and no specific immunohistochemical markers differentiate both cell types in tissue sections. Hence, these cells have often been collectively referred to as macrophages/microglia. Nonetheless, it appears possible to differentiate these two cell types at the level of scanning electron microscopy, where microglia cells have a surface covered with spines while macrophages have a smooth or ruffled surface with fewer spines (31). Using flow cytometry, microglia are noted to be low in CD45 expression in comparison to macrophages that are high expressors of CD45 (32).

It has been controversial whether blood-borne monocytes transform into brain microglia. While Rivest *et al.* document extensive replenishment of microglia by blood-derived monocytes of bone marrow origin in chimeric mice subjected to whole body irradiation (33), this was thought to be rare in non-injured, non-irradiated adult mice (22, 34).

The accumulation of macrophages/microglia in the injured CNS has been examined. For example, activated macrophages/microglia are clearly evident in the brains of patients with Alzheimer's disease and MS (35). In experimental spinal cord injury (36), there is a notable increase in the number of activated macrophages/microglia by 24h of insult (37) around the lesion site, with a maximum occurrence at day 7-10 post injury (38). In the development of experimental autoimmune encephalomyelitis (EAE), the leading animal model for many aspects of MS, there is an elevation of pro-inflammatory monocytes in blood followed by their entry into the CNS coincident with microglia activation; these occur just prior to the development of clinical signs (39). Indeed, the entry of monoyctes may guide the infiltration of T lymphocytes into the CNS parenchyma. In support, when macrophages are depleted by the use of clodronate liposomes, lymphocytes are not able to cross the glia limitans and are trapped in the perivascular space (40). Additionally in EAE, comparable to MS, disease severity can be correlated with the presence of activated macrophages in the CNS (41). The representation of macrophages/microglia is extensive throughout active demyelinating plaques in MS (42, 43) outnumbering lymphocytes by as much as 10-20 times (44), and is still remarkable in the borders of chronic active plaques of patients with secondary progressive MS (45); indeed, the predominant type of immune cell subsets in most MS autopsy studies comprise activated macrophages/microglia. In active plaques of MS, macrophages/microglia with engulfment of myelin debris is evident. Therefore, the type, cellular content and extent of macrophages/microglia infiltration can reflect the different disease stages of MS (46).

4. DETRIMENTS OF MACROPHAGES/MICROGLIA ACTIVITY AFTER CNS INJURY

In the healthy brain, CNS resident microgliaare shielded from soluble factors produced in the periphery through a tight blood-brain barrier that helps to confer the relative immune privilege of the CNS. Furthermore, the cytokine profile in the healthy CNS, and molecules expressed by neurons (eg CD200), may keep the microglia population in a down regulated phenotype (21).

Microglia respond very rapidly when changes occur in their surroundings such as disruption of the blood brain barrier, an alteration of levels of neurotransmitters including glutamate, or when they detect danger signals from damaged cells (21, 28). The excessive activation of microglia in response to CNS injury, along with a tremendous influx of macrophages, help shape the described detrimental effects of activated macrophages/microglia. For example, in MS and its animal model EAE, the excessive presence of activated macrophages/microglia in the CNS has detrimental roles. Experiments in EAE have shown that when macrophages/microglia activation is inhibited or reduced by using agents such as a macrophage deactivating agent (CN-1493) (47) or macrophage inhibitor factors (TKP) (48), disease onset or severity is reduced. Furthermore, when macrophages/microglia are depleted by methods such as the administration of ganciclovir to CD11b thymidine kinase-1 mice (49), or by clodronate liposomes (40, 50), EAE clinical signs may be completely eleminated (51-54). It was also noted that products released from activated microglia impair neurogenesis (55). More recently, a subclass of blood-derived monocytes characterized by the chemokine receptor CCR2 and by high Ly6C expression is thought to sustain disease activity during the effector phase of EAE when symptoms have appeared (34). Furthermore, Rasmussen *et al.* reported that in chronic EAE, microglia but not T cell over-representation persisted and that this was associated with neuronal injury (56).

In MS, there is evidence in some lesions that microglia promotes lesion development long before the infiltration of immune cells from the periphery (57). Additionally, it is reported that microglia can kill oligodendrocytes (58, 59) and that myelin is stripped off axons by macrophages/microglia in active MS lesions (60, 61).

As in MS, the excessive activation of macrophages/microglia in other neurological conditions is also thought to be detrimental. In acute traumatic injuries to the CNS such as in spinal cord injury, it was shown that when the macrophages/microglia response was attenuated by the use of chloroquine (62), minocycline (63), clodronate liposome (64), or in MMP-12 null mice (65), neurologic outcomes following spinal cord injury are improved and the extent of myelin/axon damage is reduced.

There has been a number of studies supporting the hypothesis that the excessive activation of macrophages/microglia constitutes the "bad" aspects in the response to CNS injury. This concept guided the literature for a long time, but more recent evidence suggests that activation of macrophages/microglia may not be solely detrimental.

5. BENEFITS OF MACROPHAGES/MICROGLIA ACTIVITY AFTER CNS INJURY

In recent years, the view that macrophages/microglia only have detrimental outcomes has shifted. Supporting data have come from results such as the reduced remyelination occurring in TNF-α deficient compared to wildtype mice, which suggest that the reduced extent of macrophages/microglia activity has a detrimental outcome for remyelination (66). Additionally, depletion of macrophages slows remyelination (67) and there are reports that promoting acute inflammation locally enhances remyelination in areas of chronic demyelination (68) mainly due to the elevated response of macrophage/microglia.

An explanation for the benefits of macrophages/microglia is that these cells after activation increase their levels of beneficial neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) (69, 70).

The earlier mentioned more rapid remyelinating capacity in young versus old mice has been correlated with a faster recruitment of macrophages in the younger animals (71, 72). Further evidence that macrophages/microglia can have beneficial features come from experiments in demyelinating animal models induced by toxins such as lysophosphatidylcholine and cuprizone. In these models, remyelination was impaired after depletion of macrophages with clodronate liposomes (67, 73). The usage of silica dust depletes circulating monocytes with the effect that myelin debris, a significant hindrance in the process of remyelination, was not cleared effectively from lesion sites (74). A reduction of myelin clearance and delayed remyelination was shown in the lysophosphatidylcholine model when corticosteroids, which suppress inflammatory responses, were given (75, 76), but it has to be mentioned that the opposite effect has been reported (77). Another member of the glial cell family, namely the astrocyte, is also important for endogenous repair. It is suggested that reactive astrocytes, in coordination with macrophages, contribute to OPC differentiation and thereby stimulate repair. Talbott and colleagues demonstrated that remyelinating oligodendrocytes are closely associated with reactive astrocytes (78). Additionally a recent study demonstrated that the chemokine receptor CXCR4 and its ligand CXCL12, the latter of which is up-regulated within activated astrocytes, are important factors to enhance repair (79). Taken together, in toxin-induced demyelinating animal models such as those elicited by lysophosphatidylcholine, cuprizone or ethidium bromide, the literature reveals an association between myelin debris clearance, macrophage presence, coordination by astrocytes, and remyelination (80-85).

Evidence for the beneficial effect of macrophages/microglia has also been reported in a spinal cord contusion model, where recovery was impaired in toll-like receptor (TLR) -2 and -4 null mice; TLR signalling is important to activate TLR-expressing cells of the innate immune system such as macrophages/microglia (86). In spinal cord injury models, the implantation of activated macrophages depending on time and location can be beneficial for wound repair (87-89). As well, the activation of macrophages/microglia has been reported to promote axonal regeneration (90). Furthermore, the use of lipopolysaccharide to stimulate microglia via TLR-4 improves remyelination, further supporting the importance of TLR signalling in repair processes (85, 91). In other conditions, the reduction of beta-amyloid deposits in a mouse model of Alzheimer's disease (92, 93) was facilitated by macrophage/microglia, with improved functional recovery. Another important function of macrophages/microglia cells in Alzheimer's disease is that they appear to restrict plaque formation (33); Rivest *et al.* used macrophage colony-stimulating factor (M-CSF) to increase the representation of macrophages/microglia at lesions and this resulted in the prevention of the cognitive decline associated with beta-amyloid deposition in a transgenic mouse model for Alzheimer's disease (94).

Experiments on the optic nerve by Benowitz and others have supported a beneficial effect for macrophages/microglia (95-97). These authors used a TLR-2 agonist to increase macrophage activity in the retina following optic nerve injury, and demonstrated that axonal regeneration was improved. Moreover, they demonstrated that the beneficial macrophage activity was associated with a molecule called oncomodulin. In other experiments, the transplantation of peripheral nerve-activated macrophages into a transected optic nerve increased axonal regrowth as well (98). These experiments support the contention of David and colleagues who as early as 1990 reported that macrophages convert the non-permissive nature of the CNS white matter into a permissible state for neurite growth (99).

There has been also a number of studies performed *in vitro* to support the concept that macrophages/microglia can be beneficial after CNS injuries. When oligodendrocytes are co-cultured with microglia, they increase their content of myelin lipids and proteins (100), and this has been attributed to soluble mediators elaborated by macrophages (101). Foamy macrophages acquire their distinctive morphology by ingestion and accumulation of vast amounts of myelin derived lipids and it was shown *in vitro* that myelin ingestion induces an anti-inflammatory program (102).

In summary, it has become evident that in certain situations, macrophages/microglia are conducive for the well being of the CNS after injury, and that they promote responses such as myelin repair in demyelinating diseases.

6. DICHOTOMY OF MACROPHAGES/MICROGLIA ACTIVITY AFTER CNS INJURY

The complex nature of macrophages/microglia being good, bad or ugly should now be obvious. While excessive activation appears to confer a balance of detrimental properties, evidence also points to the good side with the important roles of debris removal and production of beneficial soluble factors to promote repair events such as remyelination.

Table 1. Remyelination-stimulating compounds that have immune properties

Compound	Description
Amphotericin B	Anti-fungal medication with incidental microglia activating property
Fingolimod (FTY720)	sphigosine-1-phosphate receptor agonist, increases OPCs and also the number of microglia
Glatiramer acetate	Stimulation of immune cells to produce growth factors
Lipopolysaccaride	TLR-4 ligand
Prolactin	Peptide hormone, stimulates OPCs and macrophages
Zymosan	TLR-2 ligand

Under normal conditions in the CNS, there are barely detectable levels of inflammatory molecules and blood-derived leukocytes within the CNS; microglia appear to be in a non-activated state. Early following an insult, the balance of macrophages/microglia actions seems to shift more towards a detrimental status, as the CNS goes from a low/negligible state of inflammation to a highly activated one with the significant increase of several inflammatory molecules produced by these cell types. Over time, however, the initial negative consequences of macrophages/microglia appears to shift towards benefits due to the importance of myelin debris removal and the production of soluble growth factors that either directly or indirectly stimulate the endogenous repair program.

Besides the time factor following injury where the balance of inflammation may initially be detrimental but then shifts towards a more beneficial state, the nature of the inflammatory cells that are represented within the CNS is likely also a determinant of the overall outcome of inflammation. Macrophages have been subclassified into an M1 pro-inflammatory phenotype and an M2 anti-inflammatory/regulatory subclass (103, 104). Detailed information about the characteristics that differentiate M1/M2 subtypes would exceed the focus of this review. However, in myocardial infarction, the M2 subclass has been found to be pro-reparative (105) and differential roles of M1 and M2 in CNS injuries have begun to emerge. In this regard, following acute spinal cord injury in mice, Kigerl *et al.* (106) reported that M1 related gene expression was maintained for up to one month after injury while M2 related gene expression was transient and only lasted for 7 days after injury. To distinguish both subsets, they use phenotypic markers including CD86 and CD16/CD32 for the M1 subset, and CD206 and Arginase-1 for the M2 subset. It appears that in the healthy spinal cord, macrophages/microglia possess an M2 phenotype (107), while the injured microenvironment downregulates the M2 and increases the M1 phenotype (106). Furthermore, Kigerl *et al.* demonstrate that soluble factors from the M1 and M2 subsets of macrophages have distinct effects on neuronal survival and axon outgrowth in culture: M2 macrophages promote axon outgrowth even when inhibitory substrates such as proteoglycans or myelin is present (106). Therefore, M2 macrophages may alter the lesion environment to overcome inhibitory substrates that are not permissive for neurite outgrowth and repair.

With regards to demyelinating injuries of the CNS, the dynamics and roles of M1 and M2 macrophages/microglia remain to be reported. However, it would be important to allow the removal of myelin debris by macrophage/microglia, and for the elaboration of soluble trophic factors, which can then allow oligodendrocyte precursors to migrate and differentiate, in order to lead to the successful remyelination of denuded axona (108). Whether the M1 or M2 subclasses have more important roles in the removal of debris or for provision of trophic factors following demyelination will need to be elucidated.

7. PROMOTION OF MACROPHAGES/MICROGLIA ACTIVITY AFTER CNS INJURY

The idea to stimulate endogenous repair processes to improve outcomes of neurological disability, especially in MS and spinal cord injury that often affects young people in the prime of their life, is appealing. Targeting the macrophages/microglia population to facilitate a better remyelination capacity seems to be self-evident. The unanswered question so far is how to stimulate the beneficial roles, without increasing the harmful aspects, of macrophages/microglia activity (See Table 1).

It has been shown that when macrophages/microglia are activated through toll-like receptors (TLRs), some degree of CNS recovery following injury occurs. For example, the use of lipopolysaccharide (LPS, TLR-4 ligand) and zymosan (TLR-2 ligand) lead to promotion of remyelination (91, 95, 109, 110). The downside of this approach is that the probability of these bacterial and yeast derived products being used in humans is very low, l*et al*one the possibility that LPS and zymosan can both result in excessive stimulation of various immune cascades. Nonetheless, other TLR ligands that are safe for human consumption could be considered for promoting repair in humans.

Another possibility to promote remyelination could be the usage of prolactin; a peptide hormone that is primarily associated with lactation, but which also has important CNS functions (111-114). The study by Gregg *et al.* found that prolactin regulated OPC proliferation and promoted remyelination after a lysolecithin-induced demyelination of the mouse spinal cord (113). Prolactin is known to have the capability to increase T cell proliferation (115). We have found that prolactin has a stimulatory effect on macrophages as well (unpublished data, Manuscript in preparation) and it is possible that some of its pro-remyelinating activity is contributed by this effect in addition to the promotion of proliferation of OPCs (113).

Fingolimod (FTY720) is an sphigosine-1-phosphate receptor agonist that improves MS disease activity in trials in MS. While it was first used as an immunomodulator, fingolimod has been found to enhance remyelination in an ex-vivo slice culture system (116). In the study, Miron *et al.* also observed a significant increase of microglia in fingolimod-treated cultures, which may have helped account for the effect of fingolimod on remyelination.

Given the increasing evidence that activated macrophages/microglia have roles in CNS repair, we are

focusing our research on the hypothesis that medications with the capacity to stimulate monocytoid cells can be used to increase remyelination. Using cytokine production by human microglia as the initial screen, we found that one compound out of a library of 1040 medications, amphotericin B, is a microglia activator (117). amphotericin B is used primarily for treatment of patients with progressive and potentially life-threatening fungal infections and only recently it was described that it promotes axon growth via activation of an Akt pathway in neurons (118). In our hands, amphotericin B is able to stimulate remyelination in a toxin-induced model of demyelination, particularly in combination with macrophage colony stimulating factor (M-CSF) (117).

8. CONCLUSION

The lack of treatment options to promote remyelination of the central nervous system is a devastating circumstance for many patients with neurological impairments. The stimulation of endogenous components that have the capability to remyelinate denuded axons would be a direct and safe approach. This concept is exemplified by the activation of macrophages/microglia cells that promotes inflammation and trigger demyelination in the first place, and which then provide a milieu conducive for remyelination by clearing myelin and cellular debris, and by the provision of various growth factors. It is essential to control the fine balance between detrimental or beneficial effects when immune cells are being harnessed for repair; the intensity and timely stimulation would be important. There is still much to be done: the current understanding of the various functional states of macrophages/microglia, and especially the mechanisms regulating these states, would need to elucidated further. After all, there is good potential and a powerful approach in using macrophages/microglia as an endogenous resource to promote remyelination.

9. ACKNOWLEDGEMENTS

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Abbreviations: BDNF: brain-derived neurotrophic factor, CNS: central nervous system, EAE: experimental autoimmune encephalomyelitis, LPS: lipopolysaccharide, MMP: matrix-metalloproteinase, MS: Multiple sclerosis, NGF: nerve growth factor, NT-3: Neurotrophin-3, OPCs: oligodendrocyte precursor cells, TLR: toll-like receptor

Key Words: Macrophage, Microglia, Demyelination, Remyelination, Stimulation, Repair, CNS, Activation, Review

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