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Review

Insights into the Role of Neuroinflammation in the Pathogenesis of Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is a devastating disease, and with the increasing number of cases each year, it is becoming a significant socioeconomic burden for the affected people and the entire community. The aetiology of MS is largely unknown, but genetic susceptibility, exposure to infections and/or environmental toxicants are recognised as risk factors. MS is characterised by the appearance of lesions/plaques in the central nervous system, caused by destruction of the myelin sheet by auto-reactive T cells. Symptoms range from mild impairment of daily motor functions to severe sensory and cognitive disabilities necessitating mobility assistance, medical and support from caregivers. Due to the progressive nature of the disease, MS is gaining more attention and research to better understand its multifaceted pathogenesis. In the present review, we focus on some of the latest research related to the neuroinflammatory component of the disease, since it appears to play a critical role in MS pathogenesis. The goal is to shed more light on this specific domain of MS, in an attempt to assist in the identification of novel treatment trajectories and management plans.

Keywords: multiple sclerosis; neuroinflammation; cytokines; T cells; B cells; autoimmune disease

1. Introduction

Multiple sclerosis (MS), an autoimmune disease of the central nervous system (CNS) is recognised as a polymorphic disorder. MS displays a vast range of clinical symptoms, including motor, sensory and cognitive dysfunction, which are likely caused by the axonopathy that follows CNS demyelination. According to the Australian Bureau of Statistics, MS affects about 0.1% of the Australian population [1,2] with a heavy burden for patients and the community. The bureau estimates that about 48% of the MS sufferers in Australia exhibit profound limitations to their activity and autonomy. The neurological deficits of MS sufferers are an expanding list that progresses towards severe sensory dysfunction, often accompanied by the presence of cognitive dysregulation and neuropathic pain [3–5]. Some authors have also described peripheral neuropathy [3]. The pathological hallmarks of MS evolve around the idea that formation of CNS plaques impede normal nerve conduction and generate a local inflammatory process. These plaques appear because of loss of self-tolerance and subsequent activation of CD4+ and CD8+ T lymphocytes as well as Blymphocytes attacking the myelin sheath [5–9].

2. What Is MS (Multiple Sclerosis)?

MS is one of the world's most common CNS disorders. MS is considered the leading cause of non-traumatic disability in adults. Even though many people with MS will suffer a limited degree of disability, about 60% of MS sufferers may be wheelchair bound or will require mobility assistance within 20–25 years after onset [2,10,11]. This has major implications for the quality of life of afflicted people, their social network, and for the cost to society if their condition is not adequately managed.

MS is an inflammatory demyelinating condition. The demyelination sites (plaques or lesions) impair nerve conduction, thereby causing disruption in terms of speed and connectivity between the spinal cord and sub-cortical and cortical regions. In advanced forms, the disease has been shown to progress to also affect the grey matter [12].

MS onset averages around 30 years old, with a clear higher prevalence among females (about 1:3 male to female ratio); the pathological manifestations vary widely and include different degrees of myelin sheath loss and clinical symptoms including neuropathic pain, paralysis, muscle spasms and spasticity, abnormal gait control, progressive motor loss and optic neuritis. For some people, MS is characterised by periods of relapse and remission while, for others, the disease exhibits a progressive pattern. Due to the spectrum of symptoms and clinical manifestations, it is not surprising that the life of MS patients may become unpredictable [4,8,11–13].

3. MS—Causes, Risk Factors and Types

3.1. Causes

MS causes are yet to be fully understood. However, it is quite well-accepted that there are multiple risk factors contributing to the disease, including genetic predisposition, and non-genetic triggers, such as prior exposure to viral infections, changes in metabolism, or environmental factors, together potentially initiating a myelin-specific T-cell self-reactive autoimmune response that leads to the pathological presentation of the disease [11,14].

Three times as many women are affected compared to men, and people of Northern European descent seem to be at highest risk for MS. MS is diagnosed on the basis of clinical findings and evidence from additional tests, such as magnetic resonance imaging (MRI) of the CNS and analyses of the cerebrospinal fluid (CSF). MS typically presents in adults ranging from 20 to 45 years of age; occasionally, it is diagnosed in childhood or at middle age [14,15]. So far, the most accredited theory providing a viable rationale for the aetiology of MS is the loss of self-tolerance and self-reactivity of anti-myelin specific T cells. As mentioned above, there are several risk factors potentially playing a pivotal role in triggering the autoimmune response. Once this pathological cascade is triggered, auto reactive T cells target oligodendrocytes, the cells responsible for the production of the myelin sheath surrounding axons in the CNS, and destroy them. Subsequently, the damage may eventually extend to neurons [16].

3.2. Risk Factors

Although MS is thought to be primarily a CD4 T cell-mediated disease, susceptibility to the disease has been strongly linked to genetic factors, such as changes in the major histocompatibility complex (MHC) genes and/or of genes associated with T cell activation and homeostasis; other associations include genetic modifications in HLA II haplotypes including HLA-DR15 and HLA-DQ6, however these relationships are partly unresolved. It is believed that the link with MS is related to the role these MHCs play in auto-antigen presentation to the adaptive immune system as it triggers the auto-reactivity component of the disease, but the process is not clearly elucidated [8,11,16,17].

Other genetic risk factors have been described, potentially contributing to make individuals more vulnerable to developing the disease. Studies have suggested that some mutations, such as those in the genes encoding for the cytokine interleukin 17 (*IL-17*) and the interleukin 2 receptor (*IL-2R*) gene may be associated with an increased incidence of MS [18–20].

The higher prevalence of MS among women is also noteworthy; although the exact cause of such difference is yet to be fully explained. However, due to the well-known effects of estrogens in the modulation of the immune response, it is conceivable that the apparent sexual dimorphism of MS might be related to gender-specific susceptibility to some environmental factors triggered by estrogens that, for obvious reasons, are not effective in males [10,15].

A genome-wide study conducted by the International Multiple Sclerosis Generics Consortium showed a wide range of risk alleles for MS. Several single nucleotide polymorphisms (SNPs) were revealed through multiple phased studies and authors were able to identify links with genes encoding for *IL-2Rα* and, to a lesser extent, *IL-7R*. In addition, they replicated the findings demonstrating an additional link between MS and mutations in *HLA-DRs* [18,20].

Other work by Field and collaborators suggested that abnormalities in antigen presenting cells (APCs), the dysregulated expression of CD40 cell surface proteins on B-lymphocytes and dendritic cells might increase the risk of developing the disease [21]. Field's research also suggested that the population showing abnormal *CD40* gene expression might be more susceptible to develop Epstein-Barr virus (EBV) antigenic mimicry, hence increasing the risk of triggering MS [21].

Multiple studies have attempted to explore the potential association between "non-immunological risk factors" and the incidence of the disease. These studies identified a correlation between various environmental and lifestyle factors, including exposure to viral infections, especially, as mentioned above, with EBV, but also vitamin D deficiency and cigarette smoking habits [22–24].

As mentioned above, population studies have shown a strong association between the prevalence of MS and geographical latitude. These studies attributed the findings to the level of exposure to sun light and vitamin D intake through diet, demonstrating a clear association between vitamin D-deficiency and risk of MS development [15,23–25]. Many of these studies suggested that lower serum vitamin D levels could be predictive of higher incidence of relapses among MS patients [11,26–28].

Concerning EBV exposure, studies have highlighted a possible link between viral infection and susceptibility to MS [11,24]. It is believed that up to 95% of the adult population is seropositive for the EBV, having a risk of developing MS, which is fifteen times higher than the seronegative population [22,29]. The idea is that neuroinflammation induced by viral infection promotes the recruitment of inflammatory cells, mainly CD2+ cells, through the blood brain barrier (BBB). The viral theory relates to the possibility that certain sub-classes of viruses may exhibit antigenic mimicry to the myelin sheet and certain parts of the CNS, hence triggering an autoimmune response versus the latter [13,30,31].

3.3. Types

There are several ways to categorize Multiple Sclerosis; in this review, we have chosen to refresh the clinical-based grouping method and then introduce the latest suggested grouping of the disease based on the histological classification [6,15].

According to neurologists, it is agreed that MS sufferers may be grouped into four major clinical categories, based on the course of the disease [8,11,14,32]:

1. Relapsing-remitting MS: the most common form of the disease affecting 85% of MS patients. It is characterised by acute episodes of relapse or exacerbations of the symptoms, interspersed by periods of remission, when the patient's symptoms improve or disappear.
2. Secondary progressive MS: the relapsing-remitting type of the disease might progress to this form in variable degrees within ten years from the first diagnosis. The course of the condition worsens progressively with or without periods of remission or plateaus.
3. Primary progressive MS: 10% of patients suffering from MS may present with this form of the disease. As the name suggests, the debilitating symptoms progressively worsen from the onset of the disease. The pattern does not follow relapses or remissions, but there may be the occasional plateaus. This form is usually associated with a poorer outcome.
4. Progressive-relapsing MS: only 5% of the MS sufferers will experience this rare form. The disease is progressive from the beginning with spontaneous worsening of the symptoms along the way with no periods of remission.

The histological classification of MS presented by Kuhlmann and coworkers is an attempt to standardise histological parameters generally used to define the pathology [6]. It is based on the

identification of active/inactive focal lesions, degree of infiltration of macrophages and microgliosis, evidence of myelin degradation in biopsied plaques and is classified using the following items:

Active and early demyelinating
Active and late demyelinating
Active and post-demyelinating
Mixed active/inactive
Mixed active/inactive and demyelinating
Mixed active/inactive and post demyelinating

The inactive form of the disease is usually identified by the absence of the macrophages and microglial cells from the biopsied lesion and there is no evidence of the myelin degradation.

4. Pathogenesis and Pathophysiology

The central mechanisms of MS pathogenesis encompass a series of features such as changes in the permeability of the BBB, genetic modifications that render the individual susceptible to immune attacks, myelin sheath destruction, axonal damage and CNS scarring [9,13].

4.1. MS Pathogenesis

MS starts when a person is exposed to triggers and/or possesses a genetically inherent predisposition to develop autoimmunity. Among the most accepted triggers, environmental exposure to certain viral infections or other pathogens may initiate a self-sustained systemic inflammatory process and immune activation. The acute inflammation in turn upregulates endothelial cell adhesion molecules within the brain and spinal cord vascular network, facilitating the migration of larger than usual inflammatory cells to the otherwise immune obscure CNS. In a typical situation, this process will be transient and there will be no long-term consequences to this physiological response. However, if inflammatory cells are sensitised to the myelin antigen or myelin proteins' antigens, in a process believed to be utilised by pathogens to circumvent the host defense system, then this will prompt a series of neuroinflammatory cascades that will unavoidably lead to demyelination, axonopathy, and in some cases, damage to the grey matter [9,11,25]. What perpetuates the inflammatory process thereafter seems to be related to the ability acquired by reactive immune cells (mainly T cells) and other cell types to behave like APCs, thus creating a vicious cycle that causes further myelin damage and aids into disease progression [7,25,33]. Other emerging ideas on the involvement of T cells in MS pathogenesis point to the self-activating properties of these cells (CD4+), which seem to be able to recognise certain myelin sheath proteins and glycoproteins [11,34].

There is evidence suggesting that a risk factor for MS is the appearance of macrophage and dendritic cell populations overexpressing IL-23, an interleukin that is thought to be vital for the activation of the Th-17 cell lineage [35,36]. Studies have shown that the pathogenic population of pro-inflammatory IL-17-secreating cells (Th-17 cells) are regulated by IL-23 to produce autoimmune responses in patients with MS [35–38]. These highly reactive T cells become abundant in bodily fluids, such as peripheral blood and the CSF [38,39]. Further studies have demonstrated associations between this specific T-cell phenotype and their acquired ability to reach the site of demyelination/inflammation [40,41]. These insights point to the role of IL-23 and IL-17 as strong mediators of MS pathogenesis.

Pare et al. reviewed the role of ILs in the development and maintenance of experimental autoimmune encephalopathy (EAE), a murine model resembling some aspects of MS. The authors suggested that so far, the evidence indicates the essential role of IL-1, IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in MS development [42]. The correlation between neuroinflammation and IL-1 abundance has been extensively researched, to the level that pharmacological blockade of IL-1 receptors (IL-1R) has proven to be successful for the treatment of auto-inflammatory conditions for few decades [43]. Levesque

et al. subsequently confirmed that IL-1β, rather than IL-1α, is the isoform specifically involved in the neuroinflammatory process triggered in EAE mice models [44].

The effects of cytokines in autoimmune diseases like MS has puzzled researchers for a long time. Indeed, there have been a few discrepancies on the involvement of certain ILs when comparing animal models and human post-mortem samples from MS patients. Tzartos et al. [40] found that the levels of CD4+ and CD8+ T cells found in active human MS lesions show an "enrichment" of IL-17 expression which was not associated with higher IL-23 levels. These results have not been confirmed in rodent models. These human tissue analyses also demonstrated that T-regulatory cells (Tregs) activities in the perivascular area surrounding the lesions are often low or cells are not present at all.

There is mounting data suggesting that neuroinflammation in MS is mediated by the activation of toll-like receptors (TLRs) through bacterial antigenic mimicry [9]. TLR activation would stimulate the production of IL-12 and IL-23, which in turn can induce T cells differentiation into auto-reactive effector cells [45]. Auto-reactive CD4+ T cells would then produce endothelial bioactive substances to increase permeability of the CNS and facilitate the recruitment of other immune cell types from the periphery, including neutrophils and monocyte-derived macrophages (MDMs), in addition to CD4+ T cells [9,42]. Moreover, CD4+ T cells could promote chemotaxis through stimulatory effects on integrin production (a class of molecules that promote adhesion of white blood cells to the endothelium). Levesque et al. also suggested that CD4+ T cells are the main source of IL-1β both in the CNS and the CSF [44]. To date, there is still an open debate on whether or not and to what extent CD4+ T cells contribute to MS pathophysiology by regulating the inflammatory cascade triggered during the course of the disease. In fact, there are other lines of research where investigations are being centred on assessing the role of another subclass of T cells in active lesions, namely CD8+ T cells, and which are attempting to unveil the level of involvement of this specialised T cell type in the process of plaque formation [11]. Indeed, some interesting studies have identified significant increases in the population of memory CD8+ T cells in active plaques in comparison with CD4+ T cells [17,46,47]. Based on this model, the higher numbers of CD8+ T cells in the blood stream of MS patients might explain the higher levels of the circulating pro-inflammatory cytokine IL-17, since CD8+ T cells secrete IL-17 at levels comparable to Th17 cells [40]. Tzartos and his group also found that IL-23 is more efficient at recruiting CD8+ T cells than CD4+ T cells at the lesion site. The authors argue the issue regarding which specific T cell type has a major involvement in MS pathogenesis. This could basically be due the prior mislocalisation of these cell populations, in that both CD8+ and CD4+ T cells have been detected in the perivascular spaces and meninges, whereas only the former were also found in the CNS parenchyma from MS post-mortem tissues [40]. However, this issue will require additional evidence in order to be conclusive.

Aside from the involvement of T cells in MS, little attention has been given to another important immune cell type, i.e., B cells. Research conducted by Egwuagu and Yu reported that B cells also contribute to the overall inflammatory milieu in MS by co-stimulating T cells to produce and release inflammatory factors and of course, by promoting the production of monoclonal immunoglobulins, whose identification in the CSF still represents one of the hallmarks of the disease [48,49]. A research group showed that B cells in the peripheral blood from MS patients exhibit higher expression levels of GM-CSF receptors compared to controls, supporting the involvement of these cells in disease pathogenesis, in addition to T cells and natural killer cells (NK), which are also augmented in MS sufferers [50,51]. Nonetheless, B cells seem to play an active part in triggering the auto-inflammatory cascades of MS by stimulating the production of IL-6, tumor necrosis factor alpha (TNFα) and interferon gamma (IFNɣ) as well as by acting as APCs and promoting the production of auto-antibodies [45,49–53]. Finally, peripheral B cells isolated from MS patients showed an increased capacity to secrete IL-6 [54], tumor necrosis factor (TNF) [55] and lymphotoxin-α (LT-α). In this regard, the recent findings associating the early appearance of B cell subsets with high pro-inflammatory profile to an active form of MS [56] are interesting.

4.2. The Experimental Autoimmune Encephalomyelitis (EAE) Model of MS

Whilst there is not a single model that can perfectly mimic all aspects of MS, animal models are critical in understanding the triggering events and pathogenetic mechanisms underlying the disease in order to develop therapeutic strategies that may halt disease progression and eventually promote the development of treatments for the human condition. Among the several existing models of MS, by far the best studied and most commonly used is the rodent model of EAE [57].

Among the aspects that have proven the validity of the EAE model in mimicking the human condition is the differential staging of recruitment of immune cells types in the acute and chronic phases of EAE. It appears that the type of cells recruited at the injury/lesion site are, at least in part, related to the corresponding increase in the levels of IL-1β [42]. That is, as EAE progresses, the number of cells capable of producing higher IL-1β levels proportionally grows (please refer to Table 1 below).

Table 1. Association between cell type, MS (multiple sclerosis) phase and cytokine production.

Cell Type	MS Phase/Released Cytokine	Reference
Neutrophils	Acute Phase/IL-1β	[58]
Monocytes and Monocytes-derived Macrophages (MDM)	Acute Phase/IL-1β	[58]
T helper cells (Th17)	Chronic Phase/IL-1β	[59]
Microglia	Chronic Phase/IL-1β	[44]
Astrocytes	Chronic Phase IL-1β	[60]
B cells	Acute-Chronic and secondary progressive Phases	[49]
T regulatory cells (Tregs)	Chronic Phase—Remission/IL-10	[61,62]
B regulatory cells (Bregs)	Chronic Phase—Remission/IL-10 and IL-35	[48,63,64]

Nonetheless, aside from the pro-inflammatory effect driven by IL-1β, there is some evidence supporting its role in remyelination. The cytokine seems to be critical for the aggregation, proliferation and activation of oligodendrocytes progenitors around the areas of demyelination, and researchers are starting to believe that such beneficial functions might be attributed to the stimulatory activity of IL-1β on the production and local release of trophic factors, such as insulin-like growth factor (IGF) by cells that participate in the demyelination process in the first place [65]. The apparent bipartite roles of IL-1β in promoting both immune cell recruitment but also remyelination seem to be dependent on the temporal pattern of cytokine release and the cell types involved. It appears as though the initial release of IL-1β promotes the recruitment of T and B cells during the acute stages of CNS inflammation, followed by a secondary stage where IL-1β promotes CNS repair [65,66] (for further details on the role of the main interleukins in MS pathogenesis please refer to Table 2).

Table 2. Role of interleukins in MS pathogenesis.

Interleukin (IL) Type	Source	Function	Cells Recruitment/Activity	References
IL-17	Th 17 cells CD8+ T cells Glial cells Mucosal associated invariable T cells NK (natural killer) cells	Proinflammatory/acute inflammatory process	CD4+ T cells recruitment CD8+ T cells recruitment Neutrophil infiltration and migration to the CNS	[40,45,67]
IL-1α	Microglial cells APC (antigen presenting cells)	Proinflammatory/traumatic lead inflammation	CD4+ T cells recruitment	[42,44]
IL-1β	Microglial cells AP	Proinflammatory/autoinflammatory process and infective	CD4+ T cells recruitment	[42,44]
IL-23, IL-12, IL-2	APC, Microglia cells, MDMs	Proinflammatory	Th1 and Th17 cells polarization, CNS trophism by autoreactive effector cells	[35,39,40,45,68,69]
IL-10	Microglia/Macrophages, Tr1 cells	Anti-inflammatory	Reduce CD4+ T cells recruitment Promote Treg cells expansion	[61,70]
IL-2	Astrocytes	Anti-inflammatory	Regulation and recruitment of Treg cells	[61]
IL-1	Th1 cells—CD4+ T cells	Pro-remyelination	Differentiation and recruitment of oligodendrocyte progenitor cells (OPC)	[40,62,65,71]
IL-2	Treg cells	Pro-remyelination	Differentiation and recruitment of OPC	[61]

4.3. Role of Regulatory Adaptive Immune Cells in MS

4.3.1. Tregs

Tregs are a class of T cells that regulate the immune response and maintain tolerance to self-antigens to prevent autoimmune diseases. Tregs act as immunosuppressors by impeding the induction and growth of effector T cells. The novel work of Xie et al. to describe Tregs in mice cerebrum proved the fundamental role of these cells in immune surveillance in the CNS and in controlling the inflammatory response. The study suggested that Tregs regulate and impede the recruitment of CD4+ T cells in EAE mice and down-regulated LPS-induced neuroinflammation triggered by microglia/macrophages by releasing IL-10 [61]. Furthermore, the authors suggested a possible relationship between the release of IL-2 by astrocytes and the abundance of Treg cells.

A recent review explored the potential role of Treg cells in regulating oligodendrocytes activation and differentiation from the oligodendrocyte progenitor cell's (OPC) pool [72]. This was the follow up to a study conducted by Dombrowski's group which demonstrated that the remyelination process and the number of the activated/differentiated OPCs in Treg deficient mice is significantly lower compared to wild and/or Treg depleted mice. The investigators concluded that the principle function of Treg cells is to communicate with oligodendrocytes to induce remyelination. The process is believed to be associated with the production of the growth regulatory protein (CCN3) by Tregs, which triggers differentiation in oligodendrocytes towards a myelinating phenotype.

4.3.2. B Regulatory Cells

A major focus of investigation by many researchers aimed at resolving the autoimmune dilemma, is centred on researching the function of T cells, since these cells have long been recognised as the main actors in the adaptive immune system response. However, more recently there has been a growing interest in a less known class of immune modulatory cells, namely the B regulatory cells (Bregs).

Studies have demonstrated that Bregs, especially those producing high levels of the cytokine IL-35, do play a critical role in modulating the aberrant immune activation occurring in MS [48,49,73]. Unfortunately, to date there are no specific surface markers to correctly distinguish Breg cell subtypes, so these are usually recognised based on the specific set of cytokines they are capable of releasing. The most studied cytokine released by Breg cells is IL-10, which plays a very important role in immune modulation in human and experimental models, hence this class of Bregs is often labelled as B10 cells [48]. Shen et al. suggested the direct role of Bregs secreting both IL-10 and IL-35 in modulating the functions of T cells in EAE, as well as the plasma cell activation in the active phase of the disease, and suggested that reduced production of these two subtypes of B cells (i.e., B10 or B35) might be associated with less favourable outcomes [64]. Similar results were reported in another study by Wang et al., where the researchers observed a reduction of Bregs and a higher severity of autoimmune uveitis in mice following the pharmacological or genetic blockade of IL-35 [63].

5. Discussion

In this review, the overarching idea was to provide some of the latest insights into the role of neuroinflammation in the development and progression of MS. We sought to conduct a meta-analysis of current literature on the field, with emphasis on those studies addressing the role elicited by inflammation in the different phases of MS. Our studies suggested that present research is heavily focused on unravelling the specific involvement of different cell populations, as well as the cytokines released at different stages of the disease, in the pathogenic cascades that perpetuates the autoimmune response.

In the first part of this work, we described how MS is seen in the context of the neurological disorders, how it is classified from a clinical standpoint and what are the consolidated and emerging theories behind the development of this devastating disease. We also discussed why autoimmunity in MS is thought to be driven by putative environmental triggers in people with a susceptible

genetic background. We observed that there is consensus that priming of T cells towards a reduced self-tolerance is the result of a genetic predisposition and other concurring factors, which seems to facilitate the antigenic mimicry phenomenon responsible for the triggering of MS. The other part of the study was to review the role of the resident T cells (CD4+ T cells) in the CNS during inflammation as well as the potential mechanisms through which resident glia (microglia/microphages) recruit these cells at different stages of the inflammatory process [11,62,74]. In the third part of this work we introduced the concept of BBB permeability, discussing how the "incomplete" immune insulation of the CNS, especially in the course of the disease, may in part be implicated with the recruitment of immune cells from the periphery and/or allow the passage of pro-inflammatory mediators to signal inflammation in the CNS [11,62,74].

Whilst most of the research carried out to examine the involvement of different subpopulations of T cells was shown to pay more attention to T helper subclasses, we veered away towards recent discoveries in cytotoxic T cells (CD8+ T cells), trying to address why and how these cell types target the myelin sheath in the CNS during the exacerbation stages of the diseases and even more so in the secondary progressive form of the disease, where CD8+ T cells are localised at higher densities around the areas of demyelination, a factor usually associated with poor prognosis [17,33,75,76].

With regards to the role of B cells, we found that these immune cells seem to have a secondary role in MS pathogenesis, and it is clear that there is still some level of uncertainty about the exact function elicited by these cells in the course of MS progression. From what is known, B cells serve the immune system as professional APCs to prime cytotoxic T cells but are also very useful for diagnostic purposes, since the identification of oligoclonal immunoglobulin bands in the CSF of patients following a lumbar puncture is accepted as a gold standard to diagnose the condition. In addition, high levels of oligoclonal bands at the early stages of MS are often predictive of a severe prognosis [49,73].

A new field that is gaining momentum from translational researchers attempting to define a strategy to modulate the ongoing neuroinflammatory process in MS is centred on understanding the role of Tregs and Bregs. Both cells populations are diminished in MS patients, and it appears that a phenotypic shift from Tregs to CD8+ and/or CD4+ T cells occurs at some stage during disease progression, leading to a worsening of the autoimmune response. Tregs and Bregs are both active especially during the remission stage of the disease, and recent evidence suggests that this subclass of immune cells may play an active role not only in arresting the demyelination process, but also in promoting regeneration of the myelin sheath [49,61,62,67,72,73,76,77]. Several groups are exploring this possibility, and perhaps it is not surprising that in the near future, molecules boosting Tregs and/or Bregs function will be tested in clinical settings.

ILs are a class of cytokines that were first identified in leukocytes. Immune system activities largely depend on interleukins, and the sporadic deficiencies of some of these have been described, all pertaining to autoimmune diseases or immune deficiency. Most interleukins are produced by helper CD4+ T cells, but also by monocytes, macrophages, CD8+ T cells, dendritic cells, NK cells and endothelial cells. These cytokines stimulate the expansion and differentiation of T and B cells, and hematopoietic cells. Here, we summarised the pro-inflammatory ILs that actively participate in the recruitment of T cells during the different phases of inflammation in models of MS. As discussed above, the novel role of some anti-inflammatory ILs was highlighted, which is not solely to mitigate inflammation, but also to stimulate spontaneous remyelination at injury sites and contribute to functional recovery [5,62]. Among the many ILs described, we found that there is some degree of uncertainty on the exact involvement of IL-1β in controlling the differentiation process of oligodendrocytes [65,71], as well as remyelination in the EAE model. It looks like some ILs that are well known for their putative detrimental effects may indeed trigger regenerative responses.

MS drugs currently target the immune system to modulate the neuroinflammatory response and hence, prevent tissue damage. These disease-modifying drugs reduce the relapse of MS but largely fail in delaying the long-term detrimental effects of the disease. Therefore, there is an urgent need to find more targeted therapies. In recent years, new approaches aiming at targeting autoreactive immune

cells and their products have progressed, showing increased specificity and efficacy, while limiting the potential side effects arising from global immunosuppression. The development of cytokine or antigen-specific antibodies or vaccines appear to be promising immunopharmacological targets that are currently being explored for MS [78]. However, further investigations aimed at understanding these new interesting functions are warranted, as this could contribute to expanding the knowledge of immune cell-to-cell communication during neuroinflammation and in MS.

6. Conclusions

Inflammatory demyelination of the CNS is the hallmark of MS. By understanding the intricate relationship between cells and the cytokines released during the different stages of MS, including acute inflammation, endogenous immune modulatory responses, de- and re-myelination and recovery in MS patients, researchers are now being prompted to reconsider the future of the anti-inflammatory drugs currently used to treat afflicted patients. T cells and cytokines that were thought to trigger the pathological condition are now being considered active players in the recovery process. Based on these findings, it is proposed that researchers should start considering that T cells inhibitors and anti-inflammatory drugs might hinder the myelin regeneration whilst acting on the ongoing inflammation. Perhaps treatment regimens should be applied after the appropriate staging of the disease, that is, by administering drugs that suppress inflammation when it peaks and changing to Tregs/Bregs stimulators to support regeneration at a later stage or during remission.

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