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Review

Macrophages: A double-edged sword in experimental autoimmune encephalomyelitis

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ABSTRACT

Multiple sclerosis (MS) is a debilitating neurological disorder of the central nervous system (CNS), characterized by activation and infiltration of leukocytes and dendritic cells into the CNS. In the initial phase of MS and its animal model, experimental autoimmune encephalomyelitis (EAE), peripheral macrophages infiltrate into the CNS, where, together with residential microglia, they participate in the induction and development of disease. During the early phase, microglia/macrophages are immediately activated to become classically activated macrophages (M1 cells), release pro-inflammatory cytokines and damage CNS tissue. During the later phase, microglia/macrophages in the inflamed CNS are less activated, present as alternatively activated macrophage phenotype (M2 cells), releasing anti-inflammatory cytokines, accompanied by inflammation resolution and tissue repair. The balance between activation and polarization of M1 cells and M2 cells in the CNS is important for disease progression. Pro-inflammatory IFN-γ and IL-12 drive M1 cell polarization, while IL-4 and IL-13 drive M2 cell polarization. Given that polarized macrophages are reversible in a well-defined cytokine environment, macrophage phenotypes in the CNS can be modulated by molecular intervention. This review summarizes the detrimental and beneficial roles of microglia and macrophages in the CNS, with an emphasis on the role of M2 cells in EAE and MS patients.

1. Introduction

Multiple sclerosis (MS) is a debilitating T-cell mediated autoimmune disease of the central nervous system (CNS), manifested clinically as weakness and progressive paralysis [1]. While the etiology of MS is still not well clarified, a combination of several factors are thought to be involved, including genetics, environment, and viral infection, with environment likely playing a more dominant role than genetics [2–4]. Studies from experimental autoimmune encephalomyelitis (EAE), an animal model of MS, have revealed that autoreactive T cells against myelin proteins play a role in disease development. The infiltrating Th1 and Th17 cells in the CNS release a large amount of pro-inflammatory cytokines, such as IFN-γ, IL-17, IL-12, IL-23, and nitric oxide (NO), inducing demyelination and neuron death in the inflamed CNS [5–9]. Anti-inflammatory Th2 and regulatory T cells (Treg), which develop in the later phase, play an important role in controlling inflammation, and damping Th1 cell activity and pro-inflammatory cytokine release; adoptive transfer of Treg has been shown to be efficient in EAE suppression [10].

Recent studies have revealed that microglia/macrophages actively participate in the pathogenesis of EAE progression [11,12]. As the first line of cells, activated microglia/macrophages are more potent phagocytes than resting macrophages in the clearance of cell debris and inhibitory substances in the inflamed CNS. Although beneficial to remyelination, their production of pro-inflammatory cytokines is detrimental to CNS tissue integrity during the induction phase. There are difficulties in differentiating CNS resident microglia from peripheral macrophages in EAE, because they share the same F4/80+/CD11b+ phenotype. However under early stage of inflammatory condition, resident microglia cells express low levels of activation markers CD45, CCR1, CCR5, but high TGF-β; while peripheral infiltrating macrophages express high CD45, CCR1, CCR2, CCR5, but low TGF-β, that

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Table 1
Characteristics and function of macrophage subtypes.

	M1 macrophages	References	M2 macrophages	References
Phenotype marker	Arginase-2, iNOS, nitrotyrosine	[47,48,58,59,65]	CD206 (MR)+, CD163+, arginase-1, Ym1/2, RELM-α/FIZZ1	[46–48,58–61,65]
Activation marker	High CD25, CD28, CD40, CD80, CD86, MHCII, NF-κB	[5,49,55,64]	Low CD40, CD86, MHCII, NF-κB	[5,49,55,64]
Inducing mediator	LPS, IFN-γ, IL-12	[9,22,38,55,65]	IL-4, IL-10, IL-13, IL-33, IFN-β, CCL17, miR-124, Activin-A, Dectin-1, invariant NKT, glucocorticosteroids	[7,20,40,43,48,56,58,60,62,63,66,70,73,76]
Product	IL-6, IL-12/23p40, TNF-α, IL-1β, iNOS, NO, MCP-1, CCL22	[9,48,50,52,53,71]	IL-1ra, IL-4, IL-10, IL-13, TGF-β	[10,40,47,48,58,60,62,66,70]
Effect	Tissue damage, degeneration, suppress oligodendrocyte differentiation	[14,41,42,51,59]	Tissue repair, regeneration, drive oligodendrocyte differentiation	[14,41,42]
Disease	Induce EAE and MS	[23,24,28,38,52]	Suppress EAE and MS	[47,52,55,70]

might be used as markers for identification of CNS resident microglia cells and peripheral macrophages. Contaminating infiltrating lymphocytes, astroglial/oligodendroglial cells are identified as CD3+CD11b−CD45(high) and CD11b−CD45−, respectively, can be easily distinguished from microglia cells and macrophages [13–18]. Because they are conditioned in the same way during neuroinflammation in vivo, the function of activated microglia and macrophages overlaps. The review summarizes the detrimental and beneficial roles of microglia/macrophages, and discusses the importance of balance among their subpopulations in EAE development.

2. Microglia in EAE

Microglia are cells of the myeloid lineage that reside in the CNS, play an important role in pathologies of many diseases associated with neuroinflammation such as MS [11,12,19]. During induction phase of EAE, microglia are immediately activated and take on antigen presenting cell (APC)-like capacity to activate naive T cells toward Th1 cells [19]. More important, the activated microglia cells are major source of a variety of pro-inflammatory cytokines and chemokines, such as TNFα, IL-6, IL-23p19, IL-1β, reactive oxygen intermediates and proteinases [13,14,19,20]. Not only do the released cytokine mediators damage CNS tissues, but they also activate and recruit other leukocytes into the CNS, thus amplifying pro-inflammation. For example, IL-23 potently drives Th17 cells, but, less likely, drives Th2 T cell differentiation and infiltration into the CNS, ultimately increasing local IL-17 production, an important cytokine in EAE pathogenesis [21–23]. Depletion of microglia attenuates TNF-α and NO, while at the same time reducing activation and recruitment of leukocytes into the CNS [21,24]. Similar effects are also observed in the mouse model, with blockade of programmed death ligand 1 (PD-L1 or B7-H1) and migration inhibitory factor (MIF) signaling in microglia. Mice with microglia depletion or attenuated activation develop milder EAE, accompanied by lower levels of IL-1β, IL-6, IL-17, TNF-α, and inducible nitric oxide synthase (iNOS) in the CNS [4,25,26]. These findings are also supported by significantly delayed EAE onset and reduced demyelination in the CNS after microglia depletion.

In addition, activated microglia are major source of chemokines, such as MIP, CCL2, CCL3, CCL4, CCL5, CCL12, CCL22, all of which play a role in development of EAE [27–29]. For example, blocking CCL2 signaling in glial cells significantly reduces disease onset, progression, and demyelination, accompanied by a lower level of maturation and recruitment of leukocytes and monocytes into the CNS [30].

Although activated microglial cells participate in EAE pathogenesis, they are also beneficial to CNS tissue integrity during inflammation [26]. Miron et al. reported that M2 dominant type microglia was beneficial to the oligodendrocyte differentiation in vitro and remyelination in the lesions of EAE and aged mice, and their produced specific protein Activin-A plays an important role in the beneficial effects [14] (Table 1).

It is reported that microglia and astrocytes constitutively express a certain basal level of neurotrophic factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), ciliary neurotrophic factor (CNTF) and matrix metalloproteinase-9 (MMP-9) [31–34]. These factors can be up-regulated in an inflammatory environment from activated microglia/macrophages, and are beneficial to survival and differentiation of oligodendrocytes and neurons. Adoptive transfer of cells expressing these trophic factors improved neuron survival and nerve regeneration, and protected mice from EAE development [35].

3. Macrophages in EAE

There are few peripheral infiltrating macrophages in the CNS under physiological conditions. However, during induction and peak phases of EAE, massive infiltration of peripheral macrophages is seen in the meninges surrounding the CNS, the choroid plexus, and perivascular space, but the numbers of macrophages in the CNS are reduced during inflammation resolution and recovery phase, correlating with fewer lymphocyte infiltrates [36,37].

The increased migratory ability of activated macrophage into CNS is correlated to inflammation-induced high expression of chemokines and chemokine receptors, such as CCR2 from macrophages in mice [16]. It has been reported that in EAE up-regulation of CCL2, CCL3, CCL4 induces greater macrophage accumulation and effector function in the CNS [28–30,38]. At EAE onset, CCL22 (monocyte-derived thymus-specific chemokine) is greatly up-regulated in the draining LNs and spinal cord; in contrast, neutralization of CCL22 activity decreases macrophage accumulation in the CNS and causes milder EAE [38].

CCR4, a receptor for CCL17 and CCL22, is also up-regulated on macrophages of EAE mice, subsequently enhancing macrophage CNS infiltration. CCR4-deficient mice exhibit lower macrophage recruitment into the CNS and have milder EAE symptoms than wild type mice, associated with attenuated release of TNF-α from infiltrating macrophages [39].

The subtypes of macrophages and their role in the pathogenesis and regulation of MS/EAE are outlined below.

3.1. Phagocytosis of macrophages in EAE

During the peak and resolution phases, some infiltrating inflammatory cells proceed to apoptosis in the inflamed lesions, causing a decrease in the number of infiltrating cells in the inflamed

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