Polarization of macrophages and microglia in inflammatory demyelination

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Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system, and microglia and macrophages play important roles in its pathogenesis. The activation of microglia and macrophages accompanies disease development, whereas depletion of these cells significantly decreases disease severity. Microglia and macrophages usually have diverse and plastic phenotypes. Both pro-inflammatory and anti-inflammatory microglia and macrophages exist in MS and its animal model, experimental autoimmune encephalomyelitis. The polarization of microglia and macrophages may underlie the differing functional properties that have been reported. In this review, we discuss the responses and polarization of microglia and macrophages in MS, and their effects on its pathogenesis and repair. Harnessing their beneficial effects by modulating their polarization states holds great promise for the treatment of inflammatory demyelinating diseases.

Keywords: macrophage; microglia; polarization; demyelination; remyelination

Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory and demyelinating disease characterized by inflammation, demyelination, axonal damage, gliosis and destruction of the blood-brain barrier[1-3]. Although the T-helper (Th) cells Th-1 and Th-17 were thought to be the main response effectors for autoimmune inflammation, macrophages and microglia do play an important role in the pathogenesis of MS. The pathology of newly-forming lesions in relapsing-remitting MS shows only microglial activation and macrophage infiltration in demyelinating areas, with rare lymphocyte infiltration[4,5]. Moreover, macrophage depletion and microglial paralysis significantly suppress the progress of experimental autoimmune encephalomyelitis (EAE), the animal model of MS[6,7].

Macrophages and microglia play important roles in bridging the innate and adaptive immune responses. Under normal physiological conditions, macrophages monitor the tissue environment for pathogens, maintain tissue homeostasis, phagocytose dead and dying cells, and respond rapidly to perturbations in the local environment. Microglia share many phenotypic and functional characteristics with macrophages. In the adult central nervous system (CNS), microglia are on constant surveillance for perturbations resulting from injury or disease[8]. In MS, in which pro-inflammatory, neurotoxic and myelin-attacking microglia and macrophages predominate, some microglia and macrophages with anti-inflammatory, neuroprotective and remyelination-promoting properties are also present[9]. These conflicting lines of evidence have led to confusion and considerable debate regarding the harmful versus the beneficial roles of macrophages and microglia in MS.

The polarization of macrophages and microglia may underlie their differing functional properties. Taking advantage of their beneficial effects by modulating their polarization states holds great promise for the treatment of CNS demyelinating diseases[10-13]. In this review, we discuss the characteristics of various polarized states of macrophages and microglia, the factors that drive such polarization and
the functional features of these polarized macrophages in demyelinating diseases. We emphasize the roles of polarized microglia and macrophages in demyelination and remyelination in MS.

Macrophage Polarization: Phenotypes of Activated Macrophages

One of the most prominent characteristics of the monocyte–macrophage system is phenotypic plasticity. Work in non-neural systems has revealed important insights into the different types of macrophage activation, referred to as macrophage polarization, that result in cells with either pro- or anti-inflammatory properties[8].

The M1, or classically-activated macrophages, are induced by the prototypical Th-1 cytokine interferon-γ (IFN-γ) or lipopolysaccharide (LPS). They are IL-12[high], IL-23[high] and IL-10[low]. M1 macrophages mainly secrete pro-inflammatory cytokines such as TNF-α, IL-12, IL-23, IL-1β, IL-6 and chemotactic factors, as well as inducing cytotoxic mediators (reactive oxygen and NO). Macrophages activated in this way are involved in the acute pro-inflammatory response and have an increased antigen-presenting capacity. By contrast, the alternatively-activated macrophages (M2) are generally IL-12[low], IL-23[low], and IL-10[high], and are usually induced by the Th-2 cytokines IL-4 or IL-10, and IL-13. Currently, M2 macrophages are divided into M2a, M2b, and M2c subtypes, which have different functions. M2a macrophages are activated by IL-4 and/or IL-13, secreting large amounts of the anti-inflammatory cytokine IL-10, enhancing arginase-1 (Arg-1) activity and specifically expressing mannose receptor (MR; CD206) and macrophage chitinase 3-like protein 3 (Chi3l3; YM-1). They are involved in killing extracellular pathogens, debris removal, angiogenesis, and wound healing[14]. Macrophages activated by immune complexes or the TLR or IL-1R ligand are type 2-activated macrophages (M2b), which secrete low levels of IL-12 and large amounts of IL-10, TNF-α, IL-6, and IL-1β, inhibiting bacterial endotoxin-induced acute inflammation and promoting Th-2 differentiation and humoral immune responses. M2c macrophages are activated by IL-10, TGF-β and glucocorticoid, and are also known as inactivating macrophages, secreting high levels of IL-10 and TGF-β, and regulating and suppressing inflammation[15,16] (Table 1).

The presence of M1/M2 phenotypic polarization has also been suggested for microglia[17-21]. What lies between is a full spectrum of activation states which share some properties with the poles – either M1 or M2[26].

Heterogeneity and Polarization of Macrophages and Microglia in the Demyelinating CNS

There are three types of macrophages (CD11b+, CD45high) in different locations in the normal CNS: the perivascular macrophages, the choroid plexus macrophages and the meningeal macrophages[22]. These cells are reported to play a role in the early stages of EAE. The ED2 expression on these cells is up-regulated during EAE before lymphocyte infiltration and the onset of clinical symptoms. Moreover, a slight but measurable suppression of EAE clinical score occurs after selective and complete depletion of these ED2-positive macrophages[23].

During inflammatory demyelination, blood-derived infiltrating macrophages are thought to differentiate from two types of monocytes, the “inflammatory monocytes” (Ly6Clow, GR1+, CCR2+, CX3CR1low and CD62L+) and the “resident monocytes” (Ly6Chigh, GR1-, CCR2-, CX3CR1high and CD62L), and show important migratory and functional differences in mice and humans[24,25]. These two types of cells arise from a common progenitor called the “macrophage dendritic cell precursor”[26]. The Ly6Chigh monocytes are pro-inflammatory and are recruited early into inflammatory sites, whereas Ly-6Chigh monocytes are patrolling cells that replenish resident macrophages. Recently, it was shown that Ly6Chigh cells are the predominant population at the demyelinating lesions of EAE. They are rapidly recruited into the CNS and play a pathogenic role during autoimmune demyelinating disease[27-29].

The polarization of macrophages has been analyzed during EAE. In acute EAE, more M1 (iNOS+, ED1+) than M2 (Arg-1+, ED1+) macrophages are found at the early stage. The proportion of M2 macrophages increases and more M2 cells are seen at the EAE peak and in the recovery stage, indicating that they are associated with disease remission[30]. In a relapse-remitting EAE model, similar numbers of M1 and M2 lead to mild EAE, while more M1 cells promote relapse. In severe-relapsing EAE, the M1/M2 ratio is constantly high and especially higher during relapse[11,31,32].