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Diversity and plasticity of microglial cells in psychiatric and neurological disorders

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ABSTRACT

Recent advanced immunological analyses have revealed that the diversity and plasticity of macrophages lead to the identification of functional polarization states (classically activated M1 type and alternatively activated M2 type) which are dependent on the extracellular environment. M1 and M2 polarization states of macrophages play an important role in controlling the balance between pro-inflammatory and anti-inflammatory conditions. Microglial cells are resident mononuclear phagocytes in the central nervous system (CNS), express several macrophage-associated markers, and appear to display functional polarization states similar to macrophages. Like M1 macrophages, M1 polarized microglia can produce pro-inflammatory cytokines and mediators such as interleukin (IL) 1β, IL-6, tumor necrosis factor-α, CC-chemokine ligand 2, nitric oxide, and reactive oxygen species, suggesting that these molecules contribute to dysfunction of neural network in the CNS. On the other hand, M2 polarized microglia can produce anti-inflammatory cytokine, IL-10 and express several receptors that are implicated in inhibiting inflammation and restoring homeostasis. In this review, we summarize the diversity, plasticity, and immunoregulatory functions of M1 and M2 microglia in psychiatric and neurological disorders. Based on these aspects, we propose a contribution of imbalance between M1 and M2 polarization of microglia in bipolar disorder, obesity, amyotrophic lateral sclerosis, and Rett syndrome. Consequently, molecules that normalize the imbalance between M1 and M2 microglial polarization states may provide a beneficial therapeutic target for the treatment of these disorders.

Contents

Abbreviations: ACC, anterior cingulate cortex; 2-AG, 2-arachidonoyl-glycerol; AgRP, agouti-related peptide; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; Arg-1, arginase-1; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CART, cocaine- and amphetamine-regulated transcript; CCL2, CC-chemokine ligand 2; CNS, central nervous system; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; IFN-γ, interferon-γ; IGF-1, insulin-like growth factor-1; IL, interleukin; LPS, lipopolysaccharide; MeCP2, methyl-CpG binding protein 2; MRI, magnetic resonance imaging; MS, multiple sclerosis; NAc, nucleus accumbens; NO, nitric oxide; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PPARγ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; SOD-1, superoxide dismutase-1; S1P, sphingosine 1-phosphate; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

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1. Introduction

Microglial cells are resident mononuclear phagocytes in the central nervous system (CNS) and express several macrophage-associated markers, such as CD11b, CD14, CX_3C chemokine receptor 1 (CX_3CR1: fractalkine receptor), ionized calcium-binding adaptor molecule-1 (Iba-1), and F4/80 (Kettenmann et al., 2011; Saijo & Glass, 2011). Resident microglial cells are shown to be derived from hematopoietic stem cells in yolk sac and contribute to immune surveillance as primary responding cells for pathogen infection and injury in the CNS (Kettenmann et al., 2011; Saijo & Glass, 2011). Furthermore, microglial cells are involved in maintenance of tissue homeostasis and act as sentinels of infection and injury in the CNS (Ransohoff & Perry, 2009; Kettenmann et al., 2011; Saijo & Glass, 2011).

Recent advanced immunological analyses have revealed that the diversity and plasticity of macrophages lead to the identification of two distinct functional polarization states (classically activated M1 type and alternatively activated M2 type) and imbalance between M1 and M2 macrophage subsets plays an important role in chronic inflammation in the various tissues including the CNS (Mikita et al., 2011). Pathogen-associated molecular patterns (PAMPS) or damage-associated molecular patterns (DAMPS) can stimulate macrophages via toll-like receptors (TLRs) or adenosine triphosphate (ATP) receptors and the classical activation of resting macrophages leads to M1 phenotype in the presence of lipopolysaccharide (LPS) and type 1 helper T cell-derived cytokine, interferon (IFN)-γ (Mosser & Edwards, 2008). M1 macrophages produce pro-inflammatory cytokines and mediators such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, CC-chemokine ligand 2 (CCL2), reactive oxygen species (ROS), and nitric oxide (NO), and play a central role in host defense against bacterial and viral infections (Gordon & Martinez, 2010). In contrast, type 2 helper T cell-derived cytokines, IL-4 and IL-13, can induce alternative activation of macrophages to M2 (particularly 'M2a') phenotype (Gordon & Martinez, 2010). M2a macrophages express arginase-1 (Arg-1), Ym1, CD36, CD163, and CD206 on the cell surface and produce anti-inflammatory cytokine, IL-10 which can down-regulate M1 macrophage-mediated inflammation (Mosser & Edwards, 2008; Gordon & Martinez, 2010). Although three different M2 phenotypes (M2a, M2b, and M2c) are known in various conditions, these M2 phenotypes are thought to reflect a spectrum of plastic functional conditions rather than a set of distinct activation status (Prinz & Priller, 2014).

Microglial cells share certain characteristics including their diversity and plasticity with macrophages (Ransohoff & Perry, 2009; Kettenmann et al., 2011). Similar to macrophages, classically activated microglia (M1 phenotype) can produce pro-inflammatory cytokines and mediators (IL-1β, IL-6, TNF-α, CCL2, ROS, NO, glutamate, etc.) and induce breakdown of the blood brain barrier (BBB), which leads to a massive infiltration of inflammatory cells from the periphery, suggesting that M1 microglia contribute to neuronal damage and neural network dysfunction in the CNS (Fig. 1). In contrast, alternatively activated M2 microglia can produce anti-inflammatory cytokine IL-10 which inhibits M1 microglia-mediated neuroinflammation. Furthermore, M2 microglia express tissue-remodeling receptors (Arg-1, CD36, CD163, CD206, etc.), produce transforming growth factors β (TGF-β), brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), and contribute to restore homeostasis in the CNS (Fig. 1).

It has been classically considered that the abnormalities of neurotransmitters basically contribute to psychiatric disorders such as schizophrenia and major depressive disorder (Stahl, 2008), while recent studies have revealed that neuroinflammation appears to be associated with the development of these psychiatric disorders (Meyer et al., 2011;

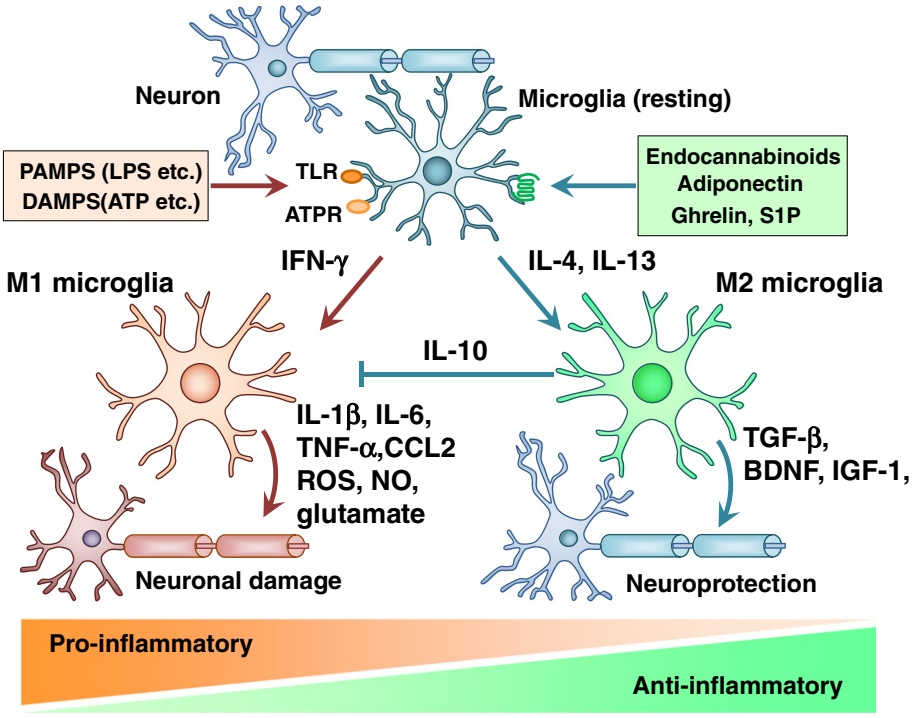

Fig. 1. M1/M2 polarization of microglia and their immunoregulatory functions. Microglial priming is seen when resting microglial cells are stimulated with pathogen-associated molecular patterns (PAMPS) or damage-associated molecular patterns (DAMPS) via TLR or adenosine triphosphate receptors (ATPR). In the presence of IFN-γ, microglia polarize to M1 phenotype and produce pro-inflammatory cytokines/mediators such as IL-1β, IL-6, TNF-α, CCL2, glutamate, ROS, and NO. In contrast, IL-4 and IL-13 induce alternative activation of microglia to M2 phenotype which down-regulates M1 functions by anti-inflammatory cytokine, IL-10. In addition, M2 microglia can promote tissue remodeling by producing neuroprotective factors, TGF-β, IGF-1, and BDNF. It is presumable that endocannabinoids, adiponectin, ghrelin, or sphingosine 1-phosphate (S1P) can induce M2 polarization of microglia and thereby showing anti-inflammatory and neuroprotective effects. These molecules may provide a beneficial therapeutic target for the treatment of psychiatric or neurological disorders and diseases.