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Research update

Functional polarization of neuroglia: Implications in neuroinflammation and neurological disorders

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ABSTRACT

Recent neuroscience research has established the adult brain as a dynamic organ having a unique ability to undergo changes with time. Neuroglia, especially microglia and astrocytes, provide dynamicity to the brain. Activation of these glial cells is a major component of the neuroinflammatory responses underlying brain injury and neurodegeneration. Glial cells execute functional reaction programs in response to diverse microenvironmental signals manifested by neuropathological conditions. Activated microglia exist along a continuum of two functional states of polarization namely M1-type (classical/proinflammatory activation) and M2-type (alternative/anti-inflammatory activation) as in macrophages. The balance between classically and alternatively activated microglial phenotypes influences disease progression in the CNS. The classically activated state of microglia drives the neuroinflammatory response and mediates the detrimental effects on neurons, whereas in their alternative activation state, which is apparently a beneficial activation state, the microglia play a crucial role in tissue maintenance and repair. Likewise, in response to immune or inflammatory microenvironments astrocytes also adopt neurotoxic or neuroprotective phenotypes. Reactive astrocytes exhibit two distinctive functional phenotypes defined by pro- or anti-inflammatory gene expression profile. In this review, we have thoroughly covered recent advances in the understanding of the functional polarization of brain and peripheral glia and its implications in neuroinflammation and neurological disorders. The identifiable phenotypes adopted by neuroglia in response to specific insult or injury can be exploited as promising diagnostic markers of neuroinflammatory diseases. Furthermore, harnessing the beneficial effects of the polarized glia could undoubtedly pave the way for the formulation of novel glia-based therapeutic strategies for diverse neurological disorders.

1. Introduction

Inflammatory reactions are inevitable pathological processes occurring in all forms of central nervous system (CNS) injuries and insults [1,2]. Macrophages are the prime and widely distributed immune cells that play a crucial role in maintaining homeostasis and defense. Tissue macrophages are present in most of the body organs including the brain, with the microglia as the representative of the resident phagocytic cells. The resident microglia mediate immune and inflammatory responses in the CNS. Per the nature of microenvironment, these cells become functionally polarized to execute specific effector programs. Microglia express specific functional reaction programs in response to diverse microenvironmental signals, and exist along a continuum of two functional states of polarization [3,4]. Microglia can be phenotypically polarized to develop either a classical (proinflammatory; M1) or an alternative (anti-inflammatory and pro-healing; M2) phenotype [5]. Diverse pro- and anti-inflammatory cytokines can polarize microglia toward distinct functional phenotypes [6]. Moreover, microglia also acquire intermediate phenotypes that display a combination of different polarization markers ranging from M1 to M2 [7], which suggests the presence of microglial cells at the crossroads of diverse pro- and anti-inflammatory mechanisms. It is the nature of the specific polarization conditions that dictates the development of microglia into any of these two distinct phenotypes [8,9]. Microglial phenotypes are most

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prominently characterized by the expression of distinct cell surface receptors and the release of soluble factors with specific functions. Microglia with M1 phenotype are characterized by upregulation of CD16 Fc receptors, CD32, CD64, CD86, interleukin (IL)-1β, IL-6, IL-12, IL-23, tumor necrosis factor (TNF)-α, inducible nitric oxide synthase (iNOS), and chemokine (C-C motif) ligand 5 (CCL5), whereas microglia of M2 phenotype display the upregulation of arginase (Arg)-1, mannose receptor (CD206), insulin-like growth factor (IGF)-1, triggering receptor expressed on myeloid cells 2 (TREM2), chitinase 3-like 3 (Ym-1), and FIZZ1. CD86 has been reported to trigger the microglial proinflammatory response [9]. In addition, upregulation of iNOS, which is expressed in diverse immune cells, is judged as a hallmark of M1 macrophages/microglia. Ability to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) is a crucial component of M1 microglia [10]. iNOS is a key microglial enzyme associated with this process, which utilizes arginine to produce nitric oxide [11]. Contrarily, upregulation of Arg-1 is one of the most specific markers of M2 macrophages/microglia [12,13]. However, microglia of M2 phenotype show diverse profiles defined as the expression of mediators or receptors with the capacity to repair or protect the body from inflammation [14]. Nevertheless, the plastic nature of microglia has made it challenging to classify these cells *in vivo*.

Microglia, an invigilator of the CNS microenvironment, serve as a major cellular component in brain inflammation [15]. In addition to performing the classical proinflammatory activity, microglia contribute to the maintenance of brain homeostasis suggesting a critical role of microglia both in the pathology and in the normal physiology of the CNS [16]. Microglia participate in the progression as well as resolution of neuroinflammation and diverse neurological disorders [17], exhibiting a range of functional states via expression of specific pattern of receptors, production of effector molecules, and acquisition of identifiable morphological feature. The nature of the inflamed microenvironment defines the overall phenotypes or functional states of microglia. Recent studies have attempted to define the microglia as a pharmacological target for diverse neurological disorders.

Astrocytes are another type of glial cells that actively participate in the substantial cross-talk between inflammatory infiltrates and CNS resident components of the innate immune system under pathological conditions [18]. In addition, astrocytes play a crucial role in higher neural processing, and actively serve to maintain the neuronal health [19]. Astrocytes become reactive under diverse pathological conditions. However, the molecular markers turned on or off during astrogliosis are not clearly determined. It is also unclear whether reactive astrocytes are beneficial or harmful to neighboring neurons. Recent advances in the field of neuroscience and glial biology have endeavored to introduce the astrocytes as immunocompetent players within the brain. Recent reports have acknowledged that astrocytes adopt neurotoxic or neuroprotective phenotypes depending on the nature of immune or inflammatory microenvironment or insults

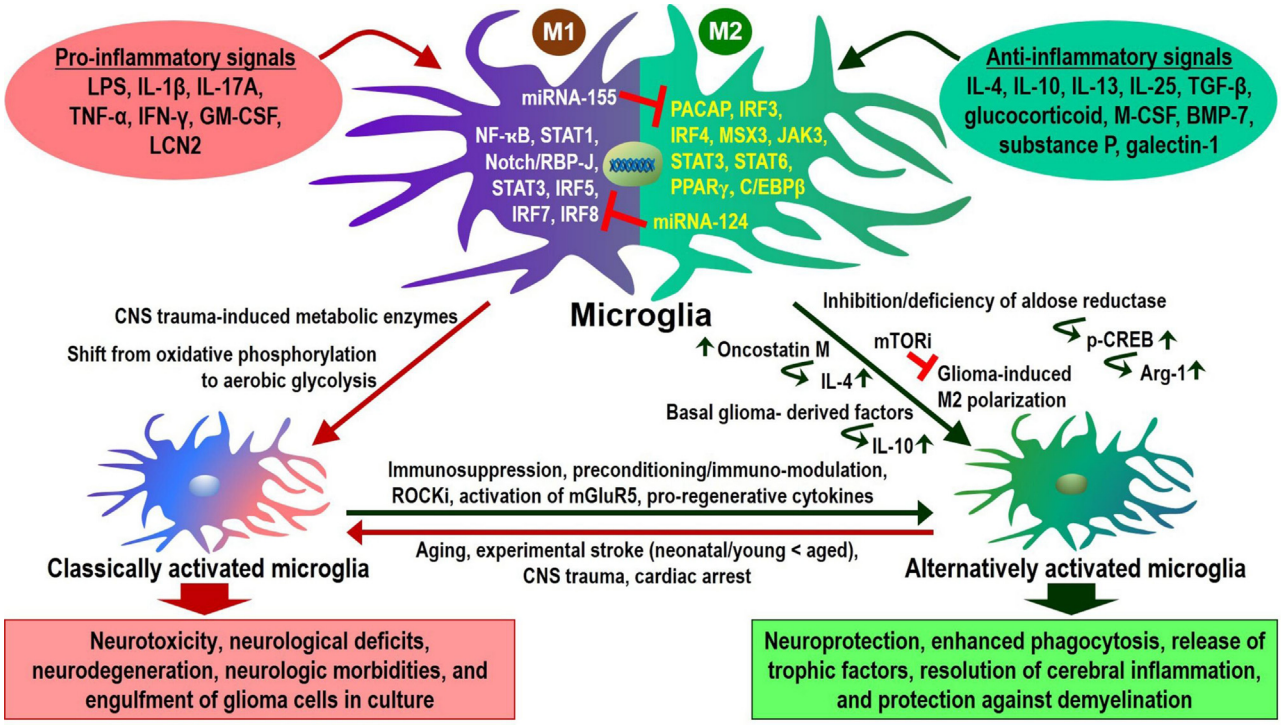

Fig. 1. Phenotypic polarization and switching of microglia. Diverse extracellular signals and intracellular molecules control the polarization and switching of microglial phenotypes. Microglia can develop into proinflammatory/classically activated (M1) or anti-inflammatory/alternatively activated (M2) phenotypes depending on the specific polarizing signals present at diverse stages after CNS injuries, and thereby revealing beneficial or detrimental responses for tissue protection and repair. M1 population releases proinflammatory mediators and free radicals to induce functional neurological deficits and neurodegeneration. In addition, M1 population engulfs glioma cells in culture. On the contrary, M2 population improves brain repair and regeneration by enhancing phagocytosis, releasing trophic factors, resolving cerebral inflammation, and protecting against demyelination. The functional polarization of microglia is found to be molecularly regulated or determined by diverse transcription factors, acute phase proteins, receptors, pathological conditions, and metabolic states. Primarily M2 phenotype inducers and/or secondarily M1 phenotype inhibitors should be explored in the future to design new therapeutics that can boost the repair function of microglia for diverse neurological disorders. LPS, lipopolysaccharide; IL, interleukin; TNF-α, tumor necrosis factor-α; IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor; LCN2, lipocalin-2; M-CSF, macrophage colony-stimulating factor; TGF-β, transforming growth factor β; BMP-7, bone morphogenetic protein 7; mTORi, mTOR inhibitor; STAT, signal transducer and activator of transcription; ROCKi, Rho kinase inhibitor; MSCs, mesenchymal stem cells; mGluR5, metabotropic glutamate receptor 5; miRNA, micro RNA; CREB, cyclic adenosine monophosphate response element–binding protein.

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