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Different Roles of Microglia/Macrophage in Ischemic Stroke and Alzheimer's Disease

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Abstract

Neuroinflammation is a double edge sword: it plays both destructive and regenerative roles in a variety of neurological diseases, such stroke and Alzheimer's disease (AD). In the central nervous system, these inflammatory changes are restricted exclusively to microglia. Ischemic stroke causes an acute cascade of events, including excitotoxicity, inflammatory responses, oxidative stress and apoptosis, whereas AD is a chronic progressive process. As the blood–brain barrier separates the central nervous system and the peripheral immune system, the brain is used to be considered an immune-privileged organ. However, accumulating evidence reveals mononuclear phagocytes and the resident microglia play a key role in modulating the development and progression of brain pathology. In this mini review, we summarize the role of microglia in the brain and in disease states. Microglia serves different roles at different stages of the diseases. We emphasize the regulatory role of CX3CR1, which may provide a novel and effective means for therapy.

Keywords: Microglia; Macrophage; Fractalkine receptor; CX3CR1

Microglia and CX3CR1 in the Brain

Microglia are the resident macrophage cells that constitute the innate immune system in the central nervous system (CNS). They account for 10% of all cells found in the brain [1]. The microglia progenitor cells are produced by primitive hematopoiesis in the yolk sac [2]. These primitive macrophages (Myb-independent) migrate to the developing neural tube to generate microglia. Thus, microglia and bone marrow-derived macrophages (Myb-dependent) are genetically distinct [3]. They proliferate and activate in most neurological diseases, ranging from multiple sclerosis to prion diseases, and play a key role in defending against infection, ischemia, trauma, inflammation, tumors and neurodegeneration [4].

Microglia constantly surveys the brain micro-environment by extremely motile processes and protrusions to remove invading micro-organisms and deleterious debris. They scavenge the CNS for infectious agents, plaques and damaged neurons and synapses. They clean up unwanted synapses by phagocytosis, playing a key role in synaptic pruning and maturation during development, thus maintaining proper neural circuit wiring [5]. Since this process must be kept efficient, microphages can be rapidly activated by even small pathological changes in the CNS. In the case of blood-brain barrier (BBB) disruption, microglia can be activated immediately and be switched from the patrolling role to the shielding role of the injured site. Activated microglia secretes growth factors to maintain the homeostasis of the brain milieu. In addition, activated microglia contributes to tissue repair and neural regeneration [4].

Any kind of pathologic insult in the brain can activate microglia to change their morphologic phenotype from highly ramified cells to amoeboid cells. Microglia have two activation phenotypes: the classic M1 state (iNOS+ microglia) is a pro-inflammatory state and the alternative M2 state (Arg+ microglia) is related to tissue repair [6]. Several signaling pathways have been proposed that contribute to the polarize M1 state, including Janus kinase (JAK)1/JAK2 signaling [7] and Toll-like receptor 4 (TLR4) [8]. In addition, IL-4 combine with IL-4Rα or IL-13 combine with IL-13Rα1 can activate transcription factors such as STAT6, peroxisome-proliferator-activated receptor γ (PPARγ), Jumonji domain-containing protein 3 (Jmjd3) and IRF4 thus activate microglia toward M2 state [9].

Fractalkine receptor (CX3CR1) is specifically expressed in microglia and macrophages. It binds solely to CX3C ligand 1(CX3CL1, fractalkine), a potent chemokine, that is mainly expressed by neurons [10]. CX3CL1/CX3CR1 signaling pathway forms an interactive crosslink between neurons and microglia. It regulates the microglial/macrophage cell migration and function [11]. CX3CL1 reduces neuroinflammation. Treatment of aged rats with CX3CL1 attenuates age-related increase in microglial activation [12]. CX3CL1 is up-regulated in the hippocampus during spatial learning by regulating glutamate-mediated neurotransmission tone [13].

Microglia and CX3CR1 in Stroke and AD

In ischemic stroke, there are evidence of microglia activation, cytokine production, blood-borne immune cells infiltration into the brain and neuronal death. The insulted brain releases defensive substances such as cytokines, chemokines and reactive oxygen species (ROS). The cytokines and ROS breakdown the BBB to facilitate peripheral immune cells, including monocytes, neutrophils and lymphocytes, to infiltrate into the brain. In the acute stage of ischemic stroke, endogenous microglia and recruited macrophages are activated and polarized to the M2 state. They gradually change into the M1 phenotype [9]. The M1 state of microglia/macrophage can release cytotoxic substances to elicit inflammation that leads to cell death. On the other hand, the M2 state of microglia/ macrophage phagocytose cellular debris and release trophic

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factors [14], which is beneficial for recovery from ischemic stroke. Among those peripheral immune cells, macrophages play a crucial role in inflammation at the post-ischemic stage.

The post-ischemic cell death releases ATP, uridine triphosphate, and CX3CL1. Because CX3CR1 is mainly expressed in microglia and macrophages, it attracts the macrophages to infiltrate into the CNS. The protection effect of CX3CR1-/- mice at the early stage of ischemic stroke is characterized by the M2 polarization markers. CX3CR1-/- mice have showed a decrease in leukocyte infiltration and therefore smaller infarcts in a transient middle cerebral artery occlusion stroke model [15,16].

The contribution of microglia activation in AD could be beneficial or detrimental [17,18]. Amyloid-β (Aβ) plaques and neurofibrillary tangles are pathological hallmarks of AD. Microglia accumulates around Aβ plaques [19]. They are thought to clear Aβ plaques by phagocytosis [20]. Microglial phenotype changes from M2 to M1 in the progression of AD [21]. Emerging evidence has pointed out that polymorphism in the microglia receptor TREM2 is a risk factor for AD [22]. However, selective depletion of microglia didn't change the plaque formation or total Aβ load [23]; implying microglia may not affect Aβ accumulation or clearance.

Aβ has been shown to initiate microglial activation and elicit chronic inflammation which lead to synaptic dysfunction and cognitive impairment [24,25]. Activated microglia accelerates tau pathology and impairs working memory in an AD mouse model [26]. Consistently, depleting microglia dramatically suppressed the propagation of tau in the brain [27].

Although CX3CR1-/- is protective against neuronal loss in a mouse model of focal cerebral ischemia, it induces microglia activation, worsening tau pathology and impaired cognitive performance in a double transgenic mouse model that carries CX3CR1-/- and human tau protein (hTau-CX3CR1-/-) [26]. This microglia activation precedes tau aggregates since at six months of age there is minimal development of tau aggregates. However, another study in the 3xTg mouse model of AD, CX3CR1 deficiency was shown to prevent neuronal loss [28]. The discrepancy in these two studies may be due to using different animal models. The 3xTg mice exhibits both Aβ and tau pathologies by including three different mutant human transgenes (APP, PSEN1 and MAPT). Blocking CX3CL1-CX3CR1 signalling actually reduces Aβ pathologies in two mouse models (APP-PS1 and R1.40) that only over-express extracellular Aβ aggregates [29]. These data suggest that CX3CR1 deficiency has opposing effects on the two primary pathologies of AD. Aβ pathologies precede tau pathologies by as much as 10 years in humans [30]. While blocking CX3CR1 may be beneficial at the early stage when Aβ pathology is dominant, its deficiency could be detrimental as the disease progresses to the late stage when activated microglia and tau aggregation become overriding.

Conclusion

Ischemic stroke and AD are different in aetiology, disease course, clinical presentation, treatment and outcomes. But both of them have evidence of neuroinflammation in which microglia plays an essential role. To understand distinctive stages of microglia and their regulatory factors, such as CX3CL1-CX3CR1 is vital to elucidate the underlying mechanism of the diseases and to develop effective therapeutic agents.

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