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FUNCTIONS OF MICROGLIAL CELLS ON NEUROGENESIS, SYPNATIC PRUNING AND NEUROTRANSMISSION: A BRIEF REVIEW

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ABSTRACT

Microglia has been known to be the immune cells of the brain where it generally responds to neuronal damage and eliminates the damaged cells by phagocytosis. Activation of microglia mediates the inflammatory response which typically hallmarks the brain pathology. However, its role in normal physiology of the central nervous system has not been clearly elucidated. In this brief review, we intend to highlight recent findings on the interesting functions of microglia in shaping the normal brain circuit including during the neurogenesis process, synaptic pruning and neurotransmission.

1.0 Introduction

Microglial cells are the primary immune cells of the central nervous system (CNS), and are basically resident macrophages that are responsible for immune defenses against invading microorganisms, stress or trauma. Intrinsically, tremendous studies were focused on microglia's capability to execute inflammatory responses in CNS and mostly weighted on their negative contribution to neurological related diseases (1, 2). Recently, there have been interesting discoveries demonstrating that microglia also plays an active role in the CNS normal physiology including neurogenesis (3, 4), synaptic pruning (5) and neurotransmission (6). In light of these findings, microglia has emerged as an important factor in shaping normal brain circuit and in turn contributing to the normal healthy cognitive and behavioral functions. Here, we aim to highlight the functions of microglial cells in regulating neurogenesis process both at embryonic and adult stages, before discussing their functions in synaptic pruning. Further, this review will also discuss the probable role of microglial in interfering with one of the neuronal activities, neurotransmission.

2.0 Roles of Microglial Cells on Neurogenesis

Neurogenesis is a complex continuous process to generate functional neurons from neural precursor cells (NPCs). The process is most active during embryonic brain development and eventually confine to several regions in adult CNS including hippocampus and subventricular zone (SVZ). NPCs will orchestrate their biological functions (proliferation,

quiescence, apoptosis as well as differentiation) depending on the interaction of cellular, genetic, and environmental factors within the brain. Microglial cells colonise the embryonic brain and selectively populate themselves into the neurogenic niches and displaying amoeboid morphology and features of their activated form (7). After embryonic neurogenesis, microglial cells are eventually distributed evenly and taken up 'resting' phenotypes. Nevertheless, it has been reported that microglial are relatively more densely populated at the neurogenic SVZ and exhibit activated phenotypes compared to other non-neurogenic regions (8, 9). The facts that microglia have been actively recruited to home at the close vicinity with neurogenic regions, intermingle with NPCs along the brain development, and prompted them to acquire activated phenotypes had strongly suggested that they may play important roles in regulating the neurogenesis process.

Most studies concerning microglial roles in neurogenesis are predominantly established on the basis of adult neurogenesis, either in vitro or *in vivo* models. It remains controversial when come to the beneficial or detrimental nature of microglial biology on neurogenesis. Several studies have described microglial and/or microglial soluble factors influencing the outcomes of NPC differentiation; either pro-neurogenic or pro-gliogenic, as well as direct NPC migration activities (10-12). On the other hand, few others showed the detrimental effects of microglial activation and inflammatory response on adult neurogenesis (13, 14). The heterogeneity of microglial effects on adult neurogenesis could be accountable on the continuum nature of their activation status that has led microglia to either acquire pro-inflammation phenotypes that are neurotoxic or anti-inflammation phenotypes that are neuroprotective. On one hand, acute activation caused by traumatic injury, ischemia or epilepsy, or triggered by administration of lipopolysaccharide (LPS) can result microglia to acquire a classical activation phenotype that is associated with inflammatory responses and negatively impact mature neuronal cells as well as neurogenesis (13, 14). Acutely activated microglial cells release pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, and Interferon-γ and in turn limit proliferation, survival and differentiation of NPCs or newly born neurons. The findings further confirmed when the biological activities of these cytokines were blocked or the use of anti-inflammatory drug to inhibit microglial activation can restore neurogenesis (13-15). Similar results were also reported in in vitro experiments (11, 16). On the other hand, chronic activation of microglia caused by T helper 2 associated cytokines (IL-4), anti-inflammatory cytokine (TGF-β), chronic dose of LPS stimulate alternative activation phenotype of microglia that favor neural stem cells (NSCs) proliferation and neurogenic differentiation (10, 17). Chronic activated microglial cells are capable to secrete neurotropic factors such as insulin-like growth factor 1 (IGF1) and TGF- β that promote neurogenesis (10, 17).

During aging there is a decline in NPC proliferation and the formation of new neurons (18). This may correlate with the fact that microglial in the aged brain displayed activated phenotypes. Aging may cumulatively stimulate microglial to develop into low grade inflammatory phenotypes and impair the homeostasis regulatory mechanisms within, resulting in unresolved inflammation (19, 20). Importantly, one should aware that the determinant of microglial protective and toxic role is context dependent. For instance, microglial could be further divided into several subpopulations gauging by their origin, phenotypic appearances, functional properties and similar activator but different dosage may cause different outcome. Moreover, microglia secretion are pleiotropic in which they can exert both neurotoxic and neurotrophic properties (21). Microglial may also acquire alternative phenotypes and become anti-inflammation/neuroprotective via phagocytosis signal from massive apoptotic milleu (17). In fact, in healthy adult brain, microglial play an important role in shaping neurogenic niche in hippocampus via phagocytosing away newborn cells that are undergoing apoptosis (3). Intriguingly, the phagocytosis is carrying out by 'resting' microglial and independent from the activation and microglial-mediated inflammation, indicating an intrinsic mechanism in normal physiology. In developing brain, microglial are shown to take part in regulating NPC pool size via phagocytosing away non-apoptosis but highly mitogenic NPCs (7). This is further confirmed with the presentation of uncontrolled expansion of NPC in animal models that lacking of microglial due to pharmacology or genetic targeted knockout/knockdown (7). Nevertheless, the functional impacts of microglial phagocytosis on neurogenesis remain to be elucidated.

3.0 Functions of Microglial Cells in Synaptic Pruning

Synaptic pruning is a process in which excessive neurons and synaptic connections are eliminated to secure the efficiency of neuronal transmissions. Microglial have been reported to play important role in removing debris and death cells in neuronal circuit and specific neuronal structures such as neurite, axon, and synapses credited to their phagocytosis capability (22-24). Several histology studies had demonstrated processes bearing 'activated' microglial were found in brain regions during postnatal synaptic remodeling period (25, 26). The role of microglial in remodeling synaptic circuits was then further confirmed in electron microscopy and two photon in vivo imaging of the primary visual cortex of healthy juvenile mice. Microglial cells are actively contacted with transient dendritic

spines and engulf intact synapses via phagocytosis in responses to changes in visual sensory experience (27, 28). Recent studies have reported defective and delayed synapses development in CX3CR1 knockout mice. Mice lacking CX3CR1 or fractalkine receptor have transient reduction of microglial number during early postnatal life resulting deficit in synaptic pruning. CX3CR1 knockout mice exhibit higher density of synapses but poor functional synaptic transmission and decrease brain connectivity compared to wild type mice leading to difficulties in social interaction and repetitive-behavior phenotypes that resembles syndrome of neurodevelopmental and neuropsychiatric disorders (5, 29).

Possible mechanism that linking microglial and synaptic remodeling is the complement cascade and major histocompatibility complex class I (MHC-I) that are expressed on neurons depending on their activity. Complement cascade components C1q and C3 are localized to immature synapses and implicated for synapses elimination (30, 31). The developmental synaptic pruning is halted and delayed in mice that lack of CR3, C3, and C1q, the initiating protein of the classical complement cascade. Pharmacological inhibition of microglial functions using minocycline also produces similar defects (32). Furthermore, both *in vitro* and *in vivo* studies suggested that microglial could also modulate synapses formation or loss via their soluble factor secretion. For example, A25T fibrils treatment can render an inflammatory phenotypes and increase secretion of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and nitric oxide resulting synapse loss and short-term memory deficits in a mouse model of transthyretin-related oculoleptomeningeal amyloidosis (33). Similarly, condition knockout of brain-derived neurotrophic factor (BDNF) from microglia can cause reduction in motor-learning-dependent synapse formation and cognitive deficit that observed in microglia depletion mice model (34). On the other hand, blocking neuronal activity in visual pathway can reduce expression of MHC-I, resulting in disruption of synaptic pruning (35). The role of MHC class I was further confirmed in mice genetically deficient for cell surface MHC-I which showed incomplete pruning of synaptic connections between retina and the central targets (36).

4.0 Microglial Cells and Neurotransmission

Apart from pruning, microglial also might interfere with neuronal activities such as neurotransmission. Microglial have been reported to express membrane receptors for all known neurotransmitters (37). This allows them to actively sample signals from neuronal cell and response to on-going neuronal activity. Microglial are also capable to express several matrix metalloproteases such as MMP2 and MMP-9 that allow proteolytic modification of the extracellular matrix (ECM) at the vicinity of synapses (38). Proteolysis of ECM can convert inactive pro-trophic factor such as EGF and TGF-β into their biological active form that may affect synapses integrity. Both pro- and anti- inflammatory mediators of microglial are implicated in modulating dendritic spines morpho-physiology and synaptic functions of neurons. In brain, microglial are the major source of TNF-α. In mice that lack of TNF-α, an accelerated maturation of the dentate gyrus region and smaller dendritic trees in CA1 and CA3 regions in young mouse has been reported (39). TNF-α was also reported to regulate synapse function such as neurotransmitter receptor trafficking, synaptic plasticity, as well as and regulation of gliotransmission (40, 41). Elevation levels of TNF-α can increase excitatory synaptic strength and decrease inhibitory synaptic strength creating differences in excitatory/inhibitory ratio (40, 42, 43). Moreover, IL-6 was reported to inhibit glutamate release and modulate excitatoxicity in cerebral cortex (44). Microglial also regulate synaptic strength via targeting synaptic adhesion molecules such as synCAM-1, N-cadherin and protocadherin (45).

5.0 Conclusion

Although the exact impacts and mechanisms underlying microglial role in neurogenesis, synaptic development, plasticity and neurotransmission remain elusive, these studies do confirm the indispensable role of microglial in modulating balance of neurogenesis, generating healthy synapse and regulating homeostasis of neurotransmission. Yet, little is known about the role of microglia in embryonic CNS development. In developing brain, neurogenesis is the core and initial step of CNS development. Regulation of embryonic neurogenesis involved not just the mechanisms that control neural precursor cells proliferation or the one that regulates the size of the NPC pool but also of those that contribute to the decision of when NPC to engage into neuronal differentiation mode. This initial step is crucial and modulates the complex organisation of molecular regulators as well as cellular components. Interestingly, microglial progenitors colonise the developing brain at early CNS development and almost concurs temporally with this transformation step. The understanding of microglial roles as the cellular modulator during embryonic neurogenesis is indeed essential to elucidate not only the embryonic neurogenesis homeostasis but also the downstream activities such as the synaptic pruning as well as neurotransmission.

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