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Physiological Function of Microglia

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Abstract

Broad interest in the rapidly advancing field of microglial involvement in forming neural circuits is evident from the accumulating findings published in leading journals. This special issue of *Neuron Glia Biology* contains a special collection of research articles and reviews concerning the new appreciation of microglial function in the normal physiology of the brain that extend beyond their traditionally understood role in pathology.

INTRODUCTION

Microglia are the resident immune cells in the central nervous system (Graeber, 2010). Although the diverse roles of microglia in pathological states have been long appreciated, recent publications are revealing physiological roles of microglia under normal conditions; for example in phagocytosis of developing (Marin-Teva et al., 2004) and adult-born neurons (Sierra et al., 2010); monitoring synapses with dynamic extension and retraction of their highly ramified cell processes (Tremblay et al., 2010; Wake et al., 2009); and phagocytosis of synapses during normal synaptic development (Paolicelli et al., 2011; Schafer et al., 2012). Dysfunction of these normal physiological functions of microglia can result in developmental disorders that were traditionally viewed only as neuronal dysfunctions (Maezawa and Jin, 2010).

Consistent with the growing appreciation that microglia have diverse functions in the brain during normal and pathological conditions, accumulating evidence is uncovering heterogeneity among microglia in different brain regions. The article by Lai et al., (2011, this issue) shows that microglia from different brain regions exhibit region-specific responses. The amount of cytokines release, receptor expression, and neurotrophic factor release are differently regulated in microglia depending on the specific brain region they occupy. These differences in turn affect neurons differently in each brain region.

As an immune cell in the central nervous system (CNS), microglia release reactive oxygen products and inflammatory molecules. The review by Nakanishi et al., (2011 this issue) considers the important question of how microglial aging affects oxidative stress and the exaggerated inflammatory responses and prolonged LPS-induced sickness behavior seen

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with increasing age. Their summary of the literature shows that accumulation of mitochondrial DNA damage in aging microglia increase production of reactive oxygen species (ROS), and promotes release of pro-inflammatory factors such as interleukin-1β. Pro-inflammatory cytokine production in the CNS leads to sickness behavior and impairs cognitive function. The review article is focused on the mitochondrial transcription factor A, which increases functional mtDNA by promoting the transcription of mtDNA and stabilizing mtDNA. Overexpression of TFAM reduces ROS even in normal aging, suggesting TFAM as a potential therapeutic target to prevent sickness behavior during aging and in response to infection (Nakanishi et al, 2011, this issue). Together this research indicates the likely possibility that microglia are involved in cognitive dysfunction with aging.

Microglia are known to be involved in neural development not only by phagocytosis of apoptotic cells, but also by controlling the fate of neurons and their progenitors. Marin-Teva et al., (2011 this issue) summarize evidence concerning microglial and neuronal cell death both during neural development and in the adult CNS. The authors summarize evidence showing that microglia phagocytize dying cells and also promote programmed cell death during neural development. Three steps in programmed cell death of neural progenitors are considered: cell attraction, recognition, and phagocytosis. Different signaling molecules are involved in each process. In the context of cell attraction signals, the authors suggest three different molecules as having a prominent role: phospholipid lysophosphatidylcholine (LPC), CX3CR1 (fractalkine) and ATP/UTP. In cell recognition for phagocytosis, the involvement of molecule such as phosphatidylserine (PS) binding with C3bi are considered. C3bi can be recognized by macrophage expressed complement-receptor-3, and another possible bridging molecules, milk fat globule epidermal growth factor-8 (MFG-E8), triggering receptor expressed on myeloid cells 2 (TREM2). These processes are also involved in regulating phagocytosis by microglia in the adult CNS after injury. Extracellular ATP acts as major cell-cell signaling molecule in the injured brain and the authors discuss how purinergic signaling is involved in microglia activation, including both on and off signaling. Fractalkine and its receptor CX3CR1, and CD200 with CD200R1 are well-established as participating in ATP-mediated on and off signaling. Studies of microglial activation involving cytokines exerting neurotoxic or neuroprotective effects on injured neurons are summarized (Marin-Teva et al., 2011 this issue).

To sense injury in the CNS, microglia must constantly monitor parenchyma in the healthy brain. Recent in vivo imaging studies have shown microglia continuously extend and retract their processes in healthy brain tissue (Nimmerjahn et al., 2005). The motility of microglia increases after application of the $GABA_A$ receptor antagonist, bicuculline, suggesting a role for this neurotransmitter receptor in activity-dependent monitoring of synaptic function by microglial cell processes.

The review by Wong et al., (2011 this issue) summarizes activity-dependent movements of microglia cell processes. These studies show that the motility of microglia is increased by bath application of AMPA and kainate and decreased by antagonist of AMPA and kainate-gated ionotrophic glutamate channels. This motility is also increased by $GABA_A$ receptor antagonist, bicuculline and decreased by bath application of GABA. Increased mobility of

microglia cell process motility is diminished by P2 receptor antagonists, suggested another cellular source of ATP might be involved in the mechanism of activity dependent movement of microglia processes. The authors concluded that motility of microglia processes is regulated by glutamate receptors on the cells which stimulate release of ATP through Pannexin channels (Wong et al., 2011, this issue)

The review by Wake et al., (2011 this issue) summarizes literature on the physiological role of microglia. Wake et al., discuss the role of microglia as a determinant of programmed cell death in neural development and also programmed cell death in adult neurogenesis. Once microglia function is impaired by CX3CR1 knock-out or immune deficient mice, adult neurogenesis is reduced and spatial learning is impaired. The authors also discuss how microglia interact dynamically with synapses to regulate synapse development and homeostasis (Wake et al., 2011, this issue)

Microglia have been known to have a function in synapse stripping since the pioneering work by Blinzinger and Kreutzberg in 1968 on regenerating motor neurons in the axotomized facial nucleus (Blinzinger and Kreutzberg, 1968). In their review Jinno et al., (2011 this issue) summarize the results of synapse “stripping” experiments in axotomized motor neurons. They discuss evidence showing that species and strain differences affect neural survival. The authors suggest that the difference in neural viability among different species is due to different types of glia cells involved in the process of neural recovery after axotomy in these strains (Jinno and Yamada, 2011, this issue). The authors also suggest that astrocytes may be involved in synapse stripping and that these glial cells may have a more neuro-protective effect than microglial intrusion on synapses. However this conclusion must be further investigated.

Tremblay (2011 this issue) provides more evidence of microglia-synapse interaction in the healthy brain. The authors discuss microglia-synapse interactions in multiple respects, including immunocytochemistry, electron microscopy, SSEM with 3D reconstruction, and two-photon *in vivo* imaging. The author also summarizes research on regulation of microglial behavior in response to neuronal activity and the possible candidate molecules involved (Tremblay 2011, this issue).

Traditionally, it has been debated whether microglia could regulate synaptic number. Paolicelli et al., (2011 this issue) summarize information on microglia function and synapse elimination in normal development, and mice which lack Cx3CR1 expression and have lost microglia function through flactalkine signaling. The authors discuss that Cx3CR1 knock-out animals show more abundant excitatory synapses, but each synapse is weaker, suggesting failure of synaptic maturation. Electron microscopy shows synaptic elements inside microglia; evidence supporting the conclusion that microglia engulf synapses during normal development. The authors suggest possible candidate immune molecules such as C1q, C3, may be involved, which has been recently supported by independent studies (Schafer et al., 2012).

As a result of dysfunction in the normal physiological role of microglia, Maezawa et al., (2011 this issue) summarize evidence that microglia are implicated in autism spectrum

disorder. Rett syndrome is one of the autism spectrum diseases, where the expression of methyl CpG binding protein 2 is abnormal not only in neurons, but also in glia. The authors discuss possible microglial involvement in disease resulting from abnormal expression of MeCp2. Abnormal expression of MeCP2 in microglia exerts glutamate toxicity of synapses without evidence of neural inflammation. This is interesting evidence that dysfunction of the physiological role of microglia contributes to the pathogenesis of developmental disorders (Maezawa et al., 2011, this issue).

In consideration of microglial function in pathological conditions, microglia have been known to have a crucial role in neuropathic pain. Trang et al., (2011 this issue) review the literature on ATP signaling in microglia with respect to the pathogenesis of neuropathic pain acting on P2X4 and P2X7 purinergic receptors. P2X4 activation promotes release of brain-derived neurotrophic factor from microglia, which changes GABA transmission from being inhibitory to excitatory as a consequence of down-regulation of the K^+-Cl^- co-transporter in neurons. The signaling pathways downstream of the P2X4 receptor and comparison with of other P2 receptors is provided (Trang et al., 2011 this issue).

In summary, the studies and review articles in this special issue demonstrate a new understanding that microglia play critical functional roles in both pathological and normal physiological states. This emerging new view of microglia in combination with traditional understanding of microglia in disease greatly increases our understanding of brain formation and disease.

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