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Physiological function of microglia

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Broad interest in the rapidly advancing field of microglial involvement in forming neural circuits is evident from the fresh 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 extends beyond their traditionally understood role in pathology.*

Keywords: Microglia, neurogenesis, synaptic plasticity, Rett syndrome, autism, chronic pain

INTRODUCTION

Microglia are the resident immune cells in the central nervous system (CNS; 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 (Marín-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 (Wake *et al.*, 2009; Tremblay *et al.*, 2010); 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, fresh 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 cytokine release, receptor expression and neurotrophic factor release is 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 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 with increasing age. Their summary of the literature shows that accumulation of mitochondrial DNA damage in aging microglia increases 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(TFAM), which increases functional mtDNA by promoting the transcription of mitochondrial DNA (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 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. Marín-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 molecules such as phosphatidylserine (PS) binding with C3bi is considered. C3bi can be recognized by macrophage expressed complement-receptor-3, and another possible bridging molecule, 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 (Marín-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 extending and retracting their processes in healthy brain tissue (Nimmerjahn *et al.*, 2005). The motility of microglia increases

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after the application of the γ-aminobutyric acid ($GABA_A$) 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 α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (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, suggesting 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 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 and Yamada (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 that 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 (Paolicelli and Gross, 2011, this isssue). 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 an 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 play 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 the other P2 receptors are 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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