Editorial

Microglia in Neuronal Circuits

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1. Introduction

Microglia comprise a unique subset of glial cells as the principal brain immune cells and are actively engaged in physiological and pathological brain functions. Unlike other resident neural cells that are of neuroectodermal origin, microglia are of mesodermal origin and invade the neuroepithelium at early embryonic stages. As resident immune response cells, microglia are extremely sensitive to almost any brain disturbance. Therefore, microglia are traditionally recognized for their immune functions during acute brain injury, such as bacterial meningitis, ischemic stroke, and spinal cord injury, as well as chronic neurological disorders, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and neuropathic pain. Recently, the role of microglia in neurodevelopment and neural plasticity in the healthy brains has gained tremendous attention. These exciting results raise an intriguing possibility that microglia can integrate into the neuronal circuits in the healthy and diseased brain.

In support of this notion, it is emerging that microglia have remarkably dynamic processes and are frequently interacting with neurons and synaptic elements. Through these interactions, microglia may monitor neuronal/synaptic activities and thus survey the microenvironment in the brain. Indeed, recent studies have apparently shown that microglia function in neuronal circuits by playing diverse roles in neural development, behavior, and pathology in the brain. Therefore, microglia research has changed the way we think about neuronal network/plasticity and increased our understanding of brain diseases associated with abnormal microglia. Contributions to this special issue provide a snapshot of microglial function in the healthy and diseased brain and propose a fundamental role of microglia in neuronal circuits.

2. Microglia in the Healthy Brain

The vivid observation of microglia in the healthy brain through in vivo imaging in 2005 was a breakthrough in microglia research. For the first time, researchers witnessed that microglia are extremely motile and their processes are constantly monitoring the microenvironment without any pathological insults. Subsequently, studies were booming to focus on the potential role of microglia in the healthy brain, including synaptic pruning in the development and regulation of synaptic transmission/plasticity. On the other hand, several lines of evidence have also indicated the neuronal control of microglial activities under physiological conditions. In this special issue, U. B. Eyo and L. J. Wu highlight recent findings on this bidirectional interaction between neurons and microglia. The review summarized how microglia signal to neurons through direct physical contact or signaling molecules such as fractalkine, complement, and DAP12, as well as how microglial activity is modulated by neuronal signals including classic neurotransmitters and chemotactic signals. In addition, the authors discussed studies of microglial depletion as an approach to understand microglial importance in neuronal development, function, and maintenance. This review on bi-directional microglial-neuronal communication provides an overview of how microglia are integrated into neuronal circuits in the healthy brain.
Recent studies have revealed a surprising role of microglia in the structural remodeling of neuronal circuits by using their immune abilities in the healthy brain. For example, microglia were demonstrated to eliminate neuronal precur-
sors, synaptic elements, and newborn cells during adult neu-
rogenesis. In this special issue, Z. Šišková and M.-E. Tremblay
further zoom in on the mi croglial function in the neuron
circuits and review recent studies on the microglia-synapse
interactions in the mature healthy brain. The focused review
discusses the emerging roles of activity-dependent microglial
elimination of synaptic elements (dendritic spines and axon
terminals) notably by phagocytosis. This microglia-synapse
interaction enables synaptic pruning and thus might be
important for the experience-dependent remodeling of neuronal
circuits in the mature brain as well as during normal aging.

In addition to structural remodeling, microglia are
able to modulate synaptic activities and plasticity. Evidence
from imaging, cellular, and electrophysiological approaches
indicates that microglia affect synaptic maturation during
development as well as the acute and dynamic regulation
of neuronal activity in the mature healthy brain. In this
special issue, S. E. Tsirka and colleagues review the recent
studies on microglia as an active player in the regulation
of synaptic activities and suggest that microglia are an
important contributor to the potential quad-partite synapse.
The review summarized some interesting mechanisms under-
lying microglial regulation of synaptic activities and synaptic
numbers; the proteases secreted from microglia to remodel
e xtracellular matrix, the release of microvesicles (shed ves-
cicles or ectosomes) derived from microglia, and connexins
and large pore channels as a way by which microglia interact
directly with neurons. A plethora of potential messengers
mediate the communication between microglia and neurons,
including cytokines, purines, glutamate, prostaglandins, and
nitric oxide. In this special issue, F. Ferrini and Y. De Koninck
particularly discuss a unique microglial signaling molecule,
brain-derived neurotrophic factor (BDNF), in controlling
neuronal excitability in both physiological and pathological
conditions.

3. Microglia in the Diseased Brain

Resting microglia rapidly transform into an activated state in
most pathological processes, including host defense against
infectious organisms, autoimmune inflammation, ischemia,
trauma, chronic pain, and neurodegeneration. Activation
of microglia is accompanied by changes in morphology,
upregulation of immune surface antigens, production of
cytotoxic or neurotrophic molecules, and phagocytosis of
pathogens, degenerating cells, and inflammatory debris.
Although microglial activation is well documented in a
variety of neurological disorders, the definitive beneficial or
detrimental roles of microglia in these diseases remain
contentious. The consensus is that microglia play different roles
based on the temporal and spatial context of brain diseases;
the proinflammatory cytotoxic aspects of activated microglia
might be important at an early stage while microglia’s anti-
inflammatory effects become more prominent later during
tissue repair. Nevertheless, microglia evidently respond and
even cause the abnormality of neuronal circuits under patho-
logical conditions.

Neuronal cell death, loss of synapses, and neuroinflam-
mation are hallmarks and emerged as a major correlate of
cognitive decline in neurodegenerative disorders. In this
special issue, Z. Šišková and M.-E. Tremblay extend the
discussion of microglia-synapse interaction to the context of
neurodegenerative disorders, such as Alzheimer’s disease,
Parkinson’s disease, and prion diseases. Chronic microglial
activation under these pathological conditions likely con-
tributes to synaptic dysfunction and elimination, thereby
exacerbating neurodegeneration. Richardson and Hossain
specifically review recent studies on the role of microglia in
Parkinson’s disease. Activated microglia and subsequent neu-
roinflammation have been consistently associated with the
pathogenesis of Parkinson’s disease. Therefore, the authors
discuss the potential of targeting microglia to reduce neu-
roinflammation, with particular focus on microglial ion
channels as novel therapeutic targets for neuroprotection in
Parkinson’s disease.

The physiology of microglia in the spinal cord is less
well studied; however, there is strong evidence of spinal
cord microglia in the genesis of chronic pain. In this special
issue, R.-R. Ji and colleagues discuss the microglial activa-
tion through the mitogen-activated kinase pathways, as
well as microglial mediators (tumor necrosis factor-alpha,
interleukin-1 beta, and BDNF) in regulating synaptic plastic-
ity of pain circuits in the spinal cord in neuropathic pain. Fer-
rini and De Koninck focus specifically on microglial BDNF
in multiple neurological conditions, including epilepsy, drug
addiction, spinal cord injury, and neuropathic pain. In
particular, microglial BDNF in the spinal cord is well
established in neuronal disinhibition in neuropathic pain in
the following signaling cascade: the BDNF activation of
neuronal TrkB receptor, downregulation of the K+-Cl-
cotransporter KCC2, disruption of Cl−homeostasis, and
hence the reduced strength of GABA_A− and glycine receptor-
mediated inhibition. Spinal cord injury triggers inflammation
with activation of innate immune responses, where both
microglia and macrophages are activated and accumulated.
In this special issue, Y. Ren and W. Young review the
beneficial mechanisms of macrophages on spinal cord injury
by inhibition of proinflammatory responses, stimulation of
angiogenesis, secretion of neurotrophic factors, and clearance
of myelin debris in the injured spinal cord, providing a
rationale of macrophage-based therapies for spinal cord
injury. Therefore, insights into the communication between
microglia/macrophages and neurons in the spinal cord will
not only further our understanding of microglia function in
neuronal network but may also lead to novel therapeutics for
ameliorating a wide array of neural dysfunctions, including
chronic pain and spinal cord injury.

4. Concluding Remarks

This special issue summarizes a broad range of topics on
microglia in neuronal circuits in both the healthy and
diseased brains, with particular emphasis on bidirectional
microglia-neuron communication, microglial remodeling
of synapse, microglial regulation of synaptic activities, microglial BDNF signaling, microglia in neurodegeneration such as Parkinson's disease, spinal microglia in neuropathic pain, and macrophages in the spinal cord injury. In spite of the controversy, it is clear that microglia are important and in need of further study in the central nervous system. We hope that papers published in this special issue will serve to increase the scientific knowledge on microglial function in the brain and offer new perspectives on the potential therapeutics targeting microglia/macrophages in various neurological disorders. The past few years have witnessed many important discoveries in the microglia field; however, there is still a long road ahead for exploring the mechanisms underlying microglial function in neuronal circuits at both the molecular and system levels.

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