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EDITORIAL

Novel Insight into Glial Biology and Diseases

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In the central nervous system (CNS), there are mainly two types of nerve cells. One is neurons, the other is glial cells. Neurons are electrically excitable, whereas glial cells are not, and this is the fundamental difference between the two types of cells. Glial cells, consisting of astrocytes, oligodendrocyte lineage cells, and microglia, contribute more than half of the total cells in the mammalian CNS. Since Rudolf Virchow coined the term 'Neuroglia' in the last century [1], studies on the structure and function of glial cells have suggested that these cells are much more than supporting cells in the CNS. Astrocytes contribute to the maintenance of brain homeostasis; oligodendrocytes form myelin for axons; microglia are primary residence immune cells in the CNS. Glial cells are vital for the regulation of a variety of physiological and pathological processes in the CNS [2, 3]. This special issue consists of 14 Reviews and 1 Insight that provides the latest advances in glial biology and disease.

Glial cells exhibit high heterogeneity, as evidenced by varied origins, locations, developmental stages, and functional states [4–6]. Therefore, the selection of specific molecular markers is crucial for studying glial cells. In this issue, Huang *et al.* summarized the immunological markers of central glial cells and discusses the pros and cons of their applications [7]. Particularly, the distinct markers for oligodendroglia help to characterize the specialization, differentiation, and maturation of oligodendrocyte progenitors, and aid in understanding the delicate process of myelin regeneration in diseases. Non-coding RNAs (ncRNAs), with epigenetic and translational regulatory activity, play a critical role in glial physiology and pathology [8]. In view of the lack of protein markers of the varied functional states in glial cells [7], studies on the expression and function of ncRNAs may also provide specific markers for the characterization of glial cells in distinct functional states.

During early CNS development, neural stem cells first give rise to neurons and are followed by glial progenitor cells, which further produce oligodendrocyte progenitor cells or astrocyte progenitor cells, and then differentiate into oligodendrocytes and astrocytes, respectively [9]. The alteration of tumor-related genes in neural stem cells and glial progenitor cells leads to the development of gliomas [10]. Meanwhile, gliomas also adopt molecular signaling pathways in glial cells to achieve proliferation and migration [11]. Therefore, elucidation of the molecular biology of glial cells may benefit the understanding of glioma origin, microenvironment, and progression, as well as developing new therapeutic strategies.

Glial cells actively regulate neural circuit functioning. As a component of the tripartite synapse, astrocytes modulate synaptic transmission and plasticity effectively with their actions on neurotransmitter clearance and gliotransmitter release, beyond maintaining ion homeostasis in the extracellular space [3]. Astrocytes contribute to information processing as well as memory formation and storage through their interaction with neurons at the local and network levels [12]. Moreover, microglia perform surveillance of neuronal activity and respond rapidly to neuron-derived signals such as glutamate, purine, and norepinephrine, by undergoing

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biochemical and morphological changes to modulate neuronal activities in turn [13]. Glia-neuron interactions also participate in many pathological processes. For example, astrocytes are involved in the regulation of nociceptive transmission and network function to amplify pain signals under chronic pain conditions [14]. In this issue, Parusel *et al.* also discuss the role of microglia in the pathogenesis of neuropathic pain and stresses the importance of the specific regional and temporal manipulations of microglial function in the study of microglia-related neurological diseases [15].

Myelination enables the saltatory conduction of action potentials along axons, and dynamic changes of the myelin sheath, including myelin segment number, distribution, length, and thickness, affect conduction velocity and information processing in neural circuits [16]. Myelin also serves as a metabolic support for axons that underlie developmental and neurodegenerative diseases [17]. In this issue, Yang *et al.* compare the differential regulation of oligodendrocyte and Schwann cell biology in CNS and PNS myelination, particularly the interaction between growth factor and amino-acid signaling pathways, and demonstrate their roles in the metabolic support of axons [18]. With a focus on multiple sclerosis, a typical demyelinating disease, Sun *et al.* comprehensively summarize the glial roles in the connections between inflammation and neurodegeneration and propose that therapeutic improvement in multiple sclerosis requires a strategy combined with immune intervention, early neuroprotection, and the promotion of remyelination [19].

Glial cells are responsible for defense functions in the CNS, contributing to the maintenance of homeostasis. When glial cells detect xenobiotics, damaged cells, or toxic proteins, they are activated to remove them by phagocytosis; meanwhile, activated glial cells also release a variety of inflammatory factors [3, 20]. However, the mechanism underlying the interaction between phagocytosis and inflammation remains elusive. In this issue, Wang *et al.* discuss the association of glial activation and α-synuclein pathology in Parkinson's disease [21]. They suggest that glial cells activated by α-synuclein at the early stage promote the phagocytosis and clearance of the protein aggregates, while sustained glial activation by α-synuclein results in chronic inflammation, leading to the inhibition of phagocytosis and α-synuclein accumulation. Microglia are versatile effector cells in the degenerating brain that have been identified as a "double-edged sword" in the progression of Alzheimer's disease, a culprit in Parkinson's disease, and a lesion component in multiple sclerosis [22]. Therefore, microglial depletion and subsequent repopulation are proposed as promising therapeutic interventions for neurodegenerative diseases [22].

The concept of a glial-vascular unit, based on the framework of a neurovascular unit, emphasizes the central role of glial cells. The interactions between astrocytes, microglia, and perivascular cells are actively involved in the regulation of cerebral blood flow, formation of the blood-brain barrier, and clearance of toxic wastes [23]. Dysfunction of the glial-vascular unit has been demonstrated in ischemic stroke, spinal cord injury, Alzheimer's disease, and major depression disorders [23]. As the fourth type of glial cells in the mammalian CNS, in addition to astrocytes, oligodendrocytes, and microglia, NG2 glial roles in the pathological process of cerebral small vessel diseases have been appreciated [24]. Aberrant NG2 glial cells lead to the failure of remyelination and immunomodulation, suggesting strategies targeting these cells to alleviate white matter lesions in cerebral small vessel diseases [24].

Generally speaking, neural networks refer to neurons forming electrically excitable circuits through synapses. However, emerging evidence shows that glial cells themselves can also form networks. For example, through connexin-mediated gap junctions, connections are formed between astrocytes and oligodendrocytes [25]. These glial networks directly exchange metabolic substances and transduction signals, which are closely associated with many neurological disorders. In this issue, Hu *et al.* discuss the effects of glial network functioning on myelin development, blood-brain barrier integrity, and neuronal energy supply [26]. They highlight the possible role of the glial connections in the occurrence and development of myelin-related neurological diseases.

In summary, a growing body of evidence demonstrates the importance of glial cells in nervous system function and disease. Glial cells are essential for the regulation of synaptic transmission and neural circuit functioning. Future studies to characterize glial heterogeneity, metabolism, development, and aging, as well as the coupling between glial and neuronal networks, by using new techniques, would allow for a more complete and in-depth understanding of brain function and diseases.

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