Symposium 20: Glial mechanisms of circuit regulation (Sat July 31, 14:00-16:00 JST)
Chairs: Woo-ping Ge (Chinese Inst for Brain Research, Beijing) and Bo Peng (Fudan Univ, Shanghai)

14:00-14:20 Soyon Hong (UKDRI, University College London, UK)
Microglia as synaptic pruners in Alzheimer's disease

14:20-14:40 Xiaoping Tong (Sch Med, Shanghai Jiao Tong Univ, China)
NG2 glia, GABA synapse and its beyond

14:40-15:00 Feng Mei (Third Military Medical Unversity, Chongqing, China)
Myelin dynamics in Alzheimer's disease

15:00-15:20 Won-Suk Chung (Dept Biol Sci, KAIST, Korea)
Phagocytic roles of glia in eliminating adult synapses

15:20-15:40 Eunji Cheong (Dept Biotech., Div. Life Sci., Yonsei University, Korea)
Astrocytic control of thalamic sensory processing

15:40-16:00 Mami Noda (Kyushu Univ, Grad Sch Pharmaceut Sci, Fukuoka, Japan)
Involvement of microglia and medical gas therapy for the persistent fatigue after COVID-19

Symposium 20 Speaker 1

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Microglia as synaptic pruners in Alzheimer's disease

My research is aimed at identifying how, on a cellular and molecular level, tissue-resident macrophages contribute to synaptic homeostasis in health and pathology in aging and neurodegenerative diseases including Alzheimer's disease (AD). One key question my lab is addressing is whether tissue-resident macrophages including microglia exist in functional clusters, and if so, which ones contribute to neuronal dysfunction in disease. Emerging data suggest heterogeneity of tissue-resident macrophages and potential functional specialization along the spatiotemporal axis. To that end, we are utilizing novel approaches to understand in situ heterogeneity of brain resident macrophages, including spatial transcriptomic approaches and proximity-based proteomics. Emerging data suggest that there are significant region-specific changes in macrophage functional clusters in AD-like hippocampus when synapses are vulnerable, before overt plaque pathology. Moreover, we have identified a novel role for a type of tissue-resident macrophages in AD-like brains, i.e., the perivascular macrophages, in synapse loss. Our data suggest that SPP1/Osteopontin secreted by perivascular macrophages is critical for beta amyloid-induced synapse loss in AD mouse models. Current experiments are underway to assess whether SPP1 and the classical complement cascade work in the same pathway to mediate synapse loss, and if so, how. These findings will help broaden our understanding of how neuroimmune interactions may go awry during aging and dementia.

Symposium 20 Speaker 2

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NG2 glia, GABA synapse and its beyond

NG2 glia, also known as oligodendrocyte precursor cells (OPCs), play an important role in proliferation and give rise to myelinating oligodendrocytes during early brain development. In contrast to other glial cell types, the most intriguing aspect of NG2 glia is their ability to directly sense synaptic inputs from neurons. However, whether this synaptic interaction is bidirectional or unidirectional, or its physiological relevance has not yet been clarified. Here, we report that NG2 glia form synaptic complexes with hippocampal interneurons and that selective photostimulation of NG2 glia (expressing channelrhodopsin-2) functionally drives GABA release and enhances inhibitory synaptic transmission onto proximal interneurons in a microcircuit. The mechanism involves GAD67 biosynthesis and VAMP-2 containing vesicular exocytosis. Further, behavioral assays demonstrate that NG2 glia photoactivation triggers an anxiety-like behavior in vivo and contributes to chronic social defeat stress.

Symposium 20 Speaker 3

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Myelin dynamics in Alzheimer's disease

Severe cognitive decline is a hallmark of Alzheimer’s disease (AD), an age-related neurodegenerative disease for which treatment has remained elusive. In addition to grey matter loss, significant alterations in white matter pathology have been identified in patients with AD. To investigate the potential contribution of myelin dysregulation to AD-related deficits in neuronal physiology and cognition, we characterized the dynamics of myelin generation and loss in the APP/PS1 mouse model of AD. Unexpectedly, we observed a dramatic increase in the rate of new myelin formation in APP/PS1 mice, reminiscent of the robust oligodendroglial response to demyelination. The increase in myelin generation was accompanied by significant degeneration of pre-existing myelin, resulting in overall decreased levels of myelination in the cortex and hippocampus of APP/PS1 mice as well as in postmortem tissue of individuals with AD. Genetically or pharmacologically enhancing myelin renewal, by oligodendoglial deletion of the muscarinic M1 receptor or systemic administration of the pro-myelinating drug clemastine, improved the performance of APP/PS1 mice in memory-related tasks. Furthermore, hippocampal sharp wave ripples – a neuronal correlate of memory consolidation – were increased in APP/PS1 mice with genetically enhanced myelin renewal. Taken together, these results identify myelin loss as a prominent feature of AD and demonstrate the potential of enhancing myelination as a therapeutic strategy to improve AD-related cognitive impairment.

Symposium 20 Speaker 4

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Phagocytic roles of glia in eliminating adult synapses

In the adult hippocampus, synapses undergo constant formation and elimination. However, the exact function and regulatory process of synapse elimination in the adult brain are largely unknown. Here, we reveal a significant role of astrocytic phagocytosis in maintaining proper hippocampal synaptic connectivity and plasticity. By utilizing mCherry-eGFP phagocytosis reporters, we find that excitatory as well as inhibitory synapses are eliminated by glial phagocytosis in the adult hippocampal CA1 region. Surprisingly, our data show that astrocytes play a major role in neuronal activity-dependent elimination of excitatory synapses. Furthermore, knocking-out the phagocytic receptor Megf10 in adult astrocytes reduces their ability to eliminate excitatory synapses, and as a result, induces the accumulation of excessive but functionally impaired synapses. Finally, we show that Megf10 knock-out mice exhibit defective long-term synaptic plasticity with impaired hippocampal memory formation. Taken together, our data provide strong evidence that astrocytes eliminate unnecessary excitatory synaptic connections in the adult hippocampus through Megf10, and that this astrocytic function is critical for homeostasis of circuit connectivity important for cognitive functions.

Symposium 20 Speaker 5

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Astrocytic control of thalamic sensory processing

Sensory discrimination is essential for survival. However, how sensory information is finely controlled in the brain is not well defined. Here, we show that astrocytes control tactile acuity via tonic inhibition in the thalamus. Mechanistically, diamine oxidase (DAO) and the subsequent aldehyde dehydrogenase 1a1 (Aldh1a1) convert putrescine into GABA, which is released through Best1. The GABA from astrocytes inhibits synaptically-elicited firing at the lemniscal synapses to bidirectionally fine-tune the dynamic range of stimulation/response relationship, precision of spike-timing, signal-to-noise ratio and sensitivity of tactile discrimination. Our findings reveal a novel role of astrocytes in the control of sensory acuity through tonic GABA release.

Symposium 20 Speaker 6

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Involvement of microglia and medical gas therapy for the persistent fatigue after COVID-19

The post-COVID-19 syndrome seems to be partly overlapped with chronic fatigue syndrome. Due to the wide spectrum of the symptoms with multiple causes, there is no specific treatment so far. In addition to the symptoms, it is proposed that neuropsychiatric sequelae of COVID-19 may include major depressive disorder, bipolar disorder, various psychoses, obsessive-compulsive disorder or post-traumatic stress disorder. Therefore, there is an urgent need to draw special attention how to avoid the serious sequelae of COVID-19 while no specific antiviral drugs are absent. The prediction of the mechanisms of the post-COVID-19 syndrome, especially on microglia and persistent fatigue, and the perspectives of the medical gas therapy as a useful tool to prevent or ameliorate the post-COVID-19 syndrome will be discussed.