Symposium 3: Reactive astrocytes as the causes of neurodegenerative diseases (Wed July 28, 16:40-18:40 JST)
Chair: C. Justin Lee (Institute for Basic Science, Daejeon, Korea)

16:40-17:10 Alexej Verkratsky (Univ of Manchester, UK)
Astrocyte iron homeostasis: links to astrogliosis and neurodegeneration

17:10-17:40 Jia-wei Zhou (Inst. of Neurosci. Chinese Academy of Sciences, China)
EBF1/RGS5 axis modulates astrocyte activation and facilitates neurodegeneration

17:40-18:10 Schuichi Koizumi (Interdisc. Grad Sch Med, Univ of Yamanashi, Japan)
Reactive astrocytes control brain pathogenesis via uncontrolled synaptogenesis

18:10-18:40 C. Justin Lee (Cntr for Cognition and Sociality, IBS, Korea)
Astrocytic urea cycle impairs memory in Alzheimer's disease.

Symposium 3 Speaker 1

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Astrocyte iron homeostasis: links to astrogliosis and neurodegeneration

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In the brain, up to three-fourths of total iron is accumulated within neuroglial cells. Plasmalemmal divalent metal ion transporter 1 (DMT1) is responsible for cellular uptake of ferrous (Fe^{2+}), whereas transferrin receptors (TFR) carry transferrin (TF)-bound ferric (Fe^{3+}). Iron ions trigger increase in $[Ca^{2+}]_i$ through two distinct molecular cascades. Uptake of Fe^{2+} by DMT1 inhibits astroglial Na^+-K^+-ATPase, which leads to elevation in cytoplasmic Na^+ concentration, thus reversing Na^+/Ca^{2+} exchanger and thereby generating Ca^{2+} influx. Uptake of Fe^{3+} by TF-TFR stimulates phospholipase C to produce inositol 1,4,5-trisphosphate ($InsP_3$), thus triggering $InsP_3$ receptor-mediated Ca^{2+} release from endoplasmic reticulum. Accumulation of iron in the brain of mice instigates reactive astrogliosis, inhibits operation of glymphatic system and aggravates depressive-like behaviours, motor disability and cognitive impairments induced by chronic stress. Analysis of *anamnesis morbi* of patients receiving iron-containing implants revealed higher incidence of Parkinson's diseases and ischemic stroke. Concentration of serum iron and ferritin were increased in subjects with metal implants. Injection of iron dextran to the brain of mice down-regulatedDMT1 in neurones through increasing the expression of Ndfip1, which degrades DMT1 and does not exist in glial cells. At the same time, excess of iron increased expression of DMT1 in astrocytes and microglial cells and triggered reactive astrogliosis and microgliosis. Facing the attack of excess iron, glial cells act as neuroprotectors to accumulate more extracellular iron by up-regulating DMT1, whereas neurones limit iron uptake through increasing DMT1 degradation. Cerebral accumulation of iron in animals is associated with impaired cognition, locomotion and mood. Excess iron from surgical implants thus can affect neural cells and may be regarded as a risk factor for neurodegeneration.

Symposium 3 Speaker 2

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EBF1/RGS5 axis modulates astrocyte activation and facilitates neurodegeneration

Emerging lines of evidence suggests that astrocytes play crucial roles in chronic neuroinflammation and contribute to the onset and progression of various neurodegenerative diseases. However, little is known about how these roles are regulated by transcription factors. Herein, we show that transcription factor early B cell factor-1 (EBF1) promotes astrocyte activation and chronic neuroinflammation via regulator of G-protein signaling 5(RGS5)/tumor necrosis factor receptor (TNFR) signaling. We found that knockout mice lacking either *Ebf1*or*Rgs5*selectively in astrocytes, but not in microglia, displayed a marked reduction in the production of proinflammatory mediators, with an attenuation in dopaminergic neuron degeneration in Parkinson's disease animal models. Mechanistically, EBF1 transcriptionally regulates the expression of RGS5 which acts to enhance the production of cytokines via interaction withTNFR1/TNFR2. Our study indicatesthatEBF1/RGS5axisis a critical determinant of astrocyte activation and chronic neuroinflammation. It provides a novel strategy for intervention of innate immune response in neurodegenerative disorders.

Symposium 3 Speaker 3:
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Reactive astrocytes control brain pathogenesis via uncontrolled synaptogenesis

Glial cells are very sensitive to environmental changes, and then, change their phenotypes into very different ones. As for astrocytes, they become “reactive astrocytes” and greatly contribute to brain diseases. Here, I show reactive astrocyte-mediated synapse remodeling and its pathophysiological consequences in the primary somatosensory cortex (S1) and the hippocampus. Mechanical allodynia is caused by peripheral nerve injury, and its pathology remains unknown. After peripheral nerve injury, we found that S1 cortical astrocytes become reactive and remodel neuronal circuits by excess synaptogenesis. Using *in vivo* two-photon imaging with genetic and pharmacological manipulations, we show that peripheral nerve injury induces a re-emergence of mGluR5 signaling in S1 reactive astrocytes, which increased spontaneous Ca^{2+} transients, release of multiple synaptogenic molecules such as TSP-1, Glypican4, and excess uncontrolled synapse formation. Then, S1 astrocytes caused misconnection of tactile- and pain-networks, thereby leading to sustained mechanical allodynia. Similar events have also occurred during formation of epileptogenesis. Four weeks after status epilepticus (SE), hippocampal astrocytes become reactive, and increased frequency of Ca^{2+} transient, followed by formation of epileptogenesis, i.e., a condition in which the brain becomes prone to epileptic seizures. The increased Ca^{2+} signals in the reactive astrocytes is a cause of epileptogenesis because inhibition of the Ca^{2+} abolished epileptogenesis. We termed these astrocytes as “epileptogenic astrocytes” and analyzed molecular profiles of them. RNAseq analysis showed that epileptogenic astrocytes re-emerged mGluR5 and increased several synaptogenic molecules. Therefore, we concluded that inappropriate network connection in the hippocampus by reactive astrocytes cause epileptogenesis. Taken together, reactive astrocytes have a key role in regulation of synaptogenesis in the adult pathological brain, for which mGluR5 and Ca^{2+} signals have pivotal roles.

Symposium 3 Speaker 4:

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Astrocytic urea cycle impairs memory in Alzheimer's disease.

Alzheimer's disease (AD) is one of the foremost neurodegenerative diseases and characterized by a significant, progressive memory loss. In AD, astrocytes have been shown to take up Aβ and degrade it to clear Aβ plaques. However, it is still unclear how Aβ induces pathogenesis and memory impairment in AD. Here, we show that Aβ induces upregulation of astrocytic urea cycle and GABA production, leading to memory impairment in AD. In astrocytes, urea cycle enzymes such as OTC, ARG1 and ODC1 are upregulated in Aβ treated condition and AD patient brain. Furthermore, we found the increased levels of citrulline-arginine-ornithine, urea cycle metabolites, leading to putrescine via ODC1 in Aβ treated astrocytes. Inhibition of ARG1 and ODC1 completely reduced GABA production in vitro and in vivo, indicating that ARG1 and ODC1 are major enzymes for putrescine production. In addition, astrocyte specific gene-silencing of ARG1 and ODC1 completely restores the impaired spike probability and memory in AD mouse model. Extending this finding, we demonstrated that memory impairment is negatively correlated with tonic GABA level in dentate gyrus granule cells, possibly as a therapeutic target of AD. Taken together, our findings indicate that astrocytic urea cycle and GABA production could be the metabolic disruption initiating neuropathogenesis in AD.