Symposium 18: Cortical Development and Organization (Sat July 31, 14:00-16:00 JST)
Chairs: Song-Hai Shi (Tsinghua University, Beijing) and Fumio Matsuzaki (RIKEN-BDR, Kobe)

14:00-14:30 Pierre Vanderhaeghen (VIB-KU Leuven Center for Brain & Disease Research, KU Leuven, Brussels, Belgium)
Human-specific temporal mechanisms of brain development

14:30-15:00 Fumio Matsuzaki (RIKEN Center for Biosystems Dynamics Research, Kobe, Japan)
Exploring the relationship of progenitor subtypes in and between gyrencephalic species at the single cell level

15:00-15:30 Xiang Yu (Peking University, Beijing, China)
Regulation of spinogenesis and functional synapse formation by experience and DHA

15:30-16:00 Itaru Imayoshi (Kyoto University, Japan)
Analysis of neural stem cell regulatory mechanisms using optogenetic

Symposium 18 Speaker 1

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Human-specific temporal mechanisms of brain development

The human brain, in particular the cerebral cortex, has undergone rapid expansion and increased complexity during recent evolution.
One striking feature of human corticogenesis is that it is highly protracted in time, from prenatal stages of neurogenesis (taking months instead of days in the mouse), to postnatal stages of neuronal maturation and circuit formation (taking years instead of weeks in the mouse). This prolonged development is thought to contribute in an important fashion to increased cortical size, but also enhanced circuit complexity and plasticity. In vitro and xenotransplantation models indicate that the developmental timing of corticogenesis is largely intrinsic to cortical progenitors and neurons. The underlying mechanisms include human-specific molecular and cellular properties, which may underlie human sensitivity to certain brain diseases.

Symposium 18 Speaker 2

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Exploring the relationship of progenitor subtypes in and between gyrencephalic species at the single cell level

The emergence of a new germinal layer (the outer subventricular zone: OSVZ) and great heterogeneity of progenitor cell types are thought to be crucial for the expansion of the mammalian brain during evolution. As distinct subtypes of neural progenitors may generate different populations of progenies, it is important to characterize the spatial and temporal pattern of individual progenitor types and their terminal fates. *In vivo* genetic manipulation and single-cell transcriptome (scTCM) analyses are two powerful approaches to understand molecular and cellular properties of particular cells. scTCM of the human brain has been extensively performed, revealing transcriptional signatures of diverse progenitor populations. However, *in vivo* mechanisms underlying the development of human radial glial (RG) cells remained less explored due to a limited experimental access. Studies using brain organoids turned out to face problems to recapitulate molecular properties of cell-types in human brain development. Under this situation, a valuable animal model to overcome difficulties in studying the human brain is the ferret (*Mustela putorius furo*), a carnivore with gyrencephalic features such as the OSVZ, forming a complex and folded brain, and also available for *in utero* electroporation (Kawasaki et al., 2012) and *de novo* genome-editing (Tsunekawa et al., 2016). Yet, the temporal pattern of molecular signatures of ferret progenitors remained largely unexplored at a high resolution. We investigated progenitor subtypes in the ferret by scTCM along the developmental course, and compared them with human information to reveal common and species-specific cell-types during the development of the complex brain. We also manipulated progenitors in ferrets by several approaches to understand subtype relationships and fates of neural progenitors.

Symposium 18 Speaker 3:
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Regulation of spinogenesis and functional synapse formation by experience and DHA

Neural circuit wiring is highly dependent on functional synapse formation, a process regulated by coordinated extracellular cues and intracellular signaling. In previous work, we showed that increasing sensory experience through environmental enrichment promoted excitatory synapse formation in the primary sensory cortices, via oxytocin signaling. What other environmental factors could have similar effects? Here we demonstrated that docosahexaenoic acid (DHA), a brain-enriched polyunsaturated fatty acid and important nutritional supplement, also regulated excitatory synaptic transmission in the primary sensory cortices. DHA is an endogenous ligand for Retinoid X receptor α (RXRA), an important nuclear receptor that binds to nonpolar regulatory molecules, and directly transduces extracellular signal to mediate changes in transcriptional programming. DHA deficiency is associated with various neurological and psychiatric disorders. We showed that DHA and RXRA contribute to synapse development in vivo as a ligand-receptor pair. In Nex-Cre-mediated Rxra conditional knockout (Rxra cKO) mice, significant reduction in dendritic spine density of neocortical L2/3 pyramidal neurons were observed in both developing and adult mice. Correspondingly, significant downregulation of excitatory synapse number and mEPSC frequency were observed. We further showed the effects of RXRA were mediated through its DNA-binding domain. Importantly, intracerebroventricular injection of unesterified DHA significantly upregulated spine density and synaptic transmission in wildtype mice, but not in Rxra cKO mice. Blocking DHA release from brain phospholipid significantly reduced spine density, an effect rescued by unesterified DHA supply. Together, these results demonstrate that unesterified DHA signals through RXRA to regulate spinogenesis and functional synapse formation, providing insight into the mechanism through which DHA promotes brain development and cognitive function.

Symposium 18 Speaker 4:
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Analysis of neural stem cell regulatory mechanisms using optogenetics

The mammalian brain consists of a complex ensemble of neurons and glial cells. Their production during development and remodeling is tightly controlled by various regulatory mechanisms in neural stem cells. Among such regulations, basic helix-loop-helix (bHLH) factors have key functions in the self-renewal, multipotency, and fate determination of neural stem cells. Here, we highlight the importance of the expression dynamics of bHLH factors in these processes. We propose the multipotent state correlates with oscillatory expression of several bHLH factors, whereas the differentiated state correlates with sustained expression of a single bHLH factor. We also developed new optogenetic methods that can manipulate gene expressions in neural stem cells by light. We used this technology to manipulate the growth and fate-determination of neural stem cells. We are also analyzing dynamic changes in downstream gene expressions and cellular states caused by systematic light-induced manipulations of bHLH transcription factors.