Special Lecture

Sat. Jul 11, 2026 11:45 AM - 12:10 PM JST | Sat. Jul 11, 2026 2:45 AM - 3:10 AM UTC | Room1（Conference Hall A）

[SL1] Special Lecture 1（III-SL1）

Deciphering the mysteries of sleep: toward the molecular substrate for “sleepiness”

Chair:Osamu Nakagawa(National Cerebral and Cardiovascular Center Research Institute / Ritsumeikan University)
Chair:Hiroyuki Yamagishi(Tokyo Metropolitan Children’s Medical Center)

[III-SL1-1] Deciphering the mysteries of sleep: toward the molecular substrate for “sleepiness”

○Masashi Yanagisawa (International Institute for Integrative Sleep Medicine, University of Tsukuba)

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Keywords：Sleep、Orexin、Sleep-Wake Regulation、Forward Genetics

Although sleep is a ubiquitous behavior in animal species with a nervous system, many aspects in the neurobiology of sleep remain mysterious. Our discovery of orexin, a hypothalamic neuropeptide involved in the maintenance of wakefulness, has triggered intensive research examining the exact role of the orexinergic and other neuronal pathways in the regulation of sleep/wakefulness. Orexin receptor antagonists, which specifically block the endogenous waking system, have been approved as a new strategy to treat insomnia. Also, since the sleep disorder narcolepsy-cataplexy is caused by orexin deficiency, orexin receptor agonists are expected to provide mechanistic therapy for the disease; they will likely be also useful for treating excessive sleepiness due to other etiologies.
Even though the executive neurocircuitry and neurochemistry for sleep/wake switching, including the orexinergic system, has been increasingly revealed in recent years, the mechanism for homeostatic regulation of sleep, as well as the neural substrate for "sleepiness" (sleep pressure), remains unknown. To crack open this black box, we have initiated a large-scale forward genetic screen of sleep/wake phenotype in mice based on true somnographic (EEG/EMG) measurements. We have so far screened >10,000 heterozygous ENU-mutagenized founders and established several pedigrees exhibiting heritable and specific sleep/wake abnormalities. By combining linkage analysis and the next-generation whole exome sequencing, we have molecularly identified and verified the causal mutation in several of these pedigrees. Since these dominant mutations cause strong phenotypic traits, we expect that the mutated genes will provide new insights into the elusive pathway regulating sleep/wakefulness. Indeed, through a systematic cross-comparison of the SIK3 Sleepy mutants and sleep-deprived mice, we have found that the cumulative phosphorylation state of a specific set of mostly synaptic proteins may represent the molecular substrate of sleep pressure. We have also found that the neuronal molecular pathway LKB1-SIK3-HDAC4/5 may represent the level of sleep pressure, regulating the amount, depth, and timing of sleep by acting in different brain regions, respectively (Kim et al. Nature 612: 512-518, 2022; Zhou et al. Nature 612: 519-527, 2022).