Paris Brain Institute

CONFERENCES DE L'ICM

MONDAY, NOVEMBER 20 AT 11:00 AM

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TOWARDS HUMAN SYSTEMS BIOLOGY OF SLEEP/WAKE CYCLES: PHOSPHORYLATION HYPOTHESIS OF SLEEP

The field of human biology faces three major technological challenges. Firstly, the causation problem is difficult to address in humans compared to model animals. Secondly, the complexity problem arises due to the lack of a comprehensive cell atlas for the human body, despite its cellular composition. Lastly, the heterogeneity problem arises from significant variations in both genetic and environmental factors among individuals. To tackle these challenges, we have developed innovative approaches. These include 1) mammalian next-generation genetics, such as Triple CRISPR for knockout (KO) mice and ES mice for knock-in (KI) mice, which enables causation studies without traditional breeding methods; 2) whole-body/brain cell profiling techniques, such as CUBIC, to unravel the complexity of cellular composition; and 3) accurate and user-friendly technologies for measuring sleep and awake states, exemplified by ACCEL, to facilitate the monitoring of fundamental brain states in real-world settings and thus address heterogeneity in human.

By integrating these three technologies, we have made significant progress in addressing two major scientific challenges in sleep research: 1) understanding sleep regulation (sleep mechanisms) and 2) determining the role of sleep (sleep functions). With regard to sleep mechanisms, we have recently proposed the phosphorylation hypothesis of sleep, which emphasizes the role of the sleep-promoting kinase CaMKIIα/CaMKIIβ (Tatsuki et al., 2016; Tone et al., 2022; Ode et al., 2020) and the involvement of calcium signaling pathways (Tatsuki et al., 2016). According to this novel perspective, the dynamics of calcium, representing neural activity during wakefulness, can be integrated and converted into the auto-phosphorylation status of CaMKIIα/CaMKIIβ, which induces and sustains sleep (Tone et al., 2022). Concerning sleep functions, we conducted computational studies to examine synaptic efficacy dynamics during sleep and wakefulness. Our findings led to the formulation of the Wake-Inhibition-Sleep-Enhancement (WISE) hypothesis, suggesting that wakefulness inhibits synaptic efficacy, while sleep enhances it.

During this talk, we will also present our discoveries regarding the identification of muscarinic acetylcholine receptors (Chrm1 and Chrm3) as essential genes of REM sleep. Furthermore, we will discuss new insights into psychiatric disorders, neurodevelopmental disorders, and neurodegenerative disorders derived from the phosphorylation hypothesis of sleep.

Hosted by **Nicolas RENIER**

If you would like to meet the speaker, please contact: **nokia.duong@icm-institute.org**

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