NCGG SEMINAR

"Achieving Productive Aging in Japan: The Systemic Regulatory Mechanism of Mammalian Aging and Longevity and Anti-Aging Intervention"

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Time and Date: at **16:00 ~ 17:00** on **22 Nov, 2016 (Tue)**

Room: The 2nd floor Conference Hall Small in the 1st Research building, NCGG

<Reference for Seminar>

Our major interest is to understand the systemic, hierarchical regulation of aging and longevity in mammals and translate that knowledge into an effective anti-aging intervention that could make our later lives as healthy and productive as possible ("productive aging"). Achieving productive aging is particularly important in Japan, due to its heavily aging society. Recent studies demonstrate that the hypothalamus functions as a high-order "control center of aging", counteracting age-associated pathophysiological changes and thereby promoting longevity in mammals. We have demonstrated that the mammalian NAD+-dependent protein deacetylase SIRT1 in the hypothalamus, particularly the dorsomedial and lateral hypothalamic nuclei (DMH and LH, respectively), is critical to counteract age-associated physiological decline and promote longevity in mice (Satoh et al., Cell Metab., 2013). In the DMH, SIRT1 and its binding partner Nkx2-1 highly colocalize, allowing us to identify a specific subset of DMH neurons, namely, SIRT1/Nkx2-1-double positive neurons. Recently, we have identified a set of genes specifically expressed in these SIRT1/Nkx2-1-double positive DMH neurons. One of these genes is Prdm13, which encodes a member of the PR domain family of transcriptional regulators. Prdm13 is one of the downstream target genes regulated by the SIRT1/Nkx2-1 signaling pathway in the DMH. DMH-specific Prdm13-knockdown mice exhibit decreased sleep quality, increased adiposity (Satoh et al., Aging Cell, 2015), and reduction in adipose Nampt, a key systemic NAD+ biosynthetic enzyme secreted from adipose tissue to remotely regulate hypothalamic function (Yoon et al., Cell Metab., 2015). We have also found that the DMH-specific knockdown of the thyrotoropin-releasing hormone (Trh) gene, another gene highly and selectively expressed in the SIRT1/Nkx2-1-double positive DMH neurons, caused defects in skeletal muscle mitochondrial gene expression, specific myokine expression, and physical activity. These results suggest that SIRT1/Nkx2-1-double positive DMH neurons contain at least two functionally distinct neuronal subpopulations, namely, Prdm13- and Trh-positive neurons, and that each subpopulation regulates distinct inter-tissue feedback loops between the hypothalamus and adipose tissue or skeletal muscle. These two feedback loops may play a critical role in mammalian aging and longevity control. Studies addressing these hypotheses are currently ongoing, and our collaborative phase I clinical study on nicotinamide mononucleotide (NMN), a key NAD+ intermediate and a potential anti-aging agent, has recently begun at Keio University School of Medicine. I will further discuss the importance of inter-tissue communications for aging and longevity control and the development of anti-aging intervention with NAD+ intermediates. and age-related diseases.

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