광주과학기술원 생명과학부
Gwangju Institute of Science and Technology School of Life Sciences

No. 2018-09

School of Life Sciences
Seminar Series

2018 Spring Semester

Tuesday, **3 April** 2018, 4:00 PM

Jukhyun Bio Auditorium(RM.121)

Can we pre-program the adult metabolic neurons in the embryo?

English

Speaker | Jae Woon Lee, Ph.D. Affiliation | Oregon Health and Science University

Host | Darren R. Williams

Abstract

Despite critical roles of the hypothalamic arcuate neurons in controlling the growth and energy homeostasis, the gene regulatory network directing their development remains unclear. Here we report that the transcription factors Dlx1/2 and Otp coordinate the balanced generation of the two functionally related neurons in the hypothalamic arcuate nucleus, GHRH-neurons promoting the growth and AgRP-neurons controlling the feeding and energy expenditure. Dlx1/2-deficient mice show a loss of GHRH-neurons and an increase of AgRP-neurons, and consistently develop dwarfism and consume less energy. These results indicate that Dlx1/2 are crucial for specifying the GHRH-neuronal identity and, simultaneously, for suppressing AgRP-neuronal fate. By analyzing the ChIPseq dataset and Otp-null mice, we show that Otp is required for the generation of AgRP-neurons and that Dlx1/2 repress the expression of Otp by directly binding the Otp gene. Together, our study demonstrates that the identity of GHRH- and AgRP-neurons is specified and segregated by the Dlx1/2-Otp gene regulatory axis.

Two particular significances are notable with our results. Firstly, this study shows for the first time that two metabolic neurons in the ARC, GHRH- and AgRP-neurons, are coordinately produced during development. Secondly, the synchronized embryonic production of these two neurons in the developing hypothalamus likely contributes to the balance of growth and energy homeostasis after birth, suggesting that we can perhaps pre-program the adult metabolic neurons during development.

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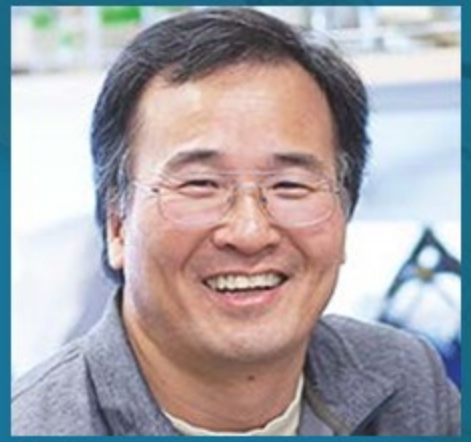

Speaker

Jae Woon Lee, Ph.D.

Education/Experience

1983	BS., Pharmacy, Seoul National University, Seoul, Korea
1990	Ph.D., Biochemistry, Texas A&M University, College Station, TX
1990-1992	Postdoctoral, Molecular Biology, Harvard Medical School/MGH, Boston, MA
1993-1994	Senior Research Scientist, Ligand Pharmaceuticals, Inc., San Diego, CA
1996-2001	Assistant/Associate Professor, Chonnam National University, Kwangju, Korea
2001-2003	Associate Professor, Pohang University of Science and Technology, Korea
2003-2010	Associate Professor, Baylor College of Medicine, Houston, TX
2010-present	Professor, Oregon Health and Science University

Research Interests

For more than the last two decades, we have been studying the molecular mechanisms by which nuclear receptors regulate transcription. In particular, I made a seminal contribution to this field through my postdoctoral work identifying a number of thyroid hormone receptor-interacting proteins (TRIPs), which function as critical transcriptional coactivators and corepressors of nuclear receptors and other transcription factors. As an independent PI, I have purified two important coactivator complexes of nuclear receptors, ASC-1 complex, which links splicing to transcription, and ASC-2 complex (ASCOM), which represents the first histone H3 lysine 4 methyltransferase (H3K4MT) complex identified in mammals (containing either the H3K4MT MLL3/KMT2C or its paralog MLL4/KMT2D). ASCOM belongs to a family of similar mammalian complexes, collectively named Set1-like complexes. Interestingly, our mouse genetics work for different subunits of ASCOM suggested that ASCOM is specialized to metabolic controls by nuclear receptors as well as early embryonic development. More recently, we discovered that our mutant mouse models for Mll4 recapitulate many features of the human neurodevelopmental disorder named Kabuki syndrome, which is mainly caused by inactivating mutations in MLL4. We also discovered that our liver-specific Mll4 knockout mice are resistant to diet-induced fatty liver formation, which is the central subject for the current proposal, and it will be highly interesting to determine if this feature is replicated in human Kabuki patients.

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