Symposium 18

Cracking the Neural Code: Understanding Obesity through the Hypothalamus, Brain Stem, and Vagus Pathways

Chairpersons

Ki Woo Kim
Yonsei University, Korea

Hyung Jin Choi
Seoul National University, Korea

Speakers

Joe Eun Son
Kyungpook National University, Korea

Chen Ran
The Scripps Research Institute, USA

Cheng Zhan
University of Science and Technology of China, China

Panel Discussion

Yong Taek Jeong
Korea University, Korea

Chan Hee Lee
Hallym University, Korea

Joe Eun Son

Kyungpook National University, Korea

• Education

Period	Affiliation	Position
– **2008-2013**	Seoul National University, Korea	Ph.D.
– **2004-2008**	Seoul National University, Korea	B.Sc.

• Affiliations / Experience

Period	Affiliation	Position
– **2014-2023**	The Hospital for Sick Children, University of Toronto, Canada	Postdoctoral Research Associate
– **2013-2014**	Seoul National University, Korea	Postdoctoral Researcher
– **2011-2013**	Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada	Visiting Scholar

• Committee Memberships

- Korean Diabetes Association
- Korea Society for Molecular and Cellular Biology
- Korean Society of Food Science and Technology
- Korean Society of Toxicogenomics and Toxicoproteomics
- Korea Society of Food Science and Nutrition

• Publications

- Son JE *, Dou Z, Kim KH, Wanggou S, Cha VSB, Mo R, Zhang X, Ketela T, Chen X, Li X, Huang X, Hui CC. Irx3 and Irx5 in Ins2-Cre+ cells regulate hypothalamic postnatal neurogenesis and leptin response. *Nature Metabolism, 3(5):701-713*
- Son JE*, Dou Z, Wanggou S, Chan J, Mo R, Li X, Huang X, Kim KH, Michaud J, Hui CC*. Ectopic expression of Irx3 and Irx5 in the paraventricular nucleus of the hypothalamus contributes to defects in Sim1 haploinsufficiency. *Science Advances, 7(44):eabh4503 (*, co-correspondence)*
- Son JE, Dou Z, Kim KH, Hui CC. Deficiency of Irx5 protects mice from diet-induced obesity and associated metabolic abnormalities. *International Journal of Obesity, 46(11):2029-2039*
- Dou Z, Son JE*, Hui CC*. Irx3 and Irx5 - novel regulatory factors of postnatal hypothalamic neurogenesis. *Frontiers in Neuroscience, 15:763856. (*, co-correspondence)*
- Son JE, Jo J.-Y, Kim S, Park MJ, Lee Y, Park SS, Park SY, Jung SM, Jung SK, Kim JY and Byun S. Rice Bran Extract Suppresses High-Fat Diet-Induced Hyperlipidemia and Hepatosteatosis through Targeting AMPK and STAT3 Signaling. *Nutrients, 15(16), 3630*

Symposium 18

Hypothalamic Function of IRX3 and IRX5, Genetic Determinants of Human Obesity

Joe Eun Son (Kyungpook National University, Korea)

Obesity has become a serious health concern worldwide, increasing the prevalence of other chronic diseases. It is critical to gain a deeper understanding of the machinery underlying the development of obesity to improve current prediction, diagnosis, and treatment options for obesity and associated metabolic disorders. While obesity is a complex condition resulting from a combination of hereditary and environmental factors, it is largely attributed to genetic defects involved in the control of appetite by the brain, particularly the hypothalamus, a major command center in energy homeostasis regulation. To this end, by using mouse genetics and multi-omics technologies, my research identified Iroquois (IRX) homeobox genes, IRX3 and IRX5, as novel genetic determinant factors of obesity and further unveiled their obesity regulatory mechanism in the control of hypothalamic neurodevelopment at the single-cell level. Specifically, IRX3 and IRX5 are genetic effectors of FTO (fat mass and obesity-associated gene) variants, the strongest genetic risk factors for human obesity, and SIM1 haploinsufficiency, a monogenic form of human obesity. Furthermore, I identified a novel neural stem cell (NSC) population in the postnatal mouse hypothalamus, and established that predominant expression of Irx3 and Irx5 in this NSC population is critical for postnatal neurogenesis and hypothalamic feeding control; and I established the molecular profiles of Sim1+ neurons in the paraventricular nucleus of the mouse hypothalamus and uncovered that ectopic expression of Irx3 and Irx5 in these neurons represents a central mechanism contributing to the neurodevelopmental defects leading to overeating in Sim1 haploinsufficiency. Given that both FTO obesity-risk alleles and SIM1 haploinsufficiency are associated with increased energy intake in human obesity, my research provides unprecedented mechanistic evidence for genetic control of human obesity. These findings could potentially lead to novel predictions and treatment options for this condition.

Chen Ran

The Scripps Research Institute, USA

• Education

Period	Affiliation	Position
– **2011-2017**	Stanford University	Ph.D.
– **2007-2011**	Peking University	B.A.

• Affiliations / Experience

Period	Affiliation	Position
– **2017-2024**	Harvard Medical School	Postdoctoral Fellow
– **2010**	Washington University in St. Louis	Research Assistant

• Publications

– Ran C, Boettcher JC, Kaye JA, Gallori CE, Liberles SD. A brainstem map for visceral sensations. Nature. 2022 Sep;609(7926):320-326. doi: 10.1038/s41586-022-05139-5. Epub 2022 Aug 31. Erratum in: Nature. 2022 Nov;611(7934):E6. doi: 10.1038/s41586-022-05414-5. PMID: 36045291; PMCID: PMC9452305

– Ran C, Hoon MA, Chen X. The coding of cutaneous temperature in the spinal cord. Nat Neurosci. 2016 Sep;19(9):1201-9. doi: 10.1038/nn.4350. Epub 2016 Jul 25. PMID: 27455110; PMCID: PMC5599125

– Ran C, Kamalani GNA, Chen X. Modality-Specific Modulation of Temperature Representations in the Spinal Cord after Injury. J Neurosci. 2021 Sep 29;41(39):8210-8219. doi: 10.1523/JNEUROSCI.1104-21.2021. Epub 2021 Aug 18. PMID: 34408066; PMCID: PMC8482863

– Ran C, Chen X. Probing the coding logic of thermosensation using spinal cord calcium imaging. Exp Neurol. 2019 Aug;318:42-49. doi: 10.1016/j.expneurol.2019.04.009. Epub 2019 Apr 20. PMID: 31014574; PMCID: PMC6993943

– Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, Tye KM, Deisseroth K, Malenka RC. Input-specific control of reward and aversion in the ventral tegmental area. Nature. 2012 Nov 8;491(7423):212-7. doi: 10.1038/nature11527. Epub 2012 Oct 14. PMID: 23064228; PMCID: PMC3493743

Symposium 18

The Coding of Internal Senses in the Brainstem

Chen Ran (The Scripps Research Institute, USA)

Our external senses of sight, smell, sound, touch, and taste enable us to perceive the external world. In addition, our interoceptive system monitors the physiological state of peripheral organs. This bodily sensory system orchestrates multi-organ physiological responses, regulating feeding, drinking, sickness behaviors, and generating the internal senses such as satiety, hunger, nausea, malaise, and visceral pain. However, despite the scientific and clinical importance, the principles that define visceral sensory processing remain poorly defined. Previously, we developed an in vivo two-photon mouse brainstem calcium imaging preparation to understand internal organ representations in the nucleus of the solitary tract (NTS), the interoceptive gateway in the brain. Combining the imaging platform with stimulation of multiple visceral organs, we uncover diverse neuronal responses to internal stimuli, while functionally defined cell types are highly organized within the NTS. Using patterned in vivo brainstem optogenetics, we precisely stimulate different neuronal ensembles and show that spatial domains of the NTS differentially modulate autonomic functions. Using mouse genetics and functional manipulations of specific brainstem circuits, we reveal viscerosensory information streams that have distinct functions. Our study defines the functional architecture of brainstem viscerosensory pathways, laying the foundation for future research to understand interoceptive processing throughout the brain.

Cheng Zhan

University of Science and Technology of China, China

Education

Period	Affiliation	Position
– **2011**	Hua Zhong University of Science and Technology	Ph.D.
– **2006**	Hua Zhong University of Science and Technology	M.S.
– **2003**	Hua Zhong University of Science and Technology	B.S.

Affiliations / Experience

Period	Affiliation	Position
– **2021-Present**	University of Science and Technology of China	Professor
– **2011-2021**	National Institute of Biological Sciences (NIBS), Beijing	Engineer
– **2006-2008**	National Institute of Biological Sciences (NIBS), Beijing	Director of the Imaging Facility

Committee Memberships

- Stress Neurobiology Branch of the Chinese Society of Neuroscience
- Autonomic Neurobiology Branch of Chinese Association for Physiological Sciences

Publications

- Liang Wang, Mingxiu Cheng, Yucheng Wang, Jing Chen, Faming Xie, Li-Hao Huang, Cheng Zhan#. Fasting-activated neurons regulate immune cell homing and suppress autoimmune diseases in mice. Nature Neuroscience
- Jing Cai, Jing Chen, Joshua Ortiz-Guzman, Jessica Huang, Benjamin R Arenkiel, Yuchen Wang, Yan Zhang, Yuyan Shi, Qingchun Tong#, Cheng Zhan#. AgRP neurons are not indispensable for body weight maintenance in adult mice. Cell Reports
- Jing Chen, Chunli Li, Zhonghua Lu, Cheng Zhan#. Optimal Timing of a Commonly-Used Rabies Virus for Neural Recording and Manipulation. Neuroscience Bulletin
- Jing Chen, Minxiu Cheng, Liang Wang, Lei Zhang, Dan Xu, Peng Cao, Fengchao Wang, Herbert Herzog, Sen Song, Cheng Zhan#. A vagal-NTS neural pathway that stimulates feeding. Current Biology
- Z. Zhao, L. Wang, W. Gao, F. Hu, J. Zhang, Y. Ren, R. Lin, Q. Feng, M. Cheng, D. Ju, Q. Chi, D. Wang, S. Song, M. Luo and C. Zhan#. A Central Catecholaminergic Circuit Controls Blood Glucose Levels during Stress. Neuron

Symposium 18

Roles of Brainstem Catecholaminergic Neurons in Control of Energy Homeostasis

Cheng Zhan (University of Science and Technology of China, China)

The brain plays a crucial role in regulating energy intake and expenditure in response to various internal and external factors and energy requirements. While extensive research has highlighted the significance of the hypothalamus in maintaining energy balance, there is limited understanding of the functional roles of other brain regions. Our comprehensive investigation focused on brainstem catecholaminergic neurons (solitary nucleus and ventrolateral medulla), exploring their brain-wide connections and functional contributions to the regulation of energy homeostasis, including food intake, blood glucose levels, and energy expenditure during fasting. This presentation will address the importance of brainstem catecholaminergic neurons in energy metabolism control, elucidating their roles and mechanisms of action.