conferenceseries.com

10th International Conference on
Neuroscience and Neurochemistry
&
6th International Conference on Vascular Dementia February 27-March 01, 2017

Vesicular trafficking of cholinergic machinery in acetylcholine signaling requires scaffold protein BNIP-H working in concert with kinesin motor and Rab GTPases

Boon Chuan Low
National University of Singapore, Singapore

The neurotransmitter acetylcholine (ACh) is essential for neuron development, memory, learning and motor movement. It is synthesized from choline and acetyl-CoA by choline acetyl transferase (ChAT). ATP citrate lyase (ACL) is a key metabolic enzyme that produces the acetyl-CoA for this process. However, the precise spatial disposition of this cholinergic machinery for both morphogenesis and neurotransmission remain largely unknown. Mutations in the *ATCAY/Atcay* gene, which encodes a BCH domain containing BNIP-H (also known as caytaxin), lead to ataxia and mental retardation in humans (cayman ataxia), as well as ataxia and dystonia in several rodent models. Recently, we used molecular genetics, biochemical and imaging methods and revealed that BNIP-H recruits the cholinergic machinery to neurite terminal to regulate cholinergic signaling. BNIP-H links kinesin-1 (KLC1) motor protein to ACL and transports ACL towards neurite terminal. Therefore, the BNIP-H/ACL complex synergistically recruits ChAT, leading to enhanced secretion of ACh. ACh then activates MAPK/ERK via muscarinic receptors to promote neuritogenesis. In mice deficient in BNIP-H, ACL fails to interact with KLC1, and formation of the ACL/ChAT complex is prevented. Significantly, Bnip-h knockdown in zebrafish causes axon defect of motor neuron through impaired cholinergic pathway, leading to motor disorder. Here, we further show that BNIP-H specifically engages Rab11 GTPases and a component of the actin-based exocyst complex to regulate its dynamic disposition and neurologic function. In conclusion, BNIP-H promotes cholinergic signaling by trafficking ACL to neurite end, where ChAT is subsequently recruited to regulate the local production of ACh. Our results provide the first molecular evidence that precise spatial regulation of the cholinergic machinery is crucial in neuronal differentiation and neurotransmission, the significance of which will be further discussed.

Biography

Boon Chuan Low is a Principal Investigator at Mechanobiology Institute and Department of Biological Sciences, National University of Singapore. His research work focuses on "Defining cellular and molecular mechanisms underlying neuronal differentiation and cancer metastasis". His discovery on the BCH domain as a versatile protein scaffold has led to our better understanding of the intricate spatiotemporal regulation of GTPases, kinases and metabolic signaling in cell morphogenesis, cell motility, cell growth and differentiation. His work also extends to BCH and other scaffold proteins that can integrate both biochemical and mechanical signals in cell-cell and cell-matrix interaction, leading to tissue organization and organogenesis.

dbslowbc@nus.edu.sg

Notes: