Vesicular Trafficking of Cholinergic Machinery in Acetylcholine Signaling Requires Scaffold Protein BNIP-H working in Concert with Kinesin motor and Rab GTPases

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Abstract

The neurotransmitter acetylcholine (ACh) is essential for neuron development, memory, learning and motor movement. It is synthesized from choline and acetyl-CoA by choline acetyltransferase (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 (*Developmental Cell, 2015*). BNIP-H links kinesin-1 (KLC1) motor protein to ACL and transports ACL towards neurite terminal. There, 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.

Recent Publications:

1. Gupta AB, Wee LE, Zhou YT, Hortsch M, Low BC (2012). Cross-species analyses identify the BNIP-2 and Cdc42GAP homology (BCH) domain as a distinct functional subclass of the CRAL_TRIO/Sec14 superfamily. *PLoS One.* 7(3):e33863.
2. Pan CQ, Sudol M, Sheetz M and Low BC (2012). Modularity and functional plasticity of scaffold proteins as p(l)acemakers in cell signaling. *Cell Signaling*. 24(11):2143-65.
3. Pan CQ and Low BC (2012). Functional plasticity of the BNIP-2 and Cdc42GAP Homolgy (BCH) domain in cell signaling and cell dynamics. *FEBS Letters* 586(17):2674-91.

4. Ravichandran A, Low BC (2013) SmgGDS antagonizes BPGAP1-induced Ras/ERK activation and neuritogenesis in PC12 cell differentiation. *Mol Biol Cell.* 24(2):145-56.
5. Peng Yi, Li Li Chew, Ziwang Zhang,' Hao Ren,' Liling Zheng, Yan Luo, Hongwei Ouyang, BC Low*, and YT Zhou* (2015) KIF5B transports BNIP-2 to regulate p38 mitogen-activated protein kinase activation and myoblast differentiation. *Mol Biol Cell* 26(1):29-42.
6. Sun, JC, Pan, CQ, Chew, TW, Liang, FY, Burmeister, M and Low, BC (2015) BNIP-H recruits the cholinergic machinery to neurite terminals to promote acetylcholine signalling and neuritogenesis. *Developmental Cell* 34(5): 555–568.
7. Jiang, TT, Pan, CQ and Low BC (2017) BPGAP1 spatially integrates JNK/ERK signalling crosstalk in oncogenesis. *Oncogene* (Jan 16. doi: 10.1038/onc.2016.466).

Biography



Prof. Boon Chuan LOW is a Principal Investigator at the Mechanobiology Institute and Department of Biological Sciences, National University of Singapore. His group 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.

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