NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

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Hosted by Professor Gong Zhiyuan

BCH domain as a versatile scaffold protein module and a key p(l)acemaker in cell signaling: a journey through space and time

By **Low Boon Chuan**

Associate Professor, Department of Biological Sciences, NUS.

Protein-protein interactions determine the efficiency and specificity in cell signaling. This process however requires precise timing and placement of interacting partners at different stages of signal transduction. Our group has identified the BCH (for BNIP-2 and Cdc42GAP Homology) domain as a versatile scaffold protein domain that regulates small GTPases, kinases and metabolic signaling at specific subcellular compartments. For examples, BCH domains control Ras, Rho and Rac small GTPases signaling by engaging these molecular switches with their immediate activators, the guanine nucleotide exchanger factors (GEFs) or their inactivators, the GTPase-activating Proteins (GAPs), leading to dynamic actin cytoskeletal rearrangement in stress fibers and membrane ruffles and also activation of membrane and endosomal Ras/MAPK for cell morphogenesis, cell motility, cell growth and differentiation. BCH domains also work in concert with other protein modules and motifs present in the same proteins to transport the metabolic enzyme ATP citrate lyase (ACL) on the kinesin motor protein from cell body to neurite termini where it orchestras the production of neurotransmitter acetylcholine at the synapses. Our studies further show that BCH domain-containing proteins could function as mechanotransducers that bridge mechanical cues from extracellular matrix and substrate rigidities to cell dynamic and tissue reorganization. Some may even function in the nucleus.

In this talk, the plasticity of BCH domains will be unfolded through integrative and interdisciplinary strategies that encompass biochemical, cellular, molecular and developmental biology studies to biophysical, structural biology, bioimaging and mechanobiology approaches using the yeast, zebrafish, mice, mammalian cells and patient samples as our comparative experimental models. The significance of BCH domain will be discussed in the context of its evolutionary origin, its unique structure and versatile functions in cell proliferation, cell morphogenesis, cell motility, embryogenesis, neuronal differentiation, neurotransmission and cardiomyocyte functions, as governed by 4 highly potent members of the BCH-containing proteins, i.e. BNIP-2, BNIP-H (Caytaxin), p50RhoGAP (ARHGAP1) and BPGAP1 (ARHGAP8), which are involved in the development of ataxia and cancer. The major implications from our findings on the important role of signaling scaffold proteins will be highlighted.

A/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 morphogenesis, 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.

Artwork by Ann Nee, DBS, NUS