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

VIRTUAL BIOLOGY COLLOQUIUM

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Hosted by A/P Cynthia He

The Bax-Binding Protein MOAP-1 negatively regulates Nrf2 signalling in liver by disrupting the p62 bodies

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Nrf2 signalling is vital for protecting cells against oxidative stress. However, its hyperactivation is often found in liver cancer through excessive build-up of p62/SQSTM1 bodies that sequester Keap1, an adaptor of the E3-ubiquitin ligase complex, from binding Nrf2. Here, we report that the Bax-binding protein MOAP-1 negatively regulates p62-Keap1-Nrf2 signalling through disruption of p62 bodies. Upon induction of cellular stresses that stimulate formation of p62 bodies, MOAP-1 is recruited to p62 bodies and reduces their levels independent of the autophagy pathway. Loss of MOAP-1 can lead to marked upregulation of p62 bodies, enhanced sequestration of Keap1 by p62 and hyperactivation of Nrf2 target genes. MOAP-1-deficient mice exhibit elevated tumor burden with excessive p62 bodies and Nrf2 activity in a diethylnitrosamine (DEN)-induced mouse liver cancer model. Moreover, analysis of the aged wild-type and MOAP-1 KO mice reveals that about half of the MOAP-1 KO mice exhibit chronic liver lesions with excessive p62 aggregation, while none of the wild-type mice display notable abnormality. We propose MOAP-1 is a negative regulator of Nrf2 signalling via dissociation of p62 bodies.

About the Speaker

Dr Victor C. Yu was born in Hong Kong. He obtained his BSc in Pharmacy from University of Houston and PhD in Pharmaceutical Chemistry from University of California San Francisco (UCSF) where he focused on studying molecular pharmacology of morphine. He undertook post-doctoral training at the Howard Hughes Medical Institute at UCSD where he made the landmark discovery in identifying the nuclear receptor RXR as the common co-regulator protein for the retinoic acid, vitamin D and thyroid hormone receptors. He moved to Singapore in 1993 as Principal Investigator at the Institute of Molecular and Cell Biology (IMCB). His team has been focusing on studying cell death mechanism and had identified several proteins important in regulating apoptosis signalling in mitochondria. In 2009, he joined National University of Singapore (NUS). His laboratory is now mainly focusing on characterizing the physiological and pathological roles of the Bax-binding protein MOAP-1 in liver and brain.

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