INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE

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Seminar Notice

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Biological Chemistry

Title : Part I: Mitochondrial calpain system in mitochondrial Ca2+ dynamics **& Part II:** CRAC channels Ca2+ microdomains in NFAT activation and gene expression

Speaker : Dr. Pulak Kar, Department of Physiology, Anatomy and Genetics University of Oxford, Oxford, U.K.

Date & Time : February 14, 2018 at 3:30 pm

Venue: Theoretical Physics seminar room (Centenary building)

Abstract:

Part I: Mitochondrial calpain system in mitochondrial Ca2+ dynamics

Calpains are a family of Ca2+-activated cysteine proteases that play a central role in cytoskeleton modulation, cell migration, cell cycle progression and apoptosis. Physiologically calpain activity is controlled by its endogenous inhibitor, calpastatin. Dysregulation of calpain activity due to elevated intracellular Ca2+ level has been correlated with the manifestation of several diseases like neurodegenerative disease, heart daises, cancer and pulmonary vasculature. Therefore, detail investigation of the distribution of calpain and their functional regulation in cellular level especially in sub-organelles is an important field of research. Our interest is to understand the mechanistic basis of calpain function in mitochondrial Ca2+ regulation in bovine pulmonary artery smooth muscle. We found that in elevated Ca2+ level, the inner mitochondrial membrane associated μ-calpain-calpastatin become dissociated, which leads to activation of μ-calpain that subsequently cleaves the mitochondrial major Ca2+ extruding protein Na+/Ca2+ exchanger (NCX). This cleavage of mitochondrial NCX by μ-calpain could lay a key role in mitochondrial Ca2+ overload and pulmonary smooth muscle demise. Therefore, regulation of calpain system in mitochondria of pulmonary smooth muscle could be potentially imperative in controlling the severity of the

pulmonary disease.

Part II: CRAC channels Ca2+ microdomains in NFAT activation and gene expression

Although a vast number of chemical signals are employed on the cell surface, only a small number of intracellular messengers are achieved into physiological consequences. Among them intracellular calcium is the most widespread, activating a range of fundamental cellular responses including gene expression, neurotransmission, beating of the heart, autophagy and apoptosis. Many different processes are activated by the same message, raising the question how elevation of intracellular calcium triggers a specific cellular response. Our aspiration is to understand how specificity is achieved in the immune system. Our research demonstrates that the formation of a store dependent signaling complex in the plasma membrane provides for selective activation of a fundamental downstream response by calcium released activated calcium channel (CRAC). CRAC channels are the major route for Ca2+ entry in all eukaryotic cells. The molecular basis of the CRAC channel has been identified, with STIM1 (ER resident protein) and ORAI1 (plasma membrane pore forming protein). Following ER store depletion STIM1 and ORAI1 are assembled and co-clustered, which lead to the opening of CRAC channels in the plasma membrane and let calcium enter in to the cell. As the calcium enters, its target is immediately and selectively activated. This mechanism explains how different ways of increasing calcium activate different cellular responses. This issue is nicely encapsulated by the nuclear factor of activated T cell (NFAT) family of Ca2+ dependent transcription factors, which are essential for vertebrate development, differentiation and immune function. NFAT proteins share the same spatial and temporal domain and are activated by the same intracellular signal. I will discuss how NFAT isoforms (NFAT1 and NFAT4) that co-exist within the same sub-cellular domain are differentially activated by CRAC channels. Our research demonstrates that NFAT1 has a private line of communication with plasma membrane calcium channels, activating in response to Ca2+ microdomains near the open channels. By contrast NFAT4 is more of a co-incidence detector, requiring both local Ca2+ entry through the same channels as well as a rise in nuclear Ca2+. I would also like to discuss the down stream regulation of NFAT-driven gene expression. Impaired NFAT activation due to aberrant CRAC channel function in immune cell causes severe combined immunodeficiency syndrome (SCID). Therefore, targeting the CRAC channel may provide a promising therapeutic approach to control the severity of an immune response.

All are cordially invited to attend the seminar

Sincerely yours,
R. Mukhopadhyay
(HoD)