CANCER SCIENCE INSTITUTE OF SINGAPORE

NUS National University of Singapore | CSI SINGAPORE



SUN Wendi

PhD Candidate

(Supervisor: Prof Lorenz Poellinger)

CSI Graduate Programme

PH.D ORAL DEFENSE

#04-01 Smart Classroom

Centre for Translational Medicine
14 Medical Drive, Singapore 117599

Mon, 25 May 2015
10:00 – 11:00 AM

No registration required. All are welcome.

Identification and Investigation of Proteins Interacting and Cooperating with the Von Hippel-Lindau Tumor Suppressor Protein

The von Hippel-Lindau (pVHL) protein is a well-known tumor suppressor that functions as a key component of the pVHL E3 ubiquitin ligase complex, mediating ubiquitination and degradation of the hypoxia-inducible factor α (HIF-α) protein. To gain new insights into the function of pVHL, we have identified and investigated novel pVHL interacting proteins. The metabolic enzymes, fatty acid synthase (FASN) and carbamoyl phosphate synthase-aspartate transcarbamylase-dihydroorotase (CAD), were identified by protein complex affinity purification and mass spectrometry analysis. Physical interactions between FASN and pVHL proteins were validated through co-immunoprecipitation assays. Several amino acid residues which are commonly mutated in VHL disease patients were found to be essential for the FASN-pVHL interaction. FASN protein knockdown led to decreased HIF-α protein levels, indicating a regulatory role of FASN on HIF-α protein. This regulation was shown to be dependent on the presence of the wild type pVHL protein but not on FASN protein's enzymatic activity. We propose that the interaction between FASN and pVHL protein disrupts the binding ability of the pVHL E3 ubiquitin ligase complex to HIF-α protein. Moreover, HIF-α was activated in the process of FASN induction during adipocyte differentiation. Treatment by 25-hydroxycholesterol, a negative regulator of FASN, also resulted in HIF-α protein down-regulation. Both findings support the physiological relevance of HIF-α regulation by FASN. Positive correlation between FASN and HIF-α target gene expression levels was observed in human prostate cancer patient specimens, indicating a potential clinical significance.