CANCER SCIENCE INSTITUTE OF SINGAPORE

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PhD Candidate

(Supervisor: Assoc Prof Chng Wee Joo)

CSI Graduate Programme

PH.D ORAL DEFENSE

CeLS Seminar Room 1

Centre for Life Sciences (CeLS) Level 1
28 Medical Drive, Singapore 117456

No registration required. All are welcome.

Mon, 6 April 2015
10:00 – 11:00 AM

Global Discovery of Dysregulated Protein Expression and Phosphorylation Networks Identified LEO1 as a Key Substrate of PRL-3 Phosphatase in Leukemogensis

PRL-3, an oncogenic dual-specificity phosphatase, is over-expressed in 50% of AML and associated with poor survival. We found that stable expression of PRL-3 in the cytokine-dependent TF-1 AML cells confers cytokine-independent growth, induces colony-forming ability in methylcellulose media and tumorigenesis in vivo. However, how PRL-3 mediates these functions in AML is unknown.

To systematically characterize novel substrates of PRL-3 in leukemia, SILAC-based mass spectrometry was performed on the parental TF-1 cells and their malignant PRL-3 transfectant counterparts. We obtained quantitative measurements on 803 proteins, where 331 were significantly up-regulated (>1.5-fold) and 67 were under-expressed (<0.6-fold). More importantly, PRL-3 altered the phosphorylation status of 192 proteins. We showed that Leo1, a component of RNA polymerase II-associated factor (PAF) complex, is a novel target of PRL-3 in AML. We described a novel mechanism where PRL-3 promotes Leo1 expression through epigenetic mechanisms. In addition, PRL-3 and Leo1 protein levels were positively associated in AML patient samples (N=24; p-value <0.01). On the other hand, inhibition of Leo1 reverses PRL-3 oncogenic phenotypes in AML. Loss of Leo1 leads to destabilization of the PAF complex and downregulation of SOX2 and SOX4, potent oncogenes in myeloid transformation.

Independent of the PAF complex, Leo1 played an important role in the activation of β-catenin. PRL-3 interacts with and dephosphorylates Leo1 in vitro and in vivo. Leo1 then forms a complex with β-catenin, and induces the nuclear retention and transcriptional activation of β-catenin target genes, including c-myc and cyclin D1. Hence, our study revealed that the functional consequences of PRL-3 overexpression in AML cells were pleiotropic and exploited the intracellular activation of two potent oncogenic pathways, SOX genes and β-catenin.