Cancer Science Institute of Singapore

Research Meeting

Date: Friday, 17 April 2015
Time: 12pm – 1pm
Venue: CeLS Auditorium, Level 1, Centre for Life Sciences
28 Medical Drive, Singapore 117456

Dennis Kappei

Special Fellow, CSI Singapore

T-Evolution – How phylointeractomics reconstructs functional evolution of protein binding

High-throughput DNA sequencing substantially advanced molecular phylogenomics to investigate evolutionary relationships based on genomic data. Seminal work has been performed in vertebrates to identify evolutionarily conserved as well as rapidly evolving genetic information. However, sequence conservation might not follow functional conservation of gene regulatory networks and homologous proteins may have different functions in different species. In fact, there is ample evidence that protein complexes evolve rapidly, associated with a functional diversification. We propose phylointeractomics as a new concept to investigate protein binding across different species to gain insight into molecular mechanisms of evolution. Using advanced label-free quantitative mass spectrometry, we investigate the telosome across 16 vertebrates ranging from zebrafish to human. In addition to the identification of previously unknown telomere-associated proteins our phylointeractomics screen unveils how protein homologs undergo functional evolution. For instance, we demonstrate that a well-characterized, core binder evolved as a telomere-binding protein in therians and we are able to recapitulate by selected single amino acid exchanges the necessary gain-of-function mutations at the evolutionary branch point. Phylointeractomics thus represents a powerful approach to reconstruct functional protein evolution.

Ng King Pan

Senior Research Scientist, Prof. Toshio Suda's group

Role of HIFs & ARG2 in hematological malignancy

Resembling that of solid tumor, leukemic stem cells (LSCs) are situated in a hypoxic microenvironment. Tissue hypoxia preserves stem cells function mainly though hypoxia-inducible factors (HIFs), the master regulators of hypoxic responses. We previously found that hypoxic leukemic cells upregulate HIFs and Arginase 2 (ARG2), an arginine metabolizing enzyme. Here, we sought to determine if HIFs regulates ARG2 expression, and whether this axis contributes to metabolic and microenvironmental alterations in leukemia. Acute myeloid leukemia (AML) cell lines expresses high level of ARG2 as compared to normal cord blood cells, whereas the other arginase isoform ARG1 negligibly expresses in both normal and leukemic cells. Indeed, hypoxic treatment upregulates ARG2 exclusively. Pharmacological inhibition or shRNA knockdown of either HIF1α or HIF2α downregulates ARG2, suggesting both HIFs contribute to ARG2 expression. Furthermore ARG2 does overexpress in primary AML case. Interestingly, AML cells release ARG2 protein into the extracellular medium, which could potentially deplete arginine from the microenvironment. Altogether, we propose that the HIFs-ARG2 axis enables the hypoxic leukemic cells to create an arginine depletion microenvironment that could interfere with normal haematopoiesis.