Cancer Science Institute of Singapore
Research Meeting

Date: Friday, 27 March 2015
Time: 12pm – 1pm
Venue: LT36, Level 3 Auditorium, MD6
14 Medical Drive, Singapore 117599

Dominic Voon

Senior Research Scientist, Prof. Yoshiaki Ito's group

A role for RUNX3 in inflammation-induced expression of IL23A in gastric epithelial cells

The transcription factor RUNX3 functions as a tumor suppressor in the gastric epithelium, where its inactivation is frequently observed during carcinogenesis. To better understand the genetic programme orchestrated by RUNX3 in gastric epithelial cells, we conducted a microarray study which identified *IL23A* as a RUNX3 target gene in gastric epithelial cells. This was confirmed in a series of *in vitro* analyses in gastric epithelial cell lines. While elucidating the underlying regulatory network, we uncovered a prominent role for the proinflammatory TNF-α/NF-κB pathway in activating *IL23A* transcription. Moreover, the activating effect of TNF-α was markedly augmented by the infection of *Helicobacter pylori*, the primary cause of human gastritis. This is achieved through the CagA/SHP2 pathway and the induction of PAMP-sensing NOD1 pathway by *H. pylori* peptidoglycan. Importantly, RUNX3 synergized strongly with these physiologically relevant stimuli to induce IL23A. Lastly, evidence will be presented for the secretion of IL23A by gastric epithelial cells in a form that is distinct from canonical IL-23 (IL23A/IL12B). Our observations suggest that RUNX3 exerts its tumor suppressor activities in part through its contribution to gastric immunity, a notion which extends beyond current appreciation of its cell autonomous functions. Through a microarray study, we identified *IL23A* as a RUNX3 target gene in gastric epithelial cells.

Yao Xiaosai

Research Fellow, Prof. Patrick Tan's group

Epigenetic aberrations in clear cell renal cell carcinoma

Large-scale exome sequencing efforts have identified dysregulation of chromatin state as a main mechanism of clear cell renal cell carcinoma (ccRCC), since inactivating mutations in histone modifying enzymes and nucleosome remodeling enzymes are frequently detected in tumor samples. Despite the identification of somatic mutations in these chromatin-modifying enzymes, the landscape of the altered chromatin state itself has not been well described in ccRCC. We compared the genome-wide histone modification profiles between tumor and patient-matched normal tissues, and found 2,000 putative cis-regulatory elements gained in ccRCC. Two thirds of these elements are enhancers and could recapitulate the ccRCC signature better than promoters could. We further examined super-enhancers - dense clusters of enhancers often controlling oncogenic drivers . We find that hypoxia-inducible factor (HIF) tends to occupy tumor-associated super-enhancers, implying HIF's role as a master transcription factor in ccRCC.