CANCER SCIENCE
INSTITUTE OF SINGAPORE
RESEARCH MEETINGS

27 October 2017, Friday | 3pm – 4pm

Auditorium, Level 1, Clinical Research Centre (MD11)

10 Medical Drive, Singapore 117597

Teoh Phaik Ju | Research Fellow, Prof Chng Wee Joo's Group (L12)

The Relationship between ADAR1 and STAT3 and its Relevance in Multiple Myeloma

Multiple myeloma (MM) is the second most common hematological cancer, characterized by the accumulation of malignant plasma cells in the bone marrow (BM). Survival of MM cells is highly dependent on the bone marrow microenvironment, which is enriched with an array of growth factors secreted by the BM stromal cells. Amongst these growth factors, interleukin-6 (IL6) has been reported to be a major driver for MM disease progression. In line with the mechanism of action of IL6, MM cells are associated with constitutive activation of the oncogenic STAT3 signaling. ADAR1, an RNA editing enzyme, exists in two distinct isoforms, namely the P110 and P150. Aberrant ADAR1 expression and activity have been reported in various cancer types, however, this remains elusive in MM. Herein, we identified that ADAR1 is overexpressed in MM and exhibited oncogenic properties *in vitro* and *in vivo*. IL6-induced activation of STAT3 signaling renders an increased expression of ADAR1 P150 isoform, at both the protein and mRNA level, indicating a transcriptional regulation by STAT3. Downstream validations revealed that ADAR1 P150 is a direct target of STAT3 transcription factor. Interestingly, we observed that IL6-induced-ADAR1 expression could in turn mediate the activity of STAT3 signaling, suggesting a potential interplay between both factors. In summary, these data provide a novel insight into the mechanism of action of IL6-conferred-oncogenic effects in MM.

Nishi Kumari | PhD Student, Dr Sudhakar Jha's Group (L13)

Identifying the Oncogenic Role of USP10 as the Regulator of PTEN Function in Breast Cancer

The PI3K pathway is the most commonly activated signaling pathway in human cancer. The lipid phosphatase PTEN is the major negative regulator of the PI3K pathway which de-phosphorylates PIP3 inhibiting downstream pathway activation. Loss of PTEN functionality has been reported in several cancer types, which further contribute to the tumorigenic impact of the PI3K pathway resulting in a more aggressive disease phenotype. Using a genome wide deubiquitinating enzyme screen we identify USP10 as a critical regulator of PI3K pathway. MAGI has recently been identified as PTEN interacting protein and along with MEK1 functions to inhibit PTEN recruitment to the plasma membrane. We find that USP10 forms a ternary complex between MEK1, MAGI1 and PTEN. Functionally, we demonstrate that USP10 stabilizes ITCH which we identified as an E3 ligase for MEK1 resulting in degradation of MEK1 and decreased PTEN plasma membrane localization. Furthermore, expression analysis of USP10 revealed significantly higher levels of USP10 in breast cancer patients and its expression is correlated with the tumour progression and poorer overall survival in the breast cancer patients. Interestingly, we show upregulation of USP10 protein level in PI3K inhibitor resistant breast cancer cells and further depletion of USP10 in these resistant cells resensitized cells to PI3K inhibitors. This study provides a new insight for designing mechanism based cancer drugs and combination therapies in breast cancer patients with the loss of PTEN functionality.

Vikas Madan | Senior Research Scientist, Prof H Phillip Koeffler's Group (L13)

ASXL2 is Recurrently Mutated in t(8;21) AML and Regulates Hematopoietic Development

Chromosomal translocation t(8;21) (q22;q22) leading to generation of oncogenic RUNX1-RUNX1T1 (AML1-ETO) fusion is a cytogenetic abnormality observed in about 10% of acute myelogenous leukemia (AML). To uncover somatic mutations that cooperate with t(8;21)-driven leukemia, we performed exome sequencing of newly-diagnosed and relapsed AML samples. We identified high frequency of truncating mutations of ASXL2 gene along with recurrent alterations of KIT, TET2, MGA, FLT3, and DHX15 in this subtype of AML. To investigate in-depth the role of ASXL2 in normal and malignant hematopoiesis, we utilized a mouse model of ASXL2 deficiency. Loss of ASXL2 caused progressive hematopoietic defects characterized by myeloid cell expansion, splenomegaly, extramedullary hematopoiesis and poor reconstitution ability of Asxl2-deficient hematopoietic stem cells in transplantation models. A parallel analysis of young and >1-year old Asxl2-deficient mice revealed age-dependent changes in the hematopoietic compartment leading to perturbations affecting not only myeloid and erythroid differentiation but also maturation of lymphoid cells. Our studies also suggest that expression of truncated ASXL2 protein confers proliferative advantage to mouse myeloid progenitors. Overall, these findings establish a critical role of ASXL2 in maintaining steady state hematopoiesis and provide insights into how its loss/mutation primes leukemic growth of myeloid cells.