GCOE Program, The University of Tokyo

Center of Education and Research for the Advanced Genome-Based Medicine

For personalized medicine and the control of worldwide infectious diseases

No advance registration required. Free Admission

IMSUT & RCAST Global COE Program

Mini-Symposium

November 9, 2012

15:00-17:00

Venue: The second floor conference room of the 1st Building,
Institute of Medical Science, The University of Tokyo (IMSUT)

Genetic and epigenetic aspects of hematological malignancies

Ross L Levine Professor, Memorial Sloan-Kettering Cancer Center, USA

Genetics and Therapy of Myeloid Malignancies

Clinical, cytogenetic, and gene-based studies have been used to inform biology and improve prognostication for patients with acute myeloid leukemia (AML), myelodysplasia (MDS), and myeloroliferative neoplasms (MPN). Most recently, a series of candidate gene and whole genome studies have identified recurrent somatic mutations in AML, MDS, and MPN patients including TET2, ASXL1, DNMT3A, and EZH2 mutations. Moreover, we have shown these mutations lead to adverse outcome in AML consistent with a biologically distinct subset of AML marked by adverse outcome.

From a biologic perspective the TET family of proteins have been shown to place a hydroxyl mark on methylated DNA and lead to DNA demethylation. We and others have found that TET2 mutationsleads to loss of DNA hydroxymethylation and a hypermethylation phenotype inleukemia patients. In addition, in vitro and in vivo studies show that TET2 loss leads to impaired hematopoietic differentiation, increased stem cell self-renewal, and myeloid transformation in vivo. Most recently studies have revealed a role of mutations in chromatin modifying enzymes in hematopoietic transformation, including mutations in the enhancer of trithorax and polycomb (ETP) gene ASXL1. We have elucidated the effects of ASXL1 mutations on chromatin state, gene expression, and hematopoietic function, and identified a specific role for ASXL1 in regulating H3K27 trimethylation and PRC2 function at specific loci in hematopoietic cells including at the HoxA cluster. We have also shown that hematopoietic specific loss of ASXL1 loss leads to myeloid transformation in vivo. These data demonstrate that novel mutationsn coopt the epigenetic state of hematopoietic stem/progenitor cells in order to contribute to transformation. Data from recent in vitro and in vivo studies delineating the role of TET2 and ASXL1 mutations in the pathogenesis of myeloid malignancies will be presented in detail.

Stephen D Nimer Professor, University of Miami, USA

Insights into the leukemogenic properties of AML1-ETO

Although the core binding factor (CBF) acute myelogenous leukemias (AMLs) have a better than average prognosis, the 5-year survival rates for these patients is only 50%1. We, and others, have shown that AML1-ETO has many gains-of-function, compared to the wild type AML1 and ETO proteins and have linked the ability of AML1-ETO to promote hematopoietic stem cell self-renewal with its ability to activate gene expression. To explain its activating effects we recently determined that AML1-ETO binds the lysine "histone acetyltransferase" (HAT) p300 via its NHR1 domain (amino acids 245-430), leading to acetylation of AML1-ETO at lysine 43 (K43) and lysine 24 (K24). It appears that acetylation at K43, but not K24, is essential for the leukemia and self-renewal promoting properties of AML1-ETO in both mouse and human AML models; this suggests several potential therapeutic strategies that could target this subtype of AML, including the use of p300 inhibitors. Alternatively, it may be possible to interfere with AML1-ETO containing transcriptional regulatory complexes to block the oncogenic functions of AML1-ETO. We continue to define the importance of specific protein-protein interactions involving AML1-ETO in leukemogenesis, and the clinical applicability of targeting its acitivty or the activity of its target genes.

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Shirokane Campus: Shirokanedai Station (Subway Namboku Line & Mita Line), Exit 2; about 3 minutes walk