Cancer Science Institute of Singapore

Distinguished Speakers' Series 2013

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Chromosomal Translocations and Transcriptional Elongation Control in Epigenetics and Cancer

Date: Thursday, 2 May 2013
Time: 11am – 12pm
Venue: LT 36, Centre for Translational Medicine, Level 3
(14 Medical Drive, Singapore 117599)
Chair: Prof. Daniel Tenen

Abstract:

Chromosomal translocations involving the *mixed lineage leukemia* (*MLL*) gene occur frequently in human acute leukemia of myeloid and lymphoid lineages. Many years ago, we identified the *Saccharomyces cerevisiae* Set1 as a MLL homologue, purified Set1/COMPASS as the first histone H3 lysine 4 (H3K4) methylase, and demonstrated that the COMPASS family and its role in H3K4 methylation is highly conserved across the evolutionary tree. Recent catalogues of somatic mutations in both hematological malignancies and solid tumors have identified a large number of mutations in the components of COMPASS. Our recent studies on the importance of the COMPASS family members and histone H3K4 methylation in development and cancer pathogenesis will be discussed. Regarding MLL's translocation role in leukemic pathogenesis, there are a large number of translocation partners of MLL with little sequence or seemingly functional similarities, yet their translocations to MLL result in the pathogenesis of hematological malignancies. Approximately 16 years ago, we identified ELL, a partner of MLL in leukemia, as an RNA polymerase II (Pol II) elongation factor. On the basis of our biochemical observations regarding ELL's role, we proposed that the regulation of the rate of transcription elongation by Pol II could have a central role in leukemic pathogenesis. Biochemical studies from our laboratory have recently demonstrated that indeed many of the MLL translocation partners in addition to P-TEFb are found within a biochemically distinct protein complex, the ELL-containing Super Elongation Complex (SEC). We have demonstrated that it is the translocation of MLL into SEC that is involved in the misrecruitment of SEC to MLL target genes, perturbing transcriptional elongation checkpoint control (TECC) at these loci and resulting in leukemic pathogenesis. Our recent finding on the role of TECC in the regulation of gene expression during development and cancer pathogenesis will be discussed.

Biography:

Dr. Ali Shilatifard is a biochemist/molecular biologist with an immense interest in understanding the molecular mechanism of the regulation of gene expression. As a Jane Coffin Childs postdoctoral fellow, Shilatifard made a seminal contribution to the field of leukemia biology by identifying the first function of any of the MLL translocation partners. Shilatifard identified ELL as a RNA Polymerase II (Pol II) elongation factor. Since its inception in 1997, the central theme in the Shilatifard laboratory has been the identification of the molecular properties of both MLL and ELL and why their translocations result in leukemogenesis. ELL is the first and best molecularly and biochemically characterized MLL partner in leukemia. In addition to his studies on ELL, within the past 15 years, Shilatifard's laboratory identified the yeast homologue of MLL, the Set1 protein in a complex named COMPASS, capable of methylating histone H3K4. Based on these fundamental yeast studies, we now know that MLL is also found in a COMPASS-like complex functioning as an H3K4 methylase. Shilatifard's laboratory also identified and demonstrated that many of the MLL partners in leukemia are found with ELL within the Super Elongation Complex (SEC) regulating the transcription of the MLL-chimera target genes. Most recently, Shilatifard's laboratory has demonstrated that Pol II elongation factors play a diverse role in regulating gene expression including the marking of both poised and inactive enhancers in the embryonic state and in the priming of future developmental gene expression patterns.