Cancer Science Institute of Singapore

SEMINAR ANNOUNCEMENT

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Regulation of Runx Complex Function by Modulating C-terminal Sequences in its Two Components

Date: Wednesday, 23 November 2016
Time: 4pm - 5pm
Venue: #04-01, Level 4, CeTM (14 Medical Drive, Singapore 117599)
Host: Prof Yoshiaki Ito

Abstract:

Runx transcription factor complexes are evolutionally conserved transcriptional regulator, and are composed of Runx protein and non-DNA binding Cbfb protein. Mammal Cbfb gene produces two functional isoforms, Cbfb1 and Cbfb2, by RNA splicing. However, functional difference between these two variants has not been clarified in animal model. We have generated two mutant mouse strains that lack either variant by targeting specific mutation at the splice donor signal. Although there was no apparent developmental defect in Cbfb1-deficient mice, we found development of many types of hematopoietic cells were impaired by loss of Cbfb2. For instance, Cbfb2-deficient mice have the small thymus due to decreased influx of hematopoietic progenitors form fetal liver during embryogenesis. Further analyses revealed that Cbfb2 was essential for differentiation of Lin−IL7R+PIRhi thymic-homing progenitors in 12.5 dpc fetal liver. In addition, induction of CCR9 chemokine receptor on these cells requires Cbfb2 binding to cell-type specific enhancers, a transcriptional program conserved in bony fishes in which RNA splicing to generate Cbfb2 was likely to be emerged during evolution. These findings not only highlight how acquisition of novel splice variant increased functional diversity of Runx complexes, which had contributed to shape the program for formation of the primary lymphoid organ, but also suggest a possible regulatory mechanism for Runx complex function by modulating C-terminal sequences in its components. We were then interested in the other evolutionally conserved C-terminal end sequences, VWRPY, in Runx proteins, and are testing what happens when VWRPY motif in Runx3 protein is changed to VWRPW in mouse model.

Biography:

After Ph.D. study at Kyushu university, I joined Dr. Dan Littman's laboratory at NYU as a post-doctoral fellow and started to examine mechanisms of *Cd4* gene silencing. During this study, I had learned a lot about epigenetic regulation, modes of transcription factors function and the methods for functional analyses of *cis*-regulatory regions. After five-years in my post-doc study, I finally identified Runx transcription factor complexes, which act as heterodimers of Runx proteins and the non-DNA binding Cbfb protein, as essential factors for *Cd4* silencing through binding to the intronic *Cd4* silencer (*Cell* 2002). In 2004, I had opportunity to open my laboratory at RIKEN Research Center for Allergy and Immunology (RCAI) and expanded my studies focusing on function of Runx complexes during development of immune system as well as in regulation of immune responses. One of my major contributions to Developmental Immunology was characterization of a transcription factors network that governs a helper versus cytotoxic lineage choice during thymocyte differentiation. Based on dense characterization of regulation of *Zbtb7b* gene expression, which encodes a central transcription factor, ThPOK, for CD4 helper T cells, we proposed a model that an antagonistic interplay between two transcription factors, ThPOK and Runx, serves as a central mechanism to separate these cell fates. We have identified several essential regulatory regions in the *Zbtb7b* locus, and continues to work on the mechanisms that control *Thpok* expression via regulating them. Beside above studies, my laboratory has been working to unravel function of Runx complexes by analyzing a series of mutant mouse strains harboring specific mutations in the Runx family genes. Recent works are unraveling roles of Runx complexes during development of innate lymphoid cells and dendritic cells, and we recently found that CC chemokine gene cluster is a novel Runx target to restrain inflammation response. We are also interested in how function of Runx complexes is modulated and started to address roles of C-terminal end sequences in Runx and Cbfb proteins.