



The Norwegian Society for Immunology hereby announces the April Guest Lecture:

"Selective Functions of the Modulatory DNA-Binding Zinc Fingers of Ikaros in Hematopoiesis and Tumor Suppression"

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Date: Wednesday 21st of April

Venue: Lunch Room IMMI 2nd floor, Rikshospitalet

When: 15.00-16.00

Program

15.00-15.15: Refreshments

15.15-16.00: Guest Lecture and discussion

Abstract

Ikaros is a Zn-finger transcription factor that has been shown to be both a critical regulator of hematopoiesis and a potent tumor suppressor. Ikaros binds DNA as a homodimer, heterodimer, or multimer, with sequence-specific DNA-binding determined by four N-terminal Zn-fingers. Although the DNA-binding domain contains 4 classic C2H2 Zn fingers, the two central fingers are sufficient for high-affinity binding to many DNA motifs, suggesting that flanking fingers 1 and 4 may modulate binding to specific target genes. One barrier toward a complete understanding of the biological functions and mechanisms of action of Ikaros has been the phenotypic complexity of Ikaros null mice. To examine the functions and mechanisms of action of Ikaros in greater depth, and to test the hypothesis that the flanking Zn fingers within the DNA-binding domain contribute to different functions, we generated two new mouse strains that lack the exons encoding either finger 1 or finger 4. Remarkably, and in contrast to the phenotype of Ikaros null mice, fingers 1 and 4 were both found to be expendable for B-cell development, suggesting that fingers 2 and 3 are sufficient for interactions with Ikaros target genes essential for B lymphopoiesis. Finger 1, which is naturally absent from one of the two abundant alternatively spliced isoforms of Ikaros in wild-type mice, was also found to be expendable for lymph node development and for tumor suppression. In contrast, mice lacking finger 4 lacked lymph nodes and consistently developed thymic lymphoma. Selective roles of these two Zn fingers in regulating other hematopoietic events have been uncovered. Further analysis of these phenotypic differences, coupled with detailed analyses of the DNA-binding preferences of different zinc finger combinations, should lead to the identification of new Ikaros target genes and a better understanding of the critical roles of Ikaros in hematopoiesis. In addition, the recent discovery by Mullighan et al (Nature, 2008) that more than 80% of all human BCR-Abl+ B-ALL's have deletions or mutations in the Ikaros locus has prompted us to initiate a collaborative project to study the interaction between the BCR-Abl proto-oncogene and loss of Ikaros tumor suppressor function. The mice lacking Zn finger 4 provide a possible model system, as these mice have lost tumor suppressor function, but in contrast to Ik null mice, these mice do have B-cells.