SIgN Immunology Seminar



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The Road to Become CD4 Helper T Cells

Host
Dr Florent Ginhaux
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Date
Thursday,
24 October 2013

Time
2pm – 3pm

Venue
SIgN Seminar Room
Immunos Building
Level 4
Biopolis

Genetic programming towards the $CD4^+$ helper lineage in post-selection thymocytes depends upon expression of the ThPOK transcription factor. Helper lineage-specific expression of *Thpok* gene with correct kinetic increase of its amount is achieved by balancing the activities of a transcriptional silencer and two functionally redundant enhancers. To address how these *cis*-regulatory elements cooperatively regulate expression of *Thpok*, we engineered a gfp reporter allele harboring mutations or positional relocations of these elements. Our results indicate that natural separation of the proximal enhancer from the silencer is critical for its enhancer activity. Structural comparison of the *Thpok* locus in several species suggest that a primordial enhancer may have been separated from the silencer via duplication, generating a locus in which two opposing regulatory functions were segregated. Based on these findings, we hypothesized that organization of local chromatin loops function as a on-off switch for *Thpok* expression. In turn, this topological switch is likely regulated by trans-acting factors that aid in the assembly of holocomplexes between the promoter and either of the two regulatory elements. In this regard, thymocytes from Bcl11b-deficient mice lack both silencer- and enhancer-mediated regulation of *Thpok* during their differentiation. The lack of this bi-functional regulatory network for *Thpok* expression uncouples TCR/MHC specificity and CD4/CD8 lineage choice in Bcl11b-deficient animals. These results will be discussed in the context of how regulatory mechanisms for *Thpok*.