HOXA transcription factors play a key role in the epigenetic regulation of TCRα enhancer activity

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Abstract

During T-lymphocyte ontogeny the ordered rearrangements of TCRδ, TCRγ TCRβ and TCRα loci determine the development into either γδ or αβ T-cell lineages. Whereas the former loci rearrange at early stages of thymic development, TCRα rearrangements occur only after the cortical β-selection stage. To understand the mechanisms involved in the developmental regulation/delay of TCRα rearrangements, we performed exhaustive epigenetic analyses of both mouse and human thymic subpopulations, including generation of Blueprint reference epigenomes. Strikingly, before β-selection the TCRα enhancer (Eα) is already bound by several lymphoid transcription factors, including the key Eα activators RUNX1 and ETS1, but is found in an open yet epigenetically silent configuration. Thorough gene expression analysis of thymic subpopulations revealed that the HOXA5-9 transcription factors are down-regulated concomitantly to Eα activation. Furthermore, we demonstrated that, by interacting with ETS1/RUNX1 via their homeodomains, HOXA proteins bind to Eα, repress Eα activity and prevent TCRα rearrangements. Accordingly, HOXA9 overexpression imposes developmental bias towards γδ T-cell lineage, which highlights the key role of HOXA proteins in the epigenetic programming controlling the onset of TCRα rearrangements and αβ vs γδ developmental cell fate.