

Cofactors Regulate Early Thymic Progenitor Development by Silencing Non-T Lineage Programs and Sustaining T-cell Identity

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Abstract

The thymus sustains the lifelong output of new T cells; however, it cannot self-renew and thus requires continuous replenishment by progenitors derived from the bone marrow. Upon thymic entry, these multipotent hematopoietic progenitors gradually differentiate and acquire T-cell identity. A network of sequence-specific transcription factors (TFs) and transcriptional coregulators regulates this process. Transcriptional coregulators interact with a wide range of TFs without directly binding to DNA; however, our understanding of their precise roles during T-cell development remains limited. Among these coregulators, the Tle family consists of several members. They were reported to promote the establishment of CD8⁺ cell lineage identity, while also inhibiting the development of CD8⁺ central memory cells and suppressing the malignant transformation of myeloid lineage cells. In this study, we found that knockout of Tle coregulators at an early stage of thymic development not only impairs the formation and differentiation of early thymic progenitors, but also leads to excessive accumulation of B cells, dendritic cells, and myeloid cells within the early thymocyte compartment. Integrated multi-omics analyses indicate that Tle coregulators repress the expression of non-T lineage transcription factors such as *Pax5*, *Irf8*, and *C/EBPα*, while simultaneously upregulating key components of the T-cell transcriptional program, including *Notch1*, *Gata3*, and *Erg*. Thus, Tle coregulators exert a dual function: they ensure the progression of T-cell specification and commitment while actively preventing cells from diverging into alternative lineages.

Keywords

Thymus, T Cells, Transcription Coregulators, Multiomics Analyse