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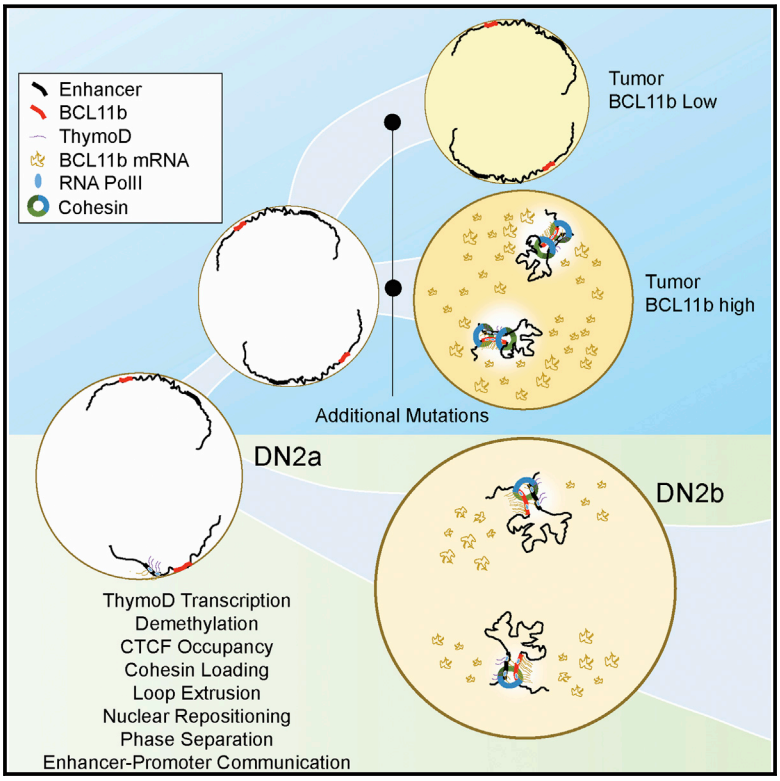
Cell

Non-coding Transcription Instructs Chromatin Folding and Compartmentalization to Dictate Enhancer-Promoter Communication and T Cell Fate

Graphical Abstract



Highlights

- Non-coding transcription directs loop extrusion
- Non-coding transcription dictates compartmentalization
- Non-coding transcription directs enhancer-promoter communication
- Non-coding transcription establishes T cell identity and blocks lymphoid malignancy

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In Brief

Transcription of a non-coding locus facilitates chromatin folding and compartmentalization to reposition T-lineage-specific enhancer and promoter elements into a single-loop domain.

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Non-coding Transcription Instructs Chromatin Folding and Compartmentalization to Dictate Enhancer-Promoter Communication and T Cell Fate

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SUMMARY

It is now established that Bcl11b specifies T cell fate. Here, we show that in developing T cells, the Bcl11b enhancer repositioned from the lamina to the nuclear interior. Our search for factors that relocalized the Bcl11b enhancer identified a non-coding RNA named ThymoD (thymocyte differentiation factor). ThymoD-deficient mice displayed a block at the onset of T cell development and developed lymphoid malignancies. We found that ThymoD transcription promoted demethylation at CTCF bound sites and activated cohesin-dependent looping to reposition the Bcl11b enhancer from the lamina to the nuclear interior and to juxtapose the Bcl11b enhancer and promoter into a single-loop domain. These large-scale changes in nuclear architecture were associated with the deposition of activating epigenetic marks across the loop domain, plausibly facilitating phase separation. These data indicate how, during developmental progression and tumor suppression, non-coding transcription orchestrates chromatin folding and compartmentalization to direct with high precision enhancer-promoter communication.

INTRODUCTION

The differentiation of T cells is orchestrated in the thymus. Upon exposure to Delta-Notch signaling, early T cell progenitors (ETPs) differentiate into multipotent DN2a cells, which in turn develop into committed DN2b cells. DN2b cells subsequently progress into DN3a cells in which TCRβ VDJ rearrangement is initiated. Once a productive TCRβ chain has been assembled, DN3b cells expand and differentiate into $CD4^+CD8^+$ double-positive (DP) thymocytes. In the DP compartment, thymocytes die by either neglect or negative selection or persist through positive selection to differentiate into CD4 single-positive (CD4SP) or CD8SP cells (Klein et al., 2014; Naito et al., 2011).

The developmental progression of T cells is regulated by the combined activities of an ensemble of transcriptional regulators. T-lineage development is initiated by the E-proteins that activate the expression of genes encoding components involved in Notch signaling (Bain and Murre, 1998; Ikawa et al., 2006; Miyazaki et al., 2017). Once instructed to respond to Notch signaling, T cell progenitors activate the expression of Bcl11b, GATA-3, and TCF1 (Yui and Rothenberg, 2014). Specifically, Bcl11b expression is initiated at the DN2a cell stage to promote developmental progression to the DN2b cell stage. At the DN2b cell stage, Bcl11b expression is further elevated and, in concert with E2A, activates a T-lineage-specific program of gene expression and suppresses the expression of genes associated with alternative cell fates (Liu et al., 2010; Ikawa et al., 2010; Li et al., 2010a; Longabaugh et al., 2017). The activation of Bcl11b expression in DN2 cells involves Notch signaling, GATA-3, TCF1, and RUNX1 that bind to an enhancer, named Major Peak, located in the Bcl11b intergenic locus control region (Guo et al., 2008; Weber et al., 2011; García-Ojeda et al., 2013; Li et al., 2013). Recent elegant studies indicated that full activation of Bcl11b expression in developing T cell progenitors requires a rate-limiting transition from an inactive to an active chromatin state (Kueh et al., 2016).

Here, we have examined how Bcl11b expression is activated to establish T cell fate and suppress the development of lymphoid malignancies. We found that, in developing T cell progenitors, the Bcl11b locus control region, containing a well-characterized enhancer, repositioned from the lamina to the nuclear interior. The repositioning of the Bcl11b enhancer was orchestrated by a non-coding RNA, named ThymoD (thymocyte differentiation factor). ThymoD transcription promoted demethylation at sites associated with CTCF occupancy across the transcribed region and activated cohesin-dependent looping, plausibly involving loop extrusion, to bring the Bcl11b promoter and enhancer into a single loop domain. These results are consistent with a model in which non-coding transcription dictates enhancer-promoter communication at multiple levels: (1) demethylation of CpG residues across the ThymoD transcribed region to permit CTCF occupancy, (2) recruitment of the cohesin complex to the transcribed region to activate cohesin-dependent looping, (3) loop extrusion to juxtapose with great precision the enhancer and promoter into a