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Definition of Regulatory Network Elements for T Cell Development by Perturbation Analysis with PU.1 and GATA-3

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Abstract

PU.1 and GATA-3 are transcription factors that are required for development of T cell progenitors from the earliest stages. Neither one is a simple positive regulator for T lineage specification, however. When expressed at elevated levels at early stages of T cell development, each of these transcription factors blocks T cell development within a different, characteristic time window, with GATA-3 overexpression initially inhibiting at an earlier stage than PU.1. These perturbations are each associated with a distinct spectrum of changes in the regulation of genes needed for T cell development. Both transcription factors can interfere with expression of the Rag-1 and Rag-2 recombinases, while GATA-3 notably blocks PU.1 and IL-7Rα expression, and PU.1 reduces expression of HES-1 and c-Myb. A first-draft assembly of the regulatory targets of these two factors is presented as a provisional gene network. The target genes identified here provide insight into the basis of the effects of GATA-3 or PU.1 overexpression and into the regulatory changes that distinguish the developmental time windows for these effects.

Keywords

T cell development; fetal thymus organ culture; GATA-3; PU.1; Ets family; retroviral transduction; IL-7 receptor; c-Myb; HES-1; pre-TCR

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