TOWARDS T-CELL SPECIFICATION: DEFERRAL OF COMMITMENT AND IRREVERSIBILITY

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Abstract

T-cell progenitors evolve into mature T-cells in the thymus under the influence of Notch. During the first steps a set of key players, Tcf7, Gata3, Bcl11b, and PU.1, develop into a stage when the commitment decision takes place for the T-cell lineage in favour of alternative cell fates. Using staged gene expression data for this gene quartet together with a putative architecture for their interactions as a basis for dynamical models, it is demonstrated that the commitment decision is irreversible. This analysis allows for different logics (AND/OR) and monomer/dimer binding options for the interactions, out of which only 3 alternatives provide irreversibility. This development of differentiation competence is accompanied by a remarkable expansion of the initial progenitor pool. Computational models are exploited in which the probability to progress is linked to division number. To satisfy differentiation kinetics and overall cell yield data, these models require that initial progenitor cells (DN1) divide multiple times prior to committing into the next stage (DN2). Most of the analysis above is based upon bulk data. Preliminary single cell data support the claims in addition to provide other features like heterogeneity.