Dynamical modeling of human T helper cell differentiation

High number of signals can be delivered by dendritic cells (DC) depending on their context of stimulation. The integrated information given by these multiple signals will then shape the T helper phenotype. We developed an integrated data-driven model of coupled measures of 36 DC communication signals and 17 Th cytokines at a protein level. A high diversity of DC and T cell phenotype was achieved by the systematic stimulation of DC with combinations of perturbators. The model predicts the synergistic induction of IL-17F by IL-12p70 combined to IL-1B independently of IL-17A (Grandclaudon et al, submitted). This model prediction has been validated experimentally.

In order to understand the contribution of IL12 in the induction of TH17-cytokines, we established a logical model of Th cell differentiation that includes T cell inputs (Th polarizing factors), downstream signaling components, and T cell outputs (Th cytokines). This predictive logical model for the network controlling T-helper cell differentiation is encoded with the GINsim software. There are evidences of differential regulation of IL-17A and IL-17F that we are validating in vitro.

The building of the model raises two questions. Firstly, can we find new mechanisms controlling Th differentiation based on our analysis? The model is based on two hypotheses. Hypothesis 1: Stat1 may regulate differentially IL17A and F production. Hypothesis 2: Stat5a inhibits IL17A but not F.

On a second hand, can we build a network model illustrating the complex intracellular signaling pathways and transcriptional factors controlling differential regulation of IL17A and IL17F production using Ginsim?

Our first results unveiled a balanced function of Stat1 and Stat5a/b in the induction of IL17A and IL17F production by human T cells. We will further improve the model with data from the literature or experimentally generated (miRNA, ChIP seq datas). The model will raise new hypotheses concerning T helper cell differentiation mechanisms that will be experimentally validated.

Keywords : IL17, model, differentiation
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