

# **Experimental and Mathematical Analysis of Regulatory Networks in T-helper Lymphocytes**

Edda G Schulz



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In this book, an interdisciplinary approach combining dynamic quantitative measurements with mathematical modelling is used to solve two different problems in molecular immunology. In the first part, structure and function of the gene-regulatory network that controls differentiation of type I T-helper (Th1) cells is investigated. By determining the network structure through an iterative process of modelling and experiments, the author shows that Th1 differentiation proceeds in two steps: In the early effector phase, the Th1 master transcription factor T-bet is controlled by an interferon-? dependent positive feedback loop, while in the later phase a second IL-12 dependent feedback maintains T-bet expression. The antigen signal acts as a switch between the two pathways. Moreover, it is shown that only T-bet expression in the late phase is predictive of the success of the differentiation process. Since T-bet expression in the late phase requires IL-12 stimulation, this work uncovers the molecular mechanisms behind the unique role of IL-12 in Th1 differentiation. In the second part, regulation of the transcription factor NFAT that mediates antigenic stimulation in T-cells is investigated. NFAT is activated by nuclear import upon dephosphorylation of multiple residues. Based on simultaneous measurements of NFAT subcellular localization and phosphorylation, a quantitative mathematical model of the NFAT regulatory network is developed and the underlying design principles are analyzed. In summary, the study exemplifies the necessity of a dynamic analysis at the systems level to understand complex biological processes.

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