



DIVERSITY AND PLASTICITY OF T-HELPER CELL TYPES PREDICTED FROM REGULATORY NETWORK MODELLING

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Alternative cell differentiation pathways are believed to arise from the concerted action of signalling pathways and transcriptional regulatory networks. However, the prediction of mammalian cell differentiation from the knowledge of the presence of specific signals and transcriptional factors is still a daunting challenge. In this respect, the vertebrate hematopoietic system, with its many alternative differentiation pathways and cell types, is a compelling case study.

Here, we report the development of an integrated, comprehensive model of the signalling/regulatory network controlling Th cell differentiation. Our main aim is to gain insight into the potential heterogeneity and plasticity of late Th cell lineages. Since available data are mainly qualitative, we rely upon a logical formalism to perform extensive dynamical analyses. To cope with the size and complexity of the resulting network, we use an original model reduction approach coupled to a stable state identification algorithm. To assess the effects of heterogeneous environments on Th cell differentiation, we have performed a systematic series of simulations, considering various prototypic environments.

As a result, we have identified stable states corresponding to canonical Th1, Th2, Th17 and Treg subtypes, but these were found to coexist with other transient hybrid cell types that co-express combinations of Th1, Th2, Treg and Th17 markers in an environment-dependent fashion.

In contrast with the classical depiction of T cell differentiation potential in terms of a branching tree, our computational study points to a reticulate network of alternative, environment-dependent, differentiation and reprogramming events.