Minimal Regulatory Network of Extrinsic and Intrinsic Factors Recovers Patterns of CD4+ T Cell Differentiation and Plasticity

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***Short Abstract* — T CD4+ lymphocytes differentiate in different cell types in response to the cytokines present in their environment, this differentiation is not terminal, as this cells are plastic. In this work we construct a minimal regulatory network which recuperates the attractors corresponding to Th0, Th1, Th2, Th17, Tfh, iTreg, Th9 and various Foxp3-independent T CD4+ cells. Using this network we studied the effect of the cytokines in the environment and of directed perturbations in the differentiation and plasticity of this cells. Finally, we determined the key nodes of the network for the differentiation and plasticity of T CD4+ lymphocytes.**

***Keywords* — Regulatory boolean networks, differentiation, plasticity, T CD4+ lymphocytes**

I. Introduction

The immune system is a complex system of biological processes and structures that protects the organism against a variety of pathogens with specialized responses and is non-reactivity to itself maintaining the homeostasis of the organism. T CD4+ lymphocytes, also known as T helper (Th) cells, play an important role orchestrating the immune responses to various infectious agents. Naive T CD4+ lymphocytes (Th0) are activated when they recognize an antigen presented by an antigen presenting cell in a secondary lymphoid organ. Depending on the cytokine milieu and costimulatory signals in their environment CD4+ T lymphocytes differentiate into different cell types, expressing specific transcription factors, membrane molecules, and cytokines, which affect the behavior of the rest of the immune system[1,2]. This cell types include: Th1, Th2, Th17, Tfh,, iTreg, Th3, Tr1 and Th9. Once differentiated, T CD4+ lymphocytes can change their expression profile, making this cells plastic[3].

The differentiation and plasticity of CD4+ T lymphocytes depends on the complex molecular interactions between the molecular elements of the network. This networks have been studied with systemic and formal approaches mainly using dynamic and autonomous regulatory network models which recuperate the differentiation of this cells[4-6]. However, the effect of specific alterations in the elements of the molecular network and the cytokines in the environment in the differentiation and plasticity of this cells is still an open question

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II. Results

We first explored models considering solely the interaction between master transcription factors as necessary and sufficient elements to explain immune system differentiation. Those models turned out to be false; they cannot explain the origin of all the expected T CD4+ cell types or their plasticity. After several refinements, we ended up with a minimal model including transcription factors, signalling pathways and, intrinsic and extrinsic cytokines as its components. This latter model was fully capable of explaining both the whole set of T CD4+ cell types (Th0, Th1, Th2, Th17, Tfh, Th9, iTreg and Foxp3-independent regulatory T CD4+ cells) and their plasticity.

The analysis of this minimal regulatory network also sheds light in the stability of the system's attractors -which correspond to different cell kinds- and the global plasticity of the differentiation process. We predict a cell fate map showing which perturbations of the components lead to transitions between subsets. This cell fate map changes in different polarizing environments, displaying how extrinsic signals alter the proportions and stability of the different T CD4+ subsets. Also, we analyzed the components of the minimal regulatory network in the global behavior of the system; in particular, the role of SOCS proteins , inhibitors of the signaling pathways, in the integration of molecular signals and plasticity is a novel discovery. The model is qualitatively congruent with the literature regarding how plasticity is affected by the micro-environment.

III. Conclusions

The quantity and diversity of the interactions involved in the differentiation of T CD4+ lymphocytes makes the behavior of this cells extremely complex, complicating the understanding and the clinic applications of the system, as the effects are not always direct. Studying the molecular network as a dynamic system lets us understand how the interactions between the components create the complex behaviors that let the immune system defend the organism against pathogens and maintain homeostasis and self-tolerance. T CD4+ lymphocytes are a complex, dynamic system, and modeling the system from this approach will give us insights into the richness of the system and its interactions.

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