A quantitative analysis of the competition for IL-2 between T_{eff} and T_{reg} cells

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***Short Abstract* — By combining *in silico* modeling with *in vitro* experiments, we show that the decision between immune tolerance and response is a highly dynamic process, in which IL-2 is crucial for both the survival of T_{eff} cells and the suppressive capacity of T_{reg} cells. The model reveals that T_{reg} cells differentially suppress weakly activated T_{eff} cells. We further show that spatial localization of cells is a critical parameter in this process and that spatial constraints add another level of complexity to cytokine signaling.**

I. Introduction

Regulatory T cells (T_{reg} cells) play a crucial role in the balance between immune tolerance and immune response and their dysfunction can lead to the onset of auto-immune diseases. Effector T cells (T_{eff} cells) need to overcome T_{reg} cell surpression in order to generate a full immune response [1]. Recent experiments showed that the consumption of the lymphocytotrophic growth hormone interleukin-2 (IL-2) by T_{reg} cells leads to apoptosis of T_{eff} cells *in vitro* and limits inflammatory bowl disorder *in vivo* [2]. However, experimental results from transwell assays suggest that IL-2 depletion is insufficient to explain the suppressive nature of T_{reg} cells [3].

Based on *in vitro* experiments, we here present a quantitative computational model of the competition for IL-2 between T_{eff} and T_{reg} cells that reconciles these seemingly contradictory findings.

II. Results

Using data from flow cytometry experiments we constructed a coarse grained model of the activation of the T cell's IL-2 receptor complex upon stimulation by IL-2. We discovered that the amplitude of the response depends on the abundance of βγ–receptor chains whereas the abundance of α–receptor chains determines the sensitivity of the T cell.

Next we extended the above model by including the phosphorylation of the key response element Stat5 and the positive and negative feedback loops regulating the expression of the receptor chains and IL-2 respectively. In order to constrain the parameters of this model, we experimentally quantified the depletion of IL-2 by T_{reg} cells and the secretion of IL-2 by T_{eff} cells. Our model correctly reproduced our experimental observations that only strongly activated T_{eff} cells with a large number of α- receptor chains are capable of escaping T_{reg} cell surveillance. The simulations revealed that T_{reg} cells not only lower the available cytokine concentration but also abrogate the positive feedback loop leading to an up-regulation of the receptor chains by reducing the amount of phosphorylated Stat5 in weakly activated T_{eff} cells. Moreover, our simulations predicted the existence of a critical number of cells that a population of strongly activated T_{eff} cells needs to overcome in order to escape suppression by an equal number of Treg cells. We next confirmed this theoretical prediction with *in vitro* experiments.

Finally, we included spatial localization of cells in our simulations. Preliminary result suggest that cells of the two different types have to be place in close proximity to one another in order for T_{reg} cells to exert an effect on T_{eff} cells. A transwell assay in which the apical well housing T_{reg} cells is situated millimeters above the surface of the basal well containing T_{eff} cells introduces a large delay in cytokine communication corrupting the timing of the competition for IL-2 between T_{reg} and T_{eff} cells.

III. Conclusion

By combining single-cell experiments with computational modeling we have characterized the critical parameters by which populations of T_{reg} and T_{eff} cells shape the decision between immune tolerance and immune response.

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