T cell fate decision through competition for IL-2

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A single cytokine can regulate multiple cell fate decisions. We have developed a mathematical model of a small cytokine network: IL-2 signaling between regulatory T cells (Treg) and conventional T cells (Tresp). The model shows how a binary decision - activation of either Tresp or Treg - is achieved through feedback-enhanced competition for IL-2. IL-2 receptor expression and spatial coupling emerges as critical processes controlling the distribution of IL-2 between the competing cell types. Different operating regions of the feedback cause the regulation of the IL-2 receptor to be binary (Tresp) or gradual (Treg). We have verified this prediction experimentally.

Keywords — **Cytokine network, Interleukin 2, regulatory T cells, positive autocrine feedback, binary decision, reaction diffusion system**

I. INTRODUCTION

CYTOKINE communication is organized in networks that link multiple cell types, releasing and taking up their messenger. To elucidate how these diffusible messengers mediate coordinated and complex cellular responses presents a formidable problem. We consider a small network of IL-2. IL-2 plays a critical role in regulating T cell numbers. It is expressed together with its high-affinity receptor by conventional antigen-responsive T cells (Tresp). Therefore IL-2 signals can initiate an autocrine loop on Tresp, which act as a positive feedback on its own expression. But it is also known that IL-2 is essential for regulatory T cells (Treg) to suppress autoimmune responses. Interestingly, Treg mediate their suppressive activity by preventing the activation of Tresp. Differences in IL-2 and IL-2 receptor expression of Tresp and Treg suggest that competition for IL-2 may be a suitable mechanism to regulate the activation of Tresp and Treg. While Tresp express IL-2 and the IL-2 receptor only after antigen stimulation, Treg express constitutively high amount of IL-2 receptors and can also upregulate them in a feedback-dependent manner. But Treg are unable to produce IL-2 at all. In addition *in vitro* co-culture experiments by de la Rosa et al. confirm this hypothesis [1]. We have developed a mathematical model to elucidate the role of the feedback loop and the parameters controlling the cell fate decision.

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II. RESULT

The reaction diffusion model includes the IL-2 receptor dynamics on Tresp and Treg as well as the intracellular IL-2 dynamics. The number of IL-2 receptors indicates the activation state on both cell types [1]. The IL-2 receptor expression exhibits bistability. With increasing strength of the antigen stimulus the IL-2 receptor expression on the Tresp switches from a very low to a high level. Above this critical activation threshold the positive feedback loop is established. If Treg are present in close proximity (<100µm), this activation threshold is shifted to much higher values. Depending on the strength of the antigen stimulus and the distance four scenarios occur: (1) no activation, (2) activation of Tresp, (3) activation of Treg, (4) activation of Tresp and Treg. Furthermore, we have shown that the number of IL-2 receptors control the outcome of the competition. The analysis also yields differences in the regulation of the IL-2 receptor expression on Tresp and Treg. Whereas Tresp show a binary expression pattern, the upregulation of the IL-2 receptors on Treg is gradual. Due to the high IL-2 receptor expression on Treg the positive feedback is always active. The differences in the IL-2 receptor expression pattern as well as the shift in the activation threshold in the presence of Treg have been verified experimentally. For this purpose Tresp has been stimulated alone or in co-culture with Treg with different concentration of antigen.

III. CONCLUSION

Competition for IL-2 regulates the alternative activation of Tresp or Treg. The intercellular distance, the strength of the antigen stimulus and the number of IL-2 receptors are important control parameters. Proximity of Tresp and Treg may not only be provided in co-culture, but also in the lymph node, when both cell types are activated by the same antigen presenting cell. The positive autocrine feedback provides a threshold number for different expression pattern of the IL-2 receptor. The different operating region of Tresp and Treg may be due to the different regulation of IL-2 receptor gene in Tresp and Treg caused by differential expression of the transcription factor Foxp3 [2].

References

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