Spatial Effects in Cytokine Signaling Between T Cells

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***Short Abstract* — The structure of diffusion-consumption fields is studied in the framework of cytokine mediated communication between T cells. The probability of autocrine consumption is measured and is shown to be low in any realistic biological scenario. The effect of tight packing of cells in tissue is treated in a novel way by fabricating well-plate designed to hold cells in a small confined volume. The screening of concentration fields due to consumption by cells is experimentally measured. Cytokine receptors on activated cells screen cytokine interactions with typical screening lengths of 1-3 cell diameters, and generally create heterogeneous and highly localized concentration fields.**

***Keywords* — cytokine dynamics, diffusion-consumption, autocrine, paracrine.**

I. Introduction

THE need for systemic and coordinated operation, throughout various biological systems, is fulfilled by the exchange of small diffusive signaling molecules which, in a naive way, allow communication between parts of a given system.

We focus on the mammalian immune system whose response to antigens is coordinated by the exchange of a variety of cytokines. Understanding the dynamics of cytokines is paramount for an accurate description of the immune system. Many forms of immunotherapy rely on modifying levels of different cytokines to provoke a desired immune response [1-3]. A deeper understanding of cytokine interactions will potentially inspire more efficacious clinical strategies.

Recent years have seen an increasing attention on the subject [4-6], but a satisfactory model is still far. The complexity of the system, the lack of accurate basic physical parameters such as diffusion coefficients, reaction rates, secretion and consumption rates, etc. and the observed natural variability in many of these parameters, have hindered modeling efforts.

II. Results

Using Interleukin-2 (IL-2) and its pathways, we focus on the two basic processes of inter-cell communications, *Autocrine* and *Paracrine* signaling.

A. *The vast majority of secreted cytokine escapes the producing cell and is released to the environment.*

We determine the prevalence of Autocrine processes by measuring the *Autocrine Probability*, i.e. the probability for a secreted cytokine molecule to be consumed by the cell which secreted it, for cells with different numbers of cytokine receptors. We show that up to unrealistically high receptor numbers, Autocrine probability tends to be low. For a physically viable number of receptors ($\sim 10^5$) we get a probability of less than a 10%. This however does not mean Autocrine responses are unimportant as cells typically exhibit a very high sensitivity to cytokine signals, with half maximal effective concentration (EC50) in the pico molar range.

B. *Cytokines are rapidly consumed by neighboring cells creating highly localized concentration fields.*

We measure how the tight packing of cells in tissue affects the extent of inter-cellular cytokine mediated interactions. IL-2 producing cells are combined with different ratios of activated and naive IL-2-/- which act as IL-2 sinks and as inert fillers, respectively. This type of arrangement simulates conditions in actual lymphoid tissue where cells are snugly packed together.

These interactions are mediated by an exponentially decaying concentration field around a producing cell which is characterized by a *Screening Length*, similarly to Debye screening in electrostatics. We see a very strong localization of cytokine concentration fields around producing cells with typical screening lengths of the order of a few (1-3) cell diameters. These short length scales for inter cellular interactions imply a highly heterogenous cytokine landscape in an active secondary lymphoid organ. This source of variability, which naturally exists *in vivo*, is mostly overlooked in most *in vitro* applications.

References

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