'Inside-Out' Signal Integration and Integrin Activation During T Lymphocyte Recruitment

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***Short Abstract* — T cell arrest within the microvasculature constitutes the fundamental mechanism for coordinating tissue-specific patterns of lymphocyte homing. We have developed and calibrated an elementary kinetic model of 'inside-out' chemoattractant signaling that precipitates integrin activation and T cell adhesion. We specifically consider the role of signaling microdomains using a stochastic, spatio-temporal model formulation and illustrate that localized network activation is essential for cell responsiveness. Furthermore, we predict a novel role for integrating multiple chemotactic stimuli and illustrate that seemingly redundant signals provide tissues a means for selectively recruiting one or more T cell subpopulations.**

***Keywords* — T lymphocyte homing, 'inside-out' integrin activation', Next Subvolume Method, Adhesive Dynamics**

I. Introduction

It is now established that the T lymphocyte trafficking program is encoded by the combinational expression of adhesion and chemoattractant receptors which act as molecular 'zip-codes' and direct unique cell sub-populations to specific target tissues [1, 2]. Transient rolling interactions in post-capillary venules allow blood borne T cells to interrogate the endothelium for surface-bound chemokines – chemotactic cytokines that positively identify tissues by signaling cell arrest and extravasation. Those lymphocyte populations bearing complimentary G-protein coupled chemokine receptors integrate these cues via 'inside-out' signal transduction that activates resting, low-affinity integrins to active, high-affinity conformations. Concurrent presentation of a complementary integrin ligand on the endothelium results in a rapid transition to stable, shear-resistant adhesion.

The elementary topology of the inside-out signaling network has begun to be elucidated, and quantitative experimental measurements of signal dynamics are becoming the focus of intense study [3]. However, it remains unclear how T cell populations expressing two or more chemokine receptors integrate multiple stimuli and whether chemokine cross-talk affects the efficacy of cell arrest. We hypothesized that multiple chemokine stimuli represent additional specificity in regulating lymphocyte traffic and generate an unrecognized level of diversity in T cell homing patterns.

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II. Methods and Results

We have constructed a kinetic mass-action model of inside-out signaling in T lymphocytes using coupled ordinary differential equations and trained the model against experimental dynamics of chemokine-triggered integrin activation. The model was subsequently reformulated using a stochastic, spatially resolved formalism – the Next Subvolume Method [4] – to examine how restricted chemokine presentation precipitates rapid and localized integrin activation in rolling cells. When integrated into Adhesive Dynamics, a simulator of cell adhesion, the kinetic model accurately predicted dynamics of cell arrest observed *in vitro* [5].

III. Conclusions

We find that inside-out signal integration occurs within spatially restricted microdomains on the cell surface, rather than in a global, cell-wide manner. This localized signaling appears to be essential for the subsecond timescales of T cell arrest observed in experimental flow assays. Moreover, the model predicts that cells expressing two or more chemokine receptors are capable of integrating multiple chemokine stimuli in a non-redundant manner. Specifically, the relatively low threshold for integrin activation ensures that multiple arrest stimuli are integrated in an additive manner rather than competing for downstream signaling effectors. Mutual priming of the inside-out network therefore appears to sensitize cells to low levels of chemotactic stimuli that would otherwise prove ineffective in promoting T cell recruitment.

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