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Adhesive Dynamics Simulations of Leukocyte Rolling and Firm Adhesion

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ABSTRACT

Leukocytes, such as neutrophils and lymphocytes, are immunological cells that must frequently leave the blood stream and enter tissue to carry out their immunological function. A neutrophil's mission is to eliminate foreign invaders in the acute inflammatory response; lymphocytes enter tissues to exchange molecular information for the correct functioning of the immune response. Despite their different functions, all leukocytes share common mechanisms by which they secure adhesion in preparation for their egress from tissues. In particular, most leukocytes are equipped with two distinct adhesion molecules, which, in a coordinated fashion, arrange for the specific location of cell arrest. One is the selectins or selectin ligands, which are responsible for both capturing leukocytes from the blood stream and for maintaining the rolling of leukocytes over the walls of the vascular endothelium. The second are the integrins, which normally exist in a passive state but which, when sufficiently many are activated through inside-out signaling, can mediate firm adhesion. A third molecular player that plays a critical role in coordinated egress is the chemokine, which expressed on the endothelium can bind to leukocyte chemokine adhesion receptors, and generate intracellular signals that can activate integrins.

Thus, the stopping of leukocytes follows the following sequence. Changes in the endothelium – expression of chemokines, and increased expression of selectins and integrin ligands (such as intercellular adhesion molecule-1, or ICAM-1) – lead to the capture and rolling of leukocytes over endothelium. After a sufficient period of rolling, chemokine receptors, selectins, or integrins – or combinations thereof – generate sufficient intracellular signals to activate integrins to switch to an active state and secure firm adhesion. In lymphocytes, a nuance is that multiple chemokine/chemokine receptor pairs might act in a coordinated fashion to develop a precise intracellular signal, tantamount to dictating the precise location of leukocyte stopping [1].

The goal of our work has been to use computer simulation to relate the precise molecular signature of both the leukocyte and the endothelium surface to the dynamics of cell stopping. The simulation methodology, Adhesive Dynamics, was developed in the Hammer laboratory, and has been previously used to simulate leukocyte rolling and stopping [2], and cell detachment from surfaces [3]. In all AD algorithms, the motion of the cell is determined from a balance of molecular adhesion and hydrodynamic forces. Each adhesion molecule is modelled individually, and the force that an adhesive bond exerts on the cell is a result of its location, strain, and mechanical stiffness. AD is also a probabilistic method, in which the formation and breakage of bonds is calculated by Monte Carlo sampling of probabilities for bond kinetics, which depend on the forces and strains (for breakage) and separation distance (for formation).

In the problem at hand, we have made two significant advances to AD. First, because there are several different molecular systems acting simultaneously (selectins, integrins, and chemokine), all of these molecular systems have been added to the method. Second, because the activation of integrins acts through an internal signalling network, we have explicitly added that molecular network inside of the cell. Using a spatio-temporal stochastic signaling network, we have modelled how chemokine ligation leads to G-protein signalling, to then activation of the intracellular intermediary (such as RAP-L), and finally to the conformational change of the integrin receptor. Because mechanical strengthening follows from integrin conformational change, this embedded signalling network allows us to calculate how signalling leads to changes in adhesion strength and thus the time for leukocyte stopping as a function of adhesion receptor density, chemokine receptor density, and hydrodynamic flow rates.

Using this method, which we refer to as Integrated Adhesive Dynamics, we can calculate the time for neutrophil stopping in controlled experiments in which the densities of adhesion molecules and chemokines have been systematically altered. For example, we show how chemokine densities can alter the time scale for stopping from several to hundreds of seconds, in agreement with in vitro experiments [4]. Further, we can predict how pharmacological alteration of G-protein activities can alter the time-scale for adhesion, making clearly testable predictions. Our ongoing work is devoted to calculating how the several chemokines can control the precise location of lymphocyte adhesion through the coordinated integration of intracellular signals.

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