427t Multiscale Modeling of Neutrophil Rolling over a Selectin-Coated Surface

Parag Pawar, Sameer Jadhav, Charles Eggleton, and Konstantinos Konstantopoulos

During inflammation, leukocytes first tether and roll on vessel walls where they become activated, due to exposure to locally produced chemokines before they firmly adhere and ultimately extravasate. These distinct types of adhesive events are mediated by highly specific receptors. The selectin family, comprising P-, E-, and L-selectin, is primarily responsible for the tethering and rolling of leukocytes on inflamed endothelium under shear stress. Even though the fast kinetics and high tensile strength of selectin-ligand bonds are primarily responsible for leukocyte rolling, experimental evidence suggests that cellular properties such as cell deformability and microvillus elasticity actively modulate leukocyte rolling behavior.

Both *in vivo* and *in vitro* studies have documented the shear threshold phenomenon in which the number of rolling leukocytes first increases and then decreases while monotonically increasing wall shear stress. There are two major theories for the shear threshold phenomenon. A receptor-ligand binding model proposed by Dembo et al. predicts the occurrence of adhesive links - termed 'catch' bonds - whose lifetime is actually prolonged by the applied force. The other theory is that shear rate can lead to an increase in bond formation rate, presumably because of increase in cell deformation with increasing shear rate, which in turn would result in increased contact area between the cell and the selectin-expressing endothelium. We wished to study the relative roles played by the receptor physical chemistry (catch bond behavior) and cellular features (such as cell deformation) in supporting the shear threshold phenomenon.

We used a three-dimensional computational model based on the Immersed Boundary Method to predict receptor-mediated rolling of deformable neutrophils in shear flow coupled to a Monte Carlo method simulating the stochastic receptor-ligand interactions. Neutrophil rolling was simulated over P-selectin coated surfaces (selectin site densities of either 15 or 45 molecules/μm^2) for shear rates between 10 s^{-1} and 200 s^{-1}. The length to height ratio, which is a measure of cell deformation, increased with increasing shear rate for both selectin site densities studied. Along these lines, the contact area between the cell and the P-selectin coated surface also increased with increasing shear rate. The average cell-rolling velocity was constant below 50 s^{-1}, beyond which it showed a marked increase - an observation that could presumably be attributed to the shear threshold phenomenon. The average bond lifetime increased with increasing shear rate, reached a maximum, and then decreased upon further increase in shear rate. The average number of selectin-ligand bonds formed during cell rolling also showed a similar trend.

The results indicate that cell deformation affects the kinetics of receptor-ligand interactions, number of bonds formed, the average bond lifetimes, and may play a key role in the shear threshold phenomenon.