Cell Adhesion in Microcirculation

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It has been found that both circulating blood cells and tumor cells are more easily adherent to curved microvessels than straight ones. In this study, the hypothesis that tumor cells prefer to adhere at the microvessels with localized shear stresses and their gradients, such as in the curved microvessels, was examined both experimentally and computationally. The fluid dynamics was carried out by the lattice Boltzmann method (LBM), and the cell dynamics was governed by the Newton's law of translation and rotation. The adhesive dynamics model is involved the effect of receptor-ligand bonds between circulating cells and endothelial cells (ECs). It was found that the wall shear stress/gradient, over a threshold, had significant contribution to tumor cell adhesion by activating or inactivating cell adhesion molecules. Our results elucidated why the tumor cell adhesion prefers to occur at the positive curvature of curved microvessels with very low Reynolds number (in the order of 10^{-2}) laminar flow.

The flow field is simulated by the lattice Boltzmann method. The adhesive dynamics model is integrated to account for the effect of stochastic receptor-ligand bonds. The interactions between receptors and ligands are realized via the compression or expansion of the ideal adhesive springs, whose kinetic expressions relate the bond association and dissociation rates. Generally, the normal bond association rate $k_f{}^n$ = 84 s^{-1} is a reasonable value that can properly recreate experimental values for velocity and dynamics of rolling in the straight vessels (Chang et al. 2000), and the normal bond dissociation rate $k_r{}^n$ in the straight vessels is force dependent based on the Bell's model (1978), $k_r{}^n = k_r^0 \exp\left(\frac{\gamma f}{k_b T}\right)$, where k_b is the Boltzmann constant, T is the temperature, k_r^0 is the unstressed dissociation rate, γ is the reactive compliance, and f is the spring force of each bond calculated from the Hooke's law: $f = \sigma(\chi - \lambda)$, where σ is the spring constant, χ is the distance between receptor and ligand, and λ is the equilibrium bond length.

We modify the Bell's model and take into account the effect of wall shear stress on bond association/dissociation rates as follows (Yan et al. 2010, 2012):

$$k_f = {k_f}^n \cdot \left(\frac{\tau}{\tau_0}\right)^{k_1} \quad , \qquad k_r = {k_r}^n \cdot \left(\frac{\tau}{\tau_0}\right)^{k_2} \tag{1}$$

and the effect of wall shear stress gradient on bond association/dissociation rates as follows:

$$k_f = {k_f}^n \cdot \exp\left(k_3 \cdot \frac{d\tau}{dl}\right) \quad , \qquad k_r = {k_r}^n \cdot \exp\left(k_4 \cdot \frac{d\tau}{dl}\right) \tag{2}$$

where τ and τ_0 are the wall shear stress along the curved vessel and along the straight part of a curved vessel, and $d\tau/dl$ is the wall shear stress gradient along the curved vessel. k_1, k_2 and k_3, k_4 are coefficients that represent the sensitivity of wall shear stress and its gradient to bond asso-/dissociation rates, respectively. In the current simulations, we assume k_1, k_2 and k_3, k_4 to be 1.0, -5.0 and 1.0 μm/Pa, -50.0 μm/Pa, respectively, to match the experimental observations.

Under real physiological conditions, the wall shear stress gradient jump or drop, over certain threshold, is a stimulus for triggering the change in the association/dissociation rates of binding. Once triggered, these rates will stay the same values until the next jump or drop occurs. Fig. 1 shows the comparison of cell trajectory between experiment *in vivo* and simulation, and they are consistent very well.

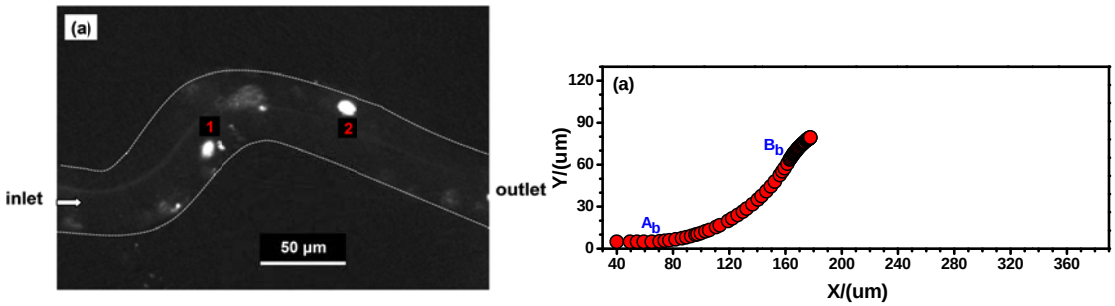

Fig. 2 Comparison of cell adhesion between experiment and simulation

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