451d Biophysical and Biochemical Characterization of Selectin-Ligand Interactions Pertinent to Metastasis

Susan L. Napier, William D. Hanley, and Konstantinos Konstantopoulos

Hematogenous metastasis is governed by a succession of cell-cell communications amidst a myriad of physiological and competitive stresses regulating the kinetics of each specific receptor-ligand pair binding. This process is governed first by the shear enhanced interactions with selectins via unknown counter-receptors which mediate cell tethering to blood platelets, leukocytes and the vascular endothelium. Our studies show that variant isoforms of CD44 (CD44v) on LS174T colon carcinoma cells possess P-, L- and E-selectin binding activity. Moreover, the selectin binding determinants on CD44v from LS174T cells are sialofucosylated structures displayed on O-linked glycans, akin to those on P-selectin glycoprotein ligand-1. The biophysical properties of selectin/carcinoma ligand binding were characterized using a cell-free flow-based adhesion assay comparing shear-dependent CD44v vs. CD44s adhesion to E-, P- and L-selectin. Furthermore, these findings were compared with the kinetic parameters of whole LS174T carcinoma cell binding to P- and L-selectin at a single molecule level. Based on these unique kinetic properties, quantitative models are employed to direct the development of carcinoma-targeted microparticles. In vitro studies to test the efficacy of the microparticle system will be performed through the use of cone-and-plate rheometry in shearing a mélange of carcinoma cells, whole blood, and microparticles. This scheme will be extended to in vivo studies in mice testing the effectiveness of the metastatic targeting particles.