578d Albumin-Derived Nanocarriers for the Display of Extracellular Matrix Ligands & Engineering Cell Adhesion and Motility

Ram I. Sharma, Marian Pereira, Jean E. Schwarzbauer, and Prabhas V. Moghe

The extracellular matrix provides cues for cell migration, adhesion, and differentiation. Cells can actively adhere to certain configurations of matrix ligands and remodel them, as part of a series of events altering cell spreading and migration. Ligand display configurations that can systematically elicit such engineered cell behaviors are not well understood. We have developed a dynamic biointerfacial model system comprised of albumin nanoscale carriers that are functionalized with recombinant fragments of fibronectin. Such carriers allow nanoscale presentation of ligand fragments but also permit active remodeling and internalization of ligands. The nanoscale carriers were fabricated from human serum albumin through controlled self-assembly during aggregation in low pH solutions. The albumin nanocarriers were synthesized to controlled sizes (30-100 nm in diameter), confirmed via dynamic light scattering and atomic force microscopy. The carriers were functionalized with truncated fragments of fibronectin that encompass the cell binding domain using standard amino-displacement chemistry. In comparison to ligand that was presented on non-tissue culture substrates, cell migration and binding was enhanced on substrates where the ligand is presented on the nanocarrier. We hypothesize that enhanced integrin-ligand binding due to cell binding domain exposure results in high levels of cell migration on substrates with ligand-conjugated nanocarriers. Investigating cell binding domain exposure by immunosorbance assays as a function of ligand presentation indicated an increase in exposure when the ligand is presented on the nanocarrier. The altered ligand conformations that result in increased exposure of cell binding domains may be caused by repulsion between the albumin derived nanocarrier and the ligand. Atomic force microscopy was used to generate force curves between a monolayer of nanocarriers and a silicon nitride cantilever is functionalized with the recombinant fragment. Quantitation of the force curves indicated that the force generated between the nanocarrier and recombinant fragment is 3.5 times larger than the force between the bare cantilever and the nanocarrier monolayer. Overall, our findings indicate that epithelial cell behaviour in response to extracellular matrix proteins can be regulated by ligand nanodisplay, suggesting that physical design strategies are critical in engineering materials that promote cell adhesion, ligand remodeling, and cell motility.