

EXTRACELLULAR AND INTRACELLULAR PHENOMENA IN MICROFLUIDIC FLOW

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Adhesion-based microfluidic cell separation techniques have been utilized for a wide range of applications, from cancer diagnostics to tissue engineering. This separation approach typically involves the functionalization of a microfluidic channel with molecules that bind to one or more cell types and the capture of cells from a flowing stream. A major advantage of the adhesion-based separation approach, particularly from the standpoint of clinical applications, is label-free operation. Traditional cell separation approaches, such as fluorescence- and magnet-activated cell sorting (FACS and MACS), by contrast, require pre-processing through labeling of sample cell suspensions with fluorescent or magnetic tags. The efficacy of adhesion-based microfluidic cell separation is governed by two factors: the affinity of cells to the ligands utilized for capture (typically antibodies or peptides) and the magnitude of fluid shear forces. The design of adhesion-based microfluidic cell separation systems is generally carried out with the implicit assumption that cells are quiescent during the separation process. In other words, it is assumed that no changes occur within the cells that would substantially affect affinity (due to receptor up/down-regulation, for example). While this assumption probably applies to the majority of applications where adhesion-based microfluidic separation has been utilized, not enough is known about how such changes might occur, particularly with respect to sensitive cells such as stem/progenitor cells and cells known to respond to shear forces.

It is proposed that these factors (shear forces) play a role in how cells adhere in microchannels and that understanding these factors will improve how cells are isolated in

microchannels. This research will directly impact the effective use of microfluidic cell separation systems for applications in tissue engineering and stem cell isolation. This proposal shows the steps that will be taken to gain an understanding of receptor-ligand interactions in microfluidic flow.

The experiments thus far have involved utilizing ligand-coated microfluidic channels of constant shear stress for adhesion studies in which cells of a selected type were incubated with known concentrations of ligand in order to block selected numbers of surface receptors. The results from this study suggest that cells respond to shear stress and chemical ligands in a synergistic manner. This synergistic effect is thought to be as result of intracellular messages being transmitted once the cells have been stimulated. Studies have also been done to determine the effect of receptor clustering when cells are under flow. These studies were performed by varying the spatial arrangement of the ligands on the microchannel surface and determining the degree of cell adhesion for selected cell types. The results from these studies suggest that receptor clustering affects how cells adhere. When the spatial arrangement of the ligand varies cells encounter with the ligand minimizes hence decreased cell adhesion.

Despite the progress thus far there are still some key things that still require completion. More studies will be performed to understand how cell's intracellular cues are linked to the extracellular stimuli that they experience. The long-term goal of this project is to 'Fingerprint' known cell types on the basis of receptor response to ligands and fluid shear stress and demonstrate 'fingerprint'-based identification of an unknown cell type. The preliminary results in this proposal have suggested that this goal has promise.