

Research Highlights

DOI: 10.1039/b911510m

Influence of substrate stiffness on cell adhesion

Cell processes such as cell growth, migration or morphogenesis are strongly influenced by the cell microenvironment, which is not only defined by the chemical composition, but also by mechanical properties such as the rigidity. Variations in rigidity have been observed, for example, in different kinds of healthy and diseased tissue in brain, bone, heart and cartilage. Hence, to recreate a heterogeneous three-dimensional extracellular matrix (ECM) as close to nature as possible, microscale variations of the ECM have to be considered. In a recent work, Samuel Sia and co-workers from Columbia University in New York developed a process that allows for microscale stiffness control in a cell-adhesive substrate.¹ Based on their former work on the fabrication of three-dimensional gels using microfluidics-based photolithography, the researchers could create stiffness differences by variations in the prepolymer solutions. In more detail, different concentrations of polyethylene glycol diacrylate (PEGDA) oligomer were added to a constant amount of PEG monoacrylate-linked bovine fibrinogen (Fig. 1). The oligomer can be crosslinked to the free thiol groups present in PEG-fibrinogen upon exposure to UV light. In several cycles, the prepolymer solution is drawn into a microfluidic channel and photo-crosslinked into hydrogel blocks. The created surfaces have varying stiffnesses with Young's modulus ranging from 0.7 to 50 kPa as confirmed by atomic force microscopy measurements. To study how the stiffness affects cells, the researchers created surfaces with a discrete stiffness gradient and studied cell growth, cytoskeleton organisation and migration of human foreskin fibroblasts (HFFs) on these surfaces. The findings suggest that the cells respond to the patterned stiffness, *e.g.* the cells migrate to regions with high stiffness. Based on these experiments, further studies on the interaction between cells and ECM are now possible and may help

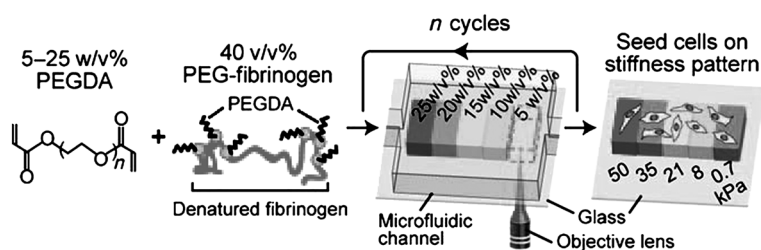


Fig. 1 Generation of surfaces with a discrete stiffness gradient to investigate cell adhesion. Experimental setup for microfluidic-based patterning of stiffness gradients. The prepolymer PEGDA is added to PEG-fibrinogen and supplied into a microchannel. During several cycles, the prepolymer solution is photo-crosslinked into hydrogel blocks of different stiffness. After removal of the microchannel, cell seeding studies are performed. (Reprinted with permission from ref. 1. Copyright 2009, Wiley-VCH).

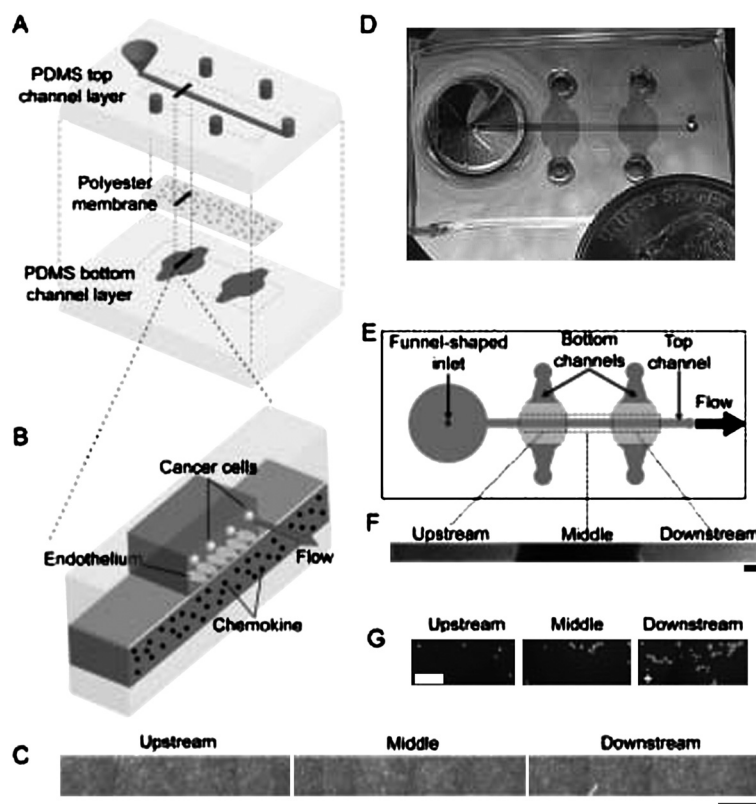


Fig. 2 Microfluidic vasculature system to study cancer cell adhesion on endothelium, a critical step in metastasis. (A) Sketch of the microdevice, showing the porous membrane that is sandwiched between two polydimethylsiloxane (PDMS) layers. (B) Cancer cells are flowing above a confluent layer of endothelial cells (images shown in (C)) that are stimulated by chemokines from the channel underneath. (D) Photograph and (E) sketch of the device from the top view. Cells cultivated in the top layer can be stimulated at the intersections with the bottom layers (F and G). (Reprinted from Song *et al.*²)

to understand the role of stiffness for cell adherence, spreading, migration and differentiation.

Microfluidic vasculature system to study intravascular cell adhesion

Transport of cells through the vasculature system and adhesion of cells on vascular endothelium at specific locations are part of immune surveillance and inflammation. Furthermore, it plays a critical role in metastatic cancer. Therefore, it is of special interest to understand the interactions of circulating cells with endothelium, and to identify molecules that are involved in arresting of circulating cells. In a recent publication, researchers from the University of Michigan describe a microfluidic system to study the parameters that influence adhesion of metastatic breast cancer cells on endothelium.² They engineered a model vasculature system, in which endothelium can be stimulated by chemokines in a spatially-restricted manner. Hence, it simulates the localised presence and polarisation of chemokines

in the human organism. To achieve this, the microdevice is comprised of two polydimethylsiloxane (PDMS) layers sandwiching a thin, porous and transparent polyester membrane (Fig. 2). On top of the membrane, a confluent monolayer of human dermal microvascular endothelial cells is cultured. Underneath, at certain positions, channels intersect with the top layer. Chemokines are transported through the channels to the intersections to activate the endothelium from the basal side, while breast cancer cells are flowing in the top channel. The chemokine (CXCL12) used in the investigation is known to be expressed in high levels in cells of organs that are commonly affected by breast cancer, such as liver, bone and brain. Indeed, at the location where the chemokine is supplied, adhesion of breast cancer cells is increased. Furthermore, the researchers investigated which receptor in the cancer cells could be involved in the cell adhesion. They used two types of cells expressing two different CXCL12-receptors and found increased adhesion for both types, suggesting a non-selective binding of cancer cells on endo-

thelium. On the other hand, prevention of adhesion was demonstrated by inhibiting specific receptors on the endothelium. These findings demonstrate that endothelium cells rather than the circulating cancer cells could be promising therapeutic targets in order to prevent metastasis. Probably the use of the microfluidic vasculature system could also help to find new therapies to block the initial cell adhesion in metastasis.

Petra S. Dittrich
ETH Zurich
dittrich@org.chem.ethz.ch

References

- 1 Y. K. Cheung, E. U. Azeloglu, D. A. Shiovitz, K. D. Costa, D. Seliktar and S. K. Sia, Microscale Control of Stiffness in a Cell-Adhesive Substrate Using Microfluidics-Based Lithography, *Angew. Chem. Int. Ed.*, 2009, **48**, DOI: 10.1002/anie.200900807.
- 2 J. W. Song, S. P. Cavnar, A. C. Walker, K. E. Luker, M. Gupta, Y.-C. Tung, G. D. Luker and S. Takayama, Microfluidic Endothelium for Studying the Intravascular Adhesion of Metastatic Breast Cancer Cells, *PLoS One*, 2009, **4**, e5756.