Design and Fabrication of a Microfluidic Device to Study Tumor Cell Mechanics During Metastasis

Michael Homsy
Chemical Engineering, The Ohio State University

NNIN REU Site: Penn State Nanofabrication Laboratory, The Pennsylvania State University, University Park, PA
NNIN REU Principal Investigator: Dr. Siyang Zheng, Department of Biomedical Engineering, The Pennsylvania State University
NNIN REU Mentor: Yiqiu Xia, Department of Biomedical Engineering, The Pennsylvania State University
Contact: homsy.3@osu.edu, siyang@psu.edu, yzx114@psu.edu

Abstract and Introduction:

The majority of cancer-related deaths do not result from the primary tumor, but rather, secondary tumors formed via metastasis [1]. During metastasis, a tumor cell migrates to distant organs or tissues through narrow gaps that are smaller than the size of the cell, such as pores in dense extracellular matrix networks. The characteristic mechanical properties of tumor cells that facilitate their movement through these paths are not well understood [2]. In addition, conventional methods of studying cell mechanics, such as micropipette aspiration, require specialized equipment and training [3]. On the other hand, microfluidics is an accessible alternative that is capable of simulating the *in vivo* environment of a metastasizing tumor cell [1].

To effectively explore the role of tumor cell mechanics during metastasis, a multilayer polydimethylsiloxane (PDMS) microfluidic device was designed and fabricated using soft lithography to contain narrow paths that mimic the small gaps through which tumor cells metastasize. Specifically, the device consisted of multiple arrays of microgaps where tumor cell behavior was observed under a microscope. Furthermore, a valve feature was incorporated in the design in order to direct the flow through one channel at a time [4]. Using human breast cancer cell line MDA-MB-231, initial experiments demonstrated that our simple device is capable of conducting intricate tumor cell experiments with the purpose of developing a more complex model of the tumor cell.

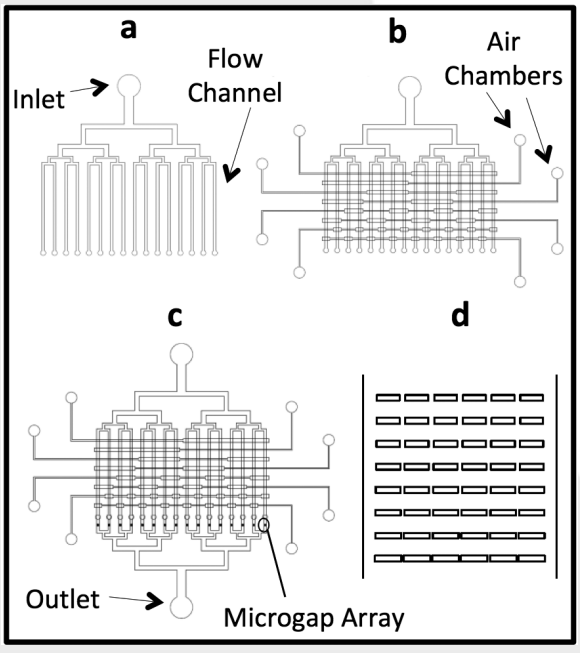

Figure 1: Design of device. (a) The first component. (b) The valve component positioned above flow channels. (c) All components. (d) Microgap array.

Methods:

The device was designed to have three components, as shown in Figure 1. The first component contained the inlet and flow channels. The second component functioned as a valve to open or shut particular flow channels. This valve component consisted of multiple air chambers and control channels that were positioned above and perpendicular to the flow channels. The third component contained the outlet and arrays of microgaps of widths varying from 5 to 10 μm. In addition, only one microgap array could be observed under a microscope. Therefore, the valve component served to direct the flow of tumor cells through one microgap array at a time. Eventually, a microgap array became clogged with cells, and the valve component was used to switch the flow to a different microgap array, allowing multiple experiments to be performed on the same device.

In order to fabricate the device, a silicon wafer was first patterned with the outlet and microgap arrays using SU-8 photoresist. Next, AZ 4620 photoresist was used to pattern the inlet and flow channels, and the wafer was baked to produce flow channels with a rounded profile. Another silicon wafer was patterned with the valve component using SU-8. Finally, PDMS was molded over each wafer, and the two molds were bonded to each other and to a glass slide.

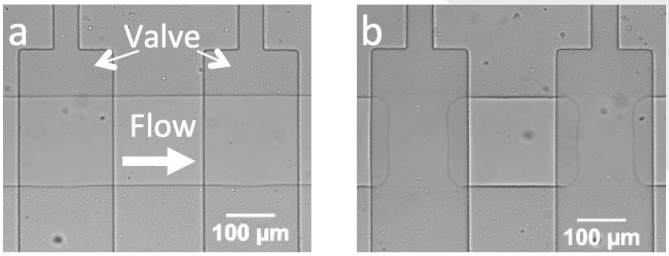

Figure 2: Valve channels (vertical) and a flow channel (horizontal). (a) Before air pressure is applied through the air chambers of the valve channels. (b) After air pressure is applied.

Results and Conclusions:

The valve component was successful in enabling and preventing flow through flow channels. Figure 2 illustrates the valve mechanism. When external air pressure was applied in air chambers, the control channels were triggered to push down and compress the flow channels below. Using a specific combination of air chambers permitted flow only through the desired flow channel.

MDA-MB-231 cells were cultured and then suspended in phosphate buffered saline (PBS). A syringe pump was used to inject the cells in suspension into the inlet at a flow rate of 1 mL per hour. Using our device, we observed tumor cell behavior at arrays of microgaps, which simulate the narrow gaps that tumor cells squeeze through during metastasis.

We observed that the extent of tumor cell deformation and success in passage through a microgap array depended on microgap width. In Figure 3, a tumor cell advanced through the first microgap with a width of 5.0 μm, but was trapped by a slightly narrower microgap with a width of 4.8 μm despite extreme deformation of the cell. Another tumor cell, in Figure 4, immediately advanced through the first microgap with a width of 6.1 μm, but took 26 seconds to pass through the next microgap with a width of 5.6 μm. These preliminary experiments indicate that our device can be used to conduct experiments to examine relationships between different factors, such as cell line and flowrate, and tumor cell behavior. In addition, different versions of the device could be designed to have altered microgap shapes and lengths. By using this device to gather data on tumor cell mechanics during metastasis, we can eventually develop a more complex model of the metastasizing tumor cell.

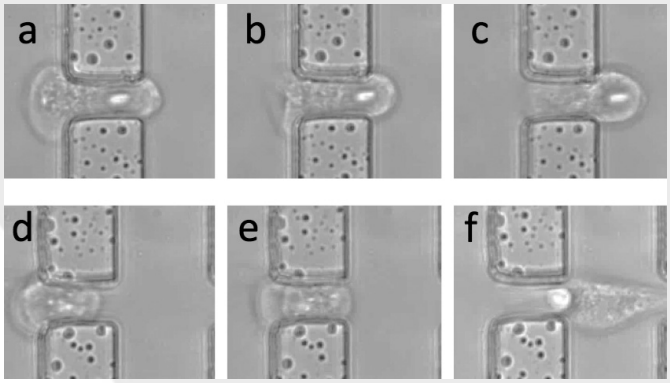

Figure 3: (a) (b) (c) A tumor cell passed through the first microgap (5.0 µm) in 18 seconds. (d) (e) (f) The same tumor cell was unable to pass through a second microgap (4.8 µm).

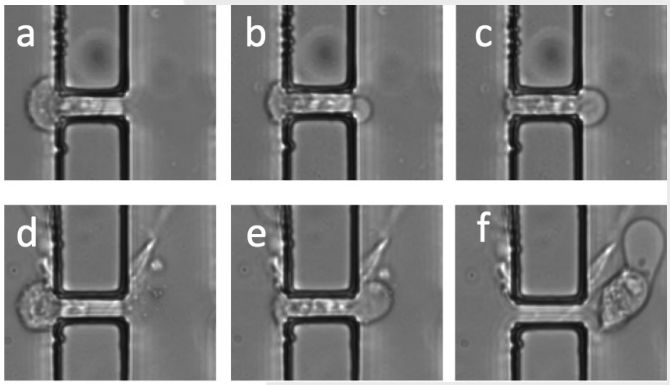

Figure 4, below: (a) (b) (c) A tumor cell passed through the first microgap (6.1 µm) in 1 second. (d) (e) (f) The same tumor cell successfully passed through a second microgap (5.6 µm) in 26 seconds.

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