Abstract:
The physical pressures and limitations associated with metastasis, the process through which cancer cells leave a primary tumor and disseminate through the blood flow, are not well understood. We have designed microstructured device which allow us to study the motion of cancer cells inside one-dimensional, blood vessel-like constrictions. We observe that the motion of a cancer cells inside 10 µm wide channels is enhanced compared to their motion on a planar surface. We find that cells migrate at a constant speed, and their unidirectional motion persists over several hours.

Research Summary:
It is known that cancer cells will use a wide variety of strategies to reach, and travel within, a blood vessel [1,2]. However, very little is known about what triggers a cell to leave the vasculature to extravasate inside a tissue. Several physical factors may influence the motion of cancer cells as they migrate within the body. For example, the cross-sectional area of a constriction have been shown to play an important role in the migration properties of certain types of cancer [4]. Here, we wish to physically recreate the forces imposed on a cancer cell as it travels through blood vessels and micro-capillaries by constraining them inside linear channels.

It has already been shown that normal epithelial cells perform a bimodal correlated random walk on a 2D planar surface [3]. The behavior of cancer cells in a capillary-like constriction, however, may be very different. By effectively limiting the motion of the cells to one dimension, we hope to be able to study in details the metastatic processes leading to cancer invasion.

We use standard photolithography and deep silicon etching techniques to fabricate a device consisting of 20 µm deep linear channels. The channels are deep enough to maintain the cells in them; i.e., once inside, they are not able to crawl out of them. We also make sure that the cells will attach only to the inside of the channels by selectively coating them with fibronectin, a ECM component which greatly enhances cell adhesion (Figure 1). We use a device in which chambers are separated by an array of several channels (Figure 2); that way, the constrained motion of cells can be compared to that on a 2D planar surface.
We use a highly metastatic type of prostate cancer cell (PC3) and monitor their behavior inside the linear constrictions. We initially inoculate cells near one end of the channels. Since all the cells are starting from the same physical location, cells entering the channels are free to move unhindered for several millimeters. The device is placed inside a custom-made microscope stage incubator which maintains a constant atmosphere of 5% CO2 and a temperature of 37°C. We monitor the cells’ motion by recording a digital micrograph every 2 minutes. Further image processing is used to extract the exact position of each cell.

Surprisingly, as the cells enter the channels, their motion is highly persistent. Most of the cells maintain their speed and direction for very long periods of time. For example, of the 21 cells observed in a device, 16 of them maintain a constant speed of ~ 150 microns per hour for more than 2 hours (Figure 4). Some of them even migrate several hundred microns over a 6 hours period, always keeping their speed constant. By contrast, during the same time, the cells on the 2D planar surface did not travel a distance greater than 50 µm.

These observations indicate that cells constrained to one dimension are much more motile than in a 2D or 3D microenvironment. Physiologically, these results indicate that the highly metastatic PC3 prostate cancer cell line is more apt to invade a tissue when it travels through a one dimensional constriction.

**References:**


