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Understanding Metastatic Growth through the Traction Force of Human Breast Cancer Cells

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Introduction

Cancer is a hard disease to control because of its ability to spread to different parts of the body. Cancer cells can spread out from a primary tumor to distant organs which gives rise to new cancer cell colonies and more tumors over time. This process is known as metastasis and causes over 90% of human cancer deaths.

Cell traction force (CTF) coordinates many cellular functions such as cell migration. Cell migration plays a critical role in the spread of cancer. Therefore, CTF plays a significant role the the biological process of metastasis.

The goal of this experiment is to simultaneously measure the deformation field around the cells and cellular responses between two different substrate rigidities. Past experiments have been mostly done with different substrate rigidities separately. However, it is more realistic to measure cellular contractility with two different substrate rigidities simultaneously. These conditions better reflect physiological conditions because there are varying rigidities within the human body.

Methods

Collagen type I from rat tail was used to make a two-layer collagen sample with different concentrations. The bottom layer of the collagen sample had a higher concentration than the top layer. Fluorescently labeled particles were added to both the top and bottom layers. Human breast cancer cells (MDA-MB-231) were placed in between the top and bottom layers.

Cytochalasin-D was added to the sample to release cellular traction force. Fluorescent images of particles and reflection images of collagen fibers and cells were captured using confocal microscopy before and after the addition of cytochalasin-D. Fluorescently labeled particle images were analyzed with a particle image velocimetry (PIV) algorithm.

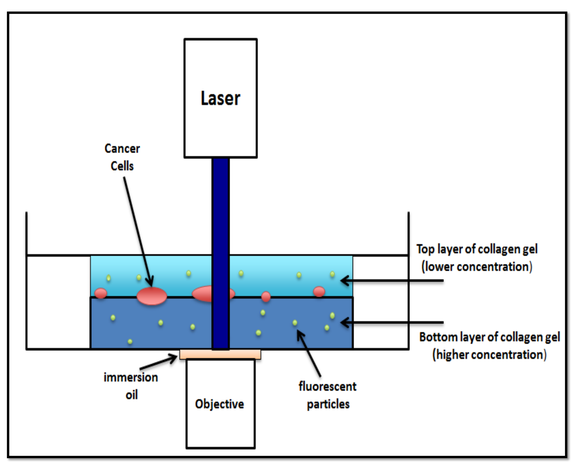

Fig. 1 Schematic diagram of the experimental set-up. The collagen sample is created in a glass bottom dish. Fluorescence and confocal microscopy is then used to image the sample.

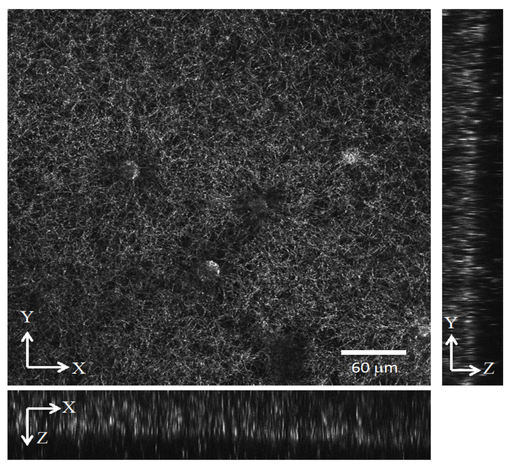

Fig. 2 This reflection image shows a planar view of the sample at the boundary between the top and bottom layer and a cross sectional view of the entire sample.

Results

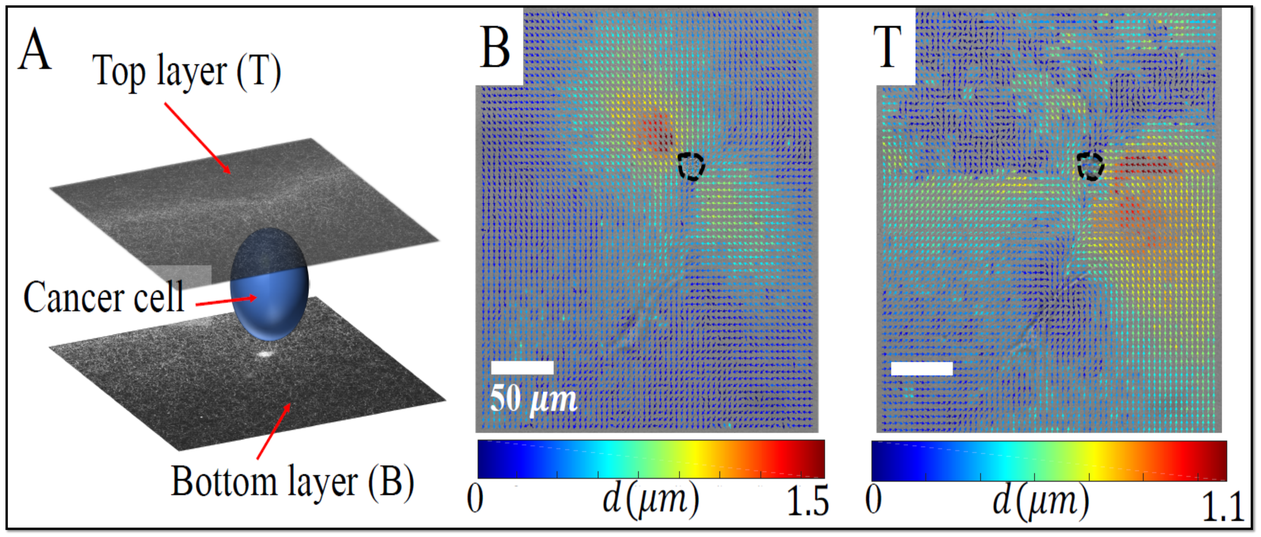

Fig. 4 (A) Illustration of confocal reflection image planes. (B) Deformation field of the bottom layer plotted using color coded arrows. The color represents the magnitude and the arrows represent the direction of the deformation. (T) Deformation field of the top layer. The black dashed line represents the membrane of the cancer cell.

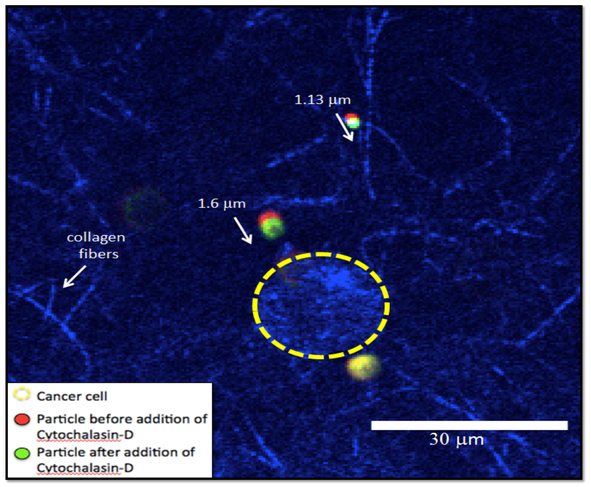

Fig. 3 Demonstration of PIV analysis. By comparing the positions of the particles before and after treatment with cytochalasin-D, deformation can be calculated.

The bottom layer is more rigid because it has a higher collagen density than the top layer. For that reason, we expected that there would have been less deformation in the bottom layer because we thought that cells applied traction force with equal magnitude. However, the results show that larger deformation occurred in the bottom layer compared to the top layer. This demonstrates that cells can sense different rigidities and apply more traction force in stiffer regions. Our results also show that the bottom layer has a more localized deformation field compared to the top layer due to its stiffness.

Discussion

In this experiment, we only measured the deformation field around the cells. In the future, we will measure the density of actin fibers and myosin activity to study cellular responses at the molecular level. Using this technique, we will also be able to measure the distance and direction of migration of cancer cells to study long-term cellular responses.

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