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A Mechanically Tunable Microfluidic Cell-Trapping Device

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Abstract

Controlled manipulation, such as isolation, positioning and trapping of cells, is important in basic biological research and clinical diagnostics. Micro/nanotechnologies have been enabling more effective and efficient cell trapping than possible with conventional platforms. Currently available micro/nanoscale methods for cell trapping, however, still lack flexibility in precisely controlling the number of trapped cells. We exploited the large compliance of elastomers to create an array of cell-trapping microstructures, whose dimensions can be mechanically modulated by inducing uniformly distributed strain via application of external force on the chip. The device consists of two elastomer polydimethylsiloxane (PDMS) sheets, one of which bears dam-like, cup-shaped geometries to physically capture cells. The mechanical modulation is used to tune the characteristics of cell trapping to capture a predetermined number of cells, from single cells to multiple cells. Thus, enhanced utility and flexibility for practical applications can be attained, as demonstrated by tunable trapping of MCF-7 cells, a human breast cancer cell line.

Keywords

Cell Trapping; Cell Array; Elastomeric Polymer; Mechanical Modulation; Microfluidics; Tunability

1. Introduction

Cell manipulation, such as separation, isolation, positioning, trapping and sorting of cells, has important applications in basic biological research and clinical diagnostics. For example, in order to study the effect of anticancer drugs, cell groups with multiple cells are needed for testing multicellular resistance [1]. However, the analysis of a large population of cells obscures the heterogeneous information within cell groups, such as the large genetic

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variation between individual cells [2, 3]. Therefore, in addition to multicellular analysis, investigations on single cell or a small number of cells are necessary. For instance, in order to study the phenotypic heterogeneity driven by cell cycle, cell aging, and epigenetic regulation, single cells must be isolated and identified [4]. Furthermore, in the study of cell-cell contact, such as the communication through junctional proteins [5] and membrane-receptor to membrane-ligand interactions [6], or cell fusion that enables the study of nuclear reprogramming [7], pairing of two cells, either the same type or different types, is required. As a result, target cells have to be trapped in particular positions without any mechanical or biochemical damage, and the number of cells trapped should be able to be adjusted according to the application.

Microfluidic technologies have been developing to allow more effective and efficient cell trapping and cell positioning, offering numerous advantages not possible with conventional platforms [8, 9]. Microfluidic cell trapping that employs either physical barriers, such as microwells [10, 11], microcups [7, 12] and cell-based valves [13, 14], or molecular interactions, such as micropatterning surfaces with polymers [15] or ligands [16], is easy to handle, does not require complicated fabrication procedures, and can realize high-throughput operation. With different dimensions of microwells [11] or microcups [12], or variant diameters of patterned spots [17], cell trapping with different numbers of cells can be achieved. For example, by utilizing weir-like capture cups with different depths, cell trapping with different numbers of cells in each trap have been reported [12]. However, once the design and fabrication of the device have been completed, it is no longer possible to alter the characteristics of the cell traps. Thus, these methods lack flexibility in precisely controlling the number of trapped cells, while cell arrays of single, two and multiple cells are all needed in cell biology applications [7, 18, 19]. On the other hand, cell trapping methods such as optical trapping [20], acoustic trapping [21], dielectrophoretic trapping [22], dynamically controlled hydrodynamic trapping [23], and their combination [24], which employ different kinds of external force during the experiment to separate and restrict cells in particular locations, allow dynamic and precise control over the number of cells trapped. However, the application of these methods is also limited by either sophisticated operation systems or complicated microfabrication processes.

These limitations can potentially be addressed by utilizing physical barrier based cell trapping techniques and employing elastomeric polymers, whose large deformability could provide flexibility and controllability in cell manipulation. In relevant work, large compliance of polymers has been used in micro- and nanofluidic applications. For example, deformable elastomeric microdevices have been used in the gating and regulation of fluids in microflow control, in which a thin compliant flap was used to alter the flow resistance by varying the applied pressure [25]. A nanofluidic system has also been designed and fabricated using oxidized polydimethylsiloxane (PDMS), in which transport characteristics were dynamically manipulated by the modulation of channel dimensions [26]. In addition, a pneumatically controlled elastomeric microstructure has been reported for patterning and manipulation of a large number of cells at the macro scale [27]. These demonstrate the feasibility of using polymers to achieve flexible and precise control in micro-/nanofluidic applications.

This paper presents a tunable cell trapping microchip that utilizes the large deformability of elastomeric polymers to precisely control the number of cells captured at the single and individual cell level. The device consists of two thin sheets of the elastomer PDMS, one of which bears microstructures to physically capture cells [28]. The microstructures each feature a dam-like, cup-shaped geometry (called a capture cup) with supporting pillars on both sides. We for the first time exploit the large compliance of elastomers to create an array of cell-trapping microstructures, whose dimensions can be mechanically modulated by inducing uniformly distributed strain via the application of an external force on the chip. The mechanical modulation is used to tune the characteristics of cell trapping to capture a predetermined number of cells, from single cells to multiple cells. The microchip is applied to MCF-7 cells to verify the significant influence of microstructure deformation on the number of cells trapped, and thus demonstrate the effectiveness of using physical modulation to enable nondestructive and flexible cell manipulation, which can potentially be used in cell biology research and clinical diagnostics.

2. Experimental

2.1. Design and Fabrication

The tunable cell trapping microchip consists of two thin sheets of elastomer PDMS, one of which bears microstructures to physically capture cells. The microstructures each have a dam-like, cup-shaped geometry (approximately 40 μm in height, henceforth called a capture cup) with supporting pillars (approximately 7 μm in height) on both sides (Fig 1). When a cell approaches a microstructure, the carrier fluid passes over the dam, while the cell is trapped in the capture cup. If one or more cells are trapped in the microstructure, the flow field upstream will immediately change, attaining a higher velocity component in the transverse direction. Therefore, cells moving into this region will gain more significant transverse kinetic energy and may be more likely to flow around the microstructure, rather than being trapped in the capture cup.

The cell trapping characteristics can be tuned through mechanical modulation of microstructures via the application of strain to the chip (Fig 2). The microchip is stretched by mounting it onto a motherboard. This induces uniform uniaxial tensile strain in the cell trapping region, which is situated in a slender bar-shaped portion of the microchip. Using different microchip mounting pin locations, the strain in the cell trapping region can be varied. This mechanical modulation changes the geometry of the microstructures, which will also alter the flow field, thereby allowing the number of cells trapped in each microstructure to be actively tuned according to practical needs.

The tunable cell trapping microchip was fabricated using standard soft lithography techniques. Briefly, the SU-8 (Micro Chem Corp., Newton, MA) mold that defines microfluidic features was first fabricated (Fig 3A). Then two PDMS (Sylgard 184, Dow Corning Inc.) sheets, one bearing the microfluidic structures and the other used as the substrate, were casted (Fig 3B) and punched with the inlet and outlet (Fig 3C). Subsequently, the two PDMS sheets were bonded to each other after oxygen plasma treatment (Fig 3D). Finally, an acrylic motherboard, onto which the fabricated microchip

was mounted, was fabricated with a laser cutter. The assembled device is shown in Fig 4A, and the details of cell trapping microstructures are shown in Fig 4B and C.

2.2. Materials

Chlorotrimethylsilane, and bovine serum albumin (BSA) were obtained from Sigma-Aldrich (St. Louis, MO). 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide (JC-1), MEM media, fetal bovine serum (FBS), penicillin-streptomycin (P/S, penicillin 10,000 unit/mL, streptomycin 10,000 µg/mL), 0.25% Trypsin-EDTA, Dulbecco's phosphate-buffered saline (D-PBS) and Vybrant® multicolor cell-labeling kit (DiI, DiO and DiD) were purchased from Life Technologies (Grand Island, NY). MCF-7 cell line was obtained from the American Type Culture Collection (ATCC, Manassas, VA).

2.3. Experimental Procedure

MCF-7 cells were incubated with the complete culture media, including MEM media supplemented with 10% FBS and 1% P/S, and were kept at 37 °C in a humidified incubator containing 5% CO₂. Before microfluidic experiments, cells were labeled by incubating them with 0.5% (v/v) DiO in the complete culture media for 20 min and then treated in the 3mL of trypsin-EDTA for at least 15 min to be detached from substrate and to prevent the nonspecific adsorption. Next, a triple volume of the complete culture media was added to stop trypsinization. Cells were then collected through centrifugation, resuspended at 1×10^8 cells/mL in complete culture media supplemented with 5 mg/mL BSA, and kept on ice.

Prior to experimentation, the microfluidic channel was incubated with 5 mg/mL BSA in D-PBS for at least half an hour to prevent the unspecific adsorption. Then, the cell suspension was diluted to 1×10^6 cells/mL in D-PBS supplemented with 5 mg/mL BSA, and introduced into the microchip with or without extension at 10 µL/min for 1 min. Afterward, D-PBS was used to rinse the channel at 10 µL/min for 1 min. Finally, a fluorescent image of cell-laden chamber was taken and used to manually count the number of cells in each trap.

3. Results and Discussion

3.1. Microstructure Deformation

The mechanical modulation of microstructures is realized by mounting the microchip onto different locations of a motherboard, initially free of extension (Fig 5A) to a tensile strain of approximately 79% (Fig 5B). According to the extension experiments, along with the increased strains, the trapping cup width decreased from 28.8 ± 0.8 µm to 18 ± 0.6 µm and the cup depth increased from 25.0 ± 0.4 µm to 36.3 ± 0.7 µm (Fig 5C). This deformation will significantly alter the number of cells able to be trapped [12].

To evaluate the uniformity of microstructure deformation, we first test the strain distribution and present results from a COMSOL Multiphysics® (COMSOL, Inc., Los Angeles, CA) numerical simulation using a three-dimensional structural model, consisting of the trapping region. The nonlinear elasticity of the structural material (PDMS) and the large strain involved in the microstructure deformation is considered. PDMS is modeled as an isotropic, incompressible hyperelastic material [25], and the Mooney-Rivlin constitutive law is applied

[29, 30]. A Young's modulus of 387 kPa is used for PDMS, as determined by the 100:7 base-to-curing agent ratio of the prepolymer solution [31]. Our results show a highly uniform strain distribution in the xy -plane throughout the trapping region (Fig 6), indicating a uniform deformation of the microstructure array.

A further numerical analysis shows when the gap between each row of microstructures was elongated from 98 μm (Fig 7A) to 175 μm (Fig 7B), leading to a 79% relative extension along x direction in the trapping region, the cup depth increased from 25 μm (Fig 7A&C) to 37 μm (Fig 7B&D), and the cup width decreased from 28 μm (Fig 7A&C) to 19 μm (Fig 7B&D). These dimension changes are consistent with the results from the experimental analysis.

3.2. Tunable Cell Trapping

To demonstrate tunable cell trapping, a cell suspension of 1×10^6 cells/mL in D-PBS with 5 mg/mL BSA was introduced into the chip (pretreated with 5 mg/mL BSA in D-PBS) at 10 $\mu\text{L}/\text{min}$ for 1 min, after which D-PBS was used to rinse the channel. The 7 μm height gap between two pillars allows a fraction of fluid carrying cells to enter the capture cup. Based on the dimensions of the cell trapping microstructure, once one cell or multiple cells occupy the capture cup, the fraction of fluid passing through the gap significantly reduces, leading to increased transverse velocity and decreased longitudinal velocity. Thus, more of a cell's longitudinal component of kinetic energy will be converted to the transverse component, increasing the tendency for additional cells to flow around the microstructure and therefore preventing them from being trapped. As shown in Fig 8A, without extension, single cell trapping was dominant, whereas multiple cells were captured as a result of an approximately 72% strain applied to the chip (Fig 8B).

Moreover, the results indicate the number of cells trapped strongly depends on the geometrical characteristics of the microstructures (Fig 8C). Without the application of strain, 41% of microstructure trapped single cells and 31% of them captured two cells. However, when the chip was extended by approximately 72%, the fractions of single-cell trap and two-cell trap decreased to 4% and 24%, respectively, and 39% of microstructures trapped three cells. These results show that the distribution of cell capture per cup shifted up from a mode of 1 without extension to a mode of 3 with the application of 72% uniaxial tensile strain.

To evaluate cell viability after trapping, trapped cells were stained by JC-1 (10 $\mu\text{g}/\text{mL}$) at 37 $^{\circ}\text{C}$ for 30 min, and fluorescent images were taken with an inverted epifluorescence microscope (Diaphot 300, Nikon Instruments Inc., NY) with a CCD camera (Model 190CU, Micrometrics, NH). The intensity of red fluorescence caused by the accumulation of JC-1 in healthy mitochondria will decrease during depolarization occurring in the early stage of apoptosis [32, 33]. The trapped cells from both the unextended and extended (72%) device did not exhibit any degradation of red fluorescence (Fig 8D&E), indicating the trapped cells were viable.

These results demonstrate that our approach can potentially allow the formation of a cell array with a predetermined cell number in each cell trap, from single cells to multiple cells.

To explain the observed tunable cell trapping, the flow field before and after extension was analyzed by three-dimensional computational fluidic dynamics (CFD) analysis to explore the characteristic parameters that affect the number of cells trapped using ANSYS Fluent® (ANSYS, Inc., Canonsburg, PA). 3-D models for the trapping regions were developed considering the cell as a rigid body. Fluid velocity along a reference line, which is denoted a–b (Fig 9A) and lies slightly above the capture cup centerline, was measured. As a crude approximation, it is assumed the cell travels with same velocity as the carrier flow. The transverse-to-longitudinal kinetic energy ratio can be represented by a dimensionless parameter $R = V_y^2/V_x^2$. As an example, the kinetic energy ratio R for the case without mechanical chip extension and without cells trapped along the line a–b is shown in Fig 9A, in which a maximum value was denoted as $R_{\max}$. When the cell's transverse kinetic energy is significant compared to its longitudinal kinetic energy, cells are more likely to move around the microstructure instead of becoming trapped in the cup. Therefore, this maximum kinetic energy ratio can be used as an indicator of the microstructure array behavior. That is, a larger value of $R_{\max}$ indicates a lower probability of cells to become trapped.

The values of $R_{\max}$ were calculated for a microstructure that has captured a varying number of cells when the device is unstretched or extended by 72% (Fig 9B). The relatively small values of $R_{\max}$ when no cell is trapped in a cup on the unstretched device (0.0114), and when zero (0.0032), one (0.0084) or two (0.0151) cells are trapped in the stretched device, suggest that an additional cell could relatively easily access the cup and become trapped. On the other hand, the relatively large values of $R_{\max}$ when a single cell is trapped in the cup on the unstretched device (0.0218) and when three cells are trapped in a cup on the extended device (0.0207) suggest that it is difficult for additional cells to move into the cup. These results are consistent with experimental data.

4. Conclusion

Biological research and clinical diagnostics rely on controlled cell manipulation, such as isolation, positioning and trapping. We have developed an elastomeric polymeric microchip for mechanically tunable cell trapping. The device consists of two thin PDMS sheets, one of which bears microstructures to physically capture cells. Each microstructure consists of a dam-like, cup-shaped geometry with supporting pillars on both sides. The employment of PDMS, which has large deformability, enables the mechanical modulation by inducing uniformly distributed strain via application of external force on the chip. Numerical analysis shows uniform strain distribution in the cell trapping region and effective modulation of cell trapping microstructures. Further analysis of the flow field suggests that the transverse-to-longitudinal kinetic ratio (E_y/E_x) of a cell can be used to reflect the possibility of trapping this cell. The experimental results also demonstrate the application of strain can significantly deform the cell trapping microstructure, thereby allowing for the cell array capable of trapping predetermined quantities of cells. In addition, the trapped cells are shown to be viable. These results demonstrate that our approach can potentially enable effective, efficient and flexible formation of an array of cells on a microchip.

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Qiao Lin received his Ph.D. in Mechanical Engineering from the California Institute of Technology in 1998 with thesis research in robotics. He conducted postdoctoral research in microelectromechanical systems (MEMS) at the Caltech Micromachining Laboratory from

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Figure 1.

The cell trapping principle. (A) Plan view and cross-sectional views along lines (B) a-a and (C) b-b of cell trapping approach. Dimensions are given in micrometers.

Figure 2.

Principle of tunable cell trapping via modulation of microstructure dimensions. (A) Single cells are trapped in the microstructures before application of strain. (B) Multiple cells are trapped in the microstructures after application of strain. Inset: detail of microstructure geometries before and after the application of strain.

Figure 3.

The microchip fabrication process. (A) Fabrication of the SU-8 mold. (B) Casting of the PDMS microfluidic sheet and the PDMS substrate. (C) Demolding of PDMS sheet. (D) Bonding of the PDMS microfluidic sheet and PDMS substrate.

Figure 4.

(A) A fabricated and assembled tunable cell trapping microchip. (B) Scanning electron micrograph image of the cell-trapping region, showing densely packed cup-shaped microstructures (scale bar: 100 μm). (C) Detail of the trap microstructure, including a dam-like capture cup with supporting pillars on both sides (scale bar: 10 μm).

Figure 5.

Modulation of microstructures for cell trapping: Phase contrast micrographs of cell trapping microstructure before (A) and after (B) after applying 79% relative extension along x direction (scale bars: 50 μm). (C) The depth and width variations of microstructures as the normal strains increased from 0 to 0.8.

Figure 6. Numerically determined distributions of the normal strain components on the lower surface of the microchannel (xy-plane) within cell trapping region: (A) x-component; (B) y-component; and (C) z-component.

Figure 7. Numerically determined microstructure deformation (A) before and (B) after applying 79% relative extension along x direction. 3D models of the microstructure (C) before and (D) after applying 79% extension. Scale bars: (A)(B) 100 μm , (C)(D) 25 μm .

Figure 8. Fluorescent micrographs of cell trapping (A) before and (B) after application of strain. (C) The distribution of trapped cells before and after microstructure modulation. Images of JC-1 stained trapped cells (D) before and (E) after application of strain. Scale bars: 100 μm .

Figure 9.

(A) Numerically determined transverse-to-longitudinal kinetic energy ratio (R) along the reference line a–b on the middle surface of the microfluidic channel. (B) Dimensionless parameter R_{max} when a varying number of cells are trapped in a cup on an unstretched (B1 and B2) and stretched device (B3–B6).