Sensors and Actuators A 215 (2014) 197–203

Contents lists available at ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

A mechanically tunable microfluidic cell-trapping device

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ARTICLE INFO

Article history:
Received 14 April 2013
Received in revised form
12 September 2013
Accepted 18 October 2013
Available online 27 October 2013

Keywords:
Cell trapping
Cell array
Elastomeric polymer
Mechanical modulation
Microfluidics
Tunability

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.

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 multi cellular resistance [1]. However, the analysis of a large population of cells obscures the heterogeneous information within cell groups, such as the large genetic variation between individual cells [2,3]. Therefore, in addition to multi cellular 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 ligand 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 that use optical [20], acoustic [21], dielectrophoretic [22], hydrodynamic [23] methods, or their combinations [24], employ different kinds of external force during the experiment to separate and restrict cells in particular locations, and thus allow dynamic and precise control over the number of cells trapped. However, the

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http://dx.doi.org/10.1016/j.sna.2013.10.016

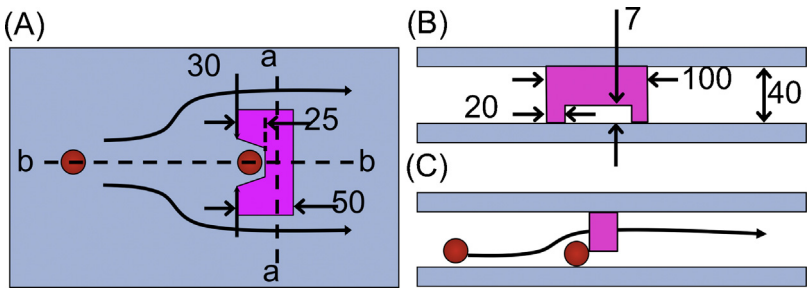

Fig. 1. The cell trapping principle. (A) Plan view and cross-sectional views along lines (B) a-a and (C) b-b of cell trapping approach. Dimensions are given in micrometers.

application of these methods is also limited by either sophisticated operation systems or complicated microfabriation 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, and also alter the flow field, thereby allowing the number of cells trapped

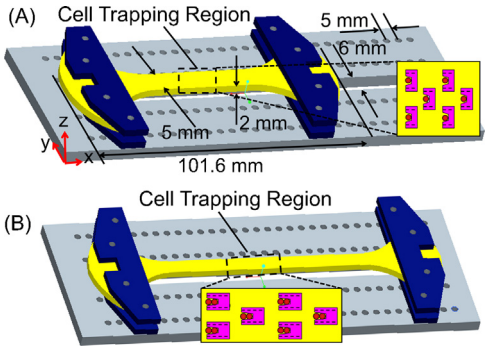

Fig. 2. Principle of tunable cell trapping via modulation of microstructure dimensions. (A) Single cells are trapped in the microstructures before application of strain. (B) Multiple cells are trapped in the microstructures after application of strain. Inset: detail of microstructure geometries before and after the application of strain.

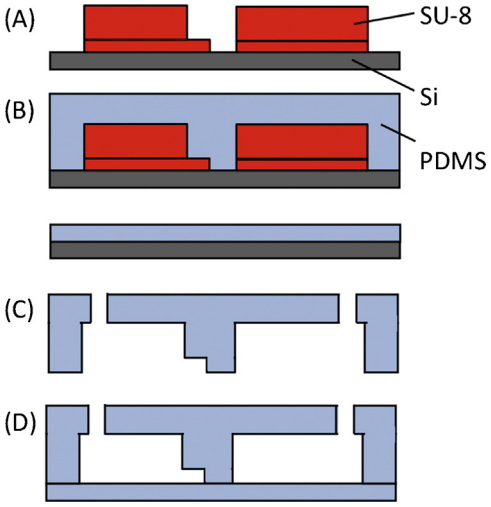

Fig. 3. The microchip fabrication process. (A) Fabrication of the SU-8 mold. (B) Casting of the PDMS microfluidic sheet and the PDMS substrate. (C) Demolding of PDMS sheet. (D) Bonding of the PDMS microfluidic sheet and PDMS substrate.