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Soft lithographic patterning of proteins and cells inside a microfluidic channel

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The control of surface properties and spatial presentation of functional molecules within a microfluidic channel is important for the development of diagnostic assays, microreactors, and for performing fundamental studies of cell biology and fluid mechanics. Here, we present soft lithographic methods to create robust microchannels with patterned microstructures inside the channel. The patterned regions were protected from oxygen plasma by controlling the dimensions of the poly(dimethylsiloxane) (PDMS) mold as well as the sequence of fabrication steps. The approach was used to pattern a non-biofouling polyethylene glycol (PEG)-based copolymer or the polysaccharide hyaluronic acid (HA) within microfluidic channels. These non-biofouling patterns were then used to fabricate arrays of fibronectin (FN) and bovine serum albumin (BSA) as well as mammalian cells.

Keywords : Microfluidics, Soft lithography, Patterning, Protein, Cell

Ⅰ. INTRODUCTION

Microdevices comprised of microfluidic components hold great promise in the development of improved bioanalytical and diagnostic devices [1]. Microfluidics allows for miniaturization of sample volumes while increasing the throughput and efficiency of analysis. Engineering the surface chemistry [2,3] and the location of surface molecules within microfluidic channels are important for many potential applications. For example, spatial patterning has been shown to induce fluid mixing [4], direct fluid flow [5] and provide means of generating functional microfluidic components such as valves [6]. In addition, controlling the location of proteins and cells within a microfluidic channel is important for the development of high throughput analytical devices [7] and multi-step bioreactors [8,9].

Currently, the most commonly used approaches to pattern within microchannels are laminar flow patterning [10] and photolithography. These techniques have been used to pattern cells, proteins [10] or hydrogels [6,8,9], direct the flow of liquids [5,11], as well as etch [12] or build microstructures [12] within microchannels. Despite the success of these approaches to control the surface properties of microchannels, there are potential limitations. For example, laminar flow patterning, a simple approach to pattern within microfluidic channels, is limited to generating geometrical patterns in the shape of the laminarly flowing streams. In addition, photolithography, a useful tool for many emerging applications [13,14], has limitations due to the potential cytotoxicity of photoinitiators [15], the need for a specialized equipment, and the difficulty in patterning the surface without modifying the surface topography [8,9]. Therefore, the development of simple and direct techniques for patterning the surface of microfluidic channels could be of benefit.

Soft lithographic approaches such as microcontact

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printing [16], microfluidic patterning [10,17,18], micromolding [19-21] and capillary force lithography [22] have served as inexpensive, convenient and scalable tools for patterning surfaces. Despite these attractive traits, the merger of soft lithographic patterning approaches and microfluidics has not been realized. To pattern microfluidic channels using soft lithography, the surface patterning must occur prior to the attachment of the PDMS mold to the substrate. However, the formation of an irreversible seal between the PDMS mold with the substrate requires oxygen plasma treatment, which can destroy the patterns. To overcome exposure to oxygen plasma, patterned membranes have been sandwiched between two plasma treated PDMS surfaces [7], However, this approach is time consuming and requires multiple steps. Furthermore, the presence of a non-adherent polycarbonate membrane may affect the robustness of the channels.

Here, we introduce soft lithographic techniques to directly pattern the substrate of microfluidic channels. The technique allowed for selective adsorption of FN and BSA onto the patterned microfluidic channels and the deposition of various proteins within multiple or individual patterns using laminar flows. In addition, cells were patterned to generate cell-based biosensors and bioreactors that are capable of enzymatic reactions.

Ⅱ. EXPERIMENTAL SECTION

2.1 Chemicals and Materials

Poly(dimethylsiloxane) (PDMS) elastomer composed of prepolymer and curing agent was purchased from Essex Chemical Sylgard 184 (Edison, NJ). Fluorescein isothiocyanate (FITC)-labeled bovine serum albumin (FITC-BSA), anti-FN antibody, 3-(trimethosysilyl) propyl methacrylate (TMSMA), poly(ethylene glycol) methyl ether methacrylate (PEGMA) (average Mn =ca. 475), FITC-labeled anti-rabbit secondary antibody, 2,2'-azobisisobutyronitrile (AIBN), propedium iodide (PI) and phosphate buffered saline (PBS) were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO). HA was obtained from Genzyme Inc. (Cambridge, MA). All cells were obtained from American Tissue Type Collection (Manassas, VA). For cell culture, Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), fibronectin (FN), trypsin, and other cell culture reagents were purchased from Gibco Invitrogen Corporation (Carlsbad, CA). Calcein AM, ethidium homodimer and Texas-red labeled BSA (TR-BSA) were purchased from Molecular Probes (Eugene, OR).

2.2 PDMS mold fabrication for surface patterning and microfluidics

PDMS molds were fabricated by curing the prepolymer on silicon masters patterned with SU-8 photoresist. The masters used for patterning had protruding cylindrical features (ranging in diameter from 15 μm to 150 μm), which resulted in PDMS replicas with the opposite sense. The masters used for microfluidics had protruding features with the impression of microfluidic channels (ranging from 50 μm to 600 μm in width and ~80 μm in height). To cure the PDMS prepolymer, a mixture of 10:1 silicon elastomer and the curing agent was poured on the master and placed at 70℃ for 2 h. The PDMS mold was then peeled from the silicon wafer and cut into narrow strips (~0.3 cm × 3 cm). These strips were sufficiently large to allow for the formation of patterns, while being small enough to allow for the major portion of the glass slide to be plasma cleaned.

2.3 Fabrication of patterned microfluidic channels

We generated patterned surfaces using microcontact printing and molding to demonstrate the versatility of the approach to pattern microchannels

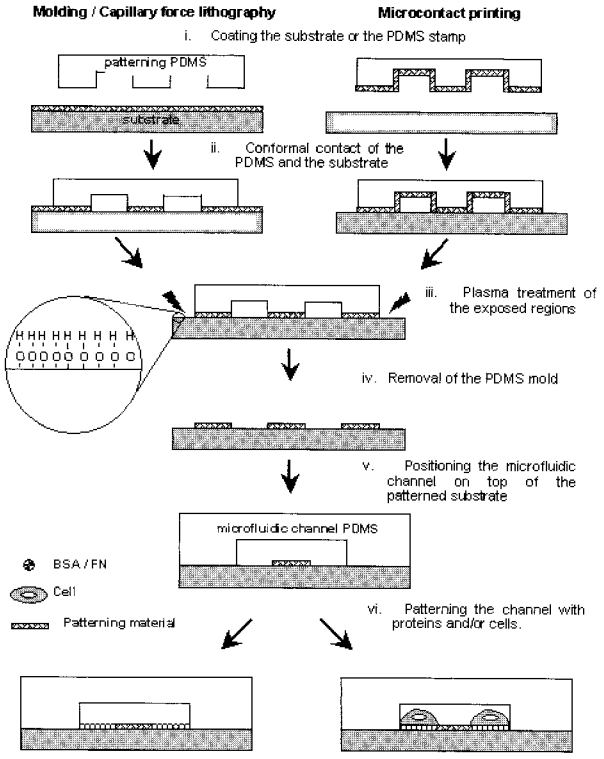
with various soft lithographic techniques. HA films were prepared by spin-coating (Model CB 15, Headaway Research Inc.) a solution containing 5 mg HA/mL of distilled water onto silicon dioxide substrates (glass slides or wafers) at 1500 rpm for 15 s. Immediately after coating, a plasma cleaned PDMS stamp with negative features was brought into conformal contact with the stamp and left to be dried for 12 h at room temperature. The patterned surfaces were then washed with PBS to remove the non-chemisorbed HA from the surface.

To synthesize poly(TMSMA-*r*-PEGMA), PEGMA and TMSMA and AIBN were dissolved in tetrahydrofuran at a molar ratio of 1.0 : 1.0 : 0.01 and degassed for 20 min and were reacted using free radical polymerization at 70 ℃ for 24 h. The solvent was then evaporated leaving behind a viscous liquid. The synthesized poly(TMSMA-*r*-PEGMA) was used to pattern surfaces using both micromolding and microcontact printing. To pattern using micromolding, glass slides were plasma cleaned for 3 min and the poly(TMSMA-*r*- PEGMA) solution (10 mg/mL in MeOH) was spin-coated onto each glass slide (1000 rpm for 10 s). A PDMS stamp was then immediately placed in conformal contact with the spin coated surface and left undisturbed for 1 h[26]. To pattern the PEG-based copolymer using microcontact printing, the PDMS mold was plasma cleaned for 3 min and subsequently a few drops of a solution of 10 mg/mL of polymer in MeOH was placed on the stamp. To generate a uniform coating on the PDMS stamps, the mold was either spin coated at 1000 rpm for 10 s or air dried until a thin film remained. The pattern on the PDMS mold was then transferred onto the substrate by firmly pressing the mold and the substrate together. All patterns were cured at 110 ℃ for 15 min.

To complete the device fabrication, a second PDMS mold with the features of the microfluidic channel and a patterned glass slide were plasma cleaned for 15-300 s (60 W, PDC-32G, Harrick Scientific, Ossining, NY), without disturbing the first PDMS mold (i.e. in conformal contact with the substrate) (Scheme 1). After plasma treatment, the first PDMS mold was peeled from the substrate and the microfluidic channel PDMS mold was brought in conformal contact with the substrate and firmly pressed to form an irreversible seal. The microfluidic molds were aligned on the patterns either manually or after the addition of a drop of anhydrous ethanol (to assist in the alignment by delaying the irreversible binding) under the microscope. Fluids were driven through the channels using a SP200i syringe pump (World Precision Instruments, Sarasota, FL) that was connected to the device using polyethylene tubing (BD, Franklin Lakes, NJ).

2.4 Protein adsorption within channels

FITC-BSA, TR-BSA and FN were dissolved in PBS (pH = 7.4) at a concentration of 50 μg/mL, 50 μg/mL and 20 μg/mL, respectively. To test for adhesion of protein within the patterned microfluidic channels, the primary protein was pumped through the microchannels for 30 min at a flow rate of 5 μL/min. For



Scheme 1. Schematic diagram of the approach to pattern within microfluidic channels.

FN staining, a solution of anti-FN antibody was run through the channel for an additional 45 min, followed by 1 h of FITC-labeled anti-rabbit secondary antibody. Protein patterns on patterned glass slides were generated by evenly distributing a few drops of the protein solution on the surfaces and storing the samples at room temperature for 30 min and then rinsing the patterns with PBS. All patterned surfaces were analyzed using an inverted fluorescent microscope (Axiovert 200, Zeiss). All protein staining experiments were done in triplicate to ensure that multiple pictures were captured. Fluorescent images of various samples were then taken and quantified using NIH-Scion Image viewer. Blank glass slides analyzed under the same light exposure were used as background controls.

2.5 Cell seeding and analysis within channels

NIH-3T3 murine embryonic fibroblasts were maintained in DMEM supplemented with 10 % FBS at 37 ℃ and 5% CO_2 environment. For cell attachment experiments, a solution of 20 μg/mL of FN in PBS was flowed through the channel for 15 min followed by a suspension of cells (~1-5 × 10^7 cells/mL) in medium containing serum at a flow rate of 5 μL/min. Once the cells were inside the channel, the fluid flow was redirected by closing the outlet of the channel and redirecting the fluid through a Y-connector. Cells were maintained in the channels for at least 3 h. Periodically, the cells were perfused with the medium at low flow rates (~0.1 mL/min) to ensure a constant supply of oxygen and nutrients. Once the cells adhered, the medium flow rate was increased to 1-3 μL/min and maintained throughout the experiment. The experiments involving cells and microfluidics were performed on an Axiovert 200 microscope (Zeiss, Germany) with an environmental chamber designed to maintain the temperatures at 37 ℃ and 5% CO_2. The resulting cell patterns were directly examined under a phase-contrast microscope after removing the non-adhered cells by flowing PBS through the channel.

2.6 Cell reactions and lyses within channels

Calcein-AM and ethidium homodimer were dissolved at a concentration of 1 μg/mL in PBS. Once the cells adhered and excess cells were washed, the calcein- AM and ethidium homodimer were flowed through the channel for 30 min at a flow rate of 3 μL/min. For experiments in which the cells were lysed, a solution of 0.1% Triton-X in PBS was flown through the channel for 5 min at 3 μL/min. The cells were then stained with calcein-AM and ethidium homodimer as described above and analyzed under a fluorescent microscope.

III. RESULTS AND DISCUSSION

3.1 Protection of micropatterns from plasma treatment

Although the direct placement of a microfluidic mold on a glass slide, without any chemical modification, could be used to make channels with patterned substrates, the resulting channels can only be operated under low pressures, which would limit the range of fluid flows and the minimum size of the channels. To generate robust microchannels, the surfaces must be treated with oxygen plasma, which generates surface hydroxyl groups that can form covalent bonds between two plasma treated surfaces. However, the oxidation reaction associated with plasma treatment can potentially destroy the micropatterns. We hypothesized that surface patterns could be protected against plasma treatment by preventing their exposure to oxygen plasma. In our approach, the patterns were protected from oxidation by leaving the PDMS mold intact during the plasma treatment. To ensure that only a small region of the substrate was protected while the remainder of the substrate was treated, the size of the PDMS mold was limited to dimensions slightly greater than the channel. Thus a small section of the substrate was patterned and remained protected while the rest

of the substrate facilitated irreversible binding to the microfluidic mold.

Micropatterns were fabricated using both micro-contact printing and molding techniques. The micro-contact printed patterns were formed by transferring the polymer from the PDMS mold to the substrate by direct contact. A thin layer of the PEG-based polymer was deposited on the PDMS mold and the pattern was subsequently transferred to the mold by firmly pressing the mold onto the substrate. The molded patterns were generated by capillary force lithography [22]. In this approach a thin film was spin coated onto the substrate, and a PDMS mold was subsequently brought into conformal contact with the surface and left until dried. The molding occurred as a result of capillary depression within the void spaces (i.e. repulsion of the hydrophilic polymer solution from the PDMS mold) as well as the hydrodynamic forces at the contact regions. Therefore, a thin film remained at the contact regions while the void regions dewetted from the surface to expose the substrate.

3.2 Patterned substrates within microfluidic channels

We utilized the oxygen plasma protective features of the PDMS mold to design an approach to fabricate stable microchannels with patterned substrates (Scheme 1). In this approach, the polymers were patterned on oxide-based substrates. Unless noted otherwise, we patterned the channels using microcontact printed PEG-based copolymers or molded HA. Details on the micropatterning method and resistant properties of PEG and HA have been published earlier [23-26]. After patterning, the substrate was plasma cleaned while maintaining the conformal contact between the PDMS mold (used for patterning) and the glass slide. The PDMS mold was then removed and a microfluidic channel was then aligned on the patterns and irreversibly attached to the substrate.

As shown in the light microscope images in Fig. 1, channels were fabricated with PEG-based copolymer (Fig. 1A) or HA (Fig. 1C-D) patterns. The pattern edges

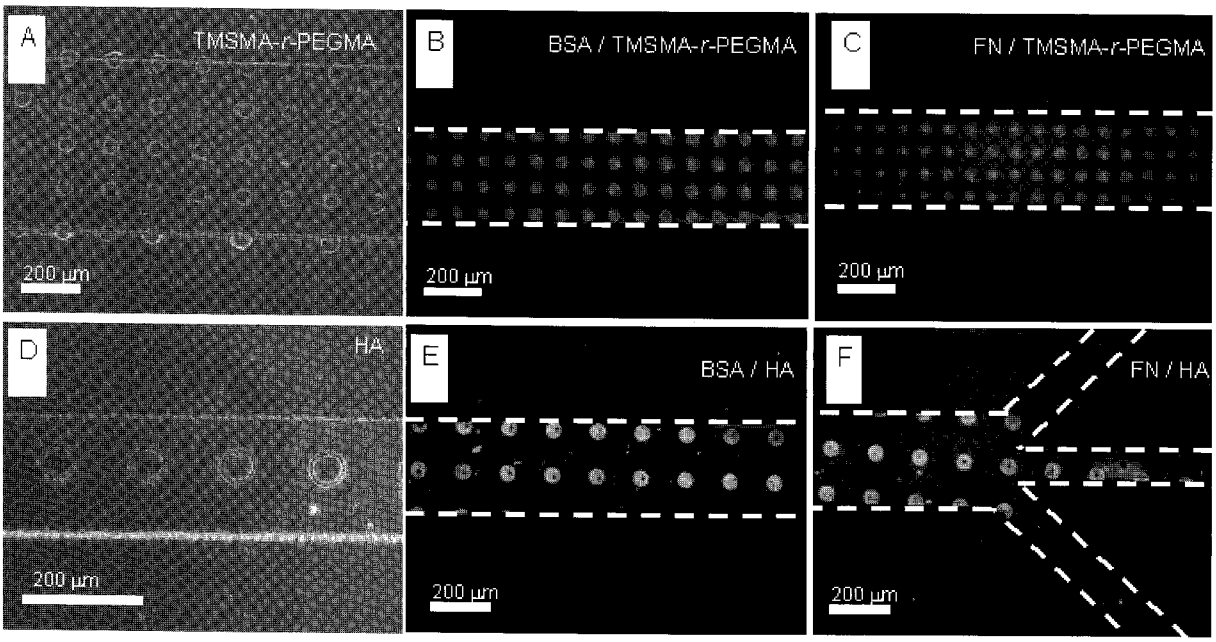


Fig. 1. Light micrograph (A, D) and fluorescent images (B, C, E, F) of patterned microfluidic channels. (A-C) represent microfluidic devices that were patterned with the PEG based copolymer, poly(TMSMA-*r*-PEGMA) while (D-F) represent microfluidic devices that were patterned with HA. The substrates were stained either with TR-BSA (B), FITC-BSA (E), or FN (C, F). The dashed lines indicate the boundary of the microfluidic channels.

in these images were clearly visible which provided an easy way to detect pattern fidelity and to align the channel. To characterize the non-biofouling properties of these patterned microfluidic channels, protein adsorption experiments were performed by flowing FITC-BSA, TR-BSA or FN through the channels. Fluorescent images in Fig. 1 are representative protein patterning images under various tested conditions. The fluorescence was limited to the exposed regions indicating that proteins attached directly to the patterns. Both PEG-based polymer as well as HA showed excellent protein resistance for BSA (95±2% and 97±3% respectively) and FN (96±3% and 95±3% relative to bare glass) within the channels. These values were not significantly different from the protein adhesion results obtained immediately after patterning [23], indicating that the additional steps involved in fabrication and the shear stress associated with the flowing fluid did not alter the intrinsic non-biofouling properties of the patterned films.

In addition, to control the adsorption of multiple proteins to various regions of an exposed substrate, we used laminar flow patterning. It was demonstrated that laminar flow of multiple proteins could be used to generate patterned arrays of proteins within channels. As can be seen from Fig. 2A, TR-BSA and FITC-BSA were adsorbed onto the various patterns within the channel. The adsorption of multiple proteins within single channels could be potentially useful for fabricating arrays of immunoassays for biosensors. Furthermore, individual patterns can be coated with two (or more) different proteins as illustrated in Fig. 2B. In this case, TR-BSA and FITC-BSA were flowed side by side in a microfluidic channel directly above an exposed pattern being aligned at the region in between the two streams.

3.3 Patterning of cells within microfluidic channels

To examine the potential of the patterned microfluidic channels for generating cellular arrays within microfluidic channels, we fabricated patterned microfluidic channels using both HA and PEG-based copolymer. Prior to cell seeding, a solution of FN was flowed through the channels for 15 min. A cell suspension of 5×10^7 cells/mL was found to be optimum to form cellular monolayers or arrays. Concentrations of $<1 \times 10^7$ cells/mL did not form confluent cell layers while concentrations $>1 \times 10^8$ cells/mL clogged the channels. The morphology of the cells within the microchannels resembled that of the cells plated under normal tissue

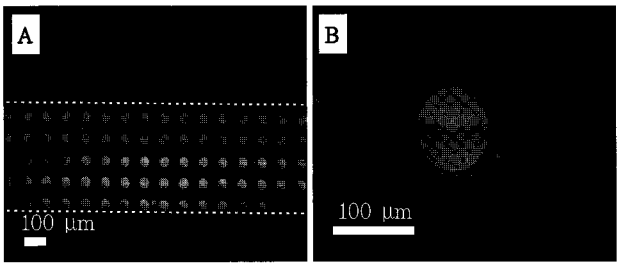


Fig. 2. Fluorescent images of microfluidic channels in which laminar flow was used to immobilize two different proteins on the patterned substrate. (A) TR-BSA (red) and FITC-BSA (green) were flown through a channel resulting in the formation of red or green patches on various sides of the channel. (B) individual patterns were coated with TR-BSA and FITC-BSA.

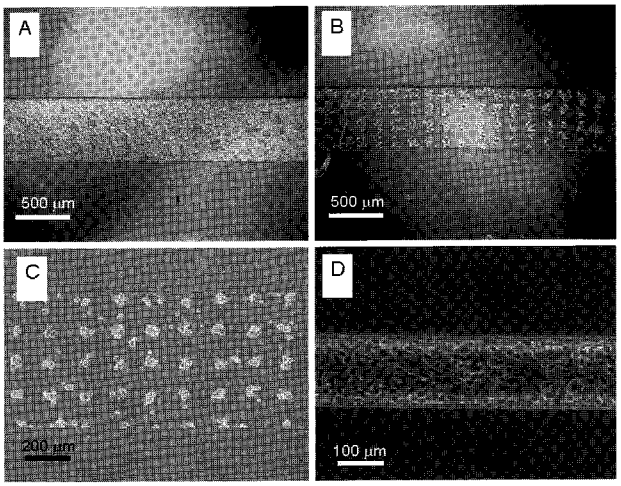


Fig. 3. NIH-3T3 fibroblast adhesion and patterning within microfluidic channels at t = 0 h (A) and after 6 h (B-D). (A) shows the initial cell density within the microfluidic channels while (B) and (C) represent the cell patterned channels on poly(TMSMA-*r*-PEGMA) and HA respectively. (D) represents fibroblast adhesion to non-patterned microchannels.

culture conditions. The cells entered the channels as spherical cell suspensions (Fig. 3A) and started to spread on the surface within 2 h. At this time, the non-adherent cells were removed by a gentle fluid flow, leaving behind partially adhered cells that fully adhered by 6 h. Cells adhered to the FN coated regions on patterns generated from HA or PEG-based copolymer (Fig. 3B-C); while inside non-patterned channels, cells formed a confluent monolayer (Fig. 3D). Once adhered in the channels, the cells did not stain for PI or Trypan blue dyes indicating that they remained viable. These results indicate that the cells could be patterned within microfluidic channels at high confluency and with high precision. We have maintained these cells within the microfluidic channels for 24 h indicating that they can be maintained for durations that are relevant for bioanalytical and biosensing applications.

To analyze the potential of this patterning approach for various analytical applications, we tested the ability of the immobilized cells to carry out enzymatic reactions using ethidium homodimer and calcein-AM molecules. The membrane permeable calcein-AM enters all cells, and is enzymatically converted to green-fluorescent calcein in the cytoplasm. Cells with an intact plasma membrane (viable cells) retain calcein, and thus fluoresce green. Only cells with a compromised plasma membrane (dead cells) take up ethidium homodimer (seen as a red dye). Thus, we were able to analyze the viability and functionality of these cells within the channels. As illustrated in Fig. 4A, NIH-3T3 cells remained viable and were also capable of performing enzymatic reactions (>98% of the cells stained only as green). To examine the potential of releasing the contents of the cells, a solution of Triton-X, a commonly used surfactant used to permeabilize cell membranes in culture, was flowed through the channel. This was followed by solution of calcein AM/ethidium homodimer after which the cells were analyzed under a fluorescent microscope. As shown in Fig. 4D, 58±8% of the cells that were treated with Triton-X were lysed as indicated by the permeation of ethidium homodimer across the membrane (red color). Interestingly, cells that were closer to the center of cellular aggregates remained viable indicating that the mass transfer limitations associated with the diffusion of Triton-X to the center of these aggregates protected these cells.

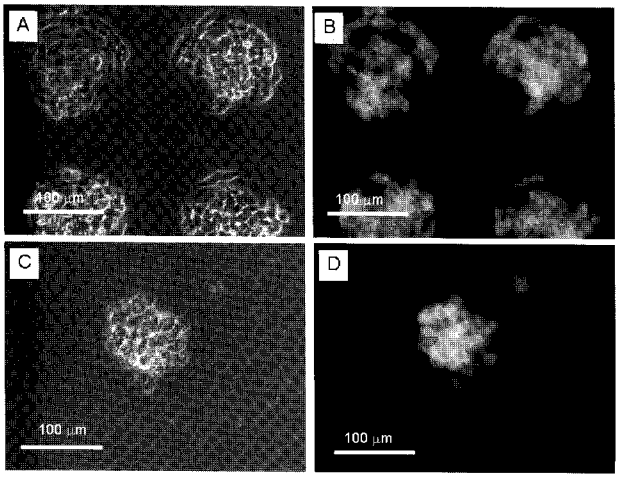


Fig. 4. (A) Light and (B) fluorescent images of NIH-3T3 fibroblasts patterned on microfluidic channels that have been treated with ethidium homodimer and calcein AM. (C-D) NIH-3T3 cells that were lysed by a pulse of Triton-X and subsequently treated with ethidium homodimer and calcein AM.

IV. CONCLUSIONS

In this study, soft lithographic methods were developed to fabricate stable microfluidic channels with precise control over the spatial patterning of the substrate. First, the patterned regions were protected from oxygen plasma by controlling the dimensions of the PDMS mold as well as the sequence of fabrication steps. Proteins were immobilized with precision on the substrate of the microfluidic channels. Fibroblasts were patterned within the channels through adhesion to FN coated regions. The cells remained viable and performed enzymatic reactions and could be lysed to potentially release intracellular components (i.e. proteins). The approach presented here can be potentially used with various soft lithographic patterning techniques to

design and fabricate more sophisticated microfluidic devices for analytical applications and microreactors.

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소프트 리소그라피를 이용한 마이크로유체 채널 내의 단백질 및 세포 패터닝

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마이크로유체 채널 내에서 표면 성질과 기능성 분자들의 공간적인 위치를 제어하는 것은 진단소자, 마이크로 반응기, 또는 세포와 마이크로 유체역학의 기본적인 연구를 위해 매우 중요하다. 이 논문에서는 소프트 리소그라피 방법을 이용하여 채널 안에 패턴된 구조물을 포함하는 안정적인 마이크로 채널을 제작하는 방법을 소개하려 한다. 먼저 패턴된 영역을 폴리디메틸실록세인(PDMS) 몰드의 치수와 제작 과정을 적당히 조절함으로써 산소 플라즈마로부터 보호한다. 마이크로 구조물은 대표적인 생물오손(biofouling) 억제 물질인 폴리에틸렌 글리콜(PEG)계 공중합 고분자 혹은 다당류인 히알루산(HA)을 패턴하여 얻었으며 이러한 패턴을 이용하여 피브로넥틴(FN), 소의 혈장 알부민(BSA) 등의 단백질과 동물 세포의 어레이를 제작하였다.

주제어 : 마이크로유체역학, 소프트 리소그라피, 패터닝, 단백질, 세포

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