Development of a Noninvasive Single Cell Manipulator Utilizing a Temperature-Responsive Polymer

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1. Introduction

Along with the recent miniaturization of physical objects in such fields as medicine, engineering, agriculture, and biology, there is an increased demand to establish methods for working in microscopic environments, such as operating and processing methods. With the developments in biotechnology over the past several years, there is an increasing need for cell microinjection and micromanipulation technologies in particular. The objective of this study is to provide an entirely new concept of micromanipulation aimed at greatly improving cell operability and achieving low invasiveness by developing a micromanipulation technique that uses temperature responsive polymers.

2. Temperature control for cell attachment and detachment

In this study, a temperature-responsive polymer, polyisopropylacrylamide (PIPAAm) was grafted onto the end surface of the manipulator. The properties of the polymer changes in response to temperature. By controlling temperature with a small Peltier device, the property of the PIPAAm was switched between hydrophilic and hydrophobic to control cell attachment and detachment (Fig. 1). The cell-trapping domain was ordered in an array by controlling the thickness of the temperature-responsive polymer layer on the order of nanometers and ablating the layer with UV excimer laser (Fig. 2).

3. Conclusion

It has been pointed out that cells can be damaged through single-cell traps and other manipulation using physical techniques, such as optical tweezers and electric fields. The technique for manipulating single cells used in the present study, using temperature changes to control the chemical nature of the manipulator surface, was found to be less invasive than existing methods. This technique is expected to have practical applications once the switching speed is improved.

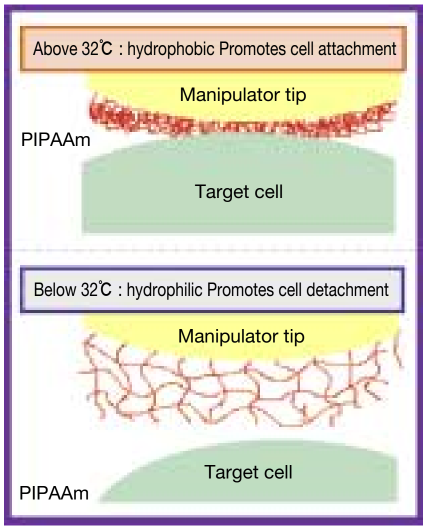

Fig. 1 Single cell manipulator employing a temperature-responsive polymer

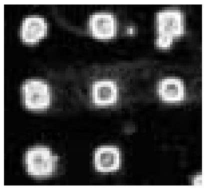

Fig. 2 Array of orderly arranged hepatocytes

Construction of Micro-Lens Array by Micro-Fabrication of Stimuli-Responsive Gel

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A gel that expands and contracts in response to physical stimuli, such as thermal, electrical, and optical variations, and chemical stimuli, such as pH and chemical substances, has begun to attract much attention for its use as a soft functional material. Now we have discovered a method enabling micromachining of this type of stimuli-responsive gel. The objective of this study is to produce a compound-eye lens as an application of the gel. While the use of this gel for optical lenses has been considered before, the greatest weakness of this substance is its lengthy stimulation-response time. For example, a gel having a size of centimeters requires several hours to respond to stimulation. However, this response time can be shortened when reducing the size to micrometers. In this study, we designed a compound-eye gel micro-lens array with this gel, as shown in Fig. 1. We attempted to form the gel in a convex shape between micro-patterned ITO (indium tin oxide) transparent electrodes, controlling the thickness and focal length of the lenses individually by voltage. Micro-lenses having a diameter of about 500 micrometers were arranged at regular intervals. Variations in response to pH and electrical stimuli were observed within 1 second. Fig. 2 shows an image acquired using this micro-lens array. A toy dinosaur was used as the subject of imaging. Variations in focal length in response to stimuli were observed from pH 7 to pH 2.

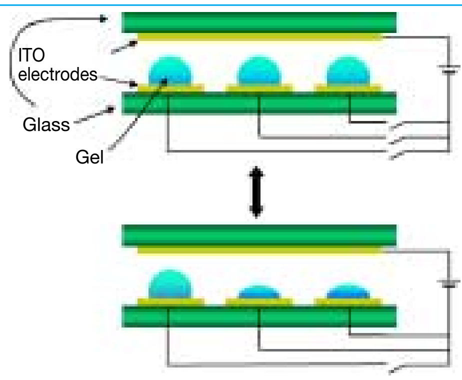

Fig. 1 Principles of the compound-eye system having an array of gel micro-lenses

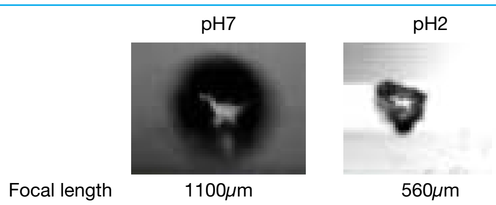

Fig. 2 An image taken by the compound-eye micro-lenses showing variations in focal length in response to pH stimuli