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Sensors and Actuators A 135 (2007) 16–22
SENSORS AND ACTUATORS A PHYSICAL
www.elsevier.com/locate/sna

MEMS based force sensors for the study of indentation response of single living cells

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Received 24 February 2006; accepted 19 May 2006
Available online 7 July 2006

Abstract

This paper presents bio-microelectromechanical systems (MEMS) force sensors, consisting of a probe and flexible beams, to study mechanobiological response of single living cells subjected to mechanical injury. Mechanical injuries are simulated by the application of large indentation on the cells by the sensor probe. The green fluorescent protein (GFP) technique is used to visualize the evolution of the actin network in the cells. The lateral indentation force response measurement capability of the sensors is shown. The cell force response is strongly linear for the initial indentation stage and the cells become yielded due to further indentation, which were not observed before. Two new types of remodeling, large buckling of stress fibers and actin agglomeration, in the actin network in a cell due to mechanical stimuli are also reported.

Keywords: Cell mechanics; Indentation; Microelectromechanical systems (MEMS); Green fluorescent protein (GFP); Actin fibers

1. Introduction

The study of mechanobiological response of living cells has received increased attention during the past decade [1–3]. The existing experimental tools developed for inducing mechanical stimuli onto cells and measuring the cell force response include the magnetic twisting cytometry (MTC), atomic force microscopy (AFM), optical traps, and many others [4]. But most of these tools, such as MTC, AFM, and optical tweezers, can only induce small cell deformations and measure small cell force response. Large cell deformations are common in normal physiological conditions, e.g., skin may need to double its length when it is deformed by bending over a joint [5], a skeletal muscle can contract or expand by 50% [6], and cell may undergo large deformations during injuries [7].

In this paper, we describe two novel micromachined force sensors (a one-component force sensor and a two-component force sensor) for the study of mechanobiological response of single living cells subject to large lateral indentations simulating mechanical injuries. The one-component force sensor is used to measure the cell indentation force response. The two-component force sensor is used to monitor the cell active response after the cell is indented for a certain deformation. The one-component force sensor is also used to study the remodeling of the actin network in green fluorescent protein (GFP)–actin transfected fibroblasts due to large indentations. New observations on the response of the actin network are shown.

2. Materials and methods

The sensors are made from pure single crystal silicon, and consist of a probe and flexible beams. The probe is used to contact and indent the cell and the flexible beams to monitor cell force response [8]. Fig. 1A–C shows a force sensor which can monitor the indenting force in the x direction only, i.e., the one-component force sensor. In this sensor, the two fixed–fixed flexible beams are the sensing beams, and the probe is connected to these beams through a backbone. The deflection of the beams, δ, is measured by the relative movement between the measurement point and reference point in the x direction, and the cell force response, F, is obtained by multiplying the deflection of the beams with the combined spring constant of the beams, k, i.e., $F=k\delta$. Each of the two fixed–fixed flexible beams has the dimensions, length: 1.96 mm,

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doi:10.1016/j.sna.2006.05.019

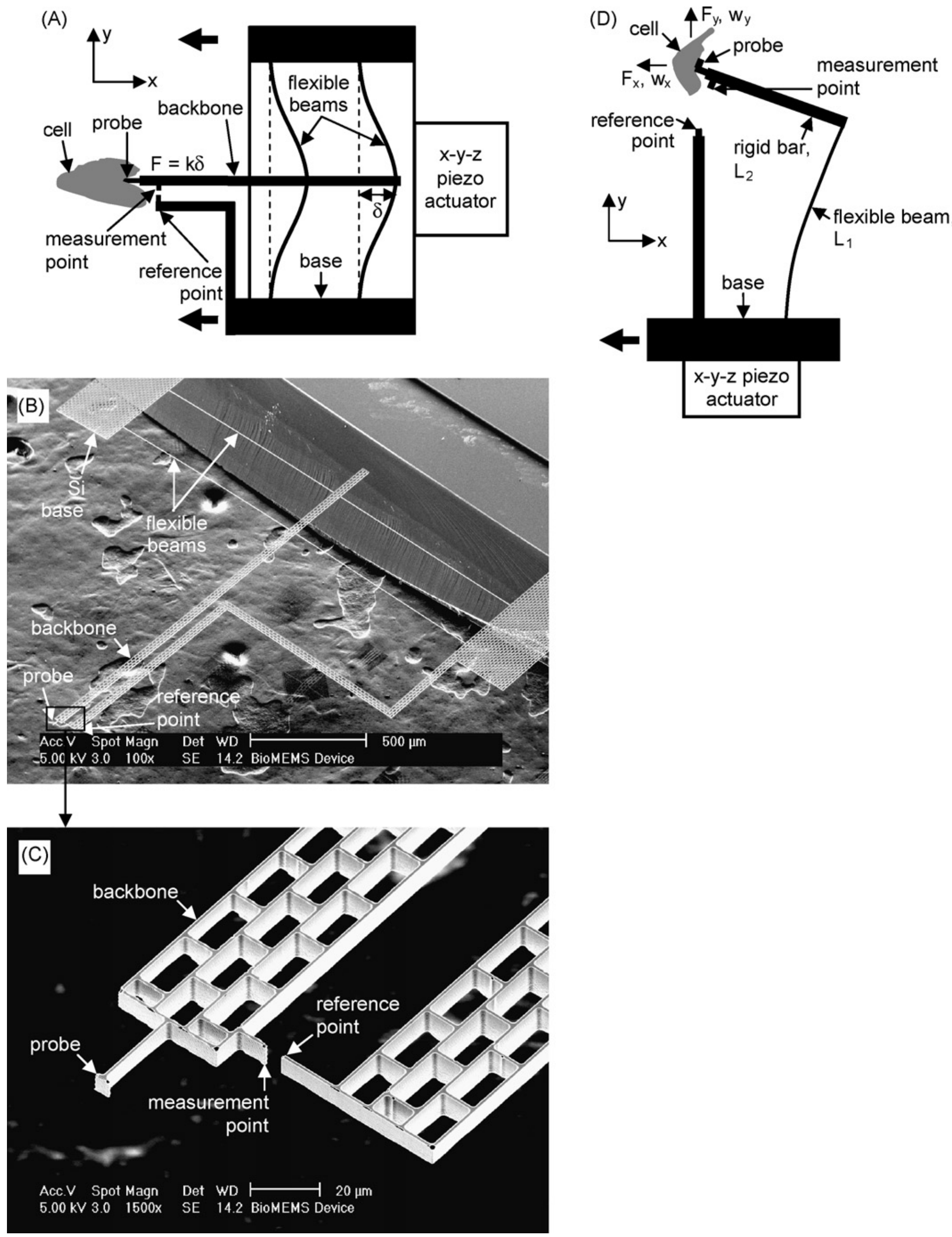

Fig. 1. Micro-force sensors for the study of single living cells: (A) schematic drawing; (B and C) SEM images of a one-component force sensor and its probe part, respectively; (D) schematic drawing of a two-component force sensor.

in plane width: 1.18 μm, and out of plane depth: 4.99 μm. The probe of the sensor is 2.0 μm wide and 4.99 μm deep, and the combined spring constant of the two flexible beams is 5.9 nN/μm.

Fig. 1D schematically shows the two-component force sensor, which can monitor the indenting force in both the x and y directions. In this sensor, a rigid bar is attached to the free end of the cantilevered flexible (sensing) beam and the probe is attached to the other end of the rigid bar, which results in the movements of the probe in both the x and y directions when the sensing beam is deflected. The spring deflections, w_x and w_y, in the x and y directions, are measured by the relative movements between the measurement point and reference point in the x and y directions, respectively. The cell force response components, F_x and F_y, in the x and y directions, respectively, can be obtained from the spring deflections by

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \frac{2EI}{L_1^3} \begin{bmatrix} 6 & 3\dfrac{L_1}{L_2} \\ 3\dfrac{L_1}{L_2} & 2\left(\dfrac{L_1}{L_2}\right)^2 \end{bmatrix} \begin{bmatrix} w_x \\ w_y \end{bmatrix}, \tag{1}$$

where E and I are the Young's modulus and moment of inertia of the sensing beam, respectively, and L_1 and L_2 are the lengths of