PERIODIC PRESSURE PULSE GENERATOR IN CELL CULTURE CHIP
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ABSTRACT
For studying the effect of stress on cell growth, this paper presents a design of cell culture chip, which can generate periodic pressure pulses via fluidic control system and generate pressure pulses with different amplitudes via hydrodynamic pressure. Pressure pulses ranging from 180 mmHg to 80 mmHg are obtained. This chip features wide frequency range (from 0 to 100 pulses/min), tunable duty cycle (from 0 to 1) and no shear stress effect, making the cell culture chip promising for many applications, for example, biological research on the relationship between hypertension and cancer.

Keywords: Cell culture, stress, pressure pulse, microfluidic chip

1. INTRODUCTION
In order to simulate on-chip in vivo microenvironments for cell culture, microfluidic chip with accurate fluidic control system is applied recently [1]. Compared with the traditional cell culture research, microfluidic cell culture systems focus on regulating the fluid mechanical environment but not the chemical environment. In prior studies, the shear stress is mainly considered for endothelial cells lining the inner lumen of blood vessels [1,2]. This paper presents a design of microfluidic cell culture chip, which has no shear stress effect on cells, can generate periodic pressure pulses via fluidic control system and generate pressure pulses with different amplitudes via hydrodynamic pressure. These features make the microfluidic chip possible for the culture of most cells under periodic pressure. It’s significant for many applications, for example, to research on the relationship between hypertension and cancer [3] in the cell level.

2. THEORY AND DESIGN
In micro channel, the typical flow is a Poiseuille flow. In a steady-state Posieuxille flow, there is a simple relationship between the flow rate $Q$ and the pressure drop $\Delta p$ as given by

$$Q = \frac{\Delta p}{R}$$

(1)

where $R$ is the fluidic resistance, which is dependent on the channel’s cross-section, the length $L$ and the viscosity of the liquid $\eta$. For a rectangular channel with a width $w$ and a height $h$ ($w > h$), the fluidic resistance is

$$R = \frac{12 \eta L}{h^3 w} \left[ 1 - \sum_{n, odd}^{\infty} \frac{192 h}{n^5} \frac{1}{w} \frac{1}{n^5} \tanh \left( \frac{n\pi w}{2h} \right) \right]$$

(2)
Therefore, along the direction of Posieulille flow in a channel, the pressure is decreased continuously. A suspended branch (no flow) connecting to the channel at different locations can achieve different pressures.

Fig. 1a presents the schematic of the microfluidic cell culture chip with integral fluidic systems. The chamber a, b and c are filled with air. An air chamber functions as a capacitor, and the micro channel resembles a resistance. They are combined together to form the integral fluidic system, and similar to the integral circuit. Inlet 1, 2 and 3 are used for cell loading, and after that, they are clamped to stop the flow in the cell culture chambers. Periodic flow of cell culture medium from the inlet to the outlet generates periodic pressures with different amplitudes on different suspended branches. But shear stresses caused by the flow will be kept out of the cell culture chambers by the integral fluidic system, and only the stress caused by the pressure will affect the cell functions. Nutritional exchange between the flow of cell culture medium and the medium in cell culture chambers is mainly dependent on diffusion. Fig. 1b is the related circuit model, in which the differences of pressure pulse shape and amplitudes at different locations are shown.

Figure 1. (a) The schematic of cell culture array chip with the integral fluidic system. (b) the circuit model and the shape of pressure pulse at several key points.
3. EXPERIMENTS AND RESULTS

The microfluidic cell culture chip (Fig. 2) fabricated by three PMMA layers through laser engraving and thermal bonding. UV glue is used for the sealing of the connection between the chip and the tubes. Syringe pump controlled by computer is used to generate initial rectangular wave with arbitrary period and duty cycle. The time resolution of the syringe pump is 1 ms. Micro-sized water droplets in air chamber a, b and c are used to monitor the real time pressures on different branches through interferometry method. The capacitor-like functions of air chamber are observed under microscope through the shift of air-liquid interface, as enhanced by dash lines in Fig. 3. Under a high pressure (Fig. 3a), the liquid flow into the air chamber and its pressure is increased. Under a low pressure (Fig. 3b), the compressed air push the liquid to flow out. Velocity distribution can also be measured by a μPIV system.

Pressure pulses with ranging amplitudes from 80 to 180 mmHg can be obtained by changing location and volume flow rate. A typical rectangular wave, with a period of 800 ms and a duty circle of 0.15, is shown in Fig. 4, and is deformed into a triangular wave. There is a delay about 30 ms between the two pressure waves. Frequency can be adjusted in the range from 0 to 100 pulses/min, and duty cycle from 0 to 1.

MDCK cells with cell culture medium (Dulbecco’s modified eagle media with 10% fetal bovine serum) were loaded into the chambers through inlet 1, 2 and 3. After 2 days, cell monolayer is formed and attached on the base of the chambers (Fig. 5).

5. CONCLUSIONS

In summary, microfluidic cell culture chip with periodic pressure pulses is developed for studying the effect of pressure/stress on cell morphology and pathology, which has advantages as easy design, simple microfluidic manipulation and no shear stress caused by flow.

REFERENCES