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REAL-TIME OPTICAL MONITORING OF CELL CULTURE IN CENTRIFUGAL MICROFLUIDICS

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ABSTRACT

We present a cellular-resolution ($2\ \mu\text{m}$) optical microscope that is rotating with a disc shaped centrifugal microfluidics cell culture platform, inside an incubator. The microscope is powered wirelessly and is composed of a homemade optics and a wireless spy camera. The human cervical cancer cell line was seeded and cultured on the disc, where their attachment and growth was monitored with the microscope. The microscope can wirelessly transmit microscopic images through the incubator to an external PC, which enables real-time (30 frames per second), continuous (without time limit) and remote (live Internet streaming) monitoring of the cell-based assays.

KEYWORDS: Lab-on-a-disc, Optical microscope, Cell culture, Wireless power, Wi-Fi transmission

INTRODUCTION

Cell-based assays under a perfusion model enables several benefits, such as continuous nutrient supply, active waste removal, lower reagent consumption and easier environmental parameter control [1]. The perfusion model is conventionally realized in microfluidics on lab-on-a-chip platforms which needs auxiliary tubing and pump. To further eliminate the complexity of overall system, a cell culture disc was proposed for the perfusion based cell cultivation [2]. Furthermore, a miniature and wireless optical microscope was developed for observing cells on a disc [3]. However, the temperature-sensitive cell culture, with the optimal culture temperature of 37°C , was affected by the heat from the wireless microscope, which lead to cell death. Additionally, we found that the miniaturized camera, could not provide the suitable magnification and resolution needed to image in detail cell growth and morphological changes during attachment, division and growth.

EXPERIMENTAL

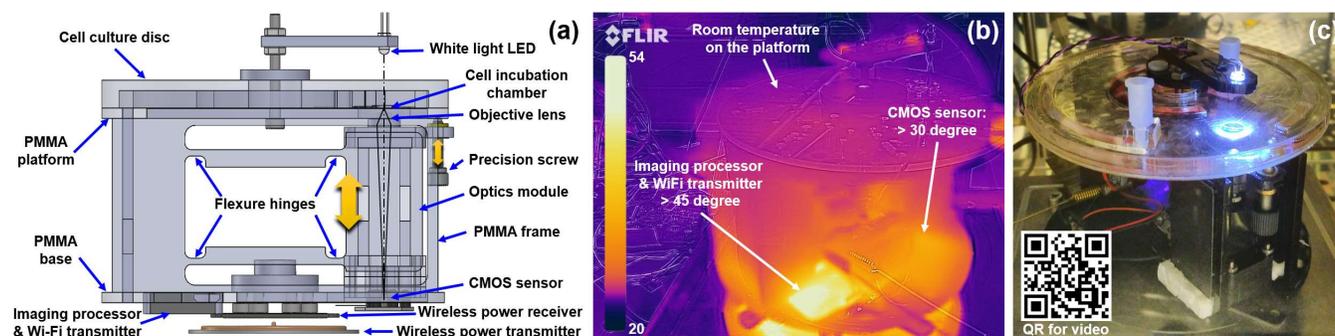


Figure 1: Microscope on a disc with integrated optical imaging, where (a) is the schematic diagram of the wireless microscope design combined with the cell culture disc; (b) shows the thermal imaging analysis of the microscope; and (c) is the photograph of the wireless microscope on a spin stand inside an incubator. Scan the QR for opening an operating video of the microscope and time-lapse cell culture images.

To solve the challenges due to the heat from the camera and to improve the magnification and resolution of the miniaturized microscope, we developed a new wireless optical microscope that implements in house optics to magnify the imaging resolution, as shown in Figure 1(a). The microscope is made of 3 mm poly(methyl methacrylate) (PMMA) framework. Inside an optics module, a 1920×1080 pixels complementary metal-oxide-

semiconductor (CMOS) image sensor is placed under an objective lens. The optics module provides a 400 x 225 μm field of view and a theoretical resolution of 200 x 200 nm per pixel. A four-linkage flexure provides rigid and linear guiding for the optics module. The precision screw is used to precisely adjust the focal point to the cells (Figure 1(a)). A white light LED provides a homogeneous illumination for imaging. Figure 1(b) shows a thermal analysis that the cell culture disc will not be thermally affected by all the heat sources (wireless power, Wi-Fi transmitter and CMOS sensor). The Wi-Fi interface enables a temporal resolution of 30 images per second. The images are captured by a freeware iSpy [4] that provides functions such as time-lapse capturing, cloud storage and real-time video streaming through the Internet. The disc was sterilized with sodium hydroxide, rinsed with ultrapure water and phosphate buffer saline and the cell chamber was coated with Matrigel. After coating the culture chamber was filled with cell culture medium and the human cervical cancer cell line (HeLa) were seeded.

RESULTS AND DISCUSSION

We found that inside an incubator, the microscopic imaging was not affected by the rotational movement (< 2 Hz) of the centrifugal cell culture platform and the flow rate. The heat generated by the wireless power and the spy camera did not interfere with the attachment and proliferation of the HeLa cell. Figure 2 (a) shows that the microscope can achieve a cellular-resolution and spot a dead cell five hours after seeding. Moreover, 2 μm features (inside a dotted circle) on top of the dead cell can be resolved as well. The cell division process can also be monitored wirelessly and remotely, as shown in Figure 2 (b), (c). One drawback is that the microscope can only monitor one spot inside the cell incubation chamber.



Figure 2: HeLa cell inside a cell culture disc imaged by the wireless optical microscope, (a) 5 hours; (b) 8 hours; and (c) 10 hours after seeding. The microscope was transmitting one image per minute during the cell culture.

CONCLUSION

The preliminary experiment shows that the newly developed wireless microscope is capable of monitoring cell cultivation process and monolayer formation on the cell culture disc. The high resolution of the camera enabled detailed real-time monitoring without the need to remove the culture unit from the incubator as commonly done when imaging cell cultures with traditional microscopes. The optical monitoring and cell cultivation on a disc could be a stepping stone for drug screening assays and various biomedical applications.

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