REAL-TIME MONITORING GLUCOSE UTILIZATION IN SINGLE CELL USING A CELL CULTURE CHIP WITH AN EMBEDDED DETECTOR

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ABSTRACT

We present a systematic study of a novel microfluidic platform capable of *in situ* detection of [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG), a glucose analog, in living cell(s), which is unprecedented using conventional technology. We investigated various operation parameters (e.g., [^{18}F]FDG concentration and cell types) by performing sensitive detection of [^{18}F]FDG utilization in a small number of cells (i.e., 1-100 cells).

KEYWORDS: Cell culture, FDG uptake, PSAPD, Glucose utilization

INTRODUCTION

This platform was composed of two major components: (i) an integrated microchip [1] for automated cell handling and (ii) a PSAPD detector [2] for real-time detection of positrons emitted from [^{18}F]FDG trapped inside the cell(s). [^{18}F]FDG is an important radiolabeled probe because it mimics glucose characteristics. Clinically, elevated levels of [^{18}F]FDG utilization in tissue is an indication of cancer, due to the activated glucose metabolism of most cancers [3]. Progressing from our initial proof-of-principle experiments for detecting radioactivity with microchip [4] and the module of micro cell culture [5], we recently implemented a complete system capable of detecting [^{18}F]FDG from a small amount of cells.

EXPERIMENTAL

Figure 1 (a) shows the fabricated multi-layer PDMS microfluidic chip for radioactive detection of [^{18}F]FDG utilization by living cells cultured inside 4×3 chambers. The detection of positrons emitted from [^{18}F]FDG was achieved with an embedded PSAPD detector located underneath the microchip; Figure 1 (b). Calibration of the PSAPD detector through the confinement of [^{18}F]FDG inside the cells was conducted with a well-type gamma counter. A linear correlation was obtained; Figure 1 (c). The middle inset picture shows the PSAPD radiograph where intact cells were detected in situ (right inset picture: cells were on-chip during the whole detection course).

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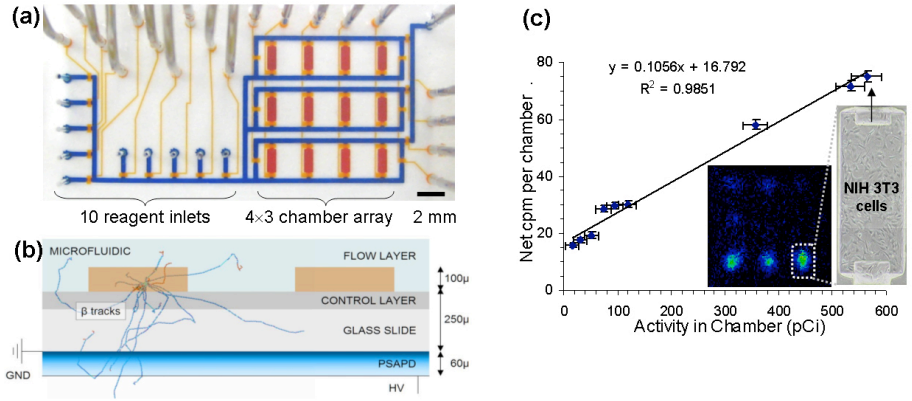

Figure 1. (a) Illustration of the micro culture chip. Color code: Blue: micro-channel network; red: micro culture chambers; and yellow: micro valves. (b) The cross section of the integrated microfluidic imaging platform. (c) Calibration of the PSAPD detector (count per min, cpm).

RESULTS AND DISCUSSION

The [^{18}F]FDG utilization of individual U87 glioblastoma (brain cancer) cells was determined by exposing cells to [^{18}F]FDG solution. We found that [^{18}F]FDG utilization depended linearly on the [^{18}F]FDG concentration for a large dynamic range of concentration, from 0.01 to 1 mCi/mL; Figure 2 (a). Moreover, normal U87 cell morphology was observed even in the maximum radioactive concentration (right inset picture). Second, the [^{18}F]FDG radioactivity per U87 cells depended on the time of incubation; Figure 2 (b). However, the [^{18}F]FDG uptake of cells seemed to saturate with a long incubation times.

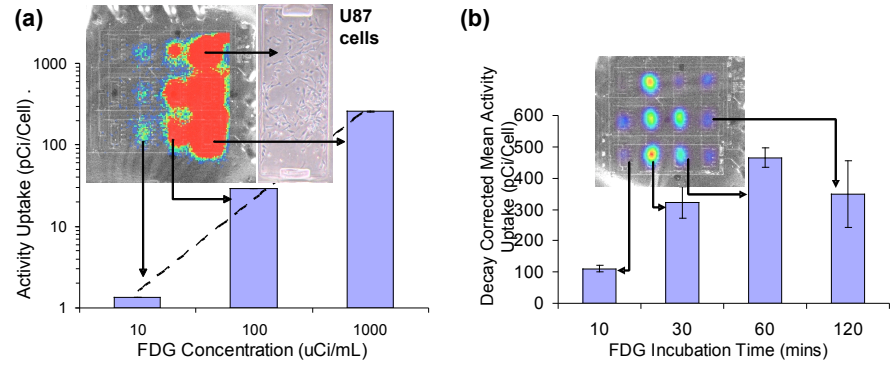

Figure 2. The [^{18}F]FDG radioactivity of individual cells as a function of (a) [^{18}F]FDG concentration and (b) the time of [^{18}F]FDG incubation.

Cellular [^{18}F]FDG utilization was studied with different cell types (brain cancer cells: U87 and LN229) as well as different numbers of cells incubated in the chambers (from 0, 1, 2 to hundred cells); Figure 3. The signal emitted from a single cell

was relatively low; however, the PSPAD detector was sensitive enough to capture the signal. Analysis of the signals revealed that both cell types transported similar amounts of [^{18}F]FDG per cell. This indicates that the [^{18}F]FDG uptake is independent of the number of cells plated per chamber.

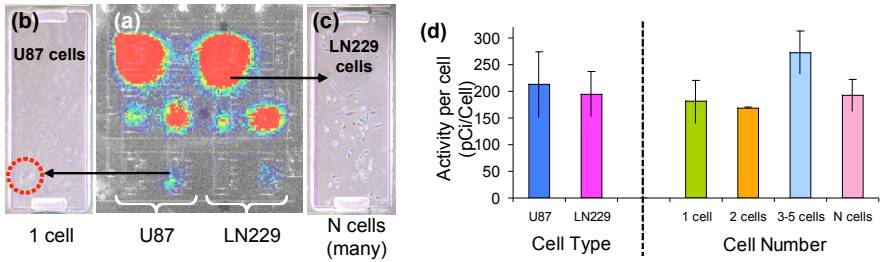

Figure 3. (a) Simultaneous detection of cellular [^{18}F]FDG utilization in response to cell types and numbers of cells plated. (b) and (c) are micrographs showing single and hundred cells. (d) Quantization according to cell types and cell populations.

CONCLUSIONS

This platform thus enables a broad range of radioactive imaging at a cellular level which will be a valuable tool for the clinical diagnosis of cancer tissue from patients. Several interesting studies are ongoing using this integrated platform.

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