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Towards a high throughput impedimetric screening of chemosensitivity of cancer cells suspended in hydrogel and cultured in a paper substrate

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ABSTRACT

In order to achieve high predictive value of cell chemosensitivity test for clinical efficacy, cancer cells were suggested to be encapsulated and cultured in hydrogel to mimic the natural microenvironment of tumors. However, handling 3D cells/hydrogel culture construct is tedious and cellular response is difficult to be quantitatively analyzed. In the current study, a novel platform for conducting 3D cell culture and analyzing cell viability has been developed towards a high throughput drug screening. Cells encapsulated in the hydrogel were cultured in the microwells of a paper substrate. The substrate was then immersed in the culture medium containing drug for 2 days. At 24 and 48 h during the culture course, the paper substrate was placed on the measurement electrodes for conducting the impedance measurement in order to quantify the cell viability in the hydrogel. Cell viability of two human hepatoma cell lines (Huh7 and Hep-G2) was quantitatively investigated under the treatment of two drugs (doxorubicin and etoposide). The results represented by IC_{50} values revealed that Huh7 cells had a higher drug resistance than Hep-G2 cells and doxorubicin had a higher efficacy than etoposide for treating hepatocellular carcinoma. The current work has demonstrated a high throughput, convenient, and quantitative platform for the investigation of chemosensitivity of cells cultured in the 3D environment.

1. Introduction

Cell culture is a commonly used technique to study the cellular responses under the tested conditions. Conventionally, cells seed and grow as a monolayer on a solid surface of the culture vessel and this culture technique is referred to two-dimensional (2D) culture model. It is widely used because of the simplicity in terms of operation and observation. However, it was reported that low predictive value of chemosensitivity test was obtained for clinical efficacy (Hay et al., 2014). One of the possible reasons might be cells cultured as a monolayer expressed lower drug resistance than cells cultured in a three-dimensional (3D) environment (Koshkin et al., 2016; Longati et al., 2013). Recently, biologists proposed to encapsulate cells into hydrogel to mimic the natural *in vivo* environment, referring to 3D culture model (Abbott, 2003; Lee et al., 2008). Greater predictive capacity was reported for drug discovery applications (Lai et al., 2011). It is expected that the 3D cell culture model will become a mainstream approach on drug screening (Pampaloni et al., 2007). Thus, development of standard protocols is essential for handling 3D cells/hydrogel culture construct and analyzing cells quantitatively (Pampaloni et al., 2007).

In the 3D cell culture model, most of the studies were to encapsulate cells in the hydrogel and then load to standard multi-well microplates for the culture (Tibbitt and Anseth, 2009). The cells/hydrogel culture construct was contained in a solid culture well and the tested substance was applied to the well. In this processing, the tested substance was diffused onto the culture construct and chemical gradient may be induced within the hydrogel. Cells suspended in the hydrogel received unequal chemical concentration. Thus, miniaturized platform was proposed to culture cells in the micro-scale culture wells to provide a uniform and well-defined culture environment (Wu et al., 2011). Moreover, cells encapsulated in the hydrogel are difficult to be quantified by the conventional bio-assays such as MTT and WST-1 assay. It is because the reacted solution cannot be extracted from the hydrogel. With the micro-fabrication technology, a pair of parallel plate electrodes was embedded in the culture well for the impedimetric quantification of cellular response (Lei et al., 2014a). Non-invasive measurement was achieved for the dynamic study of the cell chemosensitivity during the culture course. High throughput and automatic cell-based

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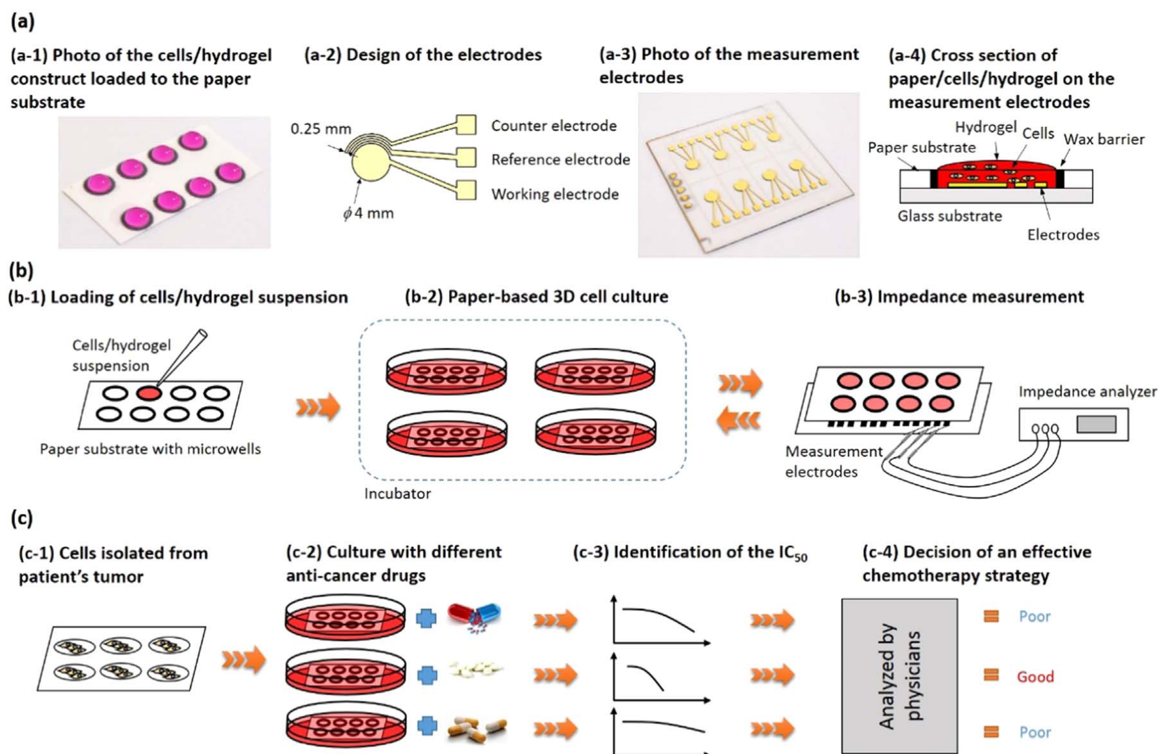

Fig. 1. Experimental setup and procedure of the paper-based cell culture and quantification platform. (a-1) Photo of the cells/hydrogel construct loaded to the microwells of the paper substrate. (a-2) Design and dimension of the electrodes based on the setup of the three-electrode system. (a-3) Photo of the glass substrate with the measurement electrodes. (a-4) Cross section of paper/cells/hydrogel on the measurement electrodes. (b) Experimental procedure of the impedimetric screening of drug sensitivity of cells suspended in the hydrogel. (c) Assessment of the chemosensitivity of the cells isolated from the patient's tissue and decision of an effective chemotherapy strategy.

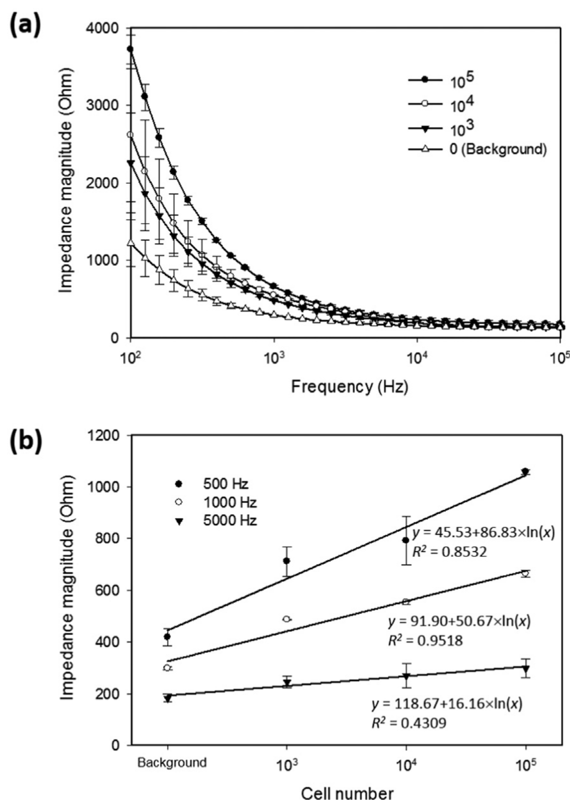

Fig. 2. Quantification of cells based on impedance measurement. Cells in different cell numbers of 0 (background), 10^3, 10^4, and 10^5 were encapsulated in the hydrogel. (a) The impedance magnitude spectrums across 100 Hz to 100 kHz. (b) The correlations between cell number in the hydrogel and the impedance magnitude measured at 500, 1000, and 5000 Hz. The error bars represent standard deviations of at least 3 repeated experiments.

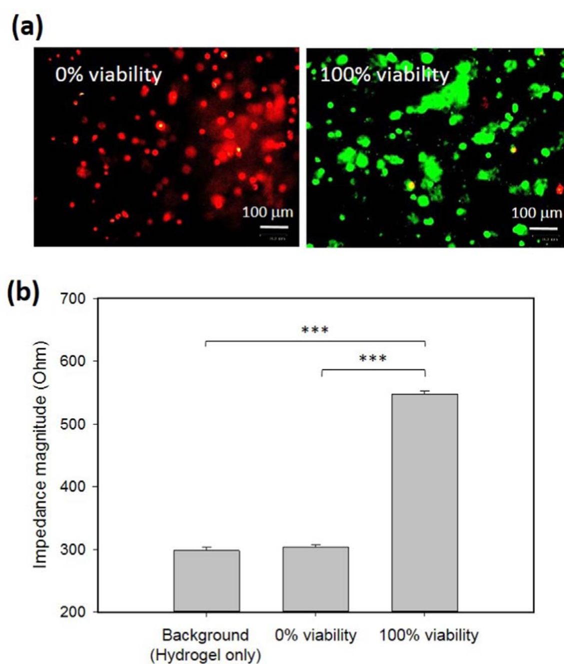

Fig. 3. Investigation of the impedance magnitude of live/dead cells in the hydrogel. (a) Fluorescent microscopic images of live/dead cells suspended in the hydrogel. (b) The impedance magnitude of 0% and 100% viability compared with the background (hydrogel only). The error bars represent standard deviations of at least 3 repeated experiments. The results were analyzed by one-way analysis of variance (ANOVA). Statistical significances are indicated as $*p < 0.05$, $**p < 0.01$, and $***\ p < 0.005$.

assays were demonstrated by the polydimethylsiloxane (PDMS)/glass microfluidic platform. Medium or tested substance was perfused to the culture wells by inserting a number of tubings to the platform.

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