Towards personalized medicine with a three-dimensional micro-scale perfusion-based two-chamber tissue model system

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ABSTRACT

A three-dimensional micro-scale perfusion-based two-chamber (3D-µPTC) tissue model system was developed to test the cytotoxicity of anticancer drugs in conjunction with liver metabolism. Liver cells with different cytochrome P450 (CYP) subtypes and glioblastoma multiforme (GBM) brain cancer cells were cultured in two separate chambers connected in tandem. Both chambers contained a 3D tissue engineering scaffold fabricated with biodegradable poly(lactic acid) (PLA) using a solvent-free approach. We used this model system to test the cytotoxicity of anticancer drugs, including temozolomide (TMZ) and ifosfamide (IFO). With the liver cells, TMZ showed a much lower toxicity to GBM cells under both 2D and 3D cell culture conditions. Comparing 2D, GBM cells cultured in 3D had much high viability under TMZ treatment. IFO was used to test the CYP-related metabolic effects. Cells with different expression levels of CYP3A4 differed dramatically in their ability to activate IFO, which led to strong metabolism-dependent cytotoxicity to GBM cells. These results demonstrate that our 3D-µPTC system could provide a more physiologically realistic *in vitro* environment than the current 2D monolayers for testing metabolism-dependent toxicity of anticancer drugs. It could therefore be used as an important platform for better prediction of drug dosing and schedule towards personalized medicine.

1. Introduction

Personalized medicine is a new healthcare paradigm where proper medication and dosage are customized to special characteristics of a patient and his/her disease. Individuals respond differently to drugs. A growing list of genetic polymorphisms in drug-metabolizing enzymes, drug transporters and drug targets have been linked to the efficacy, dosage, and toxicity profile in human [1]. Among drug-metabolizing enzymes, the cytochrome P450 (CYP) superfamily converts drugs into their primary metabolites. About 75% of drugs are eliminated via CYP-mediated metabolism, and specifically, CYP3A4, the most abundantly expressed hepatic cytochrome P450, is involved in the metabolic

process of two-thirds of all marketed drugs [2]. The genotypes of major drug-metabolizing CYPs vary significantly from person to person. This variability is believed to have resulted in different isozyme activities and contributed to the variation in drug responses among individuals [3]. Differentiating the effect of liver metabolism on drugs is therefore an important aspect of personalized medicine.

Many *in vitro* liver models have been developed to mimic the human liver function in the past few decades. Early liver models included isolated and perfused livers [4,5], liver tissue slices [6–9], freshly isolated hepatocytes in suspension [10,11], primary hepatocyte cultures [12–14], and liver microsomes [15,16]. Each of these models could reproduce certain liver functions; however, the preservation of major liver functions such as drug metabolism tended to be short-lived and the ability to integrate them into a high throughput drug screening system was lacking [17,18]. For high throughput applications, Griffith's group proposed a perfusion-based cell culture system with liver cells cultured in an array of silicon micro-wells [18–21]. Liver cells were successfully

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