Advances in Biomedical Manufacturing: 3D Tissue Model Systems for Personalized Medicine

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Abstract

Biomedical manufacturing is an emerging frontier of manufacturing, which can be represented by many areas of research and innovation, for example, biofabrication of cell-integrated micro-fluidic devices, engineered tissue substitutes and tissue model systems, innovative design and manufacturing of surgical tools, drug delivery devices, and related metrology, sensing, and control techniques. An important biomedical manufacturing area is fabrication of three-dimensional (3D) tissue model systems for personalized medicine. Individuals respond differently to drugs. A growing list of genetic polymorphisms in drug metabolizing enzymes, drug transporters and drug targets have been linked to drug efficacy, dosage, and toxicity profile in human. Among drug metabolizing enzymes, the P450 (CYP) super family converts drugs into their primary metabolites. Specifically, CYP3A4, the most abundantly expressed P450, is involved in the metabolic process of two-thirds of all the marketed drugs. The genotypes of CYP vary significantly from person to person. This variability is believed to have resulted in different isozyme activities and the variation in drug response among individuals. Understanding liver metabolic effects on drugs is therefore an important aspect of personalized medicine. A microfluidic perfusion-based, two-chamber 3D tissue model system has been developed for personalized cancer chemotherapy. The system is built on a polymer chip with two separate chambers containing porous polymeric scaffolds to culture liver and cancer cells, respectively. The two chambers are connected with microfluidic channels to mimic the blood flow through the organ-like 3D cell cultures. The cytotoxicity of anticancer drugs, including Temozolomide (TMZ) and Ifosfamide (IFO), was tested *in vitro* to treat Glioblastoma (GBM) cancer with and without the liver metabolism effect. The effects of liver cells with different expression levels of the CYP3A4 enzyme were also tested. Under the TMZ treatment, it was found that the GBM tumor cells had a much higher viability with liver cells, suggesting that the drug metabolism of liver strongly affected the efficacy of TMZ, and that the drug dosage determined in a tumor-alone culturing system may not be accurate for cancer treatment. It was also found that the liver cells converted the prodrug IFO to its cytotoxic metabolite, isophosphoramide mustard (IPM), which has a much stronger decimating effect on GBM cells. Furthermore, it was found that different expression levels of CYP 3A4 in liver cells had a significant effect on the viability of GBM cells. These tests confirmed that 3D tissue models could be used to simulate*in vivo* liver metabolism effects on anticancer drugs. Since the CYP 3A4 expression varies among individual patients, it is possible to use this device for personalized cancer treatment,*i.e.*, to use engineered liver tissue, matched with the patient's own CYP genotype or expression level, and his/her own tumor tissue to screen for the most effective drugs and determine the optimal dosage schedule. This talk will be focusing on fabrication and testing of the 3D tissue model system for personalized medicine. A brief overview of biomedical manufacturing frontier and the challenges and opportunities of 3D tissue model systems will also be discussed.