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Review

Organ/body-on-a-chip based on microfluidic technology for drug discovery

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ABSTRACT

Although animal experiments are indispensable for preclinical screening in the drug discovery process, various issues such as ethical considerations and species differences remain. To solve these issues, cell-based assays using human-derived cells have been actively pursued. However, it remains difficult to accurately predict drug efficacy, toxicity, and organs interactions, because cultivated cells often do not retain their original organ functions and morphologies in conventional in vitro cell culture systems. In the μTAS research field, which is a part of biochemical engineering, the technologies of organ-on-a-chip, based on microfluidic devices built using microfabrication, have been widely studied recently as a novel in vitro organ model. Since it is possible to physically and chemically mimic the in vitro environment by using microfluidic device technology, maintenance of cellular function and morphology, and replication of organ interactions can be realized using organ-on-a-chip devices. So far, functions of various organs and tissues, such as the lung, liver, kidney, and gut have been reproduced as in vitro models. Furthermore, a body-on-a-chip, integrating multi organ functions on a microfluidic device, has also been proposed for prediction of organ interactions. We herein provide a background of microfluidic systems, organ-on-a-chip, Body-on-a-chip technologies, and their challenges in the future.

1. Introduction

Animal testing plays a crucial role in predicting pharmacokinetics as a preclinical test in drug discovery. The efficacy and toxicity of a drug candidate in the human body are predicted based on the information previously obtained by animal testing. However, errant pharmacokinetic predictions caused by species differences between humans and experimental animals has led to abandonment of some candidate compounds prior to clinical trials [1], and directly affects the efficiency and costs of new drug development. In the European Union (EU), animal testing for cosmetic development has been completely prohibited since 2013. It is conceivable that this movement toward reduction and prohibition of animal testing might extend to drug discovery in the near future. Currently, in vitro tests with human-derived cells are used as an alternative to animal testing. These cell-based assays are an effective means for preliminary screening such as cytotoxicity. However, these methods have problems, such as cells cultured using petri dishes and multi-well plates may markedly lose their responsiveness and function, and interactions between organs cannot be directly evaluated. Thus, there are major differences between information obtained from animal testing and conventional in vitro tests for pharmacokinetics predictions.

In this decade, organ-on-a-chip based on microfluidic technology has been proposed as a novel cell-based assay tool in the μTAS (Micro Total Analysis Systems) research field. At the beginning of this research, organ-on-a-chip technology was quite far from practical use. In recent years, however, large-scale research grants at the national level have been allocated to research projects regarding organ-on-a-chip in Western countries, and expectations for practical use of this technology are increasing. In this paper, we

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review how organ-on-a-chip works, and discuss issues for practical application of these innovative technologies during drug discovery.

2. Microfluidic technology meets cells

Microfluidic devices can be used for chemical reactions and analyses in microchannels and microstructures, which are fabricated by semiconductor microfabrication technology such as photolithography and softlithography [2]. This technology called "Microfluidics" or "Lab-on-a-chip" has been established as an interdisciplinary field of research by combining micro/nano-device technologies, chemical sensor technology, and analytical chemistry in the 1990s.

In general, cell lines cultured in vitro have been largely inactivated and lack physiological functions [3]. This phenomenon also occurs in primary cultured cells, and it is extremely difficult to maintain cellular functions for prolonged periods even if these functions are normal immediately after harvest. In conventional methodology, cells are cultured in a semi-static environment, where application of experimental compounds to cells is only dependent on diffusion. On the other hand, in vivo, cells obtain oxygen and nutrients via blood flow, as well as receive chemical stimulation and physical stimulation, such as stretching and shear stress, from the surrounding environment. Such differences between in vivo and in vitro in morphology and environment might be reasons for loss or deactivation of cellular functions in cultures.

To fill the large gap between in vivo and in vitro conditions, researchers working in the μTAS and other tissue engineering research fields have applied microfluidic devices to cell culture applications since the beginning of the 2000s. Spatiotemporally liquid conditions, cell adhesion, and mechanical stimuli to cells can be controlled using microfluidic techniques. Organ-on-a-chip technology, which utilizes this microfluidic approach to replicate organ functions, has attracted a great deal of attention in recent years. Especially with the progress of a differentiation induction method for iPS cells, tissue models and disease models for drug discovery using organ-on-a-chip technology have been proposed, and are expected to serve as platforms for cell-based assays during drug discovery.

Organ-on-a-chip research in its initial stages showed improvements in functional activity by perfusion culture of 3D hepatocyte aggregations, and observation of responses to shear stress by exposing vascular endothelial cells to medium flow in a microchannel [4,5]. Recent advances in microfabrication, cell engineering, and imaging technologies have led organ-on-a-chip to become an innovative technology capable of reproducing physiological cell behaviors in vitro. Indeed, in the past few years, a substantial number of research grants have been invested in organ-on-a-chip projects from the National Institute of Health (NIH), the Food and Drug Administration (FDA), and the Defense Advanced Research Projects Agency (DARPA) in the USA, from Framework Program 7 (FP7) in the EU, and from Japan Agency for Medical Research and Development (AMED) in Japan. This investment also shows the magnitude of expectations for research related to organ-on-a-chip technology [6].

3. Organ-on-a-chip

So far, μTAS researchers have proposed organ-on-a-chip devices that reproduce various behaviors of various organs and tissues [7]. An overview of all these devices is beyond the scope of this review, but we introduce examples of in vitro research models representing major organs such as the lung, liver, kidney, and gut in this section.

3.1. Lung-on-a-chip

The most famous organ-on-a-chip is the "lung-on-a-chip," known as "breathing lung," developed by the Ingber research group at Harvard University (Fig. 1a) [8]. This device has a two-layer channel structure separated vertically by a microporous membrane made of stretchable silicone, polydimethylsiloxane (PDMS). They cultured alveolar epithelial cells on the upper surface of the membrane, vascular endothelial cells on the lower surface, and used flowing air and culture medium, respectively, to replicate the lung structure on a microfluidic device. The physiological expansion and contraction movements of the alveolus during respiration were mimicked by changing the internal pressure of the channel on both sides of the main channel at a specific cycle to extend and contract the porous membrane. They reproduced inflammatory reactions in which vascular endothelial cells highly express the integrin ligand (ICAM-1) after exposure of cells to tumor necrosis factor (TNF-α) and bacteria using this device. In addition, neutrophils flowing in the vascular side channel attached to the vascular endothelial cells following the expression of ICAM-1, then migrated to the alveolar epithelial cell surface side, through the vascular endothelial cells and the membrane's pores, and phagocytized the bacteria. A toxicity test using nanoparticles demonstrated that the amount of nanoparticle uptake into the blood vessel side of the device was increased by stretching movements of the membrane. Similar results were obtained in an animal test conducted under similar conditions. In a separate study, they also created a disease model that reproduced symptoms of pulmonary edema with the device [9]. When a low-molecular-weight drug was used for treatment of pulmonary edema in this disease model, inhibition of extravasation was observed similar to that observed in a pulmonary edema model animal. Therefore, applications as a disease model for in vitro studies have also been suggested. This device format has been widely applied to other organs such as the gut and kidney, as described later [10–12].

3.2. Liver-on-a-chip

Since the liver is the principal organ related to drug metabolism, it is extremely important to accurately predict its metabolic ability and toxicity during the drug discovery process. However, hepatocytes used for in vitro screening lose many of their original functions and activities. Powers and colleagues proposed a microfluidic device that enables morphogenesis of 3D tissue structures under continuous perfusion (Fig. 1b) [13]. Three-dimensional scaffolds were combined with a cell-retaining filter and structural support in a cell culture chamber to allow perfusion of culture medium across the top of the array and through the 3D cell aggregates in each channel. A cell culture chamber was designed so that flow rates meet estimated values of cellular oxygen consumption while providing fluid shear stress within the physiological range. The authors demonstrated that this device enables the formation of hepatocellular aggregates reminiscent of structures seen in hepatic acini, and could maintain their structure and viability for up to 2 weeks using this device.

To investigate drug responses, it is also important to maintain the polarized transport ability of hepatocytes. Bile canaliculi are formed between regularly arranged hepatocytes radially, and regularly extend from the central vein in the hepatic lobules. Bile containing metabolic products biosynthesized in the cells is excreted into the bile canaliculi. Thus, the bile canaliculi are important targets in drug metabolism studies in vitro. Nakao and colleagues developed a hepatic lobules model device that