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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

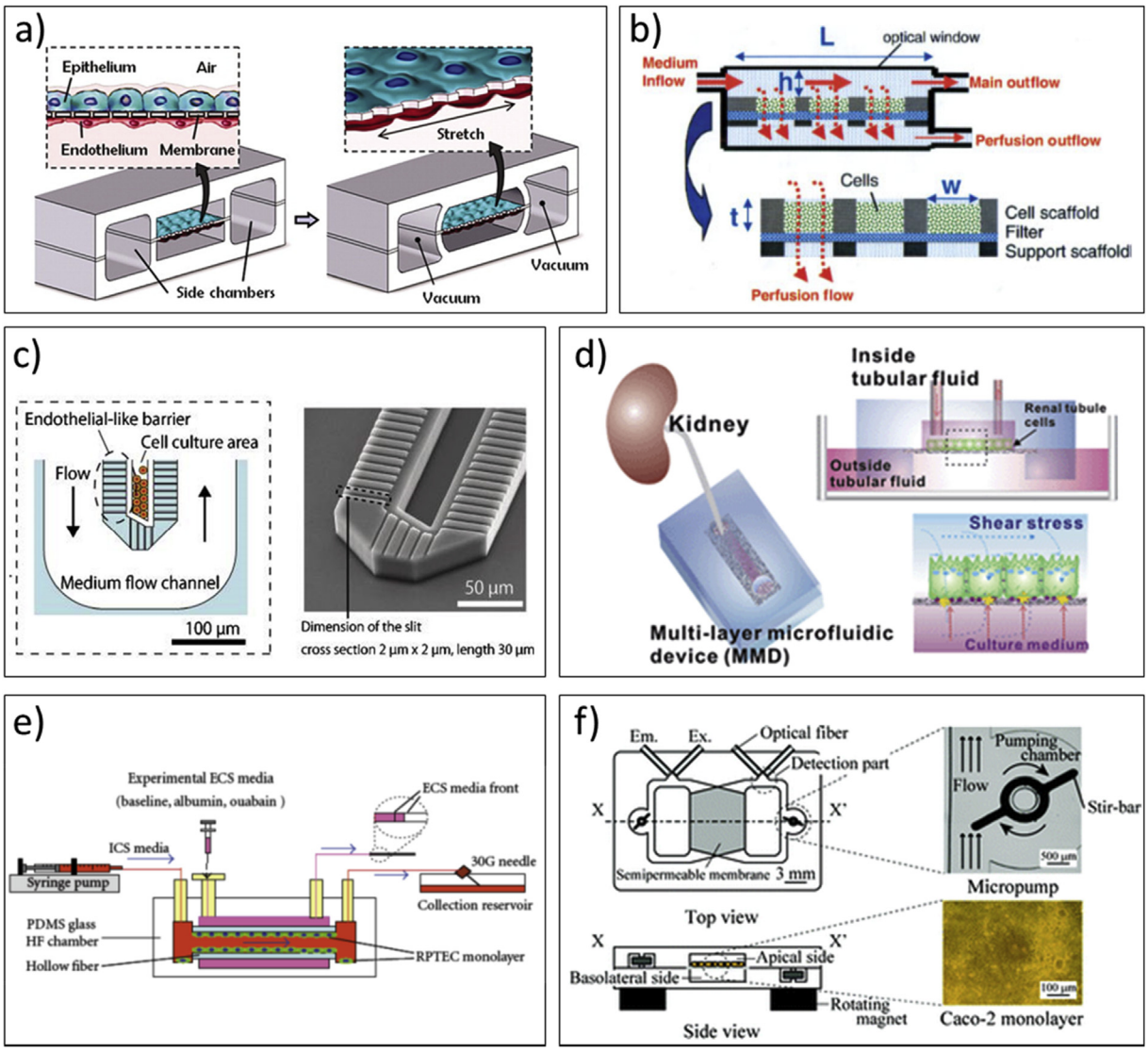

Fig. 1. Organ-on-a-chip devices: a) The lung-on-a-chip device replicates physiological breathing movements by applying vacuum to the side chambers and causing mechanical stretching of an elastic membrane forming the alveolar-capillary barrier [8]. Copyright 2010, American Association for the Advancement of Science. b) The microfluidic device for perfused 3D liver culture [13]. Copyright 2002, Wiley Periodicals. c) The liver-on-a-chip device mimics the structure of a hepatic cord [14]. Copyright 2011, American Institute of Physics. d) The kidney-on-a-chip device having a porous membrane generates in vivo-like tubular environments for collecting duct cells [19]. Copyright 2009, Royal Society of Chemistry. e) The kidney-on-a-chip device with the tubular structure of the renal tubule by incorporating a tubular hollow fiber membrane [21]. Copyright 2013, Hindawi Publishing Corporation. f) The gut-on-a-chip device has a 2-compartment structure separated by a microporous membrane, and stirrer-based micropumps and optical fiber inserts for each compartment [22]. Copyright 2008, Royal Society of Chemistry.

reproduced the microstructure of the hepatic cord, which is the smallest unit of the hepatic lobule, for physiologic bile canaliculi formation as an in vitro model (Fig. 1c) [14]. The cell culture area of the device was designed to align hepatocytes in two lines similar to hepatic cords. It was shown that aligned hepatocytes gradually self-organize and form bile canaliculi along the hepatic cord-like structure. Then, a drug metabolism test using carboxydichlorofluorescein diacetate (CDFDA) as a model metabolite was performed as an application of the drug response evaluation. CDFDA is metabolized to a fluorescent product, carboxydichlorofluorescein (CDF), by hepatocyte esterase, and is excreted into the bile canaliculi. When culture media containing CDFDA were perfused in the blood vessel flow channel, excretion of CDF into the bile canaliculi continuously formed between the cells was observed. This result is a good example showing that in vivo functions, such as metabolic pathways that maintain the shape and polarity of tissues, can be reproduced by mimicking microstructures in vivo.

3.3. *Kidney-on-a-chip*

The kidney is an important organ responsible for metabolism and excretion in vivo. During drug discovery, drug candidate efficacy and toxicity in the kidney are evaluated exclusively by animal testing because there are no suitable in vitro models. However, drug dropouts in clinical trials due to differences in metabolic mechanisms between humans and experimental animals lead to enormous losses in drug development costs. Accurate identification of nephrotoxic compounds at the preclinical testing stage would allow significant cost reductions and effectively avoid nephrotoxic drugs during development [15]. Furthermore, a highly accurate in vitro disease model brings new insights into the elucidation of mechanisms of kidney disease, and can be expected to be utilized as a promising drug screening system for new treatments.

In the simplest kidney-on-a-chip devices, Madin-Darby canine kidney epithelial (MDCK) cells and human kidney-2 (HK-2) cells

were adhered to the bottom surface of a microchannel, and loaded with physiological shear stress [16–18]. The authors showed increased cell thickness, expression of Na/K ATPase and promotion of cilia formation on the cells by the shear stress using this device. These data suggest that physiological behavior of kidney-derived cells can be replicated using the appropriately controlled shear stress load.

To model the reabsorption function of renal tubules, two-layered kidney-on-a-chip devices with porous membranes were proposed (Fig. 1d) [19,20]. In these studies, the physiological responses related to changes of sodium concentration and osmotic pressure of the apical channel were reproduced by introducing hormones such as vasopressin and aldosterone into the basal channel of the device. They also reported that shear stress not only alters cell orientation but also promotes P-glycoprotein expression, cell polarity expression, cilia growth, and albumin/glucose absorption in the cells.

To mimic a more physiologically accurate structure, a microfluidic device that reproduces the tubular structure of the renal tubule by incorporating a tubular hollow fiber membrane into a microchannel has been proposed (Fig. 1e) [21]. Musah and colleagues applied the lung-on-a-chip device to replicate the glomerulus structure by combining a human iPS-derived podocyte, and showed not only that mechanical stimuli such as shear stress and stretch contribute differentiation and maturation of podocyte, but also that the device is applicable as an in vitro kidney model through an experiment using an anticancer drug [12]. Thus, even the kidney, with its extremely complicated structures and functions, can be effectively modeled using organ-on-a-chip technology, and is an extremely effective approach for reproducing in vivo tissue structure and function.

3.4. Gut-on-a-chip

The gut is an organ responsible mainly for digestion and absorption. Particularly, the small intestine functions as a barrier against orally administered drugs, so it is important to predict its function during drug discovery. To evaluate this function, Kimura and colleagues developed a small intestine-on-a-chip device with an optical detection system (Fig. 1f) [22]. The device has two independent compartments separated by a microporous membrane on which small intestinal model (Caco-2) cells were cultured. Performance of the device was examined through long-term culture and monitoring of polarized transport activity of the cells. The cells could be cultured for more than two weeks, and monolayer transport of rhodamine 123 was successfully monitored by on-line fluorescent measurements. However, although on-line and on-chip measurement of cell dynamics was realized using this device, the cell function was not physiological.

Kim and Ingber proposed a gut-on-a-chip device that enables Caco-2 cells to be exposed continuously to physiological mechanical stimuli such as shear stress and cyclic mechanical strain that mimic peristalsis-like motions in vivo [11]. The authors showed that cells cultured using the device are reprogramed to undergo spontaneous 3D villus morphogenesis and small intestinal cell differentiation under these physiological conditions. To replicate more accurate physiological conditions, this device was used to co-culture multiple commensal microbes in contact with intestinal epithelial cells, and to analyze resulting physiological phenomena [23]. The authors demonstrated that this in vitro model replicated results like those from past animal and human studies, so they concluded that the gut-on-chip device can be used to analyze intestinal pathophysiology and dissect disease mechanisms in vitro.

4. Body-on-a-chip

Humans are composed of organs and tissues possessing multiple physiological roles and can be assumed to represent a kind of complex system. As discussed earlier, it is difficult to accurately predict interactions between organs and tissues using conventional in vitro cell culture approaches, so animal tests must be conducted to predict pharmacokinetics. In the organ-on-a-chip research field, microfluidic devices containing the functions of multiple organs and tissues, called “body-on-a-chip” or “human-on-a-chip”, have been proposed. These devices might be used to observe continuous or linked pharmacokinetic processes such as ADME (absorption, distribution, excretion, metabolism) of various drug administration routes, and the data obtained may be applied to construct mathematical models for prediction of drug efficacy.

The Shuler research group, pioneers of biochemical engineering research, has led body-on-a-chip studies ahead of the world since the 2000s [24–27]. They developed a body-on-a-chip device with multiple organ chambers called the micro cell culture analog (uCCA), and co-cultured different organ-derived cells on the device. Cell-based assays using an anticancer drug, Tegafur, were performed to observe organ interactions using the device. Their results showed that complex biological responses to a dosing scenario assuming oral or intravenous administration, previously studied conventionally using animal assays, can be reproduced using body-on-a-chip technology. Imura and colleagues developed a body-on-a-chip device that integrates small intestine model functions responsible for absorption, in addition to the liver model with metabolic functions (Fig. 2a) [28]. Using their device, they showed differences in anticancer action using drugs with different intestinal absorption rates and therapeutic mechanisms. They also succeeded in integrating kidney excretion functions by integrating a dialysis membrane into a body-on-a-chip device [29].

Although these body-on-a-chip devices could mimic multiple interactions between organs in vitro, each biological parameter measured was non-physiological. To realize accurate pharmacokinetic predictions, Kimura and colleagues developed a body-on-a-chip device that reproduces various physiological parameters such as organ volume ratios, and blood flow rate ratio on the device (Fig. 2b) [30]. This device was used for a drug efficacy evaluation of anticancer drugs, and confirmed that inhibition of absorption at the intestinal barrier, and physiological pharmaceutical benefits due to liver metabolism are reproducible using microfluidics devices.

We must consider that these body-on-a-chip devices are not capable of reproducing all biological responses. As Shuler said in his paper, the significance of body-on-a-chip is not simply to create sophisticated miniature human bodies, but to discover unknown responses that can be observed only in real-time interactions between organs. The data obtained using these devices should contribute to improvements in the accuracy of mathematical models [31]. In other words, body-on-a-chip technology needs to be used with pharmacokinetic models to predict unknown mechanisms or phenomena. The devices introduced here could be applied to various pharmacological toxicity tests by allowing combinations of cells and substances to be introduced, and a mathematical model based on the obtained experimental data using these devices could be expected to be put to practical use as an evaluation system for pharmacokinetic predictions. Indeed, Shuler et al. proposed a method for prediction of cell behavior following exposure to anticancer agents by combining data obtained using μCCA and mathematical models to predict pharmacokinetics-pharmacodynamics [26,27]. As a result, they showed the possibility of combining a body-on-a-chip approach with a mathematical modeling approach (Fig. 2c).

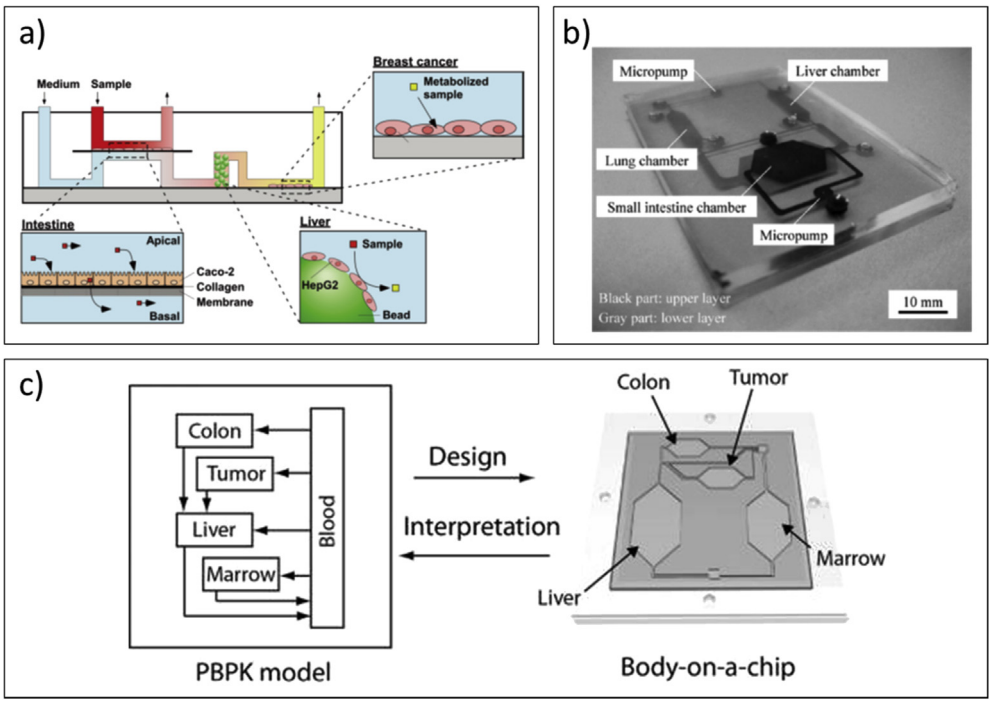

Fig. 2. Body-on-a-chip devices: a) The body-on-a-chip device having small intestine and liver models [28]. Copyright 2010, American Chemical Society. b) The body-on-a-chip device with various physiological parameters [30]. Copyright 2014, Society for Laboratory Automation and Screening. c) Design of the body-on-a-chip device based on PBPK modeling principle [27]. Copyright 2014, the Society for Experimental Biology and Medicine.

5. Issues related to practical applications of organ-on-a-chip

We have introduced trends in research related to organ-on-a-chip and body-on-a-chip. However we realize that currently these devices cannot be used directly for drug discovery as an alternative to animal testing. There are still issues to be overcome in both the engineering and biological technologies of these devices. In many proposed studies involving organ-on-a-chip, the usefulness of these devices was indicated by an evaluation of easily observed and measured functions. However, a practical in vitro model should be a system that can observe and record a variety of physiological responses to specific biological stimuli. To satisfy these requirements, we need to develop not only observation technologies which can evaluate multiply biological responses, but also biochemical technologies which can perform biochemical analysis in the micro-space of microfluidic devices, in parallel with organ-on-a-chip studies.

In addition, complicated handling requirements to use organ-on-a-chip devices greatly affects high throughput and usability, and these considerations might become a major barrier to wider practical applications. Unless cell manipulation systems and assay systems are systemized and automated in discrete equipment, organ-on-a-chip devices will not be practical. Regarding systemization, several companies in Europe and the United States, and the research group of Kanamori in Japan, have started to work toward creating organ-on-a-chip systems [32,33].

One of the main biological issues is related to sources of cells to be introduced into organ-on-a-chip technology. Although cell lines and primary culture cells were typically used for evaluation of microfluidic device functions in previous studies, immortal cell lines are usually derived from cancer cells, and have markedly lost their original organ functional activity. Although primary human derived cells could ideally be used for predicting highly accurate pharmacokinetics, there are limitations on availability of primary cell cultures due to issues of donors, and their cost. On the other hand, if human iPS-induced cells could be made readily available, the problems of loss of functional activity would be solved, so that organ-on-a-chip technology would be much closer to practical application.

6. Conclusion

In this paper, we outlined studies of organ-on-a-chip and body-on-a-chip which can be effective tools in drug discovery. Unfortunately, there are no concrete examples in which organ-on-a-chip technologies have been fully utilized in the actual drug discovery process. Griffith, who is a pioneer of organ-on-a-chip research, said that “Pharma knows what problems it needs to solve, but not how to engineer a solution. And engineers know how to build chips, but they haven't thought through how those chips will provide a solution” [30]. For the practical use of this technology, active and organic collaboration among different research fields such as medical, pharmaceutical, biological, and engineering sciences is necessary. We hope this review article will help improve understanding for such collaborative work.

Author contributions

H.K., Y.S. and T.F. designed the research. H.K. prepared the manuscript. Y.S. and T.F. commented on the manuscript.

Declaration

The authors declare no conflicts of interest associated with this manuscript.

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References

[1] Lin JH. Species similarities and differences in pharmacokinetics. Drug Metab Dispos 1995;23(10):1008–21.
[2] Wolfe DB, Qin D, Whitesides GM. Rapid prototyping of microstructures by soft lithography for biotechnology. Methods Mol Biol Clift NJ 2010;583:81–107.
[3] Rodriguez-Antona C, Donato MT, Boobis A, Edwards RJ, Watts PS, Castell JV, et al. Cytochrome P450 expression in human hepatocytes and hepatoma cell lines: molecular mechanisms that determine lower expression in cultured cells. Xenobiotica 2002;32(6):505–20.
[4] Griffith LG, Naughton G. Tissue engineering–current challenges and expanding opportunities. Science 2002;295(5557):1009–14.
[5] Borenstein JT, Terai H, King KR, Weinberg EJ, Kaazempur-Mofrad MR, Vacanti JP. Microfabrication technology for vascularized tissue engineering. Biomed Microdevices 2002;4(3):167–75.
[6] Wikswo JP, Block 3rd FE, Cliffel DE, Goodwin CR, Marasco CC, Markov DA, et al. Engineering challenges for instrumenting and controlling integrated organ-on-chip systems. IEEE Trans Biomed Eng 2013;60(3):682–90.
[7] Benam KH, Dauth S, Hassell B, Herland A, Jain A, Jang KJ, et al. Engineered in vitro disease models. Annu Rev pathology 2015;10:195–262.
[8] Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. Science 2010;328(5986):1662–8.
[9] Huh D, Leslie DC, Matthews BD, Fraser JP, Jurek S, Hamilton GA, et al. A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. Sci Transl Med 2012;4(159):159ra47.
[10] Kim HJ, Huh D, Hamilton G, Ingber DE. Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab a Chip 2012;12(12):2165–74.
[11] Kim HJ, Ingber DE. Gut-on-a-Chip microenvironment induces human intestinal cells to undergo villus differentiation. Integr Biol Quantitative Biosci Nano Macro 2013;5(9):1130–40.
[12] Musah S, Mammoto A, Ferrante TC, Jeanty SSF, Hirano-Kobayashi M, Mammoto T, et al. Mature induced-pluripotent-stem-cell-derived human podocytes reconstitute kidney glomerular-capillary-wall function on a chip. Nat Biomed Eng 2017;1(5). 0069.
[13] Powers MJ, Domansky K, Kaazempur-Mofrad MR, Kalezi A, Capitano A, Upadhyaya A, et al. A microfabricated array bioreactor for perfused 3D liver culture. Biotechnol Bioeng 2002;78(3):257–69.
[14] Nakao Y, Kimura H, Sakai Y, Fujii T. Bile canaliculi formation by aligning rat primary hepatocytes in a microfluidic device. Biomicrofluidics 2011;5(2):22212.
[15] Su R, Li Y, Zink D, Loo LH. Supervised prediction of drug-induced nephrotoxicity based on interleukin-6 and -8 expression levels. BMC Bioinforma 2014;15(Suppl.16):S16.
[16] Huang HC, Chang YJ, Chen WC, Harn HIC, Tang MJ, Wu CC. Enhancement of renal epithelial cell functions through microfluidic-based coculture with adipose-derived stem cells. Tissue Eng Part A 2013;19(17–18):2024–34.
[17] Zhou M, Ma H, Lin H, Qin J. Induction of epithelial-to-mesenchymal transition in proximal tubular epithelial cells on microfluidic devices. Biomaterials 2014;35(5):1390–401.
[18] Frohlich EM, Zhang X, Charest JL. The use of controlled surface topography and flow-induced shear stress to influence renal epithelial cell function. Integr Biol 2012;4(1):75–83.
[19] Jang KJ, Suh KY. A multi-layer microfluidic device for efficient culture and analysis of renal tubular cells. Lab a Chip 2010;10(1):36–42.
[20] Jang KJ, Mehr AP, Hamilton GA, McPartlin LA, Chung S, Suh KY, et al. Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment. Integr Biol Quantitative Biosci Nano Macro 2013;5(9):1119–29.
[21] Ng CP, Zhuang Y, Lin AWH, Teo JCM. A fibrin-based tissue-engineered renal proximal tubule for bioartificial kidney devices: development, characterization and in vitro transport study. Int J Tissue Eng 2013;2013:10.
[22] Kimura H, Yamamoto T, Sakai H, Sakai Y, Fujii T. An integrated microfluidic system for long-term perfusion culture and on-line monitoring of intestinal tissue models. Lab a Chip 2008;8(5):741–6.
[23] Kim HJ, Li H, Collins JJ, Ingber DE. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. Proc Natl Acad Sci USA 2016;113(1):E7–15.
[24] Sin A, Chin KC, Jamil MF, Kostov Y, Rao G, Shuler ML. The design and fabrication of three-chamber microscale cell culture analog devices with integrated dissolved oxygen sensors. Biotechnol Prog 2004;20(1):338–45.
[25] Sung JH, Shuler ML. A micro cell culture analog (microCCA) with 3-D hydrogel culture of multiple cell lines to assess metabolism-dependent cytotoxicity of anti-cancer drugs. Lab a chip 2009;9(10):1385–94.
[26] Sung JH, Kam C, Shuler ML. A microfluidic device for a pharmacokinetic-pharmacodynamic (PK-PD) model on a chip. Lab a Chip 2010;10(4):446–55.
[27] Sung JH, Srinivasan B, Esch MB, McLamb WT, Bernabini C, Shuler ML, et al. Using physiologically-based pharmacokinetic-guided “body-on-a-chip” systems to predict mammalian response to drug and chemical exposure. Exp Biol Med 2014;239(9):1225–39.
[28] Imura Y, Sato K, Yoshimura E. Micro total bioassay system for ingested substances: assessment of intestinal absorption, hepatic metabolism, and bioactivity. Anal Chem 2010;82(24):9983–8.
[29] Imura Y, Yoshimura E, Sato K. Microcirculation system with a dialysis part for bioassays evaluating anticancer activity and retention. Anal Chem 2013;85(3):1683–8.
[30] Kimura H, Ikeda T, Nakayama H, Sakai Y, Fujii T. An on-chip small intestine-liver model for pharmacokinetic studies. J Laboratory Automation 2015;20(3):265–73.
[31] Abaci HE, Shuler ML. Human-on-a-chip design strategies and principles for physiologically based pharmacokinetics/pharmacodynamics modeling. Integr Biol Quantitative Biosci Nano macro 2015;7(4):383–91.
[32] Dehne EM, Hasenberg T, Marx U. The ascendance of microphysiological systems to solve the drug testing dilemma. Future Sci OA 2017;3(2). Fso185.
[33] Satoh T, Narazaki G, Sugita R, Kobayashi H, Sugiura S, Kanamori T. A pneumatic pressure-driven multi-throughput microfluidic circulation culture system. Lab a Chip 2016;16(12):2339–48.