



Kidney Research and Clinical Practice

journal homepage: <http://www.kr-cp-ksn.com>
Contents lists available at ScienceDirect



Bench and Bedside - Bench

Organ-on-a-chip and the kidney

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ABSTRACT

Article history:

Received 13 July 2015

Received in revised form

3 August 2015

Accepted 5 August 2015

Available online 20 August 2015

Keywords:

Kidney

Microfluidics

Organ-on-a-chip

Traditional approaches to pathophysiology are advancing but still have many limitations that arise from real biologic systems and their associated physiological phenomena being too complicated. Microfluidics is a novel technology in the field of engineering, which provides new options that may overcome these hurdles. Microfluidics handles small volumes of fluids and may apply to various applications such as DNA analysis chips, other lab-on-a-chip analyses, micropropulsion, and microthermal technologies. Among them, organ-on-a-chip applications allow the fabrication of minimal functional units of a single organ or multiple organs. Relevant to the field of nephrology, renal tubular cells have been integrated with microfluidic devices for making kidneys-on-a-chip. Although still early in development, kidneys-on-a-chip are showing potential to provide a better understanding of the kidney to replace some traditional animal and human studies, particularly as more cell types are incorporated toward the development of a complete glomeruli-on-a-chip.

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Introduction

Technologic advances change our lifestyle in many ways. New electronic devices become ever smaller but with ever increasing functions, so they can replace large space-occupying equipment. A few decades ago, microfluidics was developed using advances in the semiconductor industry and the subsequent expansion of microelectromechanical system field [1]. The technology can manipulate at the microscale and control fluid flow precisely. Microfluidics has provided new capabilities to researchers in biology and medical science. Since early 2000, published articles and patents on microfluidics have increased dramatically in the field of engineering. Importantly, although still a smaller overall fraction, articles on

the use of microfluidics in the medical field are growing most rapidly at an exponential rate in recent years [2].

Microfluidics is characterized by the engineered manipulation of fluids at the submillimeter scale [2]. The microscale devices in microfluidics are commonly referred to as miniaturized total analysis systems or lab-on-a-chip technologies [2]. In the 1990s to 2000s, microfluidics focused on the miniaturization of previously macroscale assays. Within several years, various new technologies showed better performances than the traditional methods. For example, there are paper-based analytical devices for diagnostics [3], immunoassays assisted by surface tension [4], and organ-on-a-chip technologies [2,5] (Fig. 1). We will further focus on organs-on-chips.

Organ-on-a-chip

Organ-on-a-chip is a microfluidic cell culture device that is a more physiologically relevant *in vitro* model than cells cultured in dishes. Important features include continuously

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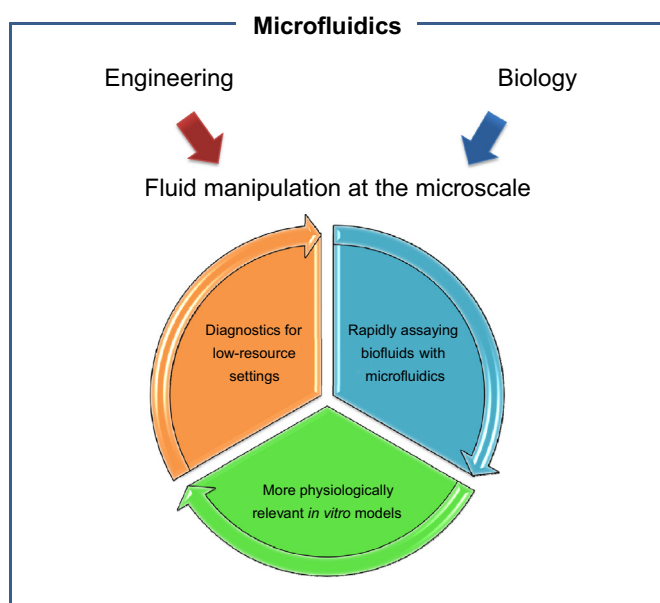


Figure 1. Concepts of microfluidics.

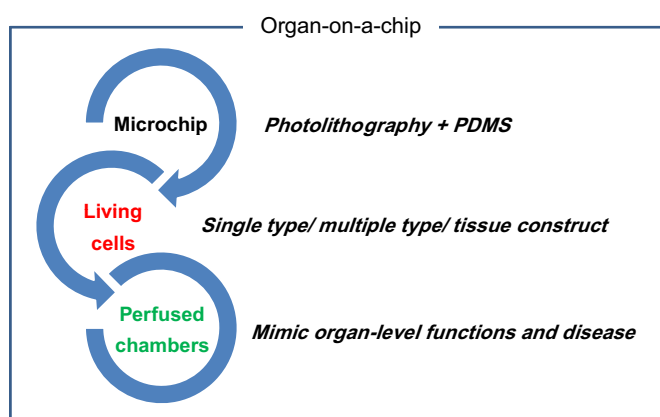


Figure 2. Concepts of organs-on-a-chip. PDMS, polydimethylsiloxane.

perfused chambers inhabited by living cells arranged to simulate tissue- and organ-level physiology [5] (Fig. 2). So far, several individual organ-on-chips have been developed, including gut-on-a-chip [6], lung-on-a-chip [7], blood vessel-on-a-chip [8], cancer-on-a-chip [9], bone marrow-on-a-chip [10], and kidney-on-a-chip [11]. In addition, multiple organs-on-a-chip has been tried, such as liver-tumor-bone marrow-on-a-chip [12] or liver-skin-intestine-kidney-on-a-chip [13].

As shown in Fig. 3, the whole experimental process using organ-on-a-chip technology consists of several steps. Photolithography, a fabricating technique that can make channels in a microscale, comes from semiconductor technology. It requires labor-intensive work, clean environments, and sophisticated training. An organ-specific microenvironment is a basic platform in the design of these devices. Briefly, researchers design the optimal condition with the proper size, numbers, and compartments of the channels. According to these designs, fine molds are cultivated and the final devices can be made out of transparent and soft polydimethylsiloxane (PDMS) [5]. Sometimes, simple ways to make replicas can be

used such as xerographic printing or three-dimensional (3D) printing of molds.

Cell sourcing is an important issue in the organs-on-a-chip field. Usually, a single cell type may be enough to mimic minimal organ function. For example, a kidney-on-a-chip for the evaluation of direct cellular toxicity may be not enough when constructed with renal tubular cells alone [11,14]. To mimic more physiologic conditions or evaluate cell-to-cell interaction, two cell types should be used like lung-on-a-chip [7], which has cultured endothelial cells on the bottom channels and alveolar cells on the top channels. This lung-on-a-chip also introduced human neutrophils with culture media to the bottom channels to observe the movement of inflammatory cells. Sometimes, cells in a tissue construct itself may be introduced into the devices, such as skin tissue or intestine constructs [13]. Humans-on-a-chip has multiple compartments to allow evaluation of the interaction among interesting organs [13].

Why is organ-on-a-chip a hot topic?

When new drugs are developed, drugs should be tested in three different stages: preclinical, clinical, and postapproval stages. Preclinical studies include two kinds of experiments: cell culture and animal studies. Cell culture methods are just culturing living cells on a dish; there is no flow of blood, and the conditions are different from cells in a real organ. In addition, the data from animal studies are not always predictive of human responses. They have fundamental limitations such as different physiology and different cellular functions. Kidney toxicity is one major cause of drug attrition and failure. Only 2% of drug development failures are screened in the preclinical stage, and serious adverse effects in > 20% of new medicines are discovered only after the clinical stages [15]. The reason why preclinical studies cannot better predict kidney toxicity is due to the limitations of current preclinical cell culture and animal models.

We need real human organ-like devices that are superior to animal models. Organ-on-a-chip may be a good solution, which has minimal functional units that use primary human cells, rather than animal cells, like a real human organ. The ideal methods will not only use human cells but also mimic 3D architecture and flow conditions within real human organs. Microfluidic devices seeded with human cells and perfused with cell culture media in a physiologically relevant manner have already been developed to provide a minimal functional unit to mimic real organs. The small size allows easy flow control and requires few cells and only small volumes of samples and reagents. Parallel experiments with large numbers of samples at the same time can also be realized. An additional advantage of the devices is optical transparency that allows visualization, at the cellular level, of the whole drug response process, something that is difficult to do in actual living organs.

What are the pros and cons of organs-on-chips?

Raw materials used in these systems are inexpensive, but specialized microengineering capabilities are needed and some, such as cleanrooms or pumps, can be expensive. Other challenges, such as bubbles, arise because of the small size. Before or during the perfusion of fluid, bubbles can form easily in the channels of devices but are difficult to remove. Cells in the device are very susceptible to detachment and injury from

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