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Review

Revolutionizing renal research: The future of kidney-on-a-chip in biotechnology

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In vitro models of kidneys have limited effectiveness owing to the complex structure and functions of the kidney when compared with other organs. Therefore many renal function evaluations are currently being carried out through animal experiments. In contrast, efforts are being made to apply biomimetic systems, such as organ-on-a-chip, which is based on microfluidic device technology, to serve as an in vitro model for the kidney. These systems aimed to recreate a physiological cultivation environment. This review has provided an overview of organ-on-a-chip research focused on glomeruli and tubules as in vitro models for the kidney and discusses future prospects.

Contents

1. Introduction

The kidney is an organ closely interconnected with blood vessels. It receives approximately 20% of the blood pumped by the heart, it filters waste products and toxins from the blood, and returns purified blood to the body. The glomerulus, which is responsible for blood filtration, consists of a complex network of capillaries that filters approximately 180 L of blood daily to produce urine [1]. The kidney is an organ targeted for safety assessments and pharmacokinetic evaluations, including metabolism and excretion, during drug development. The accurate prediction of the nephrotoxicity of potential new drugs during the experimental phase would enable cost-effective and low-nephrotoxicity drug development. Additionally, disease models contribute to the understanding of the mechanisms underlying renal disorders and serve as an effective means for developing new therapeutic

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approaches. While in vitro experiments, such as those using kidney organoids or Transwell methods, exist [2–4], their ability to faithfully replicate renal functions or potential issues such as functional inactivity currently pose concerns. Therefore, in the drug development process, the current practice involves evaluating safety and pharmacokinetic functions through animal experiments. Organ-on-a-chip technology is a novel approach to overcome the current limitations of animal and cell culture experiments. This method utilizes microfluidic devices to enable cell adhesion and cultivation, allowing for the construction of physiologically relevant in vitro organ models. Various organs and tissues, including the brain, heart, intestines, and liver, have been studied using organ-on-a-chip technology [5–8]. The kidneys have also become targets for development in this field. In kidney-on-a-chip technology, miniature kidney models are used to investigate kidney function and pathology [9]. Conversely, organ-on-a-chip technology replicates not only the kidney but also other organs, typically integrating multiple different cell types to mimic organ interactions and the body's internal environment [10]. Both methodologies fall under the purview of Microphysiological Systems (MPS), which strive to emulate the physiological functions of the human body [11]. Focusing on the “glomerulus/renal tubule-on-a-chip” can be advantageous for researching kidney diseases and function. Each approach has its own set of advantages and disadvantages. While kidney chip technology is adept at studying a single organ in isolation, organ-on-a-chip technology takes into account the interactions present among multiple organs. Moreover, the presence or absence of microfluidic systems affects the cellular environment and its interactions. Both approaches have the ability to play a significant role in advancing kidney research and therapy development, but selecting an appropriate approach requires careful consideration of their respective advantages and disadvantages. This review provides an overview of organ-on-a-chip methodologies applied to create in vitro models of glomeruli and tubules in the kidney and discusses future prospects.

2. Cells derived from induced pluripotent stem cells (iPSCs) as the cell source

Induced pluripotent stem cells (iPSCs) have garnered particular attention as a source of kidney cells [12]. iPSC-derived kidney organoids exhibit a complex 3D structure and encompass all cell lineages of the kidney, thus displaying properties similar to in vivo conditions. Consequently, cells derived from kidney organoids are more realistic cellular models for use in devices than traditional primary cells or immortalized cell lines.

For instance, one study reported the development and characterization of a 3D organoid-derived proximal tubule on-chip model using epithelial cells obtained from mature kidney organoids under static conditions. This perfusable organoid-derived proximal tubule epithelial cells tubule model, based on iPSC-derived cells, allows for a more sensitive prediction of renal toxicity than conventional models based on immortalized proximal tubular epithelial cells [13]. Furthermore, efficient differentiation of human iPSCs into podocytes and co-cultivation with human glomerular endothelial cells in an organ-on-a-chip microfluidic device were designed to mimic pulsatile blood flow in live glomeruli and apply mechanical strain by having parallel hollow channels. Under fluid flow and mechanical strain, podocytes extend protrusions towards endothelial cells through pores in the membrane. This co-culture exhibited selective filtration by retaining albumin in the capillary compartment, while excreting inulin into the urine compartment [14]. These studies highlight the crucial role of iPSC-derived kidney cells in the construction of kidney models within the devices. Advancements in iPSC technology are expected to provide more physiologically relevant kidney cells, thereby improving the accuracy of kidney disease models and advancing research on drug screening and regenerative medicine.

3. Materials used for organ-on-a-chip

Devices designed to mimic microenvironments specific to organs are crafted from various materials such as glass, polysulfone (PS), polymethylmethacrylate (PMMA), polyethylene terephthalate (PET) [15]. Polydimethylsiloxane (PDMS) has been chosen for its advantages, such as softness, transparency, biocompatibility, gas permeability, ease of replication, and low autofluorescence [16]. PDMS has various advantages; however, its absorption of hydrophobic compounds can be a limitation in drug testing. Therefore, thermoplastic materials such as polystyrene and polycarbonate are preferred microfluidic materials [17]. The development of microfluidic devices has enabled researchers to better understand and simulate the biological interactions in microenvironments.

4. Organ-on-a-chip technology

This advanced technology has been shown to provide an innovative approach for mimicking human organs and tissues by controlling the flow of minute fluids. Microfluidic devices enable interactions between cells and biomolecules in tiny spaces, allowing the precise replication of complex environments within the human body. When focusing on the kidney in particular, these devices emulate physiological functions such as glomeruli and tubules, making them an ideal platform for reproducing pathophysiological states. Microfluidic devices are constructed on the microscopic scale to allow cells and biomolecules to interact in small spaces. This enables the reproduction of cellular interactions and responses, both among cells and between cells and their environment, under conditions that closely resemble the in vivo environment [18,19]. Furthermore, these devices can control fluid flow, enabling the reproduction of fluidic dynamic factors, such as blood and lymph flow and shear stress, which cells in organs and tissues experience. Because cells in organs and tissues function when exposed to these factors, realistic reproduction of fluidic dynamics is indispensable in regard to physiological experiments [20]. Organ-on-a-chip (OoC) is not only utilized as a platform for the efficient and safe evaluation of the effects and side effects of new drugs, but also for focused research on specific organs or tissues in order to understand the mechanisms and progression of diseases [21–23]. OoC mimics in vivo reactions more realistically, thus providing more reliable results than animal experiments or in vitro models [24,25]. Particularly, OoC models that focus on specific organs or tissues are valuable for understanding disease mechanisms and progression. This is expected to mimic the progression of diseases and the effects of treatments more accurately. By replicating subtle changes within the body and the impact of drugs, the OoC technology has the potential to contribute to the development of more effective treatment methods [26,27]. As a result, OoC technology has garnered attention as an innovative means of enabling research and evaluation that is challenging using conventional methods in the fields of life sciences and medicine.

5. Kidney-on-a-chip using microfluidic devices

5.1. Glomerulus-on-a-chip

In vitro models of drug-induced renal toxicity are essential for effective pharmaceutical development. Kidney organoids mimic certain functions of the human kidney [28], like nephron-like structures, but lack full filtration capabilities and normal

glomerular basement membrane formation. Additionally, genetically modified cell lines and complex induction protocols are often used, which potentially affect their morphology and function [29]. Despite there being some success in the past in regard to recreating kidney structures using traditional 2D or 3D culture systems including spheroids and extracellular gels, the results have been inconsistent. Therefore, there is growing emphasis on developing organ-on-a-chip models of glomeruli and tubules based on cell lines to assess drug transport and renal toxicity [14,30]. The glomerular chips developed thus far face challenges in achieving a functional filtration barrier with crucial selective permeability [31]. This difficulty arises from the sensitivity of podocytes to shear stress, which leads to a high likelihood of functional loss during cultivation [32–34]. Recently, Petrosyan et al. developed a glomerulus-on-a-chip (GoC) comprising human podocytes and glomerular endothelial cells seeded on an organoplate [35]. A distinctive feature of this system is the absence of an artificial membrane between the two layers, which allows glomerular cells to form an ECM layer of extracellular matrix composed of collagen IV and laminin. The glomerular filtration barrier (GFB)-like structure of this system reproduces the functions of the GFB, including selective permeability and responsiveness to nephrotoxic compounds. Furthermore, addition of puromycin aminonucleoside, a nephrotoxic substance that induces focal segmental glomerulosclerosis, to GoC-induced podocyte damage replicates the appearance of albuminuria. Therefore, this system mimics the functionality and injury expression of the actual renal GFB. Using this platform, it is possible to study the changes in the three-dimensional structure of podocytes, endothelial cells, GBM, abnormal functionality, and intercellular crosstalk.

Another group managed to successfully replicate the podocyte damage caused by glomerular hypertension and excessive filtration using a glomerulus-on-a-chip. Filtration stimuli promote podocyte maturation in terms of morphology and gene expression [36]. However, the cells used in this study were immortalized mouse podocytes. GoC research is fundamentally aimed at human drug discovery and disease modeling, emphasizing the need for future investigations using human podocytes. In this study, GoCs were used in order to mimic podocyte damage due to glomerular hypertension and excessive filtration, revealing that filtration stimuli enhanced podocyte maturation in terms of both the morphology and gene expression. Nevertheless, the cells used were mouse podocytes, emphasizing the necessity to reassess this study using human podocytes.

Advancements in research suggest that the GoC has the potential to be a superior model for replicating human physiological conditions and disease states. Future studies using human podocytes are expected to provide deeper insight into glomerular hypertension and other pathophysiological conditions, thereby contributing to the development of more effective treatment strategies and efficient drug discovery. The glomerulus-on-a-chip used in this study is listed in Table 1.

5.2. Renal tubule-on-a-chip

In the nephron, the smallest functional unit of the kidney, the tubules present play a significant role in drug metabolism, as they reabsorb essential substances from primary urine into the body. Membrane proteins present in the epithelial cells of the renal tubules are involved in drug metabolism, making this tissue crucial for drug kinetics. Cells of the renal tubules have cilia and function as sensory organs. Primary urine flow induces shear stress, causing the cilia to bend. This bending is sensed by polycystin-1, which triggers the influx of $Ca2+$ through polycystin-2. The influx of $Ca2+$ is enhanced by the release of intracellular $Ca2+$, which activates signaling pathways to maintain renal function [37]. Efforts to reproduce the function of renal tubules in vitro have shown that renal proximal tubular epithelial cells can become vulnerable to drug-induced toxicity when there is an imbalance between inflow and outflow [38,39]. Therefore, the organ-on-a-chip models proposed to replicate renal tubular function aim to recreate a physiological culture environment by perfusing the medium through channels. Various types of flow configurations exist for the organ-on-a-chip models proposed as renal tubule models (Fig. 1). This approach is expected to enhance and also maintain the functionality of cultured cells, thereby contributing to the development of improved renal tubule models for drug-induced toxicity studies. Cultivating renal tubular cells in a monolayer microfluidic device and subjecting the cilia present in these cells to shear stress has been shown to result in cilia elongation [40]. Additionally, the use of microfluidic devices to evaluate shear stress on ureteric bud (UB) cells suggests its potential contribution to kidney development and function in kidney development [41]. In another study, tubular-derived cells and vascular endothelial cells were cultured on a porous membrane, and shear stress-induced tubular polarity was applied [42]. Furthermore, the administration of hormones to the vascular side of the device revealed changes in the osmolarity and electrolytes in the flow path of the tubular side. Although not fully replicating all of the physiological functions of renal tubules, these previous studies suggested a partial reproduction of their physiological functions. Weber et al. In their study maintained a high survival rate of human renal tubular cells by seeding them into the

Table 1
Summary of glomerulus-on-a-chip research report.

Cell types	Objectives	Findfings	References
Human induced pluripotent stem cells (hiPSCs)	Developing a functional microfluidic device that mimics the molecular filtration characteristics of the glomerular capillary wall.	This device can replicate drug-induced podocyte injury and proteinuria in vitro.	[14]
Mice glomerular endothelial cells (GEnCs) and mice podocytes (MPC-5)	Developing a multifunctional glomerulus-on-a-chip (GoC) to achieve glomerular filtration function.	The developed GoC can faithfully replicate the fundamental physiological structure and function of the glomerulus, and it can also be further developed as a modelfor hypertensive nephropathy.	[32]
Human origin: amniotic fluid-derived podocytes (hAKPC-P), immortalized podocytes (hiPOD) and primary podocytes (hpPOD)	Development of a groundbreaking system that mimics the human renal filtration barrier.	The developed chip serves as an ideal tool for studying the mechanisms of glomerular diseases and drug screening in the field.	[35]
Heat-sensitive mouse podocytes (HSMPs)	Development of a Glomerulus-Mimicking Filtration Fluidic Device (FFD) that precisely controls vertical filtration flow.	The developed system not only mimics damage to podocytes but also promotes podocyte maturation in terms of morphology and gene expression, while reproducing a drug response different from conventional culture conditions.	[36]

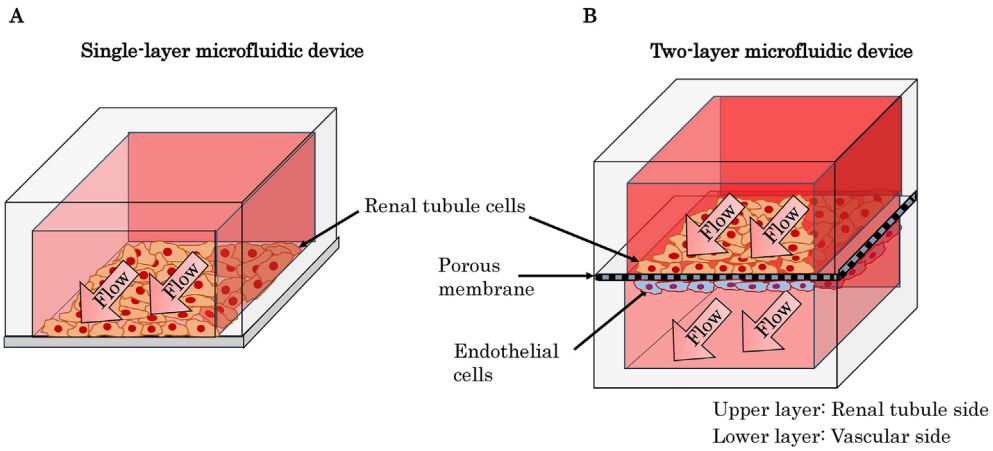

Fig. 1. Representative device structures The flow channel structures used for kidney-on-a-chip can be classified into two types: (A) single-layer microfluidic device, characterized by a simple rectangular flow channel with renal tubular cells cultured on the bottom surface. (B) Two-layer microfluidic device, featuring a porous structure dividing the upper and lower layers. Different cells are cultured on the porous upper and lower surfaces.

lumens and perfusing them in a microfluidic device, confirming that the cell morphology, including tight junctions and brush borders, resembled physiological structures. Therefore, to replicate the physiological structure of renal tubules, active research has been conducted on microfluidic devices that create a three-dimensional luminal structure by forming microchannels in the extracellular matrix (ECM) gel within the flow path, allowing cell adhesion. On the other hand, in co-culture studies, research has extended beyond renal tubular and vascular endothelial cells to include adipocytes. Co-culturing with adipocytes has been reported to stimulate hypertrophy, polarity, and differentiation of renal tubular cells [43]. In one study, co-culturing Madin-Darby canine kidney (MDCK) tubular cells with adipose tissue-derived stem cells encapsulated in a collagen gel using a microfluidic device confirmed cilia formation and the functional expression of ion transport proteins in MDCK cells [44]. Guimaraes et al. reported the coculture of renal proximal tubular epithelial cells (RPTECs) and human umbilical vein endothelial cells (HUVECs) in a polydimethylsiloxane (PDMS) microfluidic device created by a combination of 3D printing and molding techniques [45]. The proximal Tubule (PT)-on-a-chip significantly reduced high glucose levels and it also mimicked tubulopathy induced by amphotericin B, indicating albumin uptake. Notably, RPTEC/HUVEC co-cultures showed efficient cell attachment within 30 min on microchannels functionalized with plasma, 3-aminopropyltriethoxysilane, and type I collagen. This approach significantly reduces the incubation time required for perfusion of culture substrates. The PT-on-a-chip is expected to be a valuable tool for assessing the nephrotoxicity of new drug candidates, improving our understanding of drug interactions with co-cultured renal cells, reducing the need for animal testing, and fostering the safe and ethical development of new drugs. In another coculture study, we were able to develop a technique for coculturing organoid-derived cells and immortalized RPTEC on a chip. Using this technique, organoid-derived cells and RPTEC cells were co-cultured on a chip, and the transport capacity of SGLT-2 and P-gp according to cell polarity was successfully measured. Stimulation with shear stress by coculture and perfusion culture enhanced the function of both transport proteins. This allows MPS models of the proximal tubular epithelial tissue to perform drug evaluations, including reabsorption and drug excretion, in vitro [46].

Various studies have investigated the impact of shear stress on renal tubular cells, and it has become evident that certain aspects of

Table 2
Summary of renal tubule-on-a-chip research report.

Cell types	Objectives	Findfings	References
Renal cortical tubule epithelial cells (RCTEC) of distal tubule origin	The development of a device that controls the shear stress on renal tubule cilia while simultaneously monitoring real-time fluctuations in intracellular calcium levels	The developed microfluidic device is useful for morphological analysis of primary cilia under low perfusion conditions	[40]
Ureteric bud cells dissected from E15.5 mouse embryonic kidneys	Influence of fluid shear stress (FSS) on ureteric bud cells	Important correlation between due to urine flow and kidney development and function	[41]
Primary rat inner medullary collecting duct cells (IMCDC)	Developed a multilayer microfluidic device capable of mimicking renal tubule function	The microfluidic device developed is useful for mimicking the tubular system of the renal tubules in the human body	[42]
Madin-Darby canine kidney cells (MDCKC) and adipose-derived stem cells (CG-ASC)	To enhance the functionality of renal tubular cells, a microfluidic co-culture platform has been developed	In the microfluidic device co-cultured with CG-ASC, the promotion of ciliogenesis in MDCK and the functional expression of ion transport proteins were confirmed	[43]
Renal Proximal Tubule Epithelial Cells (RPTEC) and Human Umbilical Vein Endothelial Cells (HUVEC)	Development and evaluation of renal proximal tubule-on-chip	RPTEC and HUVEC co-culture demonstrated efficient cell adhesion within 30 min	[44]
RPTEC/Telomerase Reverse Transcriptase (TERT1) cells and HUVEC	Development of a technique for co-culturing organoid-derived cells and immortalized RPTEC within a chip	The morphology of proximal tubule epithelial cells improved with increased microvilli and transporter localization, leading to an increase in the transport of glucose and albumin	[45]

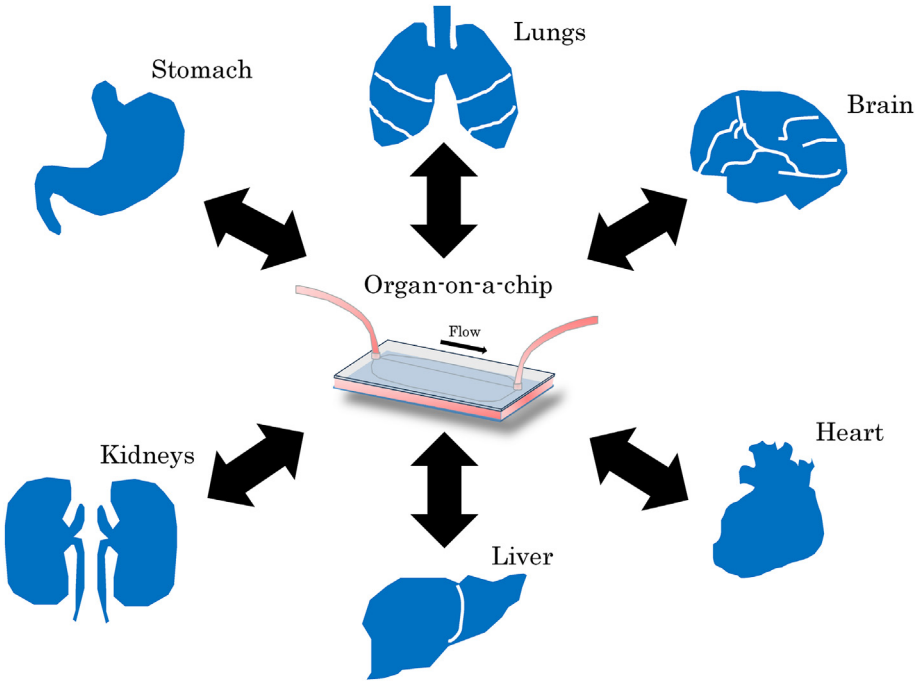

Fig. 2. Organ-on-a-chip is used for various organs Organ-on-a-chip is a system capable of artificially assembling miniature tissues that mimic the functions of various organs on a chip.

renal tubular function that are traditionally challenging to express in conventional culture experiments are achievable. The renal tubule-on-a-chip used in this study is listed in Table 2.

6. Conclusions and future perspectives

OoC technology has made significant strides in the fields of life sciences and medicine; however, several important challenges remain for its practical application. First, the issue of cell source is particularly critical in OoC models for organs such as the kidneys, which require a diverse range of cell types [47]. Human induced pluripotent stem cell (hiPSC)-derived kidney organoids show promise as cell source [48,49], further research and technological advancements are necessary to ensure their stability and reliability.

Moreover, in terms of cultivation techniques, OoC models do not currently fully reflect the physiological functions and temporal aspects of in vivo environments. Improvements in cultivation techniques are indispensable for more precise replication of functional maintenance under physiological conditions and changes over time. Although the microfluidic device technology has shown promising results so far, further engineering innovations and optimization of cell culture protocols are still required.

In order to overcome these challenges, collaborations between researchers in engineering and researchers in the fields of biology and medicine are crucial. The integration of knowledge and techniques from different disciplines is likely to lead to the realization of more physiological and reliable OoC models, thus facilitating their application in drug development and clinical research. Furthermore, OoC technology, by replicating various human organs on miniature chips, is poised to become an innovative tool in medical research, contributing to the development of new drugs and a deeper understanding of diseases in the future (Fig. 2). This has the potential to garner attention as an alternative to, and reduce, animal experiments, contributing to the development of personalized treatment methods for individual patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Disclosure statement

The author reports no potential conflict of interest.

Declaration of competing interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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