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Review

Review of microfluidics approaches to mimic the kidney

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The use of microfluidics and nanotechnology in bioscience is gaining favor among the next generation of bioscience and clinical researchers, and this field has expanded to include organ-specific applications and modeling. While certain organ-specific microfluidic chips/applications, such as those in the heart and liver, are ubiquitous in the peer-reviewed literature, the kidneys require more focus and attention to drive innovation. This review is a comprehensive overview of kidney microfluidic bio-applications and includes the current challenges and limitations that should be the focus of research efforts. More specifically, previous research efforts focused on glomerular or tubule segments of the kidney, but never both anatomical regions. This is due, in part, to the complexity of reconstituting the kidney complete with all its variable mechanical and biochemical functions.

Key words: Kidney, organs and organ systems, microfluidics.

INTRODUCTION

Research on body organs has produced new perceptions on tissue engineering, providing a framework that enables cells to preserve their phenotypic features during this process and to advance within the mesh of available proteins (Paoli and Samitier, 2016). Despite these improvements in technology, there are still challenges that need to be addressed, for example, monitoring the positions of the cells and harvesting them later for biochemical or functional analysis. Although decellularization involves a three-dimensional scaffold that provides specific essential information on the cells, including their topography and stiffness, mechanical stimuli present in the cellular microenvironment have not been elucidated in this framework. Thus, in finding solutions to this limitation, biologists, physicians, engineers, and physicists have worked together to develop unique methods of solving this problem.

Microfluidics is a field of science involving the use of technological systems to manipulate the behavior of fluids in micrometer channels (Saliterman, 2006). A microfluidic chip refers to an arrangement of microchannels that can be incised or notched. The microenvironment is linked to the network on the microfluidic chip through numerous varying dimensions that exist throughout the microfluidic disk (Li, 2004). Specifically, the patched holes create a pathway through which fluids enter or exit the chip. The fluids are then processed, which entails mixing, separating, and

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manipulating the liquid to achieve multiplexing and a mechanization system (Li, 2004). Precise and accurate management of the microchannels require essential elements that are sometimes embedded within or outside (pressure controllers) the microfluidic chip. For example, the microchannel network on the chip must be able to perform processes such as electrophoresis and DNA analysis.

Microfluidic devices (MDs) examine the chemical and physical features of fluids on the micro-scale and are better than conventional macro-scale systems in several ways. For example, MDs allow the use of lower volumes of samples and reagents, thereby reducing costs (Nguyen and Werely, 2002). MDs can also perform multiple operations simultaneously due to their compact size, which shortens the experiment time due to experimental replications and other factors surrounding this experiment (Li, 2004). Further, they offer high-quality data with significant parameter control (Saliterman, 2006).

This paper reviewed the available literature on microfluidic chips/devices focused on nephrology and the kidney. Microfluidic chips can be used in this organ must address all or any of the physiological functions, which include blood filtration to remove waste and excess fluid, limiting toxins in the bloodstream, electrolyte homeostasis, and filtrate drainage. This comprehensive review uses academic publications from the last 18 years. Publications with overly simplistic designs, such as the use of mere wells, were excluded, since they cannot mimic key physiological functions or structural aspects.

Terms used in the study

The term microfluidics refers to both a science and a technology. The scientific field of microfluidics involves the study of liquid flow in devices. As a technology, microfluidics involves the micro-scale engineering (range from 200 microns to 100 nm) of fluid flow on a substrate that contains micro-features to transport liquids like blood, bacterial suspensions, reagents, and buffers as well as to control flow, heat transfer, and mass transport. Microfluidic devices use microfluidics concepts to stimulate various controlled physiologic environments or to mimic organ functions like the kidney-on-a-chip (Sia and Whitesides, 2003). Liquids are introduced or removed from microfluidic devices using syringes or tubing (Sia and Whitesides, 2003). Flow in microfluidic devices is normally laminar but turbulent or transitional flow or a combination of both can also exist.

KIDNEY ORGAN SYSTEMS AND MICROFLUIDIC CHIPS

Microfluidic technology offers an explicit, economical, reliable, combined, and controlled environment to perform essential tasks, and microsystems can replace traditional biological laboratory methods. Microfluidic cell culture is used in diagnostics, tissue engineering, drug screening, cancer research, immunology, and stem-cell propagation. MDs offer active cell culturing within micro-perfusion arrangements to supply continuous nutrients for cell culture in the long-term. Microfluidics has the potential to reproduce the cell-extracellular matrix and cell-cell relationships in tissues through the formation of gradient solutions of biochemical indicators such as development factors, chemokines, and hormonal conditions (Perestrelo et al., 2015). Some of the areas where cell cultivation in a microfluidic system is useful include high-resolution cell design on an altered substrate using epoxy resin designs and the rebuilding of complex tissue architecture.

The initial trial to replicate the functional aspects of the kidney using an MD occurred in 2001 (Attanasio et al., 2016). Essig et al. (2001) considered the flow-prompted consequences of the proximal tubular (PT) phenotype both *in vitro* and *in vivo* (IV) by subjecting PT cells to varying flow levels. Laminar flow prompted a reformation of the actin cytoskeleton (AC) and considerably decreased the plasminogen activator level (Essig et al., 2001). *In vivo*, nephrectomy reduced the actions of fibrinolytic renal cells within the proximal tubules and strengthened the apical AC domain, which was analyzed using immunofluorescence. These effects were avoided *in vitro* when cytochalasin D was used to block AC reorganization. These findings illustrate that tubular flow affects the composition of the renal epithelial cells (ECs). Essig et al. (2001) showed how tubular flow changes the structure of renal ECs and suggested that mechanical stretching in an induced flow may contribute to interstitial tubule lacerations when renal illnesses develop. The technology or device used for this study was a modest set up, involving the assembly of slides (two) to form an analogous platter chamber, followed by the application of laminar flow (Essig et al., 2001).

Baudoin et al. (2007) established a poly-dimethylsiloxane device that could maintain cells within microchambers linked to a microfluidic system, enabling constant renal tubular (RT) nourishment and by-product elimination. This device has two layers, each 100 mm deep, where the first layer is composed of a series of microchambers and microchannels and the second is a network of microchannels that serve as an inlet and a chamber to circulate the culture medium.

Weinberg et al. (2008) established a calculative scheme for the development of a typical nephron-on-chip device using existing microfabrication technologies comprising three divisions that replicated the tubular area, the loop of Henle, and the glomerulus, which can be made of different renal cell types. Building a bioartificial loop of Henle requires a regulator with diffusion scale features. Further, using the model described earlier, this author generated a design with

transport properties, including solute and flow, that were similar to those of human nephrons. This model had functional scope for channels in every division, and the calculated flow rates were similar to practical values. However, this research was restricted to mathematical simulations of water reabsorption, and there has been no other use of the model in previous studies (Weinberg et al., 2008).

Jang and Suh (2010), developed a modest multi-layer MD by assimilating polydimethylsiloxane (PDMS), a porous tissue substrate and microfluidic channel, to culture and analyze the RT cells. Using this, they cultured a rat inner medullary collecting duct (IMCD) in a conduit. To generate IV-like tubular conditions, fluid shear stress (FSS) of 1 dyn/cm^2 was applied for 5 h. This led to the formation of an optimum fluidic environment for the developed cells, as confirmed by improved cytoskeleton reorganization, cell polarization, and molecular transport through hormone-initiated stimulation. It was concluded that MDs can effectively mimic an IV renal tubule system, a process that could be applied in advanced tissue engineering and drug screening (Jang and Suh, 2010).

An artificial kidney made of a microfluidic chip includes circulation and has two compartments. The first compartment is the top channel, which resembles the urinary lumen and has a fluid flow, and the second is the bottom chamber, which resembles the interstitial space. The compartment is filled with fluid, which is the media through which materials are transported in and out of the chip (Kim and Takayama, 2015).

During drug development, it is common to receive reports on kidney toxicity based on tissue culture and non-representative animal studies. Thus, a better approach to restoring kidney function *in vitro* is required. Jang et al. (2013) designed an MD lined with living kidney ECs, which was exposed to fluid flow imitating the vital functions of the proximal tubule of the human kidney.

Wilmer et al. (2016) showed the need for enhanced design systems to predict the efficiency of new and existing drugs by focusing on drug interactions, and drug-induced kidney injury (DIKI). Such predictions were accomplished using the most appropriate *in vitro* arrangement technology, organ-on-a-chip, because it mimics the three-dimensional microenvironment (Wilmer et al., 2016). Specifically, kidney-on-a-chip is able to reproduce the technical, organizational, transportation, reabsorption, and functional properties of the human kidney. Wilmer et al. (2016) investigated the state-of-the-art microfluidic culture systems and focused on kidney PT culturing. The kidney PT is a good model for identifying biomarkers that indicate drug relationships and DIKI. Moreover, Wilmer et al. (2016) used high-throughput screening and *in vitro* experiments for IV extrapolation.

The primary kidney ECs that are secluded from a human PT are present on the top part of the extracellular exterior and matrix-coated permeable tissue, which separates the device's primary channel into two adjacent channels: a basal interstitial channel and an apical luminal canal. Moreover, exposing the single epithelial layer to apical fluid stress improves the epithelial cell polarity and forms the primary cilia. The cells in these conditions exhibit advanced features such as the ability to transport albumin, enhanced glucose reabsorption, and increased enzyme phosphatase activity. Measuring the level of cisplatin toxicity and P-glycoprotein 1 (P-gp) efflux on-chip closely mimics the IV responses compared to the outcomes from cells kept under traditional culture conditions. Zhou et al. (2014) first investigated kidney tubular cells under flow and claimed that this is a necessary condition, since the *in vivo* microenvironment is characterized by urine flow, a stimulus that is constantly present along the epithelial brush border. These authors developed a microfluidic model that reconstitutes the renal tubular flow environment to investigate renal interstitial fibrosis by focusing on the epithelial-to-mesenchymal transition (EMT) in the proximal tubule (Zhou et al., 2014). In particular, they showed cell morphological changes and migration during the EMT of human proximal tubular epithelial cells (PTECs) (HK-2) (Zhou et al., 2014). PTEC transition is related to renal interstitial fibrosis and ultimately, proteinuria. Last, Jang et al. (2013) presented primary findings on kidney toxicity through the utilization of human PTECs in a microfluidic organ-on-a-chip micro-device.

The "kidney-on-a-chip" has different possible applications. The transfer of both AC and aquaporin-2 in the kidney-on-a-chip is likely to stress devices using cultured IMCD cells in the rat kidney (Choi et al., 2015). The condition serves as an excellent illustration of the physiological experiments performed using the kidney-on-a-chip model (Jang et al., 2011).

Fluidic studies investigate the impact of fluid shear stress (FSS) on the morphology alterations and the role of the cells in the RT. Duan et al. (2008) showed that FSS causes cytoskeletal restructuring and rectification in the renal PTECs, which may be the primary indication of FSS-prompted proximal tubule bicarbonate transportation and liquid and sodium reabsorption. Other studies have suggested that FSS-prompted cytoskeletal reorganization could be done from a device that controls cytoskeleton-related protein transportation in the tubular ECs. Jang et al. (2011) used a modest multilayer fluidic chip to show that luminal FSS improves aquaporin-2 transfer to the cells through the plasma tissue (IMCD) (Choi et al., 2012). This condition is linked to the F-actin depolymerization in the basal and apical areas of the cells, regardless of the availability of the stimulus arginine vasopressin (AVP).

There are functional limitations of the current hemodialysis method in addition to the patient being ineligible for renal transplant. A bioartificial tubule device was invented to provide metabolic function. This advancement includes the embedding of renal ECs into hollow tubes to increase the chance of survival for acute

kidney injury patients (Bonnans et al., 2014). Different cells interacting alongside extracellular matrices are mostly composed of collagen and laminin; these surround the ECs in a healthy kidney (Gattazzo et al., 2014). Huang et al. (2013) developed a microfluidic co-culture stage to increase the epithelial functioning of the cell in bioartificial microenvironments along with compound microfluidic mediums microfabricated by the use of polydimethylsiloxane. The encapsulated collagen containing the adipose-derived stem cells was then injected. Moreover, Madin-Darby canine kidney (MDCK) cells were infused; these were re-suspended in budding channels to form a single epithelial layer. In contrast to the different co-culture cells which used the commercial trans-well system, the recent work of Huang et al. (2013) on the co-culture device enabled the observation of the MDCK cell epithelial monolayer as well as CG-ASC samples in a three-dimensional microenvironment. In this experiment, the height of the cells increased because of the columnar outlines by MDCK cells.

For co-cultured MDs, ion translocation in the MDCK follows cilia formation. During fluid flow, intracellular protein undercurrents can be observed with confocal microscopy. Therefore, MD co-culture offers renal EC morphological and functional enhancements that may be essential for the development of bioartificial renal chips (Tehranirokh et al., 2013).

GLOMERULUS-ON-A-CHIP

Due to the complexity of the kidney and its variable physiological functions, kidney-on-a-chip studies have mainly been performed on proximal tubular epithelial cell barriers. However, glomerulus-on-a-chip studies have also recently been reported. The glomerulus is a vital segment of the kidney, because it is the main anatomical site for blood filtration and is akin to the blood-brain barrier, albeit in the micron range as opposed to the nano-scale. This makes it essential for drug development and toxicity investigations and a solid foundation for a variety of kidney disease models.

Wang et al. (2017) developed a novel microfluidic chip that does not mimic a single glomerulus, but rather, represents many glomerular microtissues using a series of crescent microstructures to stimulate multiple glomerular microenvironments. Their rationale was to create a system that enabled the investigation of multiple glomeruli microenvironments to establish a better *in vitro* disease model for diabetic nephropathy. The middle channel of their chip contains the glomerulus inlet where the multiple glomeruli tumble eventually settles in the crescent-shaped microfeatures to form an array that lines the parallel channels filled with 3D Matrigel (Corning, Tewksbury, MA, USA) (Figure 1) (Wang et al., 2017). According to their design, the inlet of the glomeruli flow represents the capillary lumen, and the gel channels represent the glomerular basement membrane (GBM) (Figure 1) (Wang et al., 2017). The 3D Matrigel enhances the adhesion of the arrayed glomeruli and provides a natural barrier. The gel channels are flanked by collection channels that contain the glomerular filtration barrier (GFB) filtrate and represent the Bowman's capsule (Figure 1) (Wang et al., 2017). These multiple glomeruli microfluidic approaches have been effective in mimicking endothelial and podocyte phenotypes and can demonstrate morphological changes and GFB dysfunction under high glucose scenarios.

Musah et al. (2017) chose a minimalist design but with a different bio-application than that of Wang et al. (2017). They used two linear microchannels (replicating capillary and urinary compartments) superimposed over one another and parted by flexible PDMS tissue. This membrane is flanked by vacuum channels to permit stretching and cyclic strain to better reconstitute *in vivo* physiological conditions. Musah et al. (2017) used human glomerular endothelial cells (facing the capillary compartments) and human induced pluripotent stem (hiPS) cells that differentiate into podocytes with primary and secondary processes (facing the urinary compartment). These could create a tissue-to-tissue boundary exchange that controls for selective permeability (Musah et al., 2017). The major innovation in this study, however, is not the microfluidic design, but rather, their method of directing the differentiation of hip cells into highly functional human podocytes with more than 90% efficiency. Previous attempts to differentiate these cells were restricted by heterogeneity and immature phenotypes. The differential clearance efficacy of the glomerular basement membrane was verified with only 5% inulin filtration to the urinary side and capillary retention of larger proteins such as albumin with 99% efficiency (Musah et al., 2017).

This efficiency outperformed conventional cell-line culturing which cannot recreate an endothelial/podocyte interface to study flow. This feature is essential, because the mechanical cues provided by this barrier enhance podocyte differentiation and maturation. The new model is suitable for drug toxicity investigation and renal injury models and is preferable to animal studies, which may over- or under-estimate human physiological responses. Microfluidic models allow for single organ investigation in isolation of the entire human vascular circuit, which helps to eliminate confounding factors.

Conversely, Ashammakhi et al. (2017) argued that this system could eventually be integrated into a human-on-a-chip system to investigate the effects of drugs, toxicity, and multi-factorial effects. They argued that it could replace animal testing and even dialysis. Ashammakhi et al. (2017) made another valid argument that medicine could be personalized using stem cells with patient involvement. This could replace previous less efficient methods using partially differentiated renal cells from either the Bowman's capsule or podocytes from amniotic

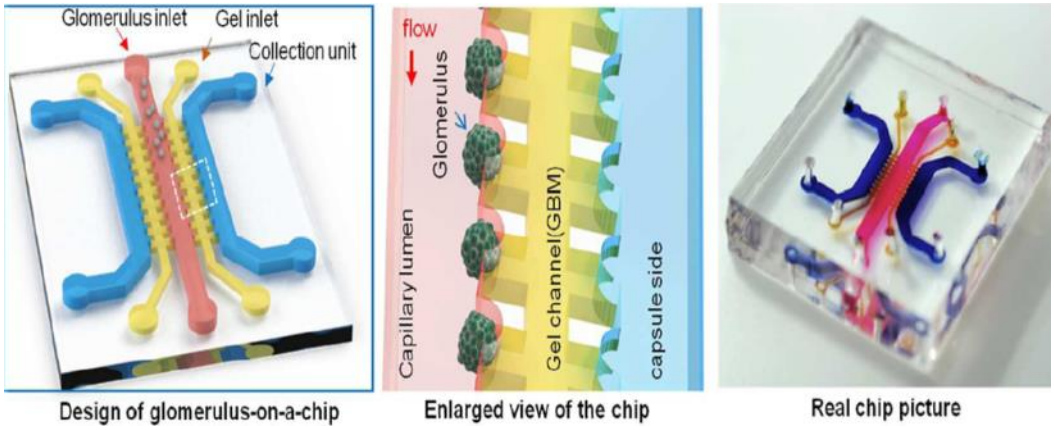

Figure 1. Real design of multiple-glomeruli-on-a-chip.
Source: Reproduced with permission from Lab Chip, 2017, DOI: 10.1039/C7LC00134G.

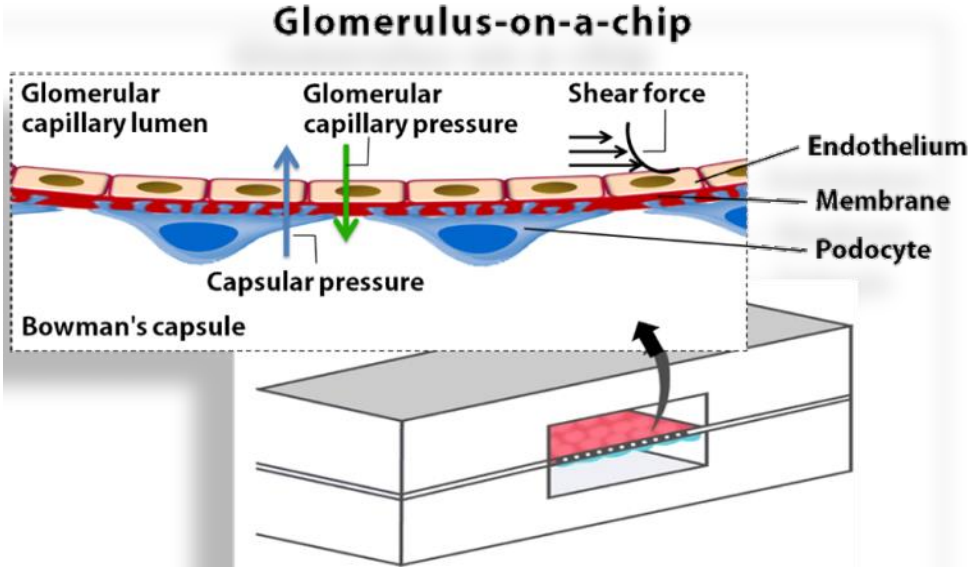

Figure 2. Schematic of endothelium and podocyte cell placement.
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fluid stem cells (Xinaris et al., 2016), or partially differentiated renal cells from either the Bowman's capsule (Lasagni et al., 2010) or urine (Lazzeri et al., 2015).

In a later study, Zhou et al. (2016) designed a novel glomerulus-on-a-chip to model hypertensive nephropathy. More specifically, their design addressed the shortcomings of previous models that did not accurately mimic the mechanical forces present under normal physiological conditions (Zhou et al., 2016). This was necessary because these mechanical and fluid forces can stress or damage cell cytoskeletal structure and rearrangement, especially in patients with diabetic nephropathy and end-stage renal failure. Zhou et al. (2016) used a dual PDMS layer approach (Figure 2) where a 10-micron thick polycarbonate filtration membrane track-etched with 10-micron diameter holes is inserted in the middle, and the three layers are aligned and sealed (Figure 2) (Zhou et al., 2016). The upper PDMS layer contains 16 culture chambers with endothelial cells that line the upper part of the polycarbonate membrane and podocytes that line the opposite side of the membrane (Figure 2) (Zhou et al., 2016). They used various flow rates and found that both 10 and 15 µL/min flow rates damaged the GFM, as reflected by an increase in inulin permeability after 12 h. However, the difference between these flows rates

suggested that the permeability of BSA and IgG occurred in 6 h with 15 µL/min as opposed to 24 h with 10 µL/min. Their chip design explains sclerotic tissue formation in the glomerulus filtration membrane, which is the critical functional site of the glomerulus.

The shear force in the diagram (Figure 2) represents the contraction and relaxation of the membrane. Glomerular capillary pressure regulates the in and out movement of fluids. The endothelium cell is used for the secretion of fluids.

The multi-layer microfluidic device (MMD) was invented by Jang and Suh (2010). The device incorporates polydimethylsiloxane (PDMS), a porous membrane substrate, and a microfluidic channel to analyze and culture renal tubular cells. It was first tested on a rat model through culturing on the inner medullary collecting duct (IMCD). In order to establish a tubular environment for the cell, a 5-h process involving the application of 1 $\mathrm{dyn/cm^2}$ of shear stress was undertaken to establish the optimal fluidic conditions for the cells, cytoskeletal reorganization, molecular transport through hormonal prompts, and boosted polarization.

Most kidney-on-chip devices, including the MMD, are placed below the microchannel and exposed to physiological shear stress. Jang and Suh (2010) established that cell thickness increased, there was Na/K ATPase expression, and cilia development promotion occurred, all of which were likely caused by shear stress through the use of the device. As a result, they noted that when using a suitably controlled shear stress load, it is possible to replicate the physiological behavior of kidney-derived cells.

The MMD uses a two-layered porous membrane to replicate the reabsorption purposes of the renal tubules. Jang and Suh (2010) found that they reproduced physiological responses related to sodium content changes and osmotic pressure of the apical channel through the introduction of hormones like aldosterone and vasopressin to the basal part of the instrument. Consequently, they noted that shear stress could result in various outcomes including the alteration of cell orientation, the promotion of p-glycoprotein expression, the absorption of glucose or albumin, cell growth, and cell polarity expression.

One main challenge related to the viability of the MMD is the podocyte-on-chip mechanism. According to Kim and Takayama (2015), a podocyte, being a glomerular visceral epithelial cell, acts as a size- and charge-selective wall to the plasma protein. Misalignment of the walls can cause harm to the podocytes and can lead to proteinuria. The researchers stated that, over the years, developers have tried to come up with a podocyte-on-a chip mechanism, but little success has been achieved. The main reason for the lack of breakthrough is that the *in vivo* exposure of intentional shear stress to podocyte cells requires innovative culturing conditions.

Practically, Jang and Suh (2010) proved that the MMD could help facilitate the rescue of cells or biomarkers that may have been harmed or lost as a result of shear stress. For instance, the shear stress facilitated the relocation of the actin cytoskeleton in the kidney-on-a-chip through the primary cultured inner medullary collecting duct cells and the translocation of aquaporin-2 on rat kidney cells. The results were a representation of the device's physiological capability. Jang and Suh (2010) established the function by taking into account the fact that renal tubular epithelial cells often experience shifts presented by the extracellular microenvironment, for example, changes in the interstitial or luminal pH and trans-epithelial osmotic gradient.

DISCUSSION

Although organ-on-a-chip systems do not require expensive raw materials, they are associated with high costs due to the development of micro engineering capabilities such as pump and clean rooms. The first challenge is that of bubbles, produced during or before perfusion of fluids, which are hard to remove and can increase the susceptibility of cells in the devices to injury or detachment. Occasionally, however, injuries associated with the air-liquid interface can be physiologically beneficial in, for instance, mimicking kidney injury. Nevertheless, bubbles or dust are generally harmful and ought to be avoided. To prevent them, Weber et al. (2016) recommended using an extracellular matrix coating for the attachment of cells on the membranes.

Second, developers of organ-on-a-chip devices face a noteworthy hindrance in culturing. According to Weber et al. (2016), prolonged culturing can degrade the matrix, affecting the viability of the cells. Moreover, it can be challenging to establish steady cell seeding and prevent microbes from being contaminated, because most experiments require long culturing periods. There is also the concern that, thus far, most of the devices' systems are yet to adequately account for certain elements such as complex system-level behavior, adaptive immune responses, nervous or skeletal systems, adaptive immune responses, and chronic disease modeling. Although the use of various kinds of attaching cells can be easy, culturing suspending cells remains a major challenge in organ-on-a-chip developments.

Previous research studies in this area have involved small-scale experiments. In order to improve future findings, greater sample sizes are required. One area that could benefit from improved research is fluid flow control. According to Kim and Takayama (2015), greater understanding of fluid flow control could enable developers to enhance the differentiation, functionality, and viability of their devices. Moreover, the enhancement of the synthetic culture system could enable different parameters to be controlled, for example, the mechanical forcing regimens, flow patterns and levels, and oxygen, molecular, and trans-cellular chemical gradients.

Weber et al. (2016) also believed that incorporating a cell culture in a 3D form could lead to more precise illustrations in *in vivo* studies. Thus far, most 3D culture methodologies have been assessed under static conditions as opposed to the recommended dynamic settings. Weber et al. (2016) noted that the use of 3D cell culture in organ-on-a-chip models could present an optimal cell culture for simulating an *in vivo*-like microenvironment.

Assuming, the challenge of developing a novel 3D biomimetic microfluidic model has been fully addressed, the focus of attention can shift to include pathological scenarios that negatively affect fluid flow and filtration. More specifically, Aghajani et al. (2019) suggested that the *Brucella* bacteria, acquired from unpasteurized milk and uncooked meat, is a major contributor to acute tubular necrosis since it can decrease blood flow and increase interstitial fluid in the kidneys.

CONCLUSION

The mimicking of organ systems through microfluidic approaches is gaining great significance within the fields of bioscience and clinical research. Attempts to emulate kidney function are within the laws of physics and fluid mechanics that mimic pathological microenvironments. The key benefit of microfluidics is the use of simple materials, which has increased the interest of current clinical researchers in this area. This review presented a comprehensive overview of kidney microfluidic bio-applications, including current challenges and limitations that should be addressed in future research efforts.

Currently, none of these organ-on-a-chip approaches are intended to replace the tissue engineering of an entire fully-functional living kidney. Rather, studies have attempted to mimic critical physiological functions of major biochemical operational units including the glomerulus or tubular epithelial cell barriers. This reconstitution of vital processes can be used instead of animal models or cell cultures. Microfluidic devices have also significantly contributed to the body-on-a-chip approach, which seeks to develop high-performing devices.

The significance of microfluidic research for clinical practice cannot be underestimated. Research has created a platform and a biomedical tool for use in everyday healthcare practice, which is especially useful for monitoring and predicting diseases. Medical diagnostics will become more affordable and faster, as microfluidics will help to reconstruct a damaged organ or tissue that has lost its functionality. Although the drawback of this method is that these man-made tissues cannot effectively work in the same ways as the natural organs of the human body, the increased complexity of the experiments has a critical effect in comparison to the petri dish. This complexity could see the development of more bio-applications, including those related to the physiological functions of major biochemical operational units such as the glomerulus or the tubular epithelial cells.

Microphysiological systems currently in production mainly include devices that use a single type of cell. Advancements in this area could incorporate prototypes that can further the capability to include, for instance, the necessary steps for secretion in the proximal tubule *in vivo*. These steps could focus particularly on the solutes' passage across the modified vascular endothelium into the tubular epithelium and interstitial matrix. Such ingenuity could act as a tight barrier to allow trans-cellular solute diffusion into the tubule lumen. For human kidney diseases, biomimetic micro-physiologic systems could help in the identification of effective and safe therapeutics (Weber et al., 2016).

The development of biomimetic microfluidic systems has indisputably provided the research community with a unique opportunity to contribute to the field of healthcare and science in general. Future researchers should continue with the quest to come up with better mechanisms that address unexplored areas, like the development of screening tools for modeling diseases affecting humans and the production of novel treatments. Furthermore, future designs could create efficient systems that can mimic vascular, interstitial, and proximal tubule characteristics including the integration of myofibroblasts, pericytes, and immune cells. Such advancements would contribute significantly to improvements in kidney physiologic function, drug development and discovery, and overall organ-on-chip technology.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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