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Review Article

Organs-on-chips Provide Insights into Molecular Mechanisms of Disease and Facilitate the Design of Newer Treatment Strategies: A Concise Review

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Abstract

Although multiple intricate and drawn-out in vivo investigations and complex in vitro assays are carried out as a part of the routine safety screening of drugs, medication failures arising out of safety-related issues continue to be an area of concern for pharmaceutical operations. Some of these failures may be explained by a lack of mathematical models to translate animal data into human data. Moreover, there may be differences in the sensitivity and drug disposition between humans and animals. Microphysiological systems may offer a way to more accurately represent these target tissues and a chance to better evaluate certain facets of human safety. As such, the ability of organs-on-chips to provide information at various development phases in drug discovery has sparked interest in recent years. This cutting-edge technology may aid in shedding light on the functioning of human organs and the pathophysiology of diseases. Also, they can be used to accurately predict the efficacy and safety of experimental medications in humans. Organs-on-chips know-how has been employed to successfully imitate specific nephron components including but not limited to the glomeruli, proximal as well as distal tubules, and collecting duct, all of which can be used in the testing of drugs for genetic kidney disorders. This review includes an overview of this technology along with some of its applications, challenges, and recommendations for the future.

Introduction

Alternatives to animal research are highly sought-after since preclinical studies are not just expensive and time-consuming but in most cases ethically questionable. Further, the abnormally high failure rates of experimental drugs in clinical settings due to the lack of reliable and predictive preclinical models have added to the researchers' difficulties. The development of organ-on-chip (OoC) devices cultured in a lab environment is a recent breakthrough in the study of in vitro human micro-physiological systems that can mimic functions at the organ and even the organismal levels.[1–5] An OoC is a biomimetic system capable of simulating the physiological microenvironment of biological tissues and organs (Fig. 1). This technology combines cell biology and engineering to create a microphysiological environment capable of nourishing and nurturing cellular architecture and function outside the biological system. Here, isolated cells are cultured in a microfluidic environment that simulates the natural physiological milieu.[6] The extracellular matrix provides structural support and biochemical signals necessary for normal physiological functioning. This microenvironment is anchored in a chip made from an inert material such as polydimethylsiloxane (PDMS), glass, or thermoplastic resin. This comprehensive review paper aims to provide new insights into the current research in the field of OoC technology. Through a meticulous examination of the latest advancements, applications, and challenges, the review seeks to offer valuable insights into the potential of OoC platforms for revolutionizing drug development, disease modeling, and personalized medicine thus contributing to the ongoing discourse on the transformative impact of OoCs on biomedical research and healthcare.

Basic structural concept of OoC

OoCs are classified into single, double, or multichannel chips. Double-channel chips consist of two separate channels connected by a porous membrane and can be used to study the interphase be-

Keywords: Organs-on-chips; Molecular mechanism; Stem cells; Kidney-on-chip; Glomerulus; Tubulopathies.

Abbreviations: 3D, three dimensional; GBM, glomerular basement membrane; KoC, kidney-on-chip; OoC, organ-on-chip; PT, proximal tubule; PDMS, polydimethylsiloxane; ToC, tumor-on-chip.

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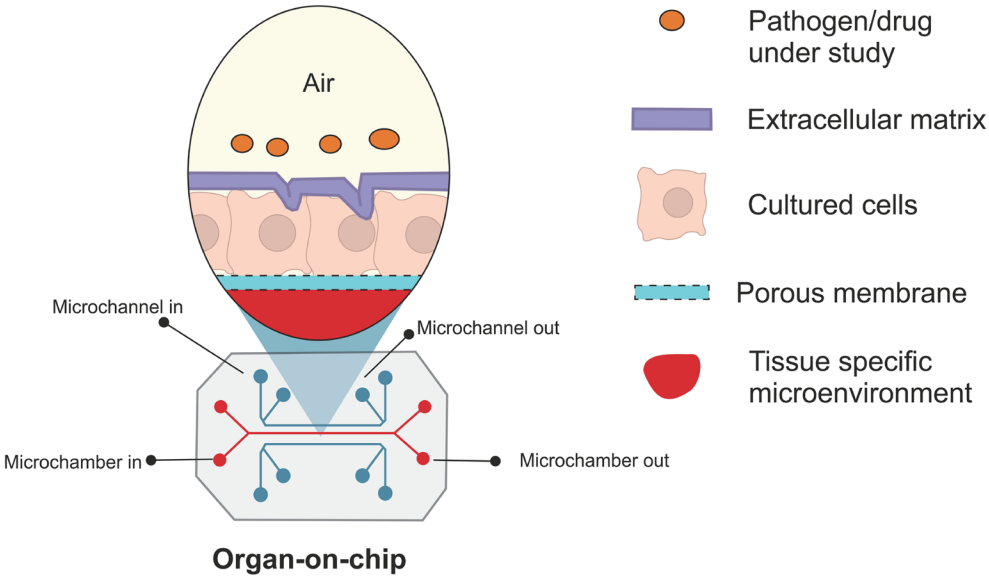

Fig. 1. An illustration of organ-on-chip simulating the biological microenvironment.

tween different cells in the same tissue. Two inlets and two outlets are built into the system to guide the entry and exit of the perfusion fluid. These channels are also used to study the effect of drugs on the cells (Fig. 2). The perfusion fluid flows through the channels in a steady manner or a pulsed manner. OoCs are fitted with physical sensors for monitoring pressure, flow rate, and other parameters and are also fitted with chemical and/or biological sensors for measuring pH, interactions, and concentration gradient as well as physiological responses. Some systems are equipped with imaging capabilities that allow researchers to observe cellular interactions in real time (Fig. 2). Interestingly, some chips can reproduce tissue-tissue interfaces and can also deliver pertinent mechanical signals, such as breathing and peristalsis-like movements, thus characterizing organ physiology and disease states. Further, human micro-level multi-organ lab-originated systems that replicate both drug metabolism and whole-body physiology can be made by interlinking two or more organ chips. Thanks to recent advancements in stem cell technologies, patient-specific stem cells can now be harvested to construct customized OoCs that can be used to study the effect of specific drugs on the patient's cells.[7]

The advancement of microphysiological systems has been facilitated by developments in stem cell engineering and regenerative medicine. Numerous culture systems have been developed to recreate tissue and organ functioning at levels that were previously unachievable. To further improve such biological mimicry, two main strategies for developing microphysiological systems are being pursued: (a) fixed 3D culture systems with intricate structural details, and (b) microfluidic 3D culture matrices with dynamic fluid flow (organ chips).[8,9]

Drawbacks of fixed 3D culture systems

Fixed microphysiological system prototypes, such as micro-engineered organoids as well as tissues grown within 3D extracellular matrix hydrogel gels, have demonstrated an impressive capacity to repeat tissue histogenesis and a wide range of biological functions such as metabolism of the drug and cell toxicity responses. However, they fail to simulate the tissue-to-tissue interface, vascular flow, interstitial movement, distribution of immune cells, and pharmacokinetic and pharmacodynamic (PK/PD) profile of administered drugs. Therefore, fixed microphysiological systems fail to accurately evaluate in vivo drug distribution, effectiveness, and toxicity. These drawbacks can be overcome by using microfluidic OoCs.[10]

History of microfluidic 3D culture devices

The lung alveolus, an important component of the respiratory system, was first recreated in the lab using an organ chip.[9] For this purpose, a soft lithography-based manufacturing technique adapted from computer hardware components was utilized. This model was a modified version of a less complex device where liq-

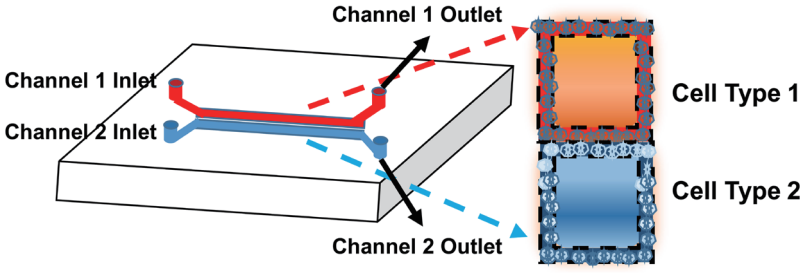

Fig. 2. Schematic representation of organ-on-chip at cellular level.

uid plugs were passed through a narrow hollow channel to create audible sounds thereby replicating fluid-filled lungs.[11] Several examples of such microfluidic 3D systems have since been reported in the literature. A few prominent ones are discussed here in brief.

Examples of organ-on-chip devices

Lung-on-chip

Since lung tissue is not capable of regeneration, any damage could be long-lasting. Additionally, smokers have a higher probability of being afflicted with lung cancer. Furthermore, several countries such as India and China have extremely high levels of air pollution, which seriously harms the lungs.

These factors have contributed to a significant rise in lung cell research, and due to the recent surge in the popularity of OoCs, numerous studies to replicate lungs for research purposes have been reportedA few important studies are cited in this section. Wang et. al. demonstrated the capability of lung-on-chip (LoC) to simulate the microenvironment of human body to carry out metabolic and regulatory activities.[12] Recent advances, challenges and applications have been discussed in detail by Francis et. al. and Dallaquila et. al.[13,14] Strategies for mimicking the physiological functions of the lung and studying the progression of lung diseases in LoC have been discussed in a review by Zhang et. al.[15] Further, Bennet et. al. published a review on the challenges, opportunities and advancements in LoC models.[16] Additionally, the role of LoC in new drug development has been reviewed by Shreshtha et. al.[17] Various case studies on the application of LoC in study of lungs and progression of disease have been published by Poojary B.[18] Zamprogno et. al. developed a second generation LoC based on a stretchable and biodegradable membrane that mimics the geometrical, mechanical, biophysical and transport properties of the lung-alveolar barrier.[19] Additionally, another noteworthy endeavor in the form of proof-of-concept studies has been reported by Huh DD.[20] In another study, a robust, versatile alveoli-on-chip was developed and studied by Richter et. al.[21] Study of the contribution of LoC to human lung structure-function relationships at cell, tissue and organ levels have been discussed by Bai & Ingber in an interesting article.[22]

Liver-on-chip

The liver is one of the most vital organs in the body that keeps regular physiological processes in check. It has a strong capacity for regeneration and can recover from any chemical or physical harm. However, unfavorable drug or disease reactions may result in permanent damage, but research in this area has been hindered due to the lack of suitable in vitro models. Therefore, these medications have been tested in vivo on animals, and when tested in humans, lethal side effects were observed. The OoC technique has been used to circumvent this drawback and liver-on-chip models have been able to predict the damaging effects of medications on liver cells. Here, the chip is seeded with liver cells and cultured, with the therapeutic and toxic effects of drugs on the liver cells then studied. Such systems may be beneficial for hepatotoxicity investigations.[23–29]

Brain-on-chip

Brain-on-chip technology utilizes a multi-step lithography technique. The technology is useful for the examination of the axon as well as its regeneration and treatment with various medicines, while several models have been developed to investigate the pathophysiology of neurodegenerative disorders. Brain-on-chip development falls into three categories: high-throughput systems, screening of experimental settings, and 3D high-content systems that imitate the environment of brain tissue. A multichip system with interconnected chips can mimic communication between many cells and organs.[30]

Blood-on-chip

The human circulatory system is a complex network of blood, blood vessels, and the heart that is difficult to replicate.[31] The critical constituents of blood such as white blood cells, red blood cells, platelets, and plasma are incorporated in the organ-on-chip models to simulate the behavior of the blood. Here, each kind of blood cell is segregated and studied to understand the interactions between the major immune system components. Such chips are constructed from polydimethylsiloxane (PDMS) prepolymer using a polylithographic technique and have 500 μ to 1 mm broad channels. These channels are packed with polystyrene beads.[23]

Pancreas-on-chip

Pancreatic cancer is resistant to most of the available anti-cancer medications and is difficult to eliminate surgically. This is due to high levels of invasiveness of the cancerous cells.[32] To overcome this drawback, Miollis et. al. used the OoC strategy where one channel was seeded with oncogenic molecules and another with mice pancreatic cancer cells. The chip was then scrutinized to investigate the drug response. The same technique was repeated with human pancreatic cancer cells in place of the mice pancreatic cancer cells.[32]

Breast tissue and tumor-on-chip

Breast cancer is the most common type of cancer reported in women. Its invasive characteristics and challenging treatment present many obstacles in its therapy. Numerous two-dimensional models have been tried with limited success as they failed to mimic the tumor characteristics. Different preclinical experiments were carried out but failed due to their inability to reproduce the obtained results.[33] These challenges were overcome by using the OoC concept to design a microfluidic 3D device called a tumor-on-chip (ToC) designed to imitate the behavior, biological processes, mechanical characteristics, and various reactions of tumor cells. Such ToC devices aid in understanding approaches for breast cancer treatment and in screening for anti-cancer drugs. The use of ToC models to research how a malignant clone interacts with the drug holds promise in the domain of cancer therapeutics.[34,35]

Kidney-on-chip

The kidney is a complex organ that contains a variety of cell types with unique functions. The coordination of their activities facilitates the removal of metabolic waste products and maintains electrolyte balance in the blood. The nephron which is the functional unit of the kidney, is subdivided into several segments, each with a specific job to do.[36] Every component is prone to genetic abnormalities with tubulopathies and glomerulopathies accounting for the majority of hereditary kidney diseases. In the recent past next-generation sequencing strategies have been utilized to provide individualized care for hereditary kidney diseases.[36] Currently, OoCs hold great promise in the diagnosis and treatment of kidney disorders. A human kidney glomerulus chip consisting of immortalized kidney podocytes and glomerular endothelial cells close to one another was used to study the role of glomerular mechanical forces in increasing glomerular leakage in hypertensive

nephropathy-diagnosed patients.[37] In another study, a human kidney glomerulus chip that replicated the glomerulus' permselectivity was used to study the renal effects of auto-immunity.[38]

In this review, recent developments in OoC-based in vitro models for the study of hereditary renal disease are discussed followed by an exploration of its proficiency to help uncover additional disease pathomechanisms and culminate into fresh therapeutic approaches. Kidney-on-chip (KoC) models aim to recreate the essential kidney functions in the laboratory. Here, the genetic profile of the diseased cell as well as its phenotype is preserved by incorporating specific mechanical and microenvironmental stimuli, thereby allowing the proliferation of the cell and promoting a better understanding of the pathophysiology of the disease.[39–44] Interestingly, the research groups have focused on specific kidney functions rather than the whole nephron and reproduced only a portion of the nephron. Although different kidney illnesses have been portrayed by a variety of in vitro cell models, the KoC platform has not yet been translated for all of them.[45]

Glomerulus-on-chip

The glomerular filtration barrier, which is made up of endothelial cells, podocytes, and the glomerular basement membrane (GBM), is crossed by solute-filled blood as the nephron's first function. A microfluidic system was employed by Petrosyan *et al*. to reproduce a glomerular filtration barrier using various kinds of podocytes and endothelial cells.[46] The model also included podocytes made from Alport syndrome (AS) patients' amniotic follicles. Reduced permselectivity for albumin due to a faulty GBM generated by the sick podocytes was reported. The appropriateness of this system to imitate the symptoms of diabetic kidney disease and drug-induced nephrotoxicity was confirmed by the clinical findings of high glucose levels and the presence of aminonucleoside puromycin.[46,47]

These findings strongly indicate that the incorporation of patient-derived cells into the KoC models is the key to successful personalized treatment. At the same time, the improved cellular milieu of KoC devices is largely responsible for highly specialized KoC models. In addition to endothelial cells, podocytes, and GBM the glomerulus also contains supportive cell types such as mesangial, granular, and macula densa. However, very few models have included mesangial cells, even though they are essential for regulating the flow rate, endocrine communication, and structural support.[48–53]

Proximal tubule-on-a-chip

The proximal tubule (PT) plays an important role in the activation of vitamin D, which is a precursor to the absorption of calcium.[54] This proximal tubule characteristic has been recreated successfully in a KoC model indicating that these OoC models are capable of replicating the maturation and functional integrity of PT cells.[55] The Lewis group investigated a different strategy for permeable channels:[56] Two neighboring channels were constructed on surfaces that resembled the extracellular matrix via bioprinting. Then, each channel was seeded with PT epithelial cells and glomerular endothelial cells. The study successfully simulated both healthy and disease conditions (hyperglycemia) through active reabsorption of solutes, including albumin and glucose.[56]

Distal tubule-on-a-chip

The distal tubule plays an important role in regulating electrolyte homeostasis and extracellular fluid volume.[57–59] Wang *et al*. worked on creating a distal-tubule-on-chip to study the effect of pseudorabies virus infection on electrolyte transport. The study demonstrated that the affected cells displayed decreased reabsorption of sodium ions due to renal dysfunction leading to serum electrolyte abnormalities and type II renal tubular acidosis.[60]

Collecting duct-on-a-chip

The last part of the nephron, the collecting duct, allows urine to be discharged as waste, and the reabsorption of water and Na^+ is the primary process in this section.[61] Regulation of body water homeostasis is a complex mechanism involving the renin-angiotensin system and is influenced by fluid shear stress, transepithelial osmotic gradient, hormones, and cytokines. Studies carried out using in vitro cell culture have met with limited success due to the poor reproducibility of the biochemical and mechanical cues of the cellular microenvironment. Jang *et al*. successfully developed a collecting-duct-on-a-chip which is a multi-layer microfluidic device wherein fluid shear stress, hormonal stimulation, and osmotic gradient were incorporated to generate tubular dynamics that emulated the luminal fluid microenvironment. This model was used to study the changes in morphology and function of renal tubular cells.[62]

Combined KoC model

In recent years, computer modeling of KoCs has been attempted using conceptual methods.[63] A chip-based system where each component of the kidney was independently cultured and subsequently joined to make a combined KoC model was reported by Sakolish and Mahler.[64] They used a combination of biological filters and PT chips to mimic glomerular filtration. Other systemic models have been created by combining KoC with distant organs, such as the liver.[65] Recently, the concept of a "body-on-a-chip" that includes the skin, heart, lung, kidney, liver, intestine, and brain has been put forth. In this model, the cells collected from the kidney and other organs of a patient were cultivated on a chip thus leading to a patient-specific chip. Such models are capable of demonstrating the effect of a diseased kidney on other organs and vice versa.[66] In conclusion, since kidney disorders also affect other organs, the "human-on-a-chip" strategy, which involves the culturing of mutated cells representing different organs on tissue-specific chips that are interconnected, could recreate the overall systemic effects of the disease.[67–70]

Evidence-based OoC approach to pharmacological study of drugs and diseases

OoCs can be used for the screening of drugs, disease modeling, and elucidating the mechanisms of drug targeting as well as drug toxicity.[71,72] The success of the OoC approach lies in the fact that it is a useful tool that can generate a large amount of data in a very short time. These systems are simple to fabricate and can be generated using indigenous materials. OoCs can be used to simultaneously study the effect of different drugs at different doses and bear a close resemblance to the in vivo microenvironment.[73] The output of OoC devices can be fed into analytical devices such as HPLC equipment or a mass spectrophotometer. DNA binding assays can also be used for the detection of chemicals released. Alternatively, assay kits can be used to identify and quantitative biomarkers, and sensors may be used to measure the decrease in nutrient levels or the secretion of metabolites.[74–78] A few case studies of pharmacological experiments using OoC devices are discussed below.

Liver-on-chip systems where liver cells of different species are cultured in adjacent microchannels have been used to study the effects of a single drug across species.[79] Liver-on-chip systems

have shown promise in the study of antibiotic effectiveness in vitro thus greatly reducing the risk of antibiotic resistance.[80] Liver-on-chip systems have greatly facilitated the study of hepatoprotective mechanisms of several drugs.[81–84]

Bang *et al*. reported the study of the pathophysiology of neurodegenerative disorders using OoCs. In another study, neurons isolated from different regions of the brain of rats were successfully cultured onto a multi-regional brain-on-chip and used to understand the pathophysiology of neurodegenerative diseases.[85–87] Also, neurological disorders such as epilepsy and Alzheimer's disease have been recreated in the labs and found to be of immense value in the screening of drugs.[88,89] It is well known that the blood-brain barrier prevents the entry of most of the drugs into the brain. Several blood-brain barrier-on-chip models have been developed to hasten the drug discovery process and to develop insights into drug delivery to the brain.[90–97]

Challenges

The above review infers that the OoCs designed to study the effect of drugs on tissues and organs at a microphysiological level can prove to be valuable alternatives for in vitro cell culture studies and reduce the extent of preclinical and clinical studies to be carried out. However, this technology has its limitations.[98–105] Instances of interaction between the microfluidic culture and the material of construction of the microchannels have been reported. This can be overcome by surface treatment of the microchannels. However, the surface treatment varies with the material of construction and the cells under study. Also, with the surface area-to-volume ratio being high, surface effects such as the adsorption of cells to the microchannel surfaces are seen. This has been observed to lead to cell cycle progression problems, especially in the proliferative phase. Due to its permeable nature, PDMS can cause drying of the media containing the cultured cells, leading to a shift in osmolarity causing cell death. Cellular respiration releases carbon dioxide that gets converted to carbonic acid causing an undesirable shift in the pH of the microenvironment. Therefore, the buffering of media and exchange of gases must be carefully monitored. Further, due to the high density of cells in the culture, nutrients are depleted rapidly while the waste products accumulate at a fast pace. This requires continuous perfusion of nutrient media into the perfusion channels. However, this exposes the proliferating cells to shear stress that may have detrimental effects. The structural features of whole cells such as peristaltic movement of the stomach, shear in blood vessels, and breathing movement of lungs are not elucidated by these cultured cells. Also, tissue-tissue interfaces are not replicated in these systems. Several research laboratories are working on overcoming these limitations and developing robust organ-on-chip prototypes that can be used to replicate the physiology of the human body and study the impact of drugs in diseased states.

Future directions

This review conclusively demonstrates the crucial role of human pluripotent stem cells and disease cells in pharmacological screening and disease modeling. Such stem cells need suitable scaffolds that provide a conducive microenvironment for their proliferation. Microfluidic devices where various cell types are co-cultured hold great promise in the study of tissue-tissue interactions, signaling, and cell recruitment in both healthy and pathological states.[106] Furthermore, the incorporation of sensors into microfluidic systems aids in the real-time assessment of cellular activity.[107–109] In line with this, several types of human kidney-on-a-chip systems that reflect the microenvironment of the kidney tubule and detect drug nephrotoxicity have been developed. Such models help to get a better understanding of the safety profile and efficacy of the drugs thus reducing the dependence on animal models and clinical trials.

Conclusions

In conclusion, the integration of microphysiological systems, particularly OoCs, into the drug discovery landscape represents a promising avenue for addressing persistent challenges in medication safety. The limitations of traditional in-vivo investigations and in-vitro assays have propelled a paradigm shift towards a more sophisticated and human-centric approach. This cutting-edge technology not only provides valuable insights into the pathophysiology of diseases but also stands as a beacon of hope for more accurate predictions of medication efficacy and safety in humans. The strides made in OoCs know-how open new horizons for advancing drug development, ushering in an era where pharmaceutical operations can navigate with greater precision, informed by a deeper understanding of human biology. However, as we embrace this innovative frontier, it is crucial to acknowledge and address the challenges associated with OoCs implementation, paving the way for continuous refinement and optimization. With ongoing dedication to research, collaboration, and technological advancements, OoCs are poised to play a pivotal role in shaping the future of drug discovery and personalized medicine.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to concept and design (SN), acquisition of the data (AS, GV), drafting of the manuscript (S Shirsath, S Shintre), critical revision of the manuscript (SN), and supervision (BV).

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