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Microfluidic Organ-Chips and Infectious Diseases: Insights from the Development and Applications Perspective

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Abstract

Artificial human organs or organ-on-chip technologies have rapidly evolved as a powerful tool for clinical diagnostics and drug discovery. Organ-on-chips, engineered microfluidic cell culture devices, reconstitute the microarchitecture and functions of living human organs by essentially mimicking the three-dimensional (3D) cross-sections of their major smallest functional units. The development of biomimetic microfluidic systems provided a bridge between the gap of *in vitro* and *in vivo* models by accommodating human cells in physiologically relevant microenvironments to accurately design and mimic the *in vivo* niche. Organ-on-chip technology is currently considered the most advanced model to recapitulate human physiology and pathophysiology with the possibility of using patient-specific cells. The implementation of new features such as the mechanical forces, blood flow, incorporation of immune cells with constant flow and the microbiome component represent a major step toward providing a window to the innerworkings of human cells and tissues. Currently, the most advanced organ-chip models include lung, intestine, kidney, liver, skin and blood-brain barrier. There are several applications of organ-chips including clinical diagnostics, drug discovery, drug delivery, biomarker discovery and disease modeling. Infectious disease research is an emerging field of organ-on-chip platforms. Investigations of bacterial, viral and parasitic pathogens and their interactions with host tissue in human-relevant systems hold the potential to drive novel advances in the biomedical field.

Keywords: Organ-on-chip, human emulation, infectious disease, drug discovery, future

INTRODUCTION

Organs-on-chips (also known as organ chips) are microfluidic cell culture systems with controlled, dynamic conditions that emulate the physico-chemical microenvironment of tissues found in the human body. Nowadays considered as one of the top emerging technologies, the micro-level approach so called microfluidic technology originates from "miniaturized total chemical analysis systems (μTAS)," a term first coined by Manz et al.[1] in 1990 and refers to performing small-volume related reaction. With the fast-evolving pace of scientific knowledge and technology, the term "microfluidics" came into existance, and denotes the concept of dealing with behaviour and manipulation of fluids through micro-channels in a precisely controlled system.[2] This concept quickly developed into microchips to perform miniaturized laboratory experiments and into their application to medicine and biomedical science as organs-on-a-chip. Organ-on-chip devices are in the size range of an AA battery and allow *in vitro* experimentation with controlled parameters.[3] Although static cell-on-chip platforms also exist which use cells trapped in a particular region of a microfluidic device for single cell analysis,[4,5] dynamic organ-on-chip platforms with constant flow have particularly

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attracted the attention of the drug industry. The microfluidic devices are engineered to culture human cells and mimic their physiological microenvironment as well as replicating both human physiology and pathology. Due to the rising ethical issues of animal experimentation, inherent differences between human and animal physiology that led to failures in clinical trials, failure of conventional *in vitro* cultures to emulate human biology, and the inability of some pathogens to grow outside the human host, organ-on-chip technology is becoming a preferred choice in the medical field and the pharmaceutical industry.[6] By providing key features that are normally lacking within conventional *in vitro* models such as the flexibility to recreate breathing motions or muscle contractions, presence of mechanical forces, expression of human receptors molecules, the possibility of creating dynamic immune cell components and tailoring patient-specific chips essential for personalized medicine, microfluidic chips are becoming a commonly used tool to study distinctive stages of pathogenesis of diverse microorganisms via merging all the interactive components of an infection. Organ-on-chips have so far been applied to viral pathogens which target the human lungs such as influenza virus and to bacterial pathogens which infect the human intestine such as enteroinvasive and enterohemorrhagic *Escherichia coli* (EIEC, EHEC), hepatitis B infection of the liver, alpha-herpesvirus infections of the nervous system, as well as parasitic infections such as malaria by modeling the human spleen.[7-12] While organs on chips are already advancing infectious disease research, the technology holds the promise of answering many open questions regarding disease mechanisms of important human pathogens such as human immunodeficiency virus (HIV) and Zika virus (ZIKV) infections in the future. In this article, we will describe organ-chip devices, microfabrication procedures, their applications to infectious diseases and pharmaceutical industry.

What are Organs-on-Chips?

Microfluidic organs-on-chips are defined as controlled microfluidic systems in which human cells are cultured in engineered microenvironments that recapitulate the essential characteristics of tissue geometry, actuation, dynamics, flow and gradients as found in a given organ of the human body.[13] The goal of organ chips is to recreate the smallest functional unit of living organs, rather than building whole organs.[14] To establish this, organ-specific cells are cultured, differentiated on chip devices recreating a 3D reconstruction of human tissue units. This technology offers numerous unique benefits over existing technologies used for functional testing by allowing control of biological, chemical and physical cell culture parameters in a single microsystem, and hence provides physiologically relevant readouts predictive of organ-level responses. A comparison of organ-on-chips and existing *in vitro* cell culture models is given in Table 1.

Microengineering technique is used to fabricate a multilayered microfluidic chip device that contains two parallel elastomeric microchannels separated by a thin porous flexible membrane[15] (Figure 1). The top channel constitutes the epithelial channel which is lined with human epithelial cells and the bottom channel, referred to as the lower vascular channel contains the microvascular endothelial cells. For each organ chip, the characteristic signals present *in vivo* need to be replicated *in vitro* via engineering methods to drive cell differentiation, tissue assembly, and functional maturation (Figure 2). The implementation of perfusion flow at a desired rate in both channels using a syringe or peristaltic pump allows the constant circulation of air, nutrients, growth factors, drugs, blood, immune cells, bacterial/viral/parasitic/fungal pathogens or toxins which can be tailored depending on the experimental model.

Microfluidic cell culture devices provide many advantages over macroscopic cell culture such as the requirement of a small number of cells, reduced reagent consumption, real-time and on-chip analysis, automation, flexibility of device design and direct coupling to downstream analysis systems. However, typical challenges associated with microfluidics technology exist and include the use of novel culture biomaterial surfaces, the complexity of operational control, and the non-standard nature of culture protocols.[3]

Various organ models have so far been developed with the lung, liver, kidney, gut, skin, brain and heart chips being the most advanced in the developmental phase.[16] The biomimetic microsystem that reconstituted the alveolar-capillary interface of the human lung was primarily developed. It comprised of alveolar epithelial cells and microvascular endothelial cells with physiological flow and cyclic suction applied to side chamber

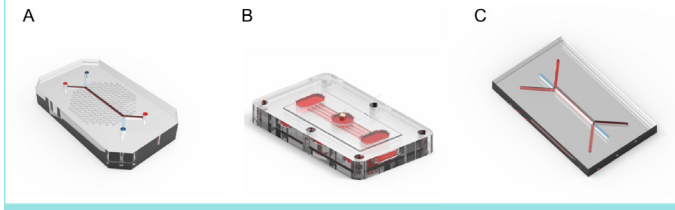

Figure 1. Prototype organ chip designs. **A)** Two-channel lung-on-a-chip microfluidic platform designating a top epithelial channel and a bottom microvascular endothelial channel **B)** Microfluidic blood-brain-barrier model consisting of a bottom perfusion layer with microchannels and bottom electrodes, a middle layer with reservoirs and neuronal chambers, and a top layer with top electrodes, **C)** Three-channel glomerulus-on-a-chip device consisting of middle channel with collagen stratification, right side channel representing the vascular space for podocytes and endothelial cells, and the left side channel depicting the urinary space where filtrate is collected.

(Adapted from Benam et al., 2016, Wang et al., 2017, Petrosyan et al., 2019).[19,20,24]

to produce rhythmic breathing movements and to create a 'breathing' lung-on-a-chip.[15,17] Alveolar chip was a step forward for assessing inflammation-induced intravascular thrombosis and toxicology of antithrombotic drugs.[18] Following the alveolus chip, small airway-on-a-chip was designed to recreate a differentiated, mucociliary bronchial epithelium exposed to air with an underlying microvascular endothelium which experiences fluid flow.[19] Many human intestine chip, 'gut-on-a chip' models have been established in which intestinal epithelial cells are cultured on polymeric scaffolds that allow crypt-villus architecture of human small intestine.[20] In further efforts, the combined effect of 3D structure and fluidic shear induced '3D gut chip' formation with absorptive permeability and enzymatic activity of the gut epithelium.[21] Efforts into modeling of human liver, a major site of drug metabolism and a target for drug-induced toxicity, have resulted in the assembly of a liver-chip consisting of human induced pluripotent stem cell (iPS)-derived hepatocytes in a perfusable platform.[22] The initial design of kidney-on-a-chip, on the other hand, contained two compartments: top channel mimicking the urinary lumen lined with renal tubular cells with fluid flow, and the bottom chamber mimicking the interstitial space.[23] A later report utilized a glomerulus-on-a-chip design with three channels using podocytes and glomerular endothelial cells representing the vascular space and the urinary space, and was proved to be a useful tool for screening therapeutic compounds.[24]

The use of biomimetic systems for the development of human skin equivalents have multiple applications including testing of pharmaceuticals and cosmetics, as well as studying the pathology of skin diseases, allergies and inflammation. The proposed models consist of three layers: epidermal, dermal and vascular components,[25] whereas more recently built full-thickness skin-on-chip devices exhibit robust epidermal and barrier function, and low skin permeability.[26] Engineering neural networks within a brain-on-a-chip platform is more challenging due to the complexity of brain tissue and multiple cell crosstalk, structural connections and cell-cell interactions representing important factors for brain function. However, progress in this area can drive breakthroughs in neurodegenerative therapies, neurodevelopmental studies and brain cancer treatments. In their study, Kilic et al.[27] generated a brain-on-chip model with pluripotent human cells differentiated into neuronal clusters interconnected with thick axonal bundles and interspersed with astrocytes, mimicking the brain parenchyma. Many microfluidic models of the blood-brain barrier (BBB) have also proposed to facilitate drug discovery targeting brain disorders, and are particularly important for understanding diseases such as Alzheimer's disease. These models usually composed of human brain microvascular endothelial cells (BMECs) interface with primary human brain astrocytes recapitulating the high level of barrier function,[28] as well as iPSC-derived neurons.[29] While the abovementioned organ chips are among the most advanced platforms, heart-on-a-chip, retina-on-a-chip, bone marrow-on-a-chip, spleen-on-a-chip, placenta-on-a-chip, as well as tumour- or cancer-on-a-chip are also being developed by researchers in the field.[12,30-34]

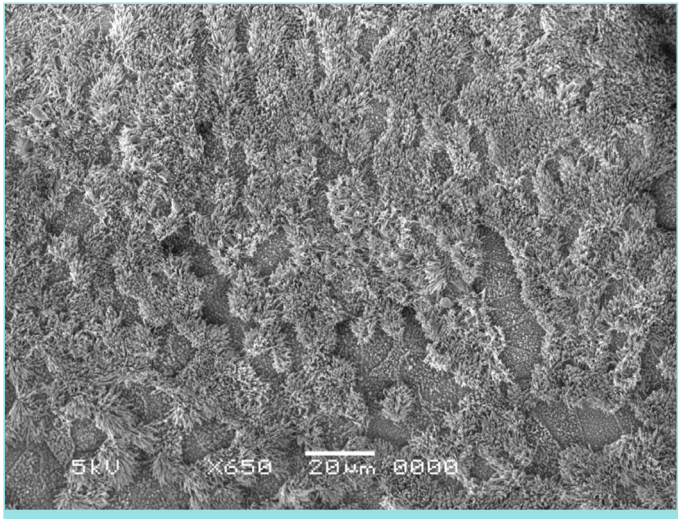

Figure 2. Ciliated airway epithelium present in a small airway-on-a-chip device imaged by scanning electron microscopy.

Production Techniques of Microfluidic Devices

Photolithography

Microfluidic prototyping mainly consists of two steps: creating of the master mold and replication into a polymeric microfluidic prototype. Master molds are often created using a complex and expensive procedure called photolithography. Photolithography is a core microfabrication technique preferably used to transfer microscale patterns to photosensitive materials by selective exposure to optical radiation.[35] During photolithographic processes, high-power ultraviolet (UV) light is projected through a photomask onto a photosensitive material (photoresist) layer to in order to fabricate patterns. A substrate such as a silicon wafer is covered with a photoresist, which is a highly viscous light-sensitive epoxy-based material. The thickness of the resist on the wafer is decided by spinning the wafer at a defined velocity via a spin-coating process, which determines the height of the subsequent microstructures. Following the photoresist uniformly covering the wafer at desired thickness, the photoresist is exposed to high-intensity UV-light. In order to create patterns in the photoresist, an opaque mask with transparent patterns is designed so that the UV-light passes through the transparent parts of the mask.[36] The result of the process is a substrate with defined structures, termed a master, which can mimic the micrometer range of sizes and ratio of *in vivo* human physiology. Photolithography processes are usually performed in a clean-room environment, which requires significant investment and maintenance costs. Alternatives to

Table 1. Comparison of advantages and disadvantages of microfluidic chips and other existing *in vitro* culture models (modified from Yu et al., 2019)[49]

In vitro cell culture models	Advantages	Disadvantages
2D cell culture (culture dish/flask, transwell membrane)	Well established protocols, easy to handle and analyze	Static condition, large media volume, lack of physiological and biochemical cues, variations in nutrient and waste concentrations, lack of immune cells
3D cell culture (engineered scaffolds, spheroids, organoids)	Cell-cell and cell-ECM interactions, mimicking of 3D architecture of human tissue	Static condition, inefficient nutrient and waste transport
Microfluidic chip (organ-on-a-chip)	Constant flow, good transport via fluid flow, fine control over microenvironment, inclusion of microbiome and immune cell elements	Difficulty in standardization and scale up, requirement for pumps, tubing and connectors

ECM: extracellular matrix, 2D: two-dimensional, 3D: three-dimensional.

photolithography including removal of the need for master molds entirely such as vinyl cutters, laser cutting, shrinking polymer, polyester-toner and paper-wax have been explored for creating master molds, however they lack the superior resolution of the photolithography technique.[37] Comparison of advantages and disadvantages of different microfabrication techniques are given in Table 2.

Soft Lithography

Much of the work in the field of microfluidics has been done using soft lithography (SL) – a collection of techniques based on printing, molding and embossing with an elastomeric stamp, which can be viewed as a complementary extension of photolithography. SL is the most common method to fabricate components of organ-on-chips, among other techniques based on molding such as injection molding and its sister technology, hot embossing. It represents a prototyping approach of several types of both microscale and nanoscale structures, and devices on planar, curved, flexible and soft substrates at a low cost. SL involves the fabrication of elastomeric stamps, i.e. mechanically soft materials, using replica-molding technique. Polydimethylsiloxane (PDMS) is a polymer with an inorganic siloxane backbone and organic methyl groups attached to silicon, and is the most commonly used material for SL applications due to its unique properties including optical transparency, biocompatibility, mechanical flexibility, chemical inertness, low toxicity, gas permeability, versatile surface chemistry, durability and importantly, low cost.[38]

The components of the organs-on-chips, both the 'rigid' chip itself as well as the flexible porous membrane that supports the cells can be fabricated using SL. The fabrication of PDMS microfluidic devices via this method has two main steps: a photolithography process for the fabrication of the stamp and the molding. The principle of replica-molding involves liquid prepolymer of PDMS being casted against the bas-relief pattern of photoresist produced by photolithography to generate a PDMS substrate that replicates the 3D topography of the original master.[35] The uncured PDMS is deposited on the microstructured mould and cured. Upon removal from the mould, the PDMS contains negative copies of the microstructures of the mould. The microfluidic device is typically created by bonding the PDMS substrate having microchannel features with a blank PDMS slab. Similarly, porous PDMS membrane can be prepared by pushing the micropillars of a silicon master through an uncured PDMS film. The punctured film can be cured to create a porous PDMS membrane on which human cells can be seeded following surface

Table 2. Advantages and disadvantages of microfluidic device fabrication techniques (adapted from Rodrigues et al., 2017 and Wu and Gu, 2011)[42, 50]

Methods	Advantages	Disadvantages
Photolithography	High (sub-micron) resolution, mass production, high wafer throughputs, ideal for microscale features	Requirement for a clean room facility, requirement for rigorous laboratory procedures and chemical post-treatment, expensive maintenance costs
Soft Lithography	Ability to fabricate 3D geometry, cost-effective, high resolution, control over surface chemistry, rapid prototyping	Pattern deformation and vulnerability to defects, low throughout, labor intensive, multi-step process
3D Printing	High throughput fabrication, single step process, quick adjustment of device features, easy to replicate in different laboratories via sharing design files	Expensive, multiple treatment sessions, need for routine maintenance and calibration of 3D printer

3D: three-dimensional.

activation and extracellular matrix (ECM) coating. Alternatively, porous membranes from commercial inserts can be used or filter membranes made of polycarbonate or polyethylene can be prepared by track etching. In track etching, electrons, heavy ions, X-ray irradiation or UV light is applied to a polymer film covered by a mask, passing through predefined openings of the mask and locally penetrating the polymer film. The production of porous polymer membranes via track etching gives control over pore size, density and share, and therefore is a preferred choice for the fabrication of organ chips.[39]

Upon microfabrication of organ-on-chip components, oxygen plasma treatment is typically applied by exposing the surface of the PDMS device components to oxygen plasma. This treatment changes surface chemistry by producing silanol terminations (SiOH) on the PDMS surface, after which the components are placed in contact to allow sealing. Plasma bonding allows a strong permanent bonding by which the properly sealed microchannels can be pumped with fluids at high pressure. The inlets and outlets of the microfluidic device are punched with a PDMS puncher in the size range of the connection tubing which will be used. Tygon (silicone, PCV, polyurethane, fluoropolymers, thermoplastic elastomers) and Teflon (polytetrafluoroethylene, PTFE) tubings are among the most frequently used material types in microfluidic setups that connect the device to a peristaltic or syringe pump for adjusting fluid flow.

3D Printing

Although photolithography and soft lithography techniques have been adopted for the fabrication of diverse organ-on-chips, they require multi-step processes and may be time consuming. More recently 3D printing and bioprinting have emerged as alternative methods owing to their ability to print multiple materials and cell types with good spatial resolution and reproducibility.[40] Stereolithography (SL) is a form of 3D printing that allows for the assembly-free production of 3D shapes in a single polymeric material from a photoresin precursor by a focused laser. In SL, a 3D object is built layer-by-layer using selective light exposure to photo-polymerize a precursor resin collected in a vat. Each layer is projected as an image obtained by digitally sectioning the 3D object into thin slices. Apart from SL, various other 3D-printing techniques have emerged such as multi-jet modeling and fused deposition (thermoplastic extrusion) modeling.[41]

Polymers Used in Microfluidic Device Production

The selection of polymer which will be applied as a matrix in a microfluidic device depends on its compatibility with the required properties of the fabrication method. There are certain required characteristics of polymers such as good optical transparency, biocompatibility, high gas permeability, multiple bonding options, flexibility to complex geometries and low cost. The most popular polymers used in microfluidic device fabrication are poly(methyl methacrylate) (PMMA), poly(dimethylsiloxane) (PDMS), poly(ethyleneterephthalate glycol) (PETG), cyclic olefin copolymer (COC), poly(styrene) (PS) and poly(carbonate) (PC) and the comparison of their properties are given in Table 3.[42]

Current Applications in Infectious Diseases

Organ-on chips have become popular tools in infectious diseases as they can be used to model organ-specific infections with various bacterial, viral and parasitic pathogens. While multiple features of an infection can be recapitulated on the chip e.g. receptor-driven adhesion to human cells, invasion, replication, intracellular survival and transepithelial migration, host responses to infection can also be evaluated by using readouts such as cytokine secretion, mucus secretion, neutrophil recruitment, integrity of cellular cytoskeletal architecture, barrier function, alterations in gene expression and protein expression levels.[43] Exploration of organ chip microfluidic technology holds a significant promise for the discovery and identification of novel drug targets, and for the preclinical evaluation of antibacterial, antiviral, antifungal and antiparasitic therapeutics in clinically relevant *in vitro* models. Most recent investigations of infectious disease research on organ-on-chip platforms are summarized below.

Infections on Lung-on-a-chip

Albeit currently being far from replacing animal models, organ chips have been used to study the interaction of pathogenic microorganisms with human tissues and organs. In one of the

Table 3. Comparison of the properties of the most commonly used polymers in fabrication of microfluidic devices (Adapted from Rodrigues et al., 2017)[42]

Polymer	Main characteristics
PMMA	Thermoplastic, transparent, UV resistant, low water absorption, good abrasion resistance
PDMS	Transparent elastomeric, biocompatible, high flexibility, high gas permeability, UV resistant, chemically inert, thermally stable
PETG	Transparent thermoplastic, chemical resistance
COC	Thermoplastic, high transparency, high heat resistance, low water absorption, high stiffness
PS	Thermoplastic, resistant to many chemicals, very good electrical properties
PC	Transparent thermoplastic, high heat resistance, high stiffness

UV: Ultraviolet.

first reports, Benam et al.[19] have used a human lung small airway-on-a-chip lined with epithelial cells from individuals with chronic obstructive pulmonary disease, and successfully demonstrated clinical exacerbation by exposure to viral pathogens such as influenza virus, in addition to increased neutrophil recruitment and selective cytokine hypersecretion. In a similar human airway-chip, investigators modeled human-to-human transmission of influenza virus infection in continued presence of antiviral drugs that have led to the discovery of novel viral drug resistance mutations and identification of host therapeutic targets.[44]

Infections on Gut-on-a-chip

Human gut-on-a-chip microdevices were also successfully applied to the study of intestinal bacterial infections and inflammation, and more importantly, the role of gut microbiome in disease by independently controlling multiple parameters on the chip. In their study, by comparing a mechanically active gut-on-a-chip to a mechanically-inactive device, Kim et al.[45] demonstrated that peristalsis-associated mechanical deformations contribute to bacterial overgrowth, a phenomenon observed in patients with inflammatory bowel disease. In their intestinal chip model, the authors also developed a chip with six commensal gut microbes, *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Bifidobacterium breve, Bifidobacterium longum*, and *Bifidobacterium infantis* and by doing so could also demonstrate that probiotic and antibiotic therapies can suppress villus injury by pathogenic bacteria such as enteroinvasive *E. coli* (EIEC).[45] Moreover, the colon chip was also applied to model damage in the human colonic epithelium induced by enterohemorrhagic *E. coli* (EHEC) infection. In this study, EHEC was observed to induce higher levels of epithelial injury when exposed to four human microbiome metabolites, and active human microbiome metabolites induced expression of flagellin associated with EHEC motility. This study itself was an example in which organ-chips provide an advantage over animal models, owing to the intrinsic species-specific differences that control the susceptibility of humans to pathogen.[9] Gut-on-a-chip platforms have also been useful for the analysis of enterovirus infection experiments that are difficult to perform in animals as they express different virus receptors to humans.[46]

Infections on Liver-on-a-chip

Hepatitis B virus (HBV) infection today remains a major public health problem with limited preventative and therapeutic options mainly due to the lack of suitable *in vitro* models, which recapitulate all steps of the viral life cycle in liver hepatocytes, and the difficulty of modeling physiologically intact host cells for HBV replication. A microfluidic primary human hepatocyte-based liver-on-a-chip system, which is permissive to HBV infection and can be maintained for at least 40 days, was recently developed. This novel model allowed dissection of complex host-pathogen interactions in HBV infections, validation of viral infection biomarkers and treatment responses, thus provided a new preclinical platform to validate potential curative therapeutic interventions.[10]

Infections on Placenta-on-a-chip

Placental inflammation, a known cause of preterm birth and neonatal mortality, has been a field in which extensive studies were limited by conventional cell and animal models due to the major variations in function and architecture of placenta. The establishment of placental barrier-on-a-chip device has provided a dynamic model of the fetal-maternal interfaces of human placenta. Acute inflammation by *E. coli* on the maternal side demonstrated complex responses including increased secretion of inflammatory cytokines by trophoblasts and adhesion of maternal macrophages following bacterial infection. These studies present a simple platform to study complex mechanisms underlying reproductive diseases.[33]

Infections on Nervous System-on-a-chip

In alternative organ models, the technology enabled the analysis of neuron-to-cell spread and axonal transport by alpha-herpesviruses in microfluidic chambers in which peripheral nervous system neurons were cultured.[11] Similarly, a 3D printed nervous system-on-a-chip reconstituting glial cell-axon interface of the nervous system revealed that Schwann cells participate in axon-to-cell spread in pseudorabies virus infection.[47]

Infections on Distal Tubule-on-a-chip

In a first-time study, Wang et al.[48] has built a distal tubule-on-a-chip to explore the pathogenesis of pseudorabies virus induced kidney disease, which demonstrated that the virus infection induced renal dysfunction in electrolyte regulation and disorder of Na^+ transporters due to disrupted tight junctions and intertwined microvilli in the reabsorption barrier.

Infections on Spleen-on-a-chip

When parasitic infections are considered, a human splenon-on-a-chip has been microengineered which reproduces the physical and hydrodynamic properties of the smallest functional unit of the splenic red pulp, the splenon. By recapitulating the function of the spleen, which is to filter erythrocytes and malaria-infected cells, Rigat-Brugarolas et al.[12] have created a microscale platform to investigate potential drugs for malaria, the parasitic infection caused by *Plasmodium* parasites.

Future Perspectives

Modeling infections in human-relevant systems is a necessity for accelerating the discovery of target-driven drugs and antimicrobials. Future applications of organ chips include real-time monitoring of infectious disease agent and human organ interactions for tackling some of the long-standing pathogens

such as HIV and ZIKV. These technologies will provide further insights into virus-host cell interactions and mechanisms associated with virulence and invasion, and hence will better aid in the design and development of safer and more potent drugs and therapeutics against HIV, ZIKV and other important human pathogens.

CONCLUSION

Bioinspired organ-on-chips are still in their infancy of development, and yet are already providing unprecedented insights into a wide spectrum of disease pathologies and infectious disease mechanisms. The possibility of using patient-specific cells on chips is allowing us to design organ-on-chip models for a specific person to evaluate that person's unique reaction to an infectious agent or a drug treatment, and will facilitate a personalized treatment plan customized to the needs of an individual patient. While physiologically linking multiple organ chips to mimic the entire human body, human-on-a-chip, has taken its place in the literature, these systems do not yet exist.

Microfluidics technology has also attracted enormous interest from infectious disease researchers as well as attention from the pharmaceutical industry aiming at developing new antimicrobials to treat infectious diseases worldwide. Although research so far has enabled the discovery of novel pathogenic mechanisms and highlighted the importance of microbiome in infectious diseases, currently the microfluidic devices are far from replacing animal models in clinical testing in the near future.

MAIN POINTS

- Organ-on-chips are engineered microfluidic cell culture devices that reconstitute the 3D microarchitecture and functions of living human organs.
- Organ-on-chips technology offers important advanced features over traditional 2D cell culture including mechanical forces, blood flow, immune cells and microbiome content.
- Organ chips offer advanced applications including clinical diagnostics, drug discovery, drug delivery, biomarker discovery, infectious disease research and disease modeling.
- The technology holds the promise of unraveling disease mechanisms of important human pathogens in the near future.

ETHICS

Peer-review: Externally peer-reviewed.

DISCLOSURES

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