Dynamic Environment in Organ-on-a-Chip Platforms

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Organ-on-a-chip (OOC) uses the microfluidic 3D cell culture principle to reproduce organ- or tissue-level functionality at a small scale instead of replicating the entire human organ. This provides an alternative to animal models for drug development and environmental toxicology screening. In addition to the biomimetic 3D microarchitecture and cell–cell interactions, it has been demonstrated that mechanical stimuli such as shear stress and mechanical strain significantly influence cell behavior and their response to pharmaceuticals. Microfluidics is capable of precisely manipulating the fluid of a microenvironment within a 3D cell culture platform. As a result, many OOC prototypes leverage microfluidic technology to reproduce the mechanically dynamic microenvironment on-chip and achieve enhanced in vitro functional organ models. Unlike shear stress that can be readily generated and precisely controlled using commercial pumping systems, dynamic systems for generating proper levels of mechanical strains are more complicated, and often require miniaturization and specialized designs.

organ-on-a-chip microfluidics mechanical strain actuators

1. Introduction

Laboratory preclinical testing is an important step in the validation and evaluation of new drug candidates before further human clinical trials, and is expected to reduce the emergency medical events caused by adverse drug reactions [1]. Pharmaceutical drug testing traditionally depends on in vivo animal models or in vitro cell culture models to evaluate pharmacological and toxicological responses to a new agent. However, it is known that in vivo animal models are sometimes challenged to precisely predict human physiological responses in drug development (e.g., metabolism, transport and oral absorption of drugs, etc.) and may poorly mimic the tissue–drug interactions. Animal testing is also hindered by issues like expensive cost, high operation difficulty, long time consumption as well as ethical approval [2][3][4].

On the other hand, in vitro cell and tissue cultures for elaborating biomimetic models have been deeply developed in recent decades to provide reliable and usable alternatives for study in various fields, such as biological research, pharmacodynamics, pharmacokinetics, drug toxicity screening, and therapy monitoring [5]. The response results are very important as a critical factor for the determination of whether the drug is safe and effective to advance to the next human clinical trials [6]. However, these responses also do not directly reflect human physiological responses because of the defective reconstitution of complex human organs.

Conventionally, cells are cultured in a 2D format to grow as a flattened monolayer independently without cell competition in flasks or well plate devices, which greatly contributes to the nascent in vitro artificial tissue for physiological-related applications [6]. More recently, 3D cell culture methods have emerged and transcended the traditional 2D method with the significant advantage of providing the in vivo-like living organ microenvironment, which is necessary to cell differentiation and specific tissue function reproduction. Cells cultured in 3D normally exhibit improved morphology, differentiation level, cell function, viability, and physiological and mechanical properties [6]. Nonetheless, static 3D cell culture technologies still desire to re-establish and integrate the dynamic microenvironment of in vivo organs. As a result, the convergence of microfluidic technologies and traditional cell culture protocol give rise to the blooming development of 3D cell dynamic culture to realise the concept of organ-on-a-chip (OOC), offering a vast opportunity for providing an alternative to animal models in preclinical drug screening.

It is well known that mechanical inputs can trigger a variety of molecular events that modulate physio-chemical outputs in microphysiological systems [7][8]. Therefore, actuators that can stretch and compress play an important role in mimicking in vivo physiologies in OOC technology with dynamic cell culture environments. Consequently, a variety of microfluidic devices utilizing integrated flexible actuators have been introduced to induce active stresses (shear, tensile, or compressive) for recreating physiological microenvironments. In most microfluidic OOC devices, highly actuate pumping systems (commercial syringe, prismatic, or pressure pumps) can be readily used to provide a precise control over shear stress induced by laminar, pulsatile, or interstitial flows. However, systems for providing mechanical strains are more complicated and may require specialized designs to generate proper levels of stimuli to tissues. To this end, this review seeks to highlight exciting microfluidic OOC platforms that are stimulated by mechanical strains. We will first provide a general overview of OOC technology. Next, mechanical strain enabled platforms with the reconstitution of mechanically dynamic microenvironments for mimicking different human organs will be elaborated. Finally, the review offers a perspective on the opportunities and challenges in developing OOC actuators for yielding future clinical advances.

2. A General Overview of Organ-on-a-Chip

Compared with traditional 3D cell culture, microfluidic OOC devices have better recapitulation of in vivo organ/tissue microstructures, cell–cell interactions, and physiological microenvironments. Therefore, OOC can take advantage of additional supporting modules to build more physiologically relevant artificial organ models so that the organ/tissue functions, activities, and physiological responses can be simulated more precisely in vitro [9]. In general, a microfluidic OOC system consists of four main modules: (1) The biological cell module that originates from various selective cell sources for dealing with the reproduced organ functionalities; (2) the microelectromechanical systems (MEMS) that provide stimulation and allows the fabrication of customized in vivo-like biomimetic frameworks; (3) the microfluidic module that reproduces the organ microenvironment; and (4) the sensing module that can monitor device operation (flow rate, strains, temperature, etc.) and detect chemicals (biomarkers, metabolites, oxygen level, etc.) [10][11]. As an early example, in 2004, Shuler's group first proposed a microfluidic-based OOC prototype—microscale cell culture analogue (μCCA) system—to predict human response

in conjunction with a physiologically based pharmacokinetic (PBPK) model in clinical trials. They fabricated a four-chamber lung–liver–other tissue–fat in vitro model with mammalian cells cultured on a silicon chip, and interconnected chambers with recirculating tissue culture medium to re-establish the circulatory system and specific organ functions [12][13].

In vivo human organs and tissues are formed as a complex structure consisting of different kinds of cells to perform specific functions. Hence, it is necessary for the in vitro model to artificially reconstitute the specific structure according to the in vivo native tissue morphology [14][15]. Since the animal model has been proved to be incapable of representing human organ physiology, human cell sources are more ideal for the artificial organ components [16][17]. Microsystems of OOC employ a microfabrication approach to build physiologically relevant cell culture incubators, which can recapitulate the functional unit tissue with minimal scaffolds of target organ, thereby reducing cost and maturation period [18][19][20]. In addition, cellular compatibility characteristics of natural or advanced synthetic hydrogel material allow a prolonged culture period and good cell attachment [21][22][23].

Microfluidics is a technology for the precise manipulation of a small quantity (from picolitre to microlitre level) of fluid. Leveraging its ability to control fluid networks in the microscale, the initial task of microfluidic technology in OOC is to continuously and precisely perfuse fresh culture medium with nutrients and oxygen to cells or tissues and remove the in situ metabolic wastes. Additional capabilities of microfluidic platforms have been further explored to provide in situ mechanical stimuli to cultured tissues, such as compression and expansion [24]. Mechanical stimuli have been demonstrated to play important roles in the regulation of biological processes at the cellular and tissue level. Living cells can be activated by mechanically changing the physiological microenvironment to maintain specific tissue/organ functions [25][26][27]. For instance, mechanical loading can increase the cardiomyocyte hypertrophy 2.2-fold and enhance proliferation rates by 21% compared to the case without stress [28]. Moreover, exposing vascular cells with fluid shear stress and cyclic stretch in a microfluidic platform to mimic the haemodynamic microenvironment can provide a better model for the in vitro study of blood vessel biomechanics [29].

Microfluidic OOCs have been tailored to mimic in vivo conditions using various materials and structures. Shear stress can be reproduced by the inherent advantages of off-chip precise fluid control systems, while strains can be generated using on-chip actuators. Pneumatic generation of mechanical stimuli on cells is the most developed technology in OOC applications, and normally incorporates the actuation of thin membranes of polydimethylsiloxane (PDMS). With the advantages of biocompatibility, low price, and precise casting, PDMS is the most widely used material for the fabrication of microfluidic OOC platforms. The elasticity of PDMS material is adjustable by tuning the ratio between elastomer base and curing agent, providing an intrinsic advantage to PDMS membranes with the potential to mimic different human tissues and organs. It has been proved that the elasticity of a substrate can affect cellular behaviours such as migration and differentiation for some types of cells [30]. For example, prostate carcinoma cells show the trend to migrate towards the less stiff substrate, while epithelial cells are more likely to move towards the stiffer substrate [31][32]; moreover, a suitable elastic substrate can contribute to the maturation of neural stem cell-derived neurons [33]. However, PDMS also has limitations for OOC applications—it can absorb small molecules such as drugs and secreted metabolites, which supresses the interaction of cells

with stimulating substance. To solve this problem, alternative materials such as polylactic acid [34], poly(methyl methacrylate) (PMMA) [35], and polystyrene [36] can be used for fabricating membranes; moreover, lipophilic coatings can be applied to PDMS material to effectively prevent the absorbing issue [37]. In addition to silicone-based elastomers, hydrogel materials also possess the intrinsic advantages of being beneficial for cell engineering by mimicking the mechanical and structural cues of the human in vivo environment, which is expected to improve cell adhesion, proliferation, differentiation, and viability [38][39].

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