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Derleme Makalesi/Review Article

Mikrofizyolojik Sistemler: Yaşam Bilimlerinin Geleceği ve Biyomedikal Mühendisliği ile Entegrasyonu

Microphysiological Systems: The Future of Life Sciences Versus Integration with Biomedical Engineering

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Öz

Mikrofizyolojik sistemler (MPS, organ-on-a-chip, OoC) minyatür fizyolojik ortamlar olarak da bilinir. Mikroortamda hücrelerin/dokuların/organların fonksiyonunu üretebilen *in vitro* hücre kültürü platformlarıdır. Organ-seviyesinde cevapları replike edebilen fonksiyonel doku birimleri olarak fabrikasyon gerçekleştirilir. Yaşam bilimleri ve sağlık araştırmalarındaki *in vivo* fizyolojik fonksiyonları çok benzer taklit ederler. Başlangıçta ilaç geliştirme ve test etme uygulamalarında kullanılmış, bir mikroçip üzerinde kritik fonksiyonlar ve mikroortam benzetişimi ile çalışmalar geliştirilmiştir. Tıbbi uygulamalar, ilaç ve toksisite taramaları gıda ve kozmetik araştırmaları ile ilerlemekte ve mekanizma çalışmaları, güvenli ve düşük maliyetli yaklaşımla yapılabilmektedir. Bu derleme, mevcut durumu, gelecekteki gelişmeleri ve multidisipliner araştırmanın önemini kısaca özetlemektedir.

Anahtar kelimeler: Mikrofizyolojik sistemler (MPS), Çip-üzerinde-organ(lar, OoC), Seri tarama, İlaç geliştirme, Ekilen hücreler, MPS cihaz üretimi, Biyolojik ürün değerlendirmesi

Abstract

Microphysiological systems (MPS, Organ-on-a-chip, OoC), also known as miniaturized physiological environments, create microenvironments replicating cellular, tissue and organ level functions in the form of *in vitro* cell culture platforms.. The functional tissues are functioning as organ units with responses specific to the organ, thereby physiological functions are mimicked *in vivo* anda re at the disposal of life sciences and health research. Initially, drug discovery and testing applications were used as microsystems able to simulate critical organ functions and microenvironments on a chip. Medical applications, drug and toxicity screening, and food and cosmetic research enable mechanistic studies and reliable research tools and require low cost. This review summarizes the current state of the art and future perspectives and emphasises the significance of multidisciplinary research.

Key Words: Microphysiological systems (MPS), Organ(s)-on-Chip (OoC), High throughput, Drug development, Seeded cells, MPS device fabrication, Biological product assessment

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INTRODUCTION

Microphysiological systems (MPS, Organ-on-a-chip, OoC), also known as miniaturized physiological environments, are *in vitro* cell culture platforms that reproduce the function of cells/tissues/organs in a microenvironment. The functional tissues are functioning as organ units with responses specific to the organ, thereby physiological functions are mimicked in vivo at the disposal of life sciences and health research.

Initially, drug discovery and testing applications were used as microsystems able to simulate critical organ functions and microenvironments on a chip. Multiple system components have been developed involving microfluidics, cell biology, and tissue engineering. MPS allow the cells to form 3D arrangements where adequate oxygen and growth factors (via microfluidic channels) should be available.

Numerous OoC platforms are presently available: "heart-on-a-chip, gut-on-a-chip, liver-on-a-chip, placenta-on-a-chip, blood-brain barrier-on-a-chip, skin-on-a-chip, bone-on-a-chip, muscle-on-a-chip", to name a few. Different platforms can be combined to study and develop applications that mimic organ interactions and better comply with *in vivo* methods. Unfortunately *in vitro* experimental designs totally stimulating all human disease facets are not completely possible at present. The MPS approach offers great potential in mechanistic studies of health and disease. Furthermore, they are miniaturized, consume less reagents and provide better modelling for cell/tissue microenvironment experiments and research. Cellular microenvironment, cell-cell interactions and associations with extracellular matrix (ECM) components are superior to cell culture, and no ethical permits are required at this level. The 3R principle is satisfied, and all data can be controlled from high technology platforms. Mass use of cultured primary human cells or stem cells have paved the way for personalized and precision medicine.. Drug screening and human disease studies can be facilitated[1,2]. Since drug discovery as sector and research/development neccesitate high-throughput cell assay systems, field called for. In addition, cell based material production and cell therapy applications reverted from small-scale to mass culture on demand. Culture vessels such as stacked flasks, culture bags, and bioreactors have been developed[3].

The traditional cell culture experimental set-ups used as models initiated a new era of organ-on-a-chip (OoC) systems as alternatives. Thus placed microfluidic technology at the center of integrating 3D bioprinting technology, microfluidic chip technology, and cell culture technology. This approach steadily moves towards method of choice status in drug screening, toxicology testing, cosmetics, food, toxicology industries as an alternative method to animal experiments and medical research. The "new *in vitro*" has achieved precision stimulatory action to *in vivo* microenvironment. Using the chip is avaible in assorted structures such as: microchannels, culture chambers, membrane structures, or multi-structured organ chips. Reconstruction of human organs' physiological environments and functional characteristics is realized with the organ-on-a-chip platform[1,2]. Interestingly, the patent's tissues/organs can be printed as personalized outputs.

While remarkable achievements have been made in OoC, such as lung chips, heart chips, intestinal chips, and skin chips and primarily used for fluid manipulation, presently the OoC allows modelling human organ properties on a slide-sized chip. Cells and tissues can be cultured using microfluidic liquid control technology: ECM provided, biochemical gradients made possible, tissue interface, blood perfusion, mechanical stimulation, and other microenvironmental conditions are possible to mimmick the *in vitro* construction of organ physiological microsystems. Thre are well defined limitations of these traditional screening methods. On the contrary interactions between complex organ-to-organ connections of different human tissues and organs *in vitro* are possible since the OoC stimulates both structure and tissue architechture and physiological activities are successfully manipulated.. 3D bioprinting, microfluidic chips, and microfluidic cell cultures are main examples of key technologies , used in chip manufacturing process. This accomodates custom designed structures using flexible chip systems to be manufactured so that multi-organ interconnections/couplings are possible with perfusion system. Nevertheless, the future will embrace integration of MPS data and in silico analyses (non-animal-based computational approach) enabling precise, high quality predictions. This is what the superior drug discovery and development upswing forward needs[1-4].

Mechanistic studies in pharmacology and

toxicology will be benefiting most with the OoC since targeted pathological analysis and crosstalk research between organs are offered for elucidating disease pathophysiology. The high cost of drug screening will be reduced, while find wider area of boosting accelerated drug research and development, opening new paths for scientific competition. In this paper, we review the progress of organ-on-a-chip technology in recent years. First, the key technologies used in OoC and MFS in general, are introduced.Thencurrent applications with future technology trends of OoC are briefly outlined. Finally, the challenges, prospects, and future trends in the development of organ-on-a-chip technology are reviewed.

Structures of organ chips[1]

As two or more tissues combine in a predefined and controlled biological system as organ, the morphology, architechture and physiology are specific to the organ studied. The vascular and structural support tissue in the organ *in situ* (the natural organ) are executed by the microfluidic chip of the OoC. Simultaneous monitoring and experimentation are facilitated. As the system dynamics provide controlled microenvironment, MPS technology has strong posistion of offering alternative to traditional cell culture systems. Here the chip is the main component of the system, and may have variable structural forms: as microchannels, as culture chambers, as membrane structures, or as multi-structured organ chips.

Microchannel-based organ-on-a-chip

One of the most universal OoC is carrying channel(s) as the main functioning component. The channel system has durable characteristics due to structural simplicity and convenient processing render the channel system advantages. Custom-designed microchannels (multiple sizes) can have different mechanical parameters. Fluid flow is versatile at idividual channels and easily regulated. The device can be manufactured to further complexity, enabling additional channels with fluid flow analysis. Similar to traditional cell co-cultures used in cancer metastasis/cellular signalling and interaction research organs of different complexity and experimental set-ups can be simulated with this chip type. Polydimethylsiloxane (PDMS) is widely used infabrication of microfluidic channels. The rationale beingsimilarity to *in vivo* blood vessel flexibility and permeability.

Chamber-based organ-on-a-chip

Different organ or tissue can be mimicked in the chamber system which has the chip with multiple chambers to facilitate fluid flow. The flow may be controlled for residence time in every chamber.This property offers organ body chamber/compartment system of physiology. . The controlled channel system delivers residence-timed transportation of nutrients, biochemicals, and signaling factors. Physiological shear stress is generated by a low-cost, programmable rocker equipment without the need for highly skilled staff. The co-culture of cells and their resistance to drug-induced hepatotoxicity also take advantage of this approach.

Membrane structure-based organ-on-a-chip

Different external pressures have been used to produce PDMS films with deformation properties. They are employed in stimulatingcell and organ contractions/expansion, to stimulate cells and tissues to produce mechanical stretching, introducing mechanical cues for research OoC. The co-cultures cited above are the suitable media for fabrication of compartmentalized bilayer microfluidic devices. Common cell lines in these experiments are human intestinal epithelial (Caco-2) cells and human umbilical vein endothelial cells (HUVECs).Cells are seeded on both sides of the membrane to construct the structural model construct for intestinal epithelial–endothelial interface. Cyclic stretching is generated during cellular growth to provide physiological mechanical strain.Fluid flow is maintained for stimulation of simulate cellular physiology *in vivo*. Medium perfusion temperature is 37◦C continuously.One significant advantage is maintenance of the cell culture and activities about a week. Another stretched mechanical stimulationexperimental use of the system is in lung-on-a-chip. Furthermore, human alveolar-capillary interface has been reported as a major achievement in human lung biomimetic microsystem design. .

Multi structure-based organ-on-a-chip

Integrated chip systems can be raised to different levels of complexity to meet the needs of variable structures and functions. The neccesity for integrated chip system are presence of more than one structure in most organ chips. Definite functional variations are baased these structural differences. Level of integration may be high

depending on complexity. A typical example is a brain cancer chip accomodating culture chambers and microchannels at the same time on the same system. Similarly the liver chip developed to represent liver circlation in blood sinüs was developed as a 3D dual-channel microfluidic membrane microchannel. The symetric parabolic flow provides different velocities and magnitudes in the two microchannels of the chip. Transport of nutrients and mass transfer to the cellular system is successfully mimicked. The hepatic sinus conteds four hepatocyte types intwo flow channels.. The third example is membrane-microchannel developed for the maintenance of gut microbial activity with a fabricated human gut-anaerobic-chip.. Accustomed organ perfusion techniques are carried further with the multi-structured organ-on-a-chip engineered devices. Exchange of nutrients and metabolites are made possible under controlled conditions; so that tissue differentiation is possible. Disease pathophysiology research had taken most advantage of this approach.,

Analytical tools for precise monitoring and control of cells within OoCs

All parameters of experimental set-ups are monitored during the time-course of the study. This precise monitoring is continuous with all planned analytical techniques integrated. Cellular states are assessed using dynamic parameters, the most common of which are cell survival/viability, cellular growth, organization, differentiation, metabolism, cellular functions, and responses to the stimuli.The cellular microenvironment are monitored for physical parameters:ion concentration, oxygen concentration, temperature, osmotic pressure, etc. Biosensors of all types: electrical, electrochemical, and optical been developed and integrated into OoC platforms, facilitating real-time monitoring of cell states and their microenvironment since invasive methods do not allow material reuse. OoC experimental monitoring with biosensors offer advantages of miniaturization, rapid responses, high specificity and sensitivity, a wide dynamic linear range, and low detection limits[2]. To this end, multidisciplinary collaboration among research areas is a necessity, with engineers solving complex problems using technology and coordinating all stages of research with life sciences to overcome challenges. A highly motivated early-stage researcher workforce will shape the future of MPS, pave the way for new collaborations, meet needs of the sector for boosting discoveries, and impress innovation with enriched/novel problem-solving methodologies. The invasive methodologies are: fluorescence immunostaining, flow cytometry, mass spectrometry, electrophoresis, PCR, RT-PCR. The end-point measurement is invasive, sample is not available for further isolation and/or kinetic work.

Biosensor-integrated MPS platforms

As mentioned above, the biochemical and physiological parameters need close and precise monitoring in all MPS, metabolism need special attention since it impacts all cellular activities. Standard metabolic parameters are glucose, oxygen, and lactate, which are to be measured to monitor cellular energy metabolism.

Cellular biology and the microenvironmental changes in OoCs are routinely monitored with electrochemical, optical, and electrical biosensors Second most common biosensors are those used for mechanical and strain parameters. External stimuli (i.e., electrical, chemical, or physical stimuli) and the cellular responses generate most valuable information/data for physiological and pathophysiological cases and the vital state of cells or organs. It is possible to link multiple biosensors for comprehensive and detailed evaluation. As mentioned above cell survival/viability is essential for intact cell status. Meaning the cell membrane has to be intact and form a barrier to control material transport in and out of the cell.Cellular barriers are present in skin, intestinal, pulmonary, hepatic, and renal systems.They have significant functions in drug/xenobiotic absorption, toxicity and biodistribution. Parameters to be routinely monitored in MPSs are those of the local microenvironment: ion concentration (e.g., pH), dissolved oxygen (DO), temperature, osmotic pressure, refractive index, and other parameters.

Data processing in multiple function MPS

Using MPS neccesitates huge data sets acquired from online biosensors to be handled and evaluated. This vast biomedical information is a group of integrated biosensor outputs. They are diverse, dynamic, and multi-dimensional data.Their complexity brings about aother interrogation that human resources alone cannot handle efficiently all data sets and their interrelationships, therefore other tools such as artificial intelligence (AI) step in. This approach offers high throughput data analysis of high-

dimensional data as an efficient solution. Automated control is then possible fort he MPSs.

Standardization

As in any rapidly developing field the MPS also need standardisation, although biological systems are very dynamic and their standardisation is cumbersome when compared to physical systems. ISO (The International Organization for Standardization) technical committees () in association with MPS standards are multifasceted and are cross-sectoral: including health, IT, and related technologies, engineering, and materials. ISO/TC 48 Laboratory Equipment and ISO/TC 276 Biotechnology are technical committees are the most elated to MPS. The International Conference on Harmonization of Pharmaceutical Regulations (ICH) has developed guidelines for pharmaceuticals' quality, efficacy, and safety; but cells are out of their scope. Guidelines are mainly for small-molecule drugs and biopharmaceuticals. Yet pending, the ISO standards for cells are mainly targetting all research related to cellular systems addressed under different experimentation methodologies[3].

Innovative strategies for MPS utilization in biosciences and medicine

Among diverse applications of OoC platforms facilitating pharmacological drug testing is presently dominant. Another very active field of research are mammary gland models both in healthy/normal and breast cancer states where *in vivo* and *in vitro* models in are used in mimicking tissue heterogeneity and disease progression.. “Breast-on-a-chip platforms”are designed to study breast cancer-related phenomena. One major output envisaged is high throughput therapeutic drug screening *in vitro*[4]. Recent focus has been in breast tumor cell co-cultures with normal epithelia on curved duct-like surfaces versus flat surfaces or to monocultures of tumor cells where differential drug sensitivity can be investigated. . This novel experimental design accomodates high throughput screening technology with multiwell-designed biomimetic OoC ductular-like platforms, which cannot be met with customary 3D breast epithelial cell culture models. Therefore they are good alternatives to 3D monocultures of normal epithelial cells to identify and study mechanisms and interactions.

Active research on the pathological mechanisms of various diseases worldwide remains elusive due to multifaceted interactions among multiple organs and is even more challenging in the pathological mechanisms of complex diseases such as metabolic, neurodegenerative, and autoimmune diseases. Organ crosstalk and causal relationships among multiple organs can significantly damage various physiological systems and lead to serious health consequences. Organ crosstalk generally refers to the biochemical and molecular communication between different organ systems within the human body or between organ mimetics on an *in vitro* platform. This multifaceted interaction involves multiple pathways and feedback loops that can lead to functional changes across organ systems. Conventional approaches such as animal experiments have been widely used to reflect crosstalk among various organs and predict clinical outcomes. Consequently, advanced models such as multi-organ microphysiological systems (MPS) have been developed to implement interactions among various organs[5]. Technological advances in areas such as computational modeling of multicellular systems and 3D printing/bioprinting are the promising means to innovation in human organ engineering. Embryology and natüre of human systems are the sparks for using engineered organs as disease models.. The hot topic already produced several promising examples: using brain organoids, engineered heart, understanding the rules governing nephron number, relationships between tissue from and cell fate in the developing lung, modeling neurodegenerative diseases with vascular networks, increasing positive correlation between organoid and patient responses, engineering a vascularized mini-brain, 3D bioprinting to produce walking/crawling biomachines[6].

With aging populations overriding country populations the risk factor schemes have changed in parallel. A variety of diseases have impacts from aging and this isuue has attracted interest in research environments. Again MPS platforms have stepped in for mechanistic studies of aging impacts on human physiology and the pathogenesis of age-related diseases. Model organisms preferred in gerontology have beed mammals, invertebrate animals, cell/tissue cultures, spheroids. However, not all mammalian models represent satisfactory ageing process of humans. Preferred non-mammalian model organism examples are: *Caenorhabditis elegans* (nematode), *Saccharomyces cerevisiae* (yeast),

Drosophila melanogaster (fruit fly), *and Danio rerio* (zebra fish). Translating and extrapolation of non-mammalian and mammalian ageing models are not at desired level and sometimes cannot produce the same case in the animal. The reason is diversity of evolutionary levels leading to different physiological responses, different cellular, tissue level metabolism and morphological diversity. Further poor complementarity arises from organ architechture and function.. The totipotency for differentiation to all tissue types is only presented by plants. The human pluripotent stem cells used as sources for organoids facilitate circadian rhtythm research; however MPS still need time to efficiently enter use in the field of model ageing phenotypes.Human senescent fibroblasts and blood vessels were employed in a 3D *in vitro* tissue chip model to investigate mechanism of senescent fibroblasts and ageing/aged microenvironments effect in human blood vessel behaviour. Another promising study developed a human brain organoid MPS platform was using 3D printing. The aim was to study the dynamics of immune-driven brain aging and investigate contractile differences between young and old adult-derived skeletal muscle cells. Concnetration on cardiovascular health an ageing cardiac tissue chip model was designed to study effect of age in cardiac diseases. Research output was most invaluable for drug screening. Multiple kidney and nephrotoxicity markers, such as epithelial barrier function, cell polarity, membrane integrity, and mitochondrial function, were evaluated in the MPS after drug induction[7].

Technical advancements and bioethical implications in developing MPS

MPS is an umbrella term where the OoC is adopted most, with rapidly developing wide range of experimental systems. Complexity and dynamics of biological systems are at every hyerarchical level of biological organisation starting from molecules to ecosystems. Although very challenging, cellular behaviour control is the overarching goal of all these advanced and unique Technologies.As the field expands and develops further, pertinent and precise data for various applications can be generated. MPS are categorized into four distinct technologies: 3D cellular aggregates, Hydrogel, Bioprinting, and OoC. Safety assessment and immune response towards biologics facilitate a comprehensive understanding of the interactions between materials/biologics applied and the immune system. These technological advancements are constantly evolving, and the focus is to spotlight the latest technological developments both from the life sciences side and biomedical engineering[8]. At the far end future research concerning suitability of MPS for a clinical product development program is the target. Here qualification and validation processes are finalized with regulatory compliance. Suitable model selection, efficient integration of massive online data, improved analytical monitoring will be the desired issues tTo ensure the reliability and applicability of MPS. On the economy side the sector should develop means and apply control over fabrication processes, and conduct comprehensive characterization of materials and cells.

Regarding imaging, light microscopy is the crucial and indispensable equipment in cytology and histology since it provides invalubale information concerning the specimen studied. It also has advantage of examining the specimen in native form therefore, it can be used in a non-invasive way and the sample can be reused/recovered. Cell types, general structural features and any damage can be assessed. The advancements in microscopy offer in-depth analysis and measurement of cells where the image can capture a wide range of endpoints and cellular phenotypes. Single-cell level data quantification is enabled e and this offers evaluation of multiple different cell types inMPS platforms., Toxic effects are easily followed as end-points for cells. Noninvasive imaging techniques also permit longer-term studies of live tissue *in situ*. In cancer research tracking tumor morphology, growth, and metastasis are very important. Another field that benefits from this approach is embryology. Furthermore, spatial information such as the cell positioning within a chip can only be executed using microscopy. Tissues often exhibit spatial cell heterogeneity, including differences in cell morphology, metabolism, and proteomic profiles. However several drawbacks in MPS imaging such as automation for high throughput screening need to be addressed for drug development/discovery in the pharmaceutical industry. Another problem comes from thickness of the specimens hindering required intracellular imaging for detail. New generation of microscopes to accomodate chip designs and formats in a flexible way are in the optics development pipeline.

Furthermore, similar to the Human Genome Project leading to advancements in

bioinformatics and ripening poerful computers for data acquisition, storage, and analysis; the acquisition of images in 3D in the MPS field requires novel data management. This has several facets such as intensive time allocation and higher data "loads". Competent data scientists are capable of image analysis in complex 3D models, requiring qualified scientists for this task. A summary of applications that utilize the microscopy techniques outlined can be found in Peel and Jackman, 2021[9].

The use of MPS in biosciences and medicine needs to solve new ethical issues. Rapid advances where technological concepts or processes are combined increase the complexity of the resulting platform. Challenges and developments promise progress in a positive scientific and enginnering direction. Supporting non-mammalian testing, and other noew molecular biology, biotechnology assays.With all these developments, the society should be informed and made aware of all the new moves in technology and innovation, their uncertainty should be addressed, complexity, the potential impact, cons and pros should be conveyed. Bioethics can make significant contribution to societal challenges and the answers, addresses to consult, beware of "tradeoffs" they are asked to make. Positive public opinion should be sought for acceptance and engagement in novel technologies. Scientists, engineers, and healthcare providers have a duty to communicate how a particular aspect of science may benefit the community, and also what risks are entailed even when it is used correctly. Importantly, community engagement fundamentally includes two way communication: scientists and policy makers must both listen to what the public thinks about any new technology, and must recognize that the values and priorities of everyone should be respected. Scientists must also acknowledge the dangers inherent in new technology when used incorrectly or without the appropriate bioethical framework[10].

CONCLUSION and PROSPECTS

As a high-end technology in the field of human health, and with a deeper understanding of human organs and more mature development of related technologies in the future, it is expected that organ chips will be used for the perfusion of artificial blood, the integration of sensors, and the management of culture conditions. Organ chips can realize the simulation of multiple organ systems and thus establish a "human chip" model. This will become an excellent tool for disease modeling, drug screening, and precision medicine, opening a broad door for drug screening, discovering more effective drugs, and accelerating treatment advances for human diseases. The way forward holds several challenges for effective application of these platforms to pre-clinical models and guide the design of clinical trials.

Although some achievements have been made in organ-on-a-chip research, there are still many challenges for future development, such as organ compatibility issues of multi-organ chips, mass production of chips, multi-system integration (such as pumps, valves, pressure regulators), the regulation of microenvironmental parameters and stimuli, Machine learning, deep learning, and other artificial intelligence technologies may be incorporated to overcome the enormous challenges brought by massive data and to realize automatic and intelligent data analysis, help researchers discover the mechanism behind diseases faster, screen patients, and identify more suitable drugs for individuals, thereby achieving precise personalized medicine. In the future, the continuous integration of new concepts and technologies on organ-on-chip platforms will accomplish real-time, in-situ, and dynamic monitoring of various kinds of critical parameters, bridge the technological gap between preclinical and experimental translational studies, develop more appropriate clinical research models, and achieve convenient, reliable, and integrated disease analysis. Other pending serious challenges are selecting cells and fabricating culture scaffolds appropriate for a given context of use (COU), while also ensuring assay protocol robustness and improving usability of the MPS platform. Moreover, lack of standards in strategies for fabricating MPS-based cell assay systems that meet client/user needs, makes it difficult to develop and select MPS that meet the COU. The most important aspect of evaluating the function of the materials that comprise the MPS is fitness for the COUs. The COUs for the utilization of MPS are very diverse, not only in drug development but also in food and cosmetics. In order to establish an appropriate MPS-based assay method, it is desirable to clarify the requirements for MPS based on the COUs and decompose the clarified requirements for MPS into requirements for cells and requirements for culture chips. Then, it is a useful sorting process to consider, select, and develop the materials and

shape of the culture chip, keeping in mind that the requirements for the cells should also be satisfied.

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