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Review Article

Human Organoids, their Perspective, and Applications for Personalized Therapy: Rapid Review

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ABSTRACT

Organoids are cell cultures that are three-dimensional (3D) and include some of the most significant traits of the organ being modeled. These *in vitro* culture techniques can recreate some activities of the represented organ, to enable these cell types specific to organs to self-organize into a spatial arrangement comparable to that found *in vivo*. Adult stem cells from tissue samples, a single adult stem cell, or pluripotent stem cells that have undergone directed differentiation can all be used to create organoids. Since some organoid model systems have an active stem cell population, the organoids can be greatly expanded. Organoid culturing methods as of now have been generated to mimic the tissue architectures of the three principal cell lines. Although there are several techniques for cultivating cells that are unique to different tissues, Typically, Matrigel® or another acceptable extracellular matrix is used to implant the appropriate tissue-specific progenitor cells or pluripotent stem cells. The stem cell population is maintained by the cells being cultivated in cell culture environments with certain growth factors that closely resemble the *in vivo* signals needed. Under these circumstances, the interconnected cells multiply and self-organize into 3D organoids that can last forever and be accessed by many systems. In addition, these cultures have proven to be exceptionally stable genetically throughout passage; after 3 months in culture, whole genome sequencing of liver organoids made through clonal expansion from only one hepatic progenitor cell just one equivalent base mutation was found. *In vitro* cell culture is being revolutionized by organoids, which offer useful and medically accurate models that accurately reproduce the essential features of the modelled tissue.

Keywords: Organoids, Cell cultures, Pluripotent stem cells, *In vivo*, Genome sequencing

INTRODUCTION

Organoids are three-dimensional (3D) cell cultures that imitate the form, function, and cellular complexity of human organs. Pluripotent stem cells are used to make them. It is currently common practice to investigate organ development and disease using these *in vitro*, miniature models of organs, which are particularly well adapted for investigating structures of multicellular organs including the kidney, lungs, brain, and retina.[1]

WHERE DO ORGANOIDS COME FROM?

To simulate the structure and functionality of an organ *in vivo*, organoids self-organize and change into relevant cell types in a lab setting. They are also referred to as "mini-organs." They develop in a predetermined 3D setting. Organoids can be produced using adult embryonic stem cells (ESCs), neonatal stem cells, induced ESCs, and stem cells.[2]

Organoids allow the investigation of matrix-adhered cells and the understanding of organ morphogenesis. In organoid culture, a procedure that may have taken years with live model organisms now only takes months. The CRISPR genome editing technique and organoid cultures are used to mimic genetic illnesses in ordinarily inaccessible tissues, such as the brain. Organoids are good models for drug discovery and personalized cancer therapy because they may be produced from tumors or induced pluripotent stem cells (iPSCs) generated from patients. The procedures for organoid cultivation are constantly being improved, offering researchers the opportunity to concentrate on cutting-edge, specialized treatments without having to use human subjects, which poses hazards. Organoids can be created by specifically differentiating iPSCs, tissue-specific adult stem cells, or human pluripotent stem cells (hPSCs). Because organoids are made from living stem cell populations, scientists can routinely grow their cultures any time. Pluripotent cells are embedded in an extracellular matrix, like Matrigel™, to form an organoid. This extracellular matrix supports the pluripotent cells. The stem cell phenotype is preserved by certain proteins and growth factors that replicate the *in vivo* environment. Depending on the original stem cell population and growth factors selected for research, matrix-embedded cells self-assemble into 3D organoid structures that perform similarly to a particular tissue.[3-5]

Scientists can alter the majority of procedures utilizing a regular tissue culture chamber and everyday instruments. In the beginning, feeder cells are used to cultivate pluripotent cells. These cells provide the growth factors needed to maintain stem cell pluripotency while creating organoid cultures with hPSCs. In multi-well plates, the hPSCs are allowed to develop colonies before being enzymatically separated from the wells and feeder population. The pluripotent colonies are then separated and plated on low-attachment 96 well plates. The cells will start to form embryoid bodies over 1–2 weeks, and utilizing tissue-specific induction medium, they can be directed towards particular lineages. The differentiated embryoid bodies can either be cryopreserved or continuously cultured for several months using a tissue-specific medium after being embedded in Matrigel™ droplets.[6] In addition, various suppliers now offer pre-made, cryopreserved organoids for sale.

ORGANOIDS VERSUS SPHEROIDS

Spheroids are defined as the primary's rounded cell clusters or immortalized cells that are widely employed in tumor research and are frequently created by researchers using standard 3D culture procedures.[3] Organoids resemble these structures, but they develop from tissue based specific stem cells that spontaneously self-assemble into miniature replicas of an organ component.[1]

ORGANOID TYPES AND THEIR APPLICATIONS

Brain organoids

Using animal models to study the development of the human brain is completely worthless because the brain is a unique, extremely complex organ. Mouse ESCs, hPSCs, and brain-stimulating factors are the most common cell types used in 3D cell culture techniques. These methods were created by researchers to encourage cell differentiation into organoids that reflect particular brain areas. These brain organoids can simulate the evolution of the human brain throughout gestation as they grow and generate several tissue layers. To uncover unidentified brain development mechanisms, researchers are advancing their techniques and the formation of these 3D brain regions earlier in the prenatal period. However, it is still difficult to induce *in vitro* growth for many brain regions after early gestational ages. Additionally, brain organoids offer important insights into neural malignancies psychiatric, genetic, and neurodevelopmental problems.[7]

The respiratory virus known as SARS-CoV-2 affects the central nervous system (CNS) as well as the respiratory system, causing several neurological problems and neuropsychiatric disorders.[8,9] Organoids of the human brain created from pluripotent stem cells are in high demand, but clinical brain specimens from individuals are difficult to obtain for research into the molecular pathogenesis of coronavirus disease 19 (COVID-19) in the CNS. SARS-CoV-2 neurotropism was demonstrated in studies employing brain organoid models and a small number of infectious neurons, astrocytes, and glial cells.[10,11] The virus's role in the blood-cerebrospinal fluid (CSF) breakdown in zone brain organoids (CSF) barrier in humans was shown by the severely damaged choroid plexus epithelial cells (ECs) in those tissues.[12,13]

SARS-CoV-2-infected brain organoids also displayed neuronal cell death, shedding light on the neurotoxic nature of the virus. As a result, the researchers concluded that choroid plexus cells infected with SARS-CoV-2 experienced an inflammatory response and had their ability to form a protective barrier between the CSF and blood compromised. To stop the spread of SARS-CoV-2 infection, they utilize angiotensin-converting enzyme 2 receptor inhibiting antibodies, through CSF or plasma from COVID-19 patients who possesses IgG antiviral antibodies.[14]

Lung organoids

Another intricate and challenging to analyze tissue is the lung. There are few two-dimensional (2D) *in vitro* tests, and *in vivo* research is expensive because of the intricacy of its cell kinds, highly vascular system's structure, and its role in oxygen exchange. Darrell Kotton of Boston University required 30 years to successfully separate lung progenitor cells. Lung

cell differentiation is sparked by the stimulation of Bone Morphogenetic protein (BMP)/Fibroblast growth factor (FGF) signaling from mouse embryonic fibroblasts, even though the first lung organoids containing alveolar tissues were made in 1980.[15] Since then, methods have advanced as researchers use hPSCs and iPSCs to simulate the function of airway ECs, monitor the development of early lung buds, and carry out lung cancer screenings. The lung's capacity to recover from injury makes it special as well. Therefore, using adult stem cells, researchers can create lung organoids.[16] As a result, adult individuals with hereditary or environmental disorders can produce lung organoids. Lung organoids have recently grown in importance as a tool for research into how SARS-CoV-2 impacts respiratory organ/system development and function.[17]

For the investigation of the Influenza virus, airway organoids were commonly used, notably influenza types A and B viruses before the appearance of SARS-CoV-2. The organoid model was used in research of both types of virus tropism. Both an *ex vivo* human bronchus explant and an organoid model were used to demonstrate the influenza A virus's kinetics of replication and tropism.[18] In different influenza types, it has been demonstrated that some A virus strains may infect particularly ciliated cells and goblet cells, among others.[18] Compared to the lower lung, the upper respiratory tract is where the influenza B virus infects people, according to a study done by Bui *et al*., 2019. This suggests that it has a similar tropism and rate of replication to the influenza A virus.[19]

Furthermore, lung organoids showed that the influenza A virus replication tended to form specific foci as opposed to spreading randomly as shown by prior monoclonal cultures.[20] Pro-inflammatory genes and genes connected to interferon (IFN) had been triggered to cause an immunological response throughout the infection of the lung organoid.[20] Also, a mammalian airway organoid has been employed to test the infectiousness of various influenza strains.[21] Considering evidence accumulated across four distinct influenza strains, the feasibility of the organoid model was proven. The 3D human lung organoid showed a higher multiplication rate of human-infectious H1N1 and H7N9 influenza viruses compared to the avian-and-swine-infective H7N2 and H1N1 viruses.[21]

Gastric/intestinal organoids

The several germ layers that make up the gastrointestinal system must cooperate to perform its many different tasks. In 2011 and 2014, scientists created the first intestinal and stomach organoids with a variety of tissue types using hPSCs.[22,23] However, the relationship between the gastrointestinal system and immunological and brain cells makes many protocols rather ineffective at simulating internal bodily processes. The microbiomes of the stomach and intestines, which have an impact on everything from the immune response to pharmacokinetics, further complicate matters. In light of this, scientists recently created protocols that enable the co-culture of intestinal commensal bacteria with organoids, enabling the investigation of the effects of microorganisms on cancer cells as well as the modeling of stomach disorders.[24,25]

While intestinal organoids give scientists a way to study patient-specific disease pathology and organ development, precisely constructing this tissue in a laboratory setting is difficult. To enable intestine cell lines organoids with crypt-like patterns to self-organize characteristics, researchers have developed a biomaterial tissue scaffold according to research that was just published.[26] The stem cell and micro-vessel compartments in these gut organoids grow side by side and faithfully replicate *in vivo* tissue.[26]

Conventionally, developed intestinal organoids in 3D matrices feature a monolayer of fluid-filled ECs; this makes them cystic. On the basal side, the cells interact with the matrix, and inside the apical surface, the tissue interacts with nutrients and medications. The apical surface of the intestine is where host-microbe interactions take place, and this is where parasitic bacteria and viruses enter. You must gain access to this inner apical surface to research these interactions or medication and nutrition delivery. With closed organoid structures, it is quite challenging to do this. To inject materials into the apical side, a hole must be made in the tissue. This method of injecting viruses has been used successfully to research infection. That, however, is extremely challenging, labor-intensive, and has limited throughput.

Cancer organoids

Cancer organoids produced by patients are a crucial resource for understanding the development of cancer and also for the development and use of personalized medicine. Cancer organoid models are used by researchers for fundamental research and medication screening because they accurately mimic patient tumors. Interestingly, tumor-derived organoids can retain their genetic and molecular characteristics even after numerous passages.[26,27] Scientists have created technologies to make and evaluate patient-derived organoids, allowing for the rapid discovery of patient-specific medications.[28]

The first 3D tumor organoid culture was a murine intestine organoid and subsequent tumor models for additional tumor tissues were created before being translated into human cells.[29] Depending on the type of tumor, different organoids generated from tumors in patients can be cultivated. Various tumor tissues, such as cancers affecting the colon, stomach, small intestine, liver, lymph nodes, bladder, prostate, mammary glands, pancreas, and many tumor organoid models have been developed recently.[30,31] It has

been successfully attempted to produce organoids of human colorectal cancer from several anatomical locations (e.g., left-sided, right-sided, and rectal tumors).[32] For the creation of 3D tumor organoids and biobanks, various growth conditions and techniques tailored specifically for tumor tissue have recently been created. These tools could be used to determine whether organoids can predict how each patient will react to the medication. These organoid lines demonstrated the idea that "tumor organoids provide a viable platform for drug testing" as well as the connection between a gene and a medication, showing the variation in pharmacological responses across patients and within a single tumor.

Liver organoids

At the moment, liver organoids may perform functions unique to the liver, such as protein synthesis and drug processing.[33] Vascularization was also seen after organoids were implanted into mice.[33] These functioning hepatocyte-containing liver organoids are also genome-stable and have few single nucleotide mutations.[34] These properties make the liver organoid a trustworthy model for figuring out how viral diseases like chronic viral hepatitis develop. According to Baktash *et al*., 2018 a study using hepatoma organoids, the hepatitis C virus enters the organoid system through successively activating entry factors such as the cluster of diversification 81, the occludin, the claudin-1, and the epidermal growth factor receptor (CLDN1), in an actin-dependent method. Furthermore, liver organoids are a more practical way to study infections that have long periods of inactivity or are prone to relapses. This is due to the liver organoid's ability to endure worthwhile and phenotypically stable in culture for 5–10 weeks, as opposed to the 2-week maximum viable culturing length for 2D primary human hepatocytes.[35] From fetal tissue, a liver organoid may live for at least 11 months. This property of prolonged persistence is advantageous for malaria research since the underlying Plasmodium protozoan parasites' pre-erythrocytic stage of the life cycle, sometimes referred to as the liver stage, allows for the parasites to persist for weeks or months inside a hepatocyte.[36]

In addition, the organoid's 3D structure showed that Plasmodium sporozoites may pass through the extracellular matrix and infect the core.[37] Due to the infectivity being typically lower in 2D cultures, this was not evident.[37] The use of organoids could permit extended study on malaria and further contagious diseases that necessitate a long duration of incubation since they can recapitulate protracted periods of infection.

Reproductive tract, heart, and skin organoids

As a result of their ability to replicate the intricate *in vivo* properties of the reproductive organs, organoids have thus been frequently utilized to research reproductive infectious diseases.[38] Infection with Ctr serovars D, K, and E of *Chlamydia trachomatis* was studied over an extended period using human reproductive tract organoids.[39] The paper asserts that the disrupted organoid's epithelium causes compensatory cellular development and releases Ctr bacteria into the lumen. In addition, the Ctr bacteria induced the Leukemia inhibitory factor (LIF) signal transduction in the organoids, which controls pluripotency and sheds light on how the Ctr bacteria may result in high-grade serous carcinoma. Human papillomavirus promotes cervix carcinogenesis, which results in cervical cancer, using organoid-based cervical models.[40] There is little doubt that as a means of researching infectious diseases, reproductive organoids provide excellent models created *in vitro* that have an impact on human reproduction. This makes it possible for researchers to understand the disease's origin and how medication screening is used. Other sexually transmitted diseases (STDs) brought on by infections including organoid technology might be used to study Trichomonas vaginalis, Herpes simplex virus, and Neisseria gonorrhoeae.

Recent studies have shown post-acute cardiovascular symptoms and problems in SARS-CoV-2 patients. Because of this, studies of the mechanisms by which the virus causes cardiac dysfunction have used cardiac organoids to find new medications that could guard against it.[41,42] Human cardiac organoids subjected to a "cytokine storm" combination of poly(I: C), IFN-, and interleukin 1 (IL-1) showed diastolic dysfunction.[41] In addition, it has been demonstrated that inhibitors of the extra terminal family and the bromodomain (BETi) can reduce transcriptional viral responses and the frequency of cardiomyocyte in SARS-CoV-2 infection while reversing organoid cardiac dysfunction.[41] This was made possible by a greater mechanistic comprehension of how the virus damages the heart.

The study of myocarditis brought on by bacteria, such as *Trypanosoma cruzi*, and viruses may also benefit from the use of cardiac organoids.[43,44] Myocarditis is mostly caused by Chagas disease and is brought on by *T. cruzi* infection.[45] Despite the use of several *in vitro* models, including primary cell lines, immortalized cell lines, and cardiomyocytes produced from human induced pluripotent stem cells, there are still problems with the symptoms and beginning of myopathy in patients with Chagas disease.[46] Therefore, patient-produced heart organoids may shed light on the mechanism underlying *T. cruzi* persistence and the origin of Chagas disease. Human skin organoids that can replicate the delicate features of the human epidermis and are extendable for six months have been developed for use in dermatological research. To aid in the study of dermatology, 6-month extendable human epidermal models have been created. Recent studies have shown that *Trichophyton rubrum* can generate a fungal infection in the human primary

epidermal organoid system.[47] The investigation led to the conclusion that the ongoing suppression of IL-1 signaling was probably to blame for the ongoing skin infections and mild inflammation.[47] More research into infections including *Streptococcus*, *Candida* species, and *Staphylococcus aureus* that cause skin disorders may be motivated by the development of a functional skin organoid.[48] A skin organoid was also employed in a recent investigation to show that the skin's neurological system and hair follicles may both be affected by SARS-CoV-2.

3D CELL CULTURE AND ASSEMBLOIDS

The next generation of multi-tissue organoids, known as cultured assembloids, has been created by researchers as a step forward in the field of organ modeling. Researchers created methods that integrate various tissues in culture, enabling them to observe and predict the tissue interactions that affect cellular activity in organs like the brain where numerous areas and tissue types interact.[49] Assembloids are becoming a crucial tool for modeling disease as a result of laboratories adapting these protocols to more complex tissues in recent years.

HOW ARE ORGANOIDS DIFFERENT FROM *IN VIVO* TISSUE?

Typically, essential guidelines for tissue formation are absent in *in vitro* systems, which reduces the reproducibility and robustness of *in vivo* tissue development and maturation. *In vivo* has two primary control mechanisms. First, signaling molecule gradients known as morphogens provide clear instructions for the distribution of different cell types in tissues. Depending on how far away from the source signal they are, the cells decide on several cell fates. Organoids grown in a laboratory lack these signals. A physical control mechanism is the second significant one. The tissues that surround one another and grow together create boundaries in the body. Tissue growth must cease because an adjacent organ must also develop before it can proceed unchecked. Since there is no environmental effect *in vitro*, the cells are free to proliferate and develop tissues in three dimensions.[49]

Somitoids

To create the segmental pattern of the vertebral column, blocks of ECs known as somites periodically arise during embryonic development in accordance with the segmentation clock. Human and mouse pluripotent stem cells have recently been used to recreate the process of somitogenesis. However, there is still a lack of the segmentation clock, epithelialization, and an *in vitro* model of human somitogenesis.[50] When the presomitic mesoderm is segmented, somitoids exhibit distinct oscillations of the segmentation clock. The resultant somites exhibit apical-basal and anterior-posterior polarity. Matrigel is necessary for epithelialization but not for somite cell differentiation. Regardless of the initial cell number, somite size is very consistent.[50]

NEED OF HUMAN SOMITE FORMATION *IN VITRO*

The intricate developmental process of somitogenesis causes waves of altered gene expression to go at regular intervals through the front end of the tissue's presomitic mesoderm to bud off somites. Somatogenesis is typically studied in model organisms like mice, chicks, and zebrafish, yet there are some significant variances despite how similar the process is overall. We are unable to research how the process is affected by human skeletal illness-causing mutations or how this tissue develops in humans since somite creation occurs during embryogenesis. To replicate somite production and differentiation in people, an *in vitro* model was created.

CONCLUSION

Human organoids have a tremendous deal of possibilities for clinical translational research despite the remaining difficulties, thanks to the benefits mentioned above and to the quick, ongoing technological advancement. Organoid technology has advanced to incorporate genetic engineering, numerous omics, and drug-screening studies, and a range of co-culture systems involving viruses, bacteria, and parasites. Starting with isolation of patient samples and the original entire "laboratory life cycle", the next step should be the creation of organoids and their cryopreservation. The study of infectious diseases has improved greatly because of organoids produced by hPSCs. Organoids can recapitulate native tissues in a manageable way, addressing some of the difficulties with earlier conventional techniques. To address the growing threat of infectious illnesses, the organoid model is undoubtedly a helpful system for comprehending the underlying biological causes of infections. Despite its potential, there are some negative aspects, such as the lack of complexity and reproducibility required to accurately recreate *in vivo* situations. Future medical research is anticipated to continuously use organoids in conjunction with a variety of scientific and technical approaches to maximize their potential. Organoids do have some limits, but as they are used and improved, the distance between their development/creation and therapeutic applications will close. Because of this, Organoids will be used more consistently and directly in the clinical treatment of patients, creating a broad and promising future.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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