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Review

# Organoid Systems

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**ABSTRACT**

In cell culture applications, modeling cells from the original tissue in culture medium has been difficult due to limitations in cell proliferation and differentiation. These limitations have directed researchers toward the discovery of organoid systems that better represent cells from the original tissue biologically, physiologically, and functionally in the culture medium. Organoid cultures can be formed from embryonic stem cells, induced pluripotent stem cells, or adult stem cells. They play a crucial role in various fields such as biology, medicine, and stem cell biology. This chapter reports on the areas of study, advantages, and disadvantages of organoid systems.

**Keywords:** 3D cell culture, embryonic stem cells, extracellular matrix, stem cell, organoids.

The process of forming a complex organism from a single fertilized egg cell is initially quite complex. However, it has been a subject of great interest in biological research. As a result of this interest, two-dimensional (2D) cultures of adult epidermal stem cells and embryonic stem cells (ESCs) *in vitro* have emerged since the 1970s.[1] Advances in fields such as biology, medicine, and stem cell biology have led to the acquisition of much knowledge in basic human biology and medical science. In this regard, one of the most important recent developments has been the development of three-dimensional (3D) organoid models that resemble organs in the living body.[2] Although the term "organoid" has become popular only in the last decade, it actually emerged as early as 1946 in the field of oncology.[3] From the 1960s onward, it began to be used by biologists to refer to cultures of self-organizing organotypic cells in cell culture.[4,5]

Organoid systems were selected as "Method of the Year 2017" by Nature Methods.[6] Organoids are 3D cultured cells that originate from cells such as human ESCS, adult tissue-specific stem cells, and human induced pluripotent stem cells, which are derived from epithelial and mesenchymal cells. They exhibit micro-anatomical structures that closely resemble the original tissue, and are grown in culture to mimic the *in vivo* conditions. In this respect, organoids promise to eliminate many limitations encountered in biological, physiological, medical, and other research areas by obtaining patient-compatible tissues in regenerative medicine and disease modeling. Cell culture techniques, which have been used in research for about 40 years, have been sterile in terms of reflecting the original cell culture. Therefore, organoid systems have become an important tool in biological research.[1,2]

Compared to 2D cell culture techniques, 3D cell culture techniques more closely resemble their tissues of origin in terms of biological, physiological, and functional properties *in vivo*. This is because, in 2D culture, cellular interactions are limited to a single layer in the horizontal plane, while in 3D culture, cellular interactions or cell-extracellular matrix (ECM) interactions occur. In 3D cultures, efforts are made to create a suitable environment for the physiological, biological, and biochemical mechanisms that cells naturally undergo in a tissue, such as cell proliferation, differentiation, migration, and survival processes. In

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this sense, 2D cell culture techniques remain sterile.[7]

Organoids are highly suitable for modeling live tissue and cells, as well as homeostasis. Additionally, the reproducibility of a model is crucial, and organoid modeling is suitable for working in multiple laboratories. The basic formation of an organoid involves the production of adult tissue from adult tissue stem cells in a matrix environment, through growth factors secreted by the stem cell niche.[2] Therefore, understanding the ECM structure in organoid systems also facilitates 3D cell culture. The regulation of stem cell niche signaling pathways and differentiation pathways also accompanies organoid system formation.[8]

Organoid systems are commonly studied under physical conditions such as suspension culture of multipotent progenitor cells or embedded within an ECM like Matrigel. Depending on the type of cancer tissue sample being cultured, growth factors, various inhibitors, R-spondin, WNT3A, and other additives can be added to the culture medium, and mixed with a flat or dome-shaped 3D Matrigel.[8,9] All of these factors affect the proliferation of cells in the organoid environment and the degree to which they reflect the original tissue.

Organoids also provide advantages for studies such as testing therapeutic agents like chemotherapeutics and immunotherapeutics, determining cell/tissue-specific treatment methods, drug screening, and identifying toxicities. There is a need for organoid models that can mimic the natural tumor environment for pre-clinical applications. Cancer organoids can be generated from primary tumors, metastatic lesions, circulating tumor cells, and effusions using various techniques including solid and liquid biopsies, rapid autopsies, and surgical resections.[10-14] After the collection of the patient's tumor tissue, tumor samples are treated for downstream culture using 3D encapsulation in a matrix. The generated tumor organoids mimic cancer cells and provide insight into the tumor microenvironment. Using the information obtained from organoid models, the response and prognosis of tumor cells to treatments can be directed.[8]

Various genetic diseases that are difficult to study in animal experiments can also be investigated using organoid systems. For example, brain development differs between human and animal models due to the expansion of the brain in the evolutionary process.[15] The process of neurogenesis involves the proliferation and diversification of progenitor cells, resulting in brain expansion. However, there are also cases of brain shrinkage. Microcephaly, a brain shrinkage disease, involves mutations in proteins involved in deoxyribonucleic acid (DNA) replication and DNA damage repair.[16] Mutations of microcephaly genes (CDK5RAP2, ASPM) can cause severe neuronal disorders. In studies conducted on mouse models, mitotic errors and centrosome anomalies were observed in neural progenitor cells, but the variability in brain models was minimal. In contrast, the generated cerebral organoid models showed more similarity to patient phenotypes in the relevant genes.[16,17]

Other advantages offered by organoids to researchers include the ability to examine human tissues with high similarity in model organisms in a repeatable manner, provide an open environment for manipulation, summarize the morphogenetic process in tissue and organ formation, provide a pre-clinical tool, and shed light on cellular mechanisms in disease processes.[2] For example, liver organoid biobanks can be created from healthy liver cells. These biobanks can be used for the diagnosis and treatment of liver diseases, acute liver failure, and the study of drug-related liver damage.[7]

To date, some cancer types that model inter-patient differences by creating personalized live biobanks can be listed as colorectal, lung, bladder, breast, ovarian, prostate, endometrial, gastric, brain, esophageal, and pancreatic cancer.[13,14,18-29] In a report by Tiriac et al.[28] a large pancreatic cancer organoid cohort was established from tumor samples of 138 patients in terms of genetics and phenotypes. The detailed pharmacotype analysis of these organoids revealed significant results at the genetic and transcriptomic levels related to the response of patients to drug treatment at the population level in clinical settings.

One example of studies conducted using organoid systems is the use of brain, colon, and lung organoids to identify small molecule inhibitors for Zika virus and SARS-CoV-2 infections.[30-32] Additionally, drug screening combined with single-cell transcriptomics in intestinal organoid models has led to the discovery of Exportin-1 as a new drug target for regulating the number of Paneth cells, which are important for regulating the composition of the gut.[33]

In addition to their functions in the diagnosis and treatment of diseases, elucidating physiological mechanisms, and investigating drug efficacy, organoid systems have also been used to create cell types for transplantation purposes such as

pancreas, liver, kidney, retina, and intestine. In a study publication, organoid-derived cells transplanted into recipient animals can integrate and partially restore organ function.[34] On the other hand, a study is currently ongoing to investigate the transplantation of cells derived from organoid systems originating from salivary glands after radiotherapy in head and neck cancers.

In an important study, it was found that single-cell transcriptomics of kidney organoids led to an improvement in organoid quality by inhibiting the neurotrophic receptor tyrosine kinase 2 (NTRK2), which is the receptor for brain-derived neurotrophic factor (BDNF), and preventing translational errors along neuronal networks.[35]

Although organoid systems represent an important stage in personalized cancer treatment modeling, there are still various limitations to their clinical application. Current organoid culture systems cannot support the long-term heterogeneous culture of tumor microenvironment (TME) cells. Current organoid cultures generally contain neoplastic cancer cells. Moreover, drug sensitivity cannot be largely predicted due to the unknown interactions and functions of ECM. More studies on appropriate 3D culture practices are needed to overcome these limitations. Additionally, improvements and adjustments to organoid system protocols are required. Protocols should be built upon an understanding of the natural biological heterogeneity of tissue.[36,37] In studies lacking appropriate protocols, organoid models will continue to carry problems such as reproducibility and incomplete patient representation. Furthermore, although organoid systems can mimic the micro-level of the originating tissue, they are not successful in mimicking an organ as a whole. This is because the dynamic structure of the tissue can be variable. To predict this, specific tools for cells and subtypes are needed.[38,39]

Since all physiological and biological processes in the TME affect the effectiveness of anti-tumor treatment, failures in clinical treatments have increased the need for stronger models to better understand TME. While traditional 2D *in vitro* cultures, which work with immune system components obtained from peripheral blood, are used, 3D organoid models have made it possible to work with primary human tumor biopsies in culture media.[40] In addition, organoid culture systems are also used to obtain a lower-cost representative model for examining *in vitro* interactions in the TME. In the early stages of the discovery of organoid systems, Sato et al.[41] successfully created organoid models from many patient-derived tissues, including colorectal cancer (CRC), and the study protocols are still expanding.[18]

Through organotypic models, steps can be taken to understand the heterogeneity of cancer in significant tumors taken from patients, their individual effects, and personalized treatment. Based on these advantages, it can be said that organoids have the ability to mimic the genetic and proteomic structure, as well as pharmacological properties, of the origin of cells *in vitro*. At the same time, it is important that the origin cells offer a repeatable and manipulable door. For example, in an organoid modeling study on mutations in the adenomatous polyposis coli (APC) gene, which plays a role in cellular processes such as cell division and invasion, it was shown that intestinal crypt homeostasis repaired APC mutations in mouse colorectal cancer cells. Research can be conducted on the repair of promoter gene mutations in tumor organoids.[8,42]

*In vitro* tumor organoid systems are a suitable system for modeling TME microenvironment heterogeneity and intercellular interactions by culturing non-neoplastic cells, immune system components, and cancer-associated fibroblasts (CAFs) in a single environment.[29,47-50] Fujii et al.[19] have also succeeded in creating a living biobank consisting of 55 CRC organoids derived from tumor phenotypes with primary and metastatic lesions. Thus, different histopathological characterization and genetic profiles *in vivo* samples were preserved, and information about drug response phenotype was provided.

Immune cells such as intraepithelial lymphocytes (IEL) play a role in adult epithelial homeostasis in the stem cell microenvironment. Epithelial cells also regulate immune responses.[43] This relationship between epithelial cells and immune cells has been studied in intestinal mucosa in animal models. However, modeling the interaction between cells *in vitro* is quite challenging. In this regard, Nozaki and colleagues[44] cultured intestinal epithelial organoids with IEL cells to examine the interaction between the immune system and epithelial cells. IEL cells isolated from mouse intestinal epithelial tissue and intestinal organoids were embedded in Matrigel and supported with a cytokine mixture of interleukin-2 (IL-2), IL-7, and IL-15 in the organoid medium. In the two-week co-culture of CD3+ intraepithelial T lymphocytes and organoid epithelium, the lymphocytes integrated into the organoid epithelium and showed significant proliferation. Based on these results, it can be said

that immune cells can remain viable in organoid systems and respond to stimuli they are exposed to. Furthermore, embedding IEL cells in Matrigel did not affect cellular mobility and allowed for immune cell function and migration.[44]

For instance, cystic fibrosis (CF) is a genetic disease in which mutations are observed on the CF transmembrane conductance regulator (CFTR) chloride channel. CFTR mutations lead to the formation of thick mucus in the intestine, lungs, or other organs.[45] Patients with rare CFTR mutations are generally overlooked in clinical research. Therefore, determining therapeutic approaches for rare CFTR mutations is crucial. Retinal organoids obtained from patients explain functional problems in CFTR: an increase in intracellular AMP levels and swelling in the organoid due to ion and fluid transport to the lumen were observed with forskolin treatment.[45-46] Swelling was not observed in rectal organoids derived from a CF patient under normal conditions. Considering this difference, rectal organoids can be used as a model to investigate CFTR functions.

In conclusion, patient-derived organoids are a powerful resource for personalized treatment. The ability of organoid models to faithfully and reproducibly recapitulate the original tumor tissue provides an important step in clinical treatment approaches and the success of drug therapies. Creating an individual organoid profile for the patient genetically in personalized treatment will also provide insight into various variations. In addition, the model organoid can be preserved in living organoid biobanks after cryopreservation. Specific targeting of cancer cells can be achieved by creating patient-specific organoid models from a single individual, and the discovery of low-toxicity drugs becomes possible. Moreover, ideas can be obtained about intratumoral heterogeneity and the tumor microenvironment. Mutations in the target tissue can be detected, and genome sequencing can be demonstrated. All of these are important action steps in anticancer therapy. Classical animal models and *in vitro* cell culture applications can sometimes encounter some limitations. The cells being studied may acquire genetic mutations, leading to cancer heterogeneity. The lack of stromal regions, genetic differences with control cells, the pharmacokinetic response of xenograft models, and the repeatability and progression of research may be limited. Another disadvantage of working with organoids is the potential for slower growth of cancer cell organoids compared to healthy tissue-derived organoids. The slowing of organoid growth rate is associated with high mitotic problems and cell death. Despite this difference, organoid cultures can be produced from patient-derived tumor tissue, and a model close to the original can be created in research studies. Along with all these advantages, there are also disadvantages such as unstable success levels and high costs. Factors such as the laboratory environment, experimental processes, oxygen levels, multi-well plates, differentiated cell types, and the maturation processes of these cell types can affect the effect of organoids.

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