Review Article
Open Access
CrossMark

Organoids technology: an advanced meditate in tissue engineering and organ development

Abstract

Organoids are in vitro miniaturized and simplified model systems of organs that have attracted a great deal of interest for cell therapy, personalized medicine, drug screening, and the modelling of tissue development and treatment of different illness. Despite significant progress in the cultivation of physiologically appropriate organoids, obstacles still stand in the way of practical applications. Organoid systems are difficult to translate in part because of the significant diversity of self-organizing growth and the limited experimental and analytical access. Since ancient times, efforts have been attempted repeatedly to create replicas of *in vivo* organs from their tissues or cells. Organoid technology as a whole has only recently begun to systematically develop and has been demonstrated to be crucial in tissue engineering. Induced and retrieved stem cells from a variety of organs have the ability to self-organize to create three dimensional structures that are physically and functionally equivalent to their in vivo counterparts. These organoid models offer a strong foundation for understanding disease modeling, drug candidate screening, and development mechanisms. In this review it has been describe the developments to produce different organoids of tissues as well as their shortcomings and potential applications in tissue engineering.

Keywords: organoids, tissue engineering, organ development, in-vitro growth, future medicine and model

Volume 8 Issue 1 - 2023

Satish Shilpi,[1] Pranali Chimaniya,[2,3] Khyati Saini,[1] Jamal Basa Dudekula,[4] Vikas Pandey[4]
[1]Department of Pharmaceutics, Faculty of Pharmacy, DIT University Dehradun, Uttarakhand, India
[2]School of Pharmacy and Research, People's University, Bhopal (MP), India
[3]Department of Pharmaceutics, Ravishankar College of Pharmacy, Bhopal (MP), India
[4]Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior (MP), India

Correspondence: Dr.Satish Shilpi, Department of Pharmaceutics, Faculty of Pharmacy, DIT University Dehradun, Uttarakhand, India, Tel +91-9406520691, Email shilpisatish@gmail.com

Received: December 26, 2022 | **Published:** February 02, 2023

Introduction

Organoids are defined as 3D-structured in vitro biological complexes that contain one or more cell types and that only partially reproduce the form and function of their in vivo counterparts. Organoid technology began to emerge in the 1970s, when James G. Rheinwald and Howard Green produced the stratified squamous epithelial colonies that served as the foundation for the in vitro creation of 3D structures. Later, the substantial developments in extracellular biology and suspension culture technologies opened the door for the continued advancement of organoid technology. Dr. Hans Clevers' team announced in 2009 that an intestine organoid could be created from a single inte stinal stem cell without the need for a mesenchymal niche.[1] This achievement is a whirling position was an account of organoid technology, stimulating the consequent creation of major 3D arrangement similar to numerous new organs in ectoderm, mesoderm, and endoderm.[1-3]

Organoid forms three dimensional structure develop from the primary tissues and cells. They can survive for longer duration with their cellular complexity and the 3D structure. It has been found from research that organoids can divide into tiny amount of tissues. To examine a physilologic and pathologic conditions many organs are developed from murine and human organoids. Basically, they are obtained from the stem cells which further divide by forming a huge number of types of cells and act as progeny.[4] However, various scientists had work on this to maintain proper environment for making stem cells which helps them in self-organizing in genetics, making tiny structures also known as miniature organs from other cells types. The size of organoids varies from 5mm to less than width of hairs. Organoids are of different types because they form various types of tissues and organs in body. Pluripotent stem cells (PSCs) are also derived from organoids which are obtained from embryo. In the early stage of organogenesis, embryonic tissue evolutes into traditional re-aggregation experiments showing that the progenitor cells divides into forming its own three dimensional structure. Now, a day's many new technologies have been developed for exogenous tissue patterning involving growth factors that shows varieties of cell identities for progressing the movement of cell and creating the 3D tissue.[5] Adult stem cells (ASC) are also created from the organoids which forms sometimes in single ASC or the ASC consisting of various tissue units.

They are directly derived from the adult tissues. Many factors are involved for the growth of culture media, which helps in controlling the signaling at the stage of tissue homeostatic in normal condition. They have the characteristics of human tissues as they are obtained from humans. Preclinical models possess the barrier for the treatment of human disease. IPSC chronology removes the ethical concerns by using hESCs.[3]

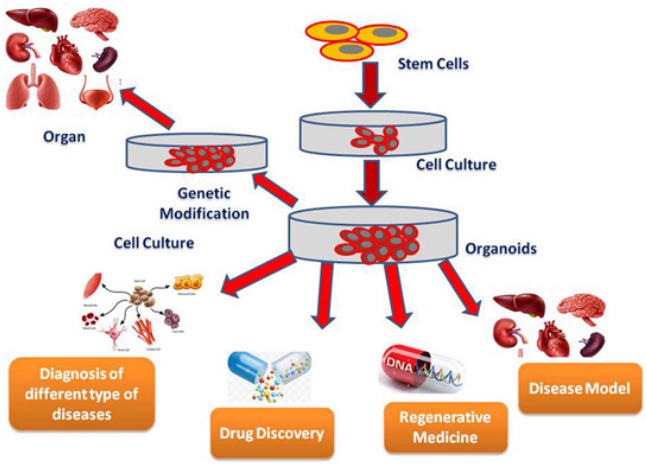

Figure 1 Application of organoids.

In order to study organ formation, adult tissue homeostasis, regeneration, disease manifestation, and potential treatments, organoids are useful research tools.[6] Organoids can now be produced in vitro using recent technical developments in the stem cell field that are similar to complete organs. The majority of these methods make use of three-dimensional (3D) culture techniques that enable cells

produced from stem cells or tissue progenitors to auto arrange in three dimensional configuration. These systems developed from traditional reaggregation experiments, which demonstrated that separated cells from embryonic organs could reassemble and recreate the original organ architecture. Organoids offer enormous opportunities for development of tissue which can help in the treatment o different type of diseases.[5]

Current organoid technologies are as follows

1. The ectoderm organoids: The outermost layer of the embryo is known as the ectoderm and it has been utilized to development of brain and skin nerve tissues.
2. The mesoderm organoids – It is used for the development of muscle, skin, gonad, and heart, kidney and blood vessel.

I. Oesophagus and lung organoids

II. Liver and pancreatic organoids

III. Stomach organoids

IV. Small intestinal and colon organoids

V. Prostate organoids.

Because distinct endoderm organs develop similarly to one another, substantial research has been done on organoid models for endoderm tissues. The establishment of organoid culture conditions that might work for other tissue engineering technologies was made possible by this commonality.[5–6]

Various organoids model

Organoids model in patient

For basic and translational research, patient organoid model shows effective tool. 57 N- glycans make 10 models across 50-94%. By examining the patient's plasma samples, chronic pancreatitis, the four EV proteins shows the biomarkers for PDAC.

Liver disease model

It is also known as Human Pluripotent stem cell .Albumin and cytokeratin 7 expression divides into hepatocytes and cholangiocytes. By incubating the organoids in free fatty acid causes structural changes same as non-alcoholic fatty liver disease.[3,7]

Intestinal organoid modeling culture

Modern intestinal organoid consists of 8 components namely LDN193189, VPA, EPZ6438 AND R-Spondin 1 conditioned medium, same as gut epithelium regeneration shows hyperplasic .In vivo stem cells shows single-cell RNA sequencing which regenerates stem cell populations.[8]

Human disease modeling and living biobanks

The use of human organoids in disease modelling is one of their main uses. Through them, individualized treatments, such as cell and organ replacement therapies, are tested for specific diseases through drug/genome screening and the formation of living biobanks. Between clinical practice and translational medicine, living biobanks are crucial. Human organoid biobanks have a lot of potential for creating live biobanks because they can collect and preserve functional tissues for a very long time, as opposed to traditional biobanks. Disease modelling has faced several difficulties because it is a fresh topic to create a model for an organ-specific disease.[3,5,9]

Therapeutic potential and application of organoids

Organoids in biomedical research

Undifferentiated stem cells have the capacity to reassemble and reproduce the organ's structural makeup. In order to create organoids for biomedical research, they are used. Organoid models are important tool in tissue engineering for restoration, regeneration, or replacement of damaged organs/tissues.[8,9,10] Organoids are currently used in the investigation of human disease and development. Organoid systems are also helping personalized and regenerative medicine advance. Compared to conventional animal models, organoids, which are produced from human stem cells or induced pluripotent stem cells, offer the genetic and physiological similarities needed for improved modelling of human development and disease.[10] Organoids are currently being employed in biomedical research to:

I. Examine tissue morphogenesis and organ development.

II. Model diseases.

III. Test drug sensitivity and toxicity.

IV. Potentially create complicated transplantable tissues.

Organoid systems that replicate organs like the heart and lungs may one day be created from successfully generated organoids of the colon, liver, kidney, and brain. By using organoids, which only need a minimal number of cells to generate a wide variety of tissue types, the modelling of human development and disease is improved. Pure cultures of particular tissue types can be used to efficiently control experiments, and advancements in bioengineering enable the production of precise models that accurately captures complicated relationships. Organoid technology could be used to create tumor biobanks or replicate the development of tumors in cancer tissue engineering. The putative driver genes involved in tumor growth in brain can be used as an experimental model by developing brain tissue in culture media with the help of CRISPRCas9 gene.[11]

It was discovered that liver organoids were an effective tool for researching liver steatohepatitis. Chemical probes could be used in 3D stomach organoids to better understand the crucial shift from the mitotic to central spindle.[10,12] According to research by Anahita Amiri and colleagues, cerebral cortical organoids made from hPSCs can represent the dynamic process of human cortical development as well as the changes in transcriptome and epigenome that occur throughout cortical development. These cerebral cortex organoids from human pluripotent stem cells were also employed to examine the differentially active genes and enhancers during the transition of stem cells to progenitors.[10]

Organoids as regenerative medicine

For developing human diseases it is need to explain the very important scientific questions in which organoid models plays as an important tool in tissue engineering for replacement of damaged organs, regeneration and restoration. Some important applications of organoids are given below. During the process of regenerative medicine diseased cells, replaced, repaired, tissues or organs. Many stem cells are obtained from 2D and 3D with a collection of organ specific cells showing self-organization, expansion, high degree of genetic stability and differentiation capacity. For longer duration, organoids proven to be for sustaining the features and functions of regenerative medicine.[13]

Organoids as model for cancer

Organoids are used in drug testing, various organ-specific diseases, and dynamic development. Cancer cells organoids are the types of tumoroids used for the treatment of cancer. There are also used for developing tumor biobanks, cancer tissue engineering, modeling the tumor formation process. In the treatment of cancer, the radiation therapy affects the cellular responses which are detected by organoids.[14] The models of organoids are used for esophagal cancer, colorectal cancer, pancreatic cancer, liver cancer, prostate cancer**.**[10] The growth factor of in-vitro shows the possibility of hair follicle by using primary cells developing from embryonic skin. This model is further used for studying the mechanism of hair follicle by increasing the hair growth, modeling skin diseases.[15] Human Lung Organoids are developed by manipulating signal pathways (HLOs).

They consist epithelial and mesenchymal lung compartments showing similarity with native lung, basal cells, myofibroblasts, smooth muscles and immature ciliated cells .The RNA sequencing shows global transcriptional profiles same as human felt lung showing the excellent model for studying human lung.[9] The study of human brain has shown many brain disorders in in viro model for the development. Cerebral cortex produces mature cortical neuron. RNA and patient specific iPS cells show difficulty disorder for replicating in mice. It reveals all the premature neuronal differentiation in patient Organoids.[14] Fovea initiate is a specialized region of retina forms cone photoreceptors with high defined vision in humans and non-humans. FoveaL cone death is the major cause of central blindness. The 3D retinal organoids which is also known as retinal organoids (ROs) developed from Liver cell proves to be effective for treating modeling and other diseases. RO cones shows a good wavelength specific light which are strong graded.[16] The tissue stem cells also act as lung alveolar epithelia; type II (ATZ) cells sometimes lacks in the models for studying human AT2 cells. To prevent this, method had been developed for making and maintaining alveolar organoids (AOs) consisting of alveolar stem cells developing from Liver cells. AOs show good effects in toxicity studies relocating the AT2-cell-specific phenotypes**.**[17]

Human disease modeling and living bio-banks

The use of human organoids in disease modeling is one of their main uses. Through them, individualized treatments, such as cell and organ replacement therapies, are tested for specific diseases through drug/genome screening and the formation of living biobanks. Between clinical practice and translational medicine, living biobanks are crucial. Human organoid biobanks have a lot of potential for creating live biobanks because they can collect and preserve functional tissues for a very long time, as opposed to traditional biobanks. Disease modeling has faced several difficulties because it is a fresh topic to create a model for an organ-specific disease.[5, 9,14]

Application in tissue engineering

Undifferentiated stem cells have the capacity to reassemble and reproduce the organ's structural makeup. In order to create organoids for biomedical research, they are used. Organoids are currently used in the investigation of human disease and development. Organoid systems are also helping personalized and regenerative medicine advance.

Endoderm organoids utilized to simulate human diseases and shed light on important scientific questions. The in vivo organs can be somewhat mimicked by a variety of previously created organoids in vitro, and these created organoids can be used to represent particular processes in dynamic development, a variety of organ-specific disorders, human cancer, and drug testing.

Cerebral cortex organoids created from hPSCs could be used to replicate the dynamic process of human cortical development as well as to display changes in the transcriptome and epigenome over the course of cortical development.

I. The growth of molecular analysis has helped organoid technology and will, in turn, assist understand molecular mechanisms more thoroughly.

II. It can be used in research on conditions or diseases affecting other organs.

III. Brain organoids could be used to represent psychiatric illnesses and ZIKV infection.[18]

IV. Organoids of the kidney were created for the individualized disease modeling of polycystic kidney disease, cystic fibrosis, and BK virus infection.

V. A function for blood vessel organoids in the modelling of diabetic vasculopathy

VI. Helicobacter pylori infection was made possible by gastric organoids.

VII. To simulate lung disease, respiratory syncytial virus infection of lung organoids is a possibility.

VIII. The ability to research hepatic steatohepatitis with liver organoids has been demonstrated.

IX. Chemical probes in 3D stomach organoids could shed light on the crucial shift from the mitotic spindle to the central spindle prior to the start of anaphase.

X. Organoid technology could also be used to create tumor biobanks or mimic the development of tumors in order to create cancer tissue engineering.

XI. The created organoids will provide new and exciting prospects for disease modelling and medication screening as well as contribute to future study on the mechanisms behind organ formation.

Human stem cells or induced pluripotent stem cells shows the same physiologic and genetic similarities as compared to conventional animal models for improvement of disease and human growth. Endoderm organoids those are indisputable. The definitive endoderm eventually transforms into the foregut, midget, and hindgut during embryonic development.[20] The pancreas, thyroid, esophagus, trachea, stomach, lung, liver, and biliary system are also produced in the foregut.[20] The small intestine develops in the midgut, while the colon matures in the hindgut. The small intestine develops in the midgut, while the colon develops in the hindgut. The organoid culture systems of numerous endoderm-derived organs, such as the thyroid,[21] lungs development,[22–24] stomach development,[25–27] liver development and colon development.[28–30]

Amiri *et al.,* (2018) developed hPSC-derived cerebral cortical organoids models for the development of human cortical and it was utilized for the investigation of various active genes and can act to enhance the stem cell to progenitor's transition.[1] Kidney organoids have been found to be used for various personalized disease models, like polycystic kidney disease, BK virus infection, and cystic fibrosis. 3D kidney organoids prepared commencing directed discrimination of pluripotent stem cells (PSCs) encompassing of numerous cell category

of kidney. They possess the a range of noteworthy hierarchical association intensity having nephron-like structures and appropriate vascularization. The economical techniques have been developed for growing kidney organoids in the media using hiPSCs oganoids.[31,32]

Liver tissue organoids are established from various induced pluripotent stem cells, hepatoblasts, embryonic stem cells and other tissue-derived cells, which will help in understanding of this complex organ. Lee et al. have explained the development of various liver model systems with their limitations and how they can be overcome. They have reported the 3D biomimetic liver models can be appropriate model and can found its promising biomedical applications and to study liver steatohepatitis.[33,34] The 3D gastric organoids application could be very helpful and can provide the key conversion from the mitotic spindle to the central spindle before anaphase onset. Also, gastric organoids provide the platform for infection caused by *Helicobacter pylori*.[34–36]

Conclusion

Research in organoids is now an emerging and rapidly growing topic finding its utility and potential in the field of tissue engineering. It has become as one of the hottest topic in the field of science to clinical appliance, connecting drug selection, toxicology, and a variety of models development like tumor models for cancer identification and in an assortment of models in human organ expansion for the treatment of diseases. In fact, organoids technologies are now providing the benefit from molecular analyses, which is helping in elucidation of the molecular mechanism. The various organoids technologies can be exploited in the studies of various disease and organs.

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

References

1. Amiri A, Coppola G, Scuderi S, et al. Transcriptome and epigenome landscape of human cortical development modeled in organoids. *Science*. 2018;362(6420):eaat6720.
2. Arjmand B, Rabbani Z, Soveyzi F, et al. Advancement of Organoid Technology in Regenerative Medicine. *Regenerative Engineering and Translational Medicine*. 2022;1–14.
3. Bose S, Clevers H, Shen X. Promises and Challenges of Organoid-Guided Precision Medicine. *Med*. 2021;2(9):1011–1026.
4. Hofer M, Lutolf MP. Engineering organoids. *Nat Rev Mater*. 2021;6(5):402–420.
5. Xinaris C, Brizi V, Remuzzi G. Organoid Models and Applications in Biomedical Research. *Nephron*. 2015;130(3):191–199.
6. Lewis A, Keshara R, Kim YH, et al. Self-organization of organoids from endoderm-derived cells. *J Mol Med.* 2021;99:449–462.
7. Corrò C, Novellasdemunt L, Li VSW. A brief history of organoids. *American journal of physiology. Cell Physiology*. 2020;319(1):C151–C165.
8. Qu M, Xiong L, Lyu Y, et al. Establishment of intestinal organoid cultures modeling injury-associated epithelial regeneration. *Cell Research*. 2021;31(3):259–271.
9. Dye BR, Hill DR, Ferguson MA, et al. In vitro generation of human pluripotent stem cell derived lung organoids. *ELife*. 2015:4:e05098.
10. He J, Zhang X, Xia X, et al. Organoid technology for tissue engineering. *Journal of Molecular Cell Biology.* 2020;12(8):569–579.
11. Bian S, Repic M, Guo Z, et al. Genetically engineered cerebral organoids model brain tumor formation. *Nat Methods*. 2018;15(8):631–639.
12. Zhang M, Liu Y, Chen YG. Generation of 3D human gastrointestinal organoids: principle and applications. *Cell Regen*. 2020;9(1):6.
13. Huang L, Bockorny B, Paul I, et al. PDX-derived organoids model in vivo drug response and secrete biomarkers. *JCI insight*. 2021;5(21):e135544.
14. Nagle PW, Coppes RP. Current and future perspectives of the use of organoids in radiobiology. *Cells*. 2020;9(12):2649.
15. Morgun EI, Vorotelyak EA. Epidermal Stem Cells in Hair Follicle Cycling and Skin Regeneration: A View From the Perspective of Inflammation. *Front Cell Dev Biol*. 2020;8:581697.
16. Saha A, Capowski E, Fernandez Zepeda MA, et al. Cone photoreceptors in human stem cell-derived retinal organoids demonstrate intrinsic light responses that mimic those of primate fovea. *Cell Stem Cell*. 2022;29(3):460–471.e3.
17. Yamamoto Y, Gotoh S, Korogi Y, et al. Long-term expansion of alveolar stem cells derived from human iPS cells in organoids. *Nature Methods*. 2017;14(11):1097–1106.
18. Lancaster MA, Renner M, Martin CA, et al. Cerebral organoids model human brain development and microcephaly. *Nature*. 2013;501(7467):373–379.
19. Yoo JJ, Cho CS, Jo I. Applications of organoids for tissue engineering and regenerative medicine. *Tissue Engineering and Regenerative Medicine*. 2020;17(6):729–730.
20. Zorn AM, Wells JM. Vertebrate endoderm development and organ formation. *Annu Rev Cell Dev Biol*. 2009;25:221–251.
21. Eldred KC, Hadyniak SE, Hussey KA, et al. Thyroid hormone signaling specifies cone subtypes in human retinal organoids. *Science*. 2018;362:6411.
22. Chen YW, Huang SX, de Carvalho A, et al. A three-dimensional model of human lung development and disease from pluripotent stem cells. *Nat Cell Biol*. 2017;19:542–549.
23. Miller AJ, Hill DR, Nagy MS, et al. In vitro induction and in vivo engraftment of lung bud tip progenitor cells derived from human pluripotent stem cells. *Stem Cell Rep*. 2018;10(1):101–119.
24. Sachs N, Papaspyropoulos A, Zomer van Ommen DD, et al. Longterm expanding human airway organoids for disease modeling. *EMBO J*. 2019;38:e100300.
25. Barker N, Huch M, Kujala P, et al. Lgr5+ve stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro. *Cell Stem Cell*. 2010;6(1):25–36.
26. McCracken KW, Cata EM, Crawford CM, et al. Modelling human development and disease in pluripotent stem-cell-derived gastric organoids. *Nature*. 2014;516(7531):400–404.
27. Bartfeld S, Bayram T, van de Wetering M et al. In vitro expansion of human gastric epithelial stem cells and their responses to bacterial infection. *Gastroenterology*. 2015;148(1):126–136.e6.
28. Yin X, Mead BE, Safaee H, et al. Engineering stem cell organoids. *Cell Stem Cell*. 2016;18(1):25–38.
29. Crespo M, Vilar E, Tsai SY, et al. Colonic organoids derived from human induced pluripotent stem cells for modeling colorectal cancer and drug testing. *Nat Med*. 2017;23(7):878–884.
30. Sugimoto S, Ohta Y, Fujii M, et al. Reconstruction of the human colon epithelium in vivo. *Cell Stem Cell*. 2018;22(2):171–176.e5.

31. Lebedenko CG, Banerjee IA. Enhancing Kidney vasculature in tissue engineering. Current trends and approaches: A Review. *Biomimetics*. 2021;6(2):40.

32. Post Y, Puschhof J, Beumer J, et al. Snake Venom Gland Organoids. *Cell*. 2020;180(2):233–247.e21.

33. Prior N, Inacio P, Huch M. Liver organoids: from basic research to therapeutic applications. *Gut*. 2019;68(12):2228–2237.

34. Ramírez Flores CJ, Knoll LJ. Breakthroughs in microbiology made possible with organoids. *PLoS Pathogens*. 2021;17(11):e1010080.

35. Ramli MNB, Lim YS, Koe CT, et al. Human Pluripotent Stem Cell-Derived Organoids as Models of Liver Disease. *Gastroenterology*. 2020;159(4):1471–1486.e12.

36. Shankaran A, Prasad K, Chaudhari S, et al. Advances in development and application of human organoids. *3 Biotech*. 2021;11(6):257.