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Organoids as models for tissue engineering and biomedical applications

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Abstract: Collagen, the primary structural protein in the extracellular matrix, has gained significant attention as a surface modification agent for biomaterials due to its exceptional biocompatibility, bioactivity, and ability to promote cellular adhesion and proliferation. Collagen coatings enhance the integration of synthetic and natural biomaterials with biological tissues, making them highly relevant in biomedical engineering, regenerative medicine, and implantable medical devices. This review explores the mechanisms by which collagen coatings improve biomaterial properties, including their role in modulating surface chemistry, hydrophilicity, and cellular interactions. Furthermore, we discuss various coating techniques, such as adsorption, covalent binding, and electrospinning, and their implications for optimizing material performance in biomedical applications. The advantages of collagen coatings in orthopedic, dental, and cardiovascular implants, as well as wound healing and drug delivery systems, are also examined. By highlighting the potential of collagen-functionalized surfaces, this article provides insight into the future directions of biomaterial innovation aimed at improving patient outcomes and medical device efficacy.

1 Introduction

Organoids are three-dimensional (3D) cellular structures that mimic key functional and structural aspects of native organs. They are derived from stem cells, including pluripotent stem cells (PSCs) and adult stem cells (ASCs), which self-organize into complex tissue-like architectures through intrinsic developmental programs (Figure 1) [1,2]. Unlike traditional two-dimensional (2D) cell cultures, organoids provide a physiologically relevant microenvironment, allowing for the study of organogenesis, disease modeling, and regenerative medicine in a way that closely resembles in vivo conditions [3-5].

Organoid formation relies on the ability of stem cells to undergo self-assembly and differentiation in response to biochemical and biophysical cues. The process is typically initiated by embedding stem cells within a supportive extracellular matrix, such as Matrigel, which provides the necessary mechanical and biochemical signals for morphogenesis. Growth factors and signaling pathways, regulate cell fate determination, guiding the organization of cells into tissue-specific structures. This recapitulation of developmental processes enables organoids to exhibit functional properties similar to their corresponding organs, including tissue-specific cell types, spatial organization, and even rudimentary physiological activity [6,7].

Due to their remarkable ability to replicate organ complexity, organoids have become powerful tools in biomedical research. They are widely employed in disease modeling, where patient-derived organoids allow for personalized medicine approaches, including drug screening and toxicity testing [8,9]. Additionally, organoids provide an innovative platform for studying developmental biology, as they enable researchers to dissect the molecular and cellular mechanisms governing organ formation. In tissue engineering and regenerative medicine, organoids offer the potential to generate transplantable tissues and serve as building blocks for bioengineered organs. Their use in stem cell-based therapies further highlights their significance in advancing regenerative strategies for treating degenerative diseases and organ failure [3,10].

Despite their promise, several challenges remain, including scalability, vascularization, and functional maturation, which must be addressed before organoid-based therapies can be fully integrated into clinical practice. Nevertheless, ongoing advancements in biomaterials, bioprinting, and microfluidic systems continue to refine organoid technology, bringing it closer to real-world applications in tissue engineering and regenerative medicine [11,12].

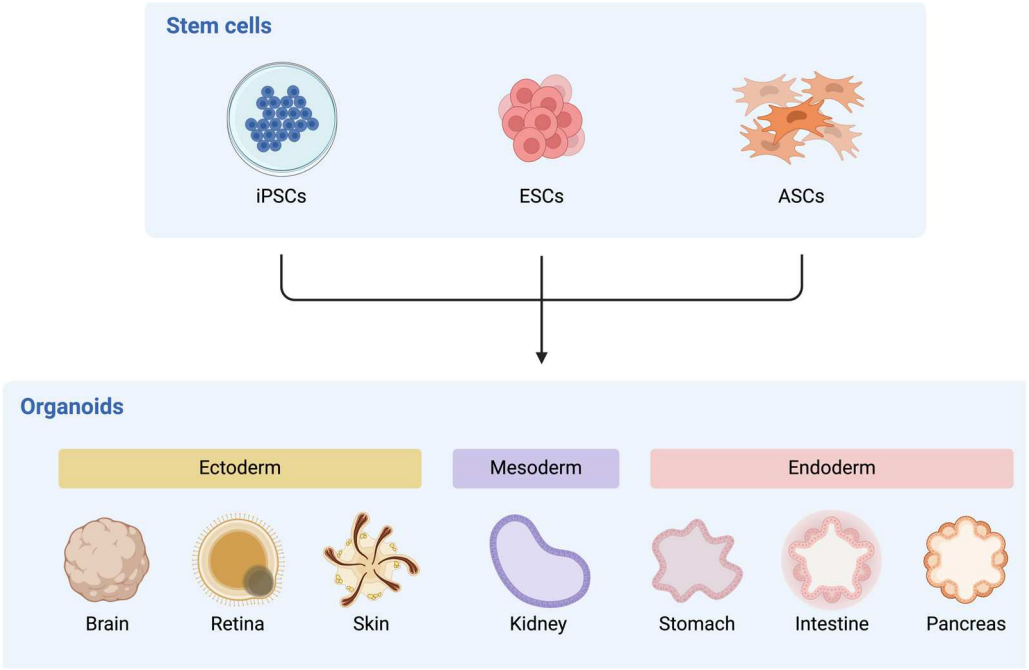

Figure 1 Differentiation of organoids from stem cells: A Visual representation of organoid development from Induced Pluripotent Stem Cells (iPSCs), Embryonic Stem Cells (ESCs), and Adult Stem Cells (ASCs), categorized by germ layer origin (Ectoderm, Mesoderm, Endoderm) (created with biorender.com)

2 Development of organoids

The development of organoids is a highly controlled process that mimics early organogenesis by guiding stem cells through self-organization and differentiation into functional tissue-like structures. This process involves key cellular mechanisms, including stem cell fate determination, spatial patterning, and microenvironmental regulation. The development of organoids can be broadly categorized into three stages: stem cell selection and initiation, directed differentiation and self-organization, and maturation and functional validation [13].

2.1 Stem cell selection and initiation

Organoids are primarily derived from two main types of stem cells: pluripotent stem cells and adult stem cells. PSCs, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), possess the ability to differentiate into any cell type of the body, making them ideal for generating diverse organoid models [14]. ASCs, on the other hand, are tissue-resident stem cells capable of differentiating into specialized cell types within their respective tissues. While PSC-derived organoids are widely used for studying early organ development, ASC-derived organoids are particularly useful for modeling tissue homeostasis and disease [15]. The initiation phase involves embedding stem cells in a three-dimensional extracellular matrix (ECM), such as Matrigel, which provides the necessary mechanical support and biochemical signals for cell adhesion and morphogenesis. The presence of specific signaling factors plays a critical role in directing initial cell proliferation and fate determination. By manipulating these signaling pathways, researchers can guide stem cells toward specific lineage commitments, forming organoid structures that closely resemble native organs [16,17].

2.2 Directed differentiation and self-organisation

One of the defining features of organoids is their ability to undergo self-organization, a process in which cells autonomously arrange into complex structures that replicate in vivo tissue architecture. This phenomenon is driven by intrinsic developmental programs that regulate cellular differentiation, polarity, and spatial patterning [18].

The differentiation process relies on a combination of growth factors and small molecules that simulate the embryonic developmental cues of specific organs. For example, in brain organoids, dual inhibition of SMAD signaling (TGF-β and BMP inhibition) promotes neural induction, while in intestinal organoids, activation of Wnt and R-spondin signaling supports crypt formation and epithelial differentiation. The interplay between cell-cell adhesion, cytoskeletal dynamics, and ECM interactions further refines tissue organization, allowing for the emergence of distinct compartments resembling different anatomical regions of the organ [19,20].

As differentiation progresses, organoids begin to exhibit key features of their respective tissues, including the presence of multiple cell types, functional domains, and, in some cases, rudimentary physiological activity. This stage is crucial for ensuring that organoid

development accurately recapitulates in vivo conditions, making them suitable for downstream applications in disease modeling and regenerative medicine [20].

2.3 Maturation and functional validation

While early-stage organoids exhibit structural and cellular similarities to their in vivo counterparts, further maturation is required to achieve full physiological functionality. Maturation involves extended culture periods, refinement of differentiation protocols, and integration of additional microenvironmental cues, such as mechanical forces and biochemical gradients. One of the major challenges in organoid maturation is vascularization, as most organoids lack functional blood vessels, limiting their size and metabolic activity [10,2]. Recent advances in co-culturing techniques, microfluidic systems, and bioengineering approaches have enabled the development of vascularized organoids that exhibit improved nutrient exchange and tissue survival. Additionally, incorporation of stromal and immune cell components has enhanced organoid complexity, bringing them closer to functional tissues found in the human body [21,17].

2.4 Applications in medicine and biomedical engineering

The continuous advancement of biomedical engineering is essential for improving medical treatments, enhancing the biocompatibility of materials, and driving innovation in personalized medicine [22]. Organoids offer an innovative platform for studying diseases at a more physiological level than traditional 2D cell cultures. Due to their complexity, they provide more accurate representations of human tissues and organs, enabling the study of disease mechanisms in a more relevant context [17]. For example, liver organoids have been used to model liver diseases such as hepatitis and cirrhosis, while brain organoids have become crucial in understanding neurodegenerative disorders like Alzheimer's and Parkinson's disease. Additionally, organoids are increasingly used in drug screening and toxicology. They can be exposed to various pharmaceutical compounds to test their effects on organ-specific functions, toxicity, and efficacy. This reduces the reliance on animal models and helps streamline the drug development process [23,24].

2.5 Drug delivery

Organoids are particularly valuable in drug delivery studies because they closely resemble the physiological characteristics of human tissues. For example, liver organoids can replicate hepatic metabolism, kidney organoids can model renal filtration and excretion, and intestinal organoids can simulate absorption and barrier functions. This allows for more realistic and predictive testing of how drugs behave within the human body, providing crucial insights into pharmacokinetics and the mechanisms of drug action. One of the primary uses of organoids in drug delivery is to study drug absorption, distribution, metabolism, and excretion (ADME) profiles. By mimicking the organs involved in drug metabolism and transport, such as the liver, intestine, and kidneys, organoids can be used to evaluate how drugs are absorbed through the gut, metabolized in the liver, or eliminated through the kidneys. This can help determine the bioavailability and effectiveness of oral drugs, as well as identify potential toxic effects or interactions with other medications. Intestinal organoids, in particular, are often used to study how drugs cross the intestinal barrier and are absorbed into the bloodstream. By incorporating human-derived cells, these models can better predict the absorption of drugs in humans compared to traditional animal models . Organoids also play a significant role in studying drug toxicity. Traditional in vitro cell cultures may fail to account for the complexity of human tissues, leading to inaccurate predictions of how a drug may affect the body.

By using organoids to simulate human tissue responses, researchers can identify potential toxicities early in drug development. For example, liver organoids can be used to assess hepatotoxicity, and cardiac organoids can be employed to investigate cardiotoxicity. By understanding the toxicity profiles of drugs in more realistic human models, researchers can reduce the likelihood of harmful side effects when the drugs are tested in clinical trials.

Although organoids present significant advantages in drug delivery research, there are still challenges to overcome. One limitation is the size and complexity of organoids, which can make large-scale production and high-throughput screening difficult. As organoid culture techniques improve, the scalability of organoid models will likely increase, allowing for more widespread use in drug delivery studies. Additionally, while organoids replicate certain aspects of human tissue, they do not fully replicate the complexity of the entire organism, meaning their predictive value for drug responses may still be limited in certain cases. Advances in organoid technology, such as incorporating immune cells, vascular networks, and other components, will help address some of these limitations and provide more comprehensive models for drug delivery research [25].

2.6 Disease modeling

One of the primary advantages of organoids in disease modeling is their ability to mimic the architecture and function of human organs. Unlike 2D cultures, which consist of a single layer of cells, organoids are three-dimensional structures that resemble the organization and complexity of actual tissues [26]. This allows researchers to study diseases in a more physiologically relevant context. For instance, intestinal organoids replicate the villous structure of the human gut, enabling the modeling of gastrointestinal diseases such as Crohn’s disease, ulcerative colitis, and infections like Clostridium difficile. These organoids can also mimic the effects of

environmental factors, such as diet or microbiome, on disease progression, providing valuable insights into the gut-brain axis and the role of the intestinal barrier in disease.

Authors Melzer et al. introduced the porcine urinary bladder (PUB) as an advanced organ culture model for creating an ex vivo pancreatic niche, which enables the study of pancreatic ductal adenocarcinoma (PDAC). This model allows pancreatic progenitor cells to develop into ductal and endocrine lineages, with pancreatic duct-like organoids (PDLOs) maturing into duct-like tissue. The PUB model supports the study of early pancreatic dysplasia and cancer [8].

Organoids have also proven crucial in modeling neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases. Brain organoids, derived from neural stem cells, can replicate the cellular diversity and complex structure of the human brain, allowing researchers to study neurodegenerative diseases in a way that was previously not possible. These organoids model the early stages of disease, including the accumulation of amyloid plaques in Alzheimer's or the loss of dopaminergic neurons in Parkinson's disease. Furthermore, they can be used to screen potential therapeutic compounds, providing a more effective method for identifying drugs that may slow disease progression (Figure 2) or alleviate symptoms.

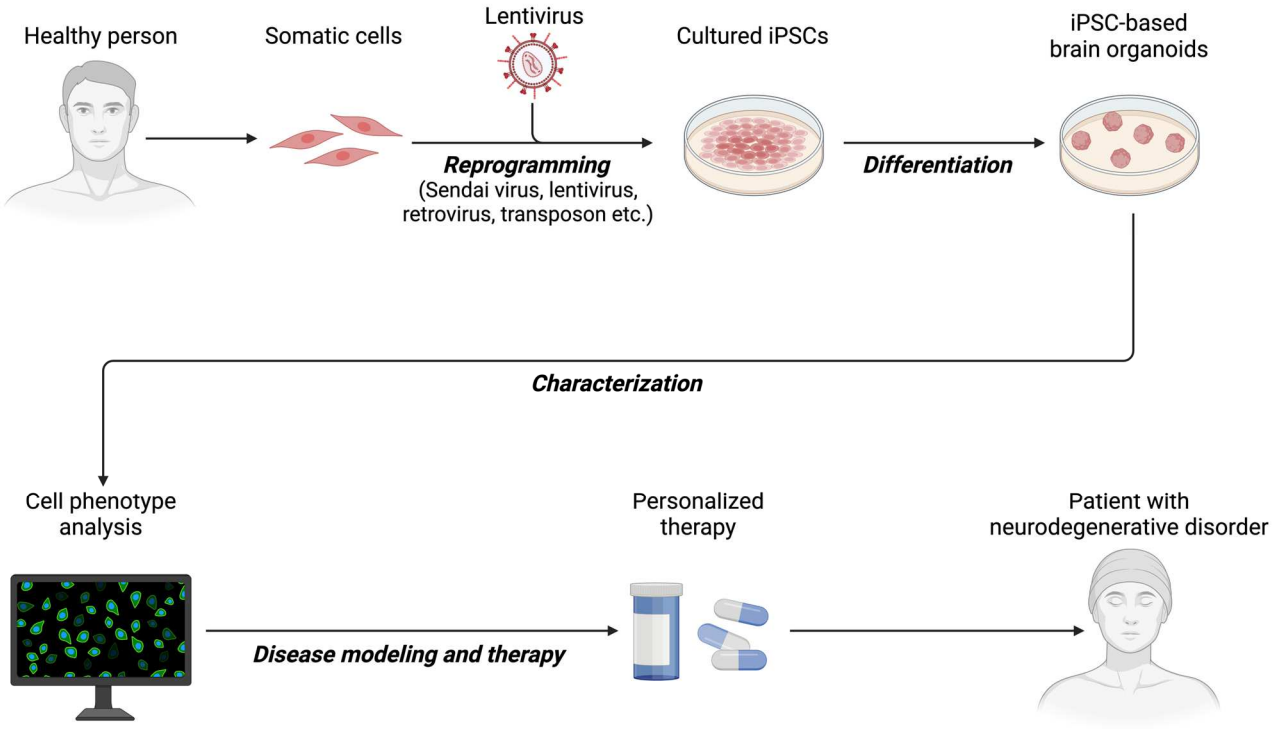

Figure 2 Disease modeling and personalized therapy using induced pluripotent stem cells (iPSCs) derived from healthy somatic cells via Lentivirus transduction (created with biorender.com)

Wang et al. explored the potential of bone organoids derived from stem cells for bone regeneration but faced challenges, such as the need for robust mechanical support through scaffolds and hybrid extracellular matrices (ECM). To overcome these obstacles, they developed a novel bioink made from gelatin methacrylate/alginate methacrylate/hydroxyapatite (GelMA/AlgMA/HAP), which was used in bioprinting to create intricate bone ECM analogs. The bioprinted scaffolds supported the long-term cultivation, maturation, and differentiation of bone organoids, mimicking the natural bone's self-mineralizing properties [9].

Organoids are also instrumental in studying rare genetic disorders. Diseases that affect specific tissues or organs, such as cystic fibrosis or Duchenne muscular dystrophy, can be modeled using patient-derived organoids. For example, organoids derived from cystic fibrosis patients can mimic the defective epithelial cell function seen in the disease, providing a platform for drug screening and studying the underlying pathophysiology. These models can also be used to explore how genetic mutations affect organ development and function, helping to identify novel therapeutic targets for rare diseases that currently lack effective treatments.

Revah et al. transplanted human stem cell-derived cortical organoids into the somatosensory cortex of newborn athymic rats, where the organoids matured and integrated into sensory and motivation-related circuits.

MRI and single-nucleus profiling showed organoid growth, corticogenesis, and activity-dependent transcriptional programs. Transplanted neurons exhibited more complex properties than in vitro counterparts, enabling the discovery of defects in neurons from Timothy syndrome patients [27].

2.7 Cancer treatment

Organoids derived from cancerous tissues offer a more accurate representation of tumors compared to traditional 2D cell cultures. They maintain the architecture, cellular diversity, and genetic features of the original tumor, which is crucial for understanding the complexity of cancer. Tumor organoids can be generated from different types of cancer, such as colorectal, breast, lung, pancreatic, and ovarian cancer, allowing for the study of tumor progression, metastasis, and the molecular mechanisms underlying cancer development. These models also provide a better means of recapitulating the tumor microenvironment (TME), which plays a critical role in cancer behavior, including immune cell infiltration, hypoxia, and extracellular matrix composition. By mimicking these factors, organoids serve as valuable platforms for exploring how tumors interact with surrounding tissue and how the TME affects tumor growth and therapy resistance.

Choi et al. developed a vascularized lung cancer model incorporating patient-derived lung cancer organoids, lung fibroblasts, and perfusable vessels using 3D bioprinting. They utilized a porcine lung-derived decellularized extracellular matrix hydrogel to mimic the biochemical composition of native lung tissue, providing physical and biochemical cues for the cells within the LC microenvironment [28].

One of the most promising applications of organoids in cancer treatment is their role in personalized medicine. Organoids derived from a patient's own tumor cells offer a unique opportunity to test a range of chemotherapies, targeted therapies, and immunotherapies before deciding on a treatment plan. This personalized approach helps determine which drug or combination of therapies will be most effective for the individual, reducing the risk of adverse side effects and improving overall treatment outcomes. Organoid-based drug screening platforms have been used in clinical settings to identify the most effective treatment options for patients. For example, patient-derived organoids (PDOs) from colorectal cancer can be exposed to various chemotherapy agents, and the response can be monitored in real-time to predict how the patient will respond to the same drugs in vivo. This helps clinicians select the best course of action for each patient, tailoring treatment to the specific molecular and genetic characteristics of their cancer.

Yuan et al. established organoid lines from human gallbladder carcinoma (GBC), normal gallbladder, and benign gallbladder adenoma tissues. These organoids accurately reflected the histopathology, genetic features, and heterogeneity of primary tissues. The study suggests that patient-derived organoids can be a valuable tool for exploring gallbladder tumor pathogenesis and developing personalized treatments [29].

Immunotherapy, which utilizes the body's immune system to fight cancer, has shown promise in treating a variety of cancers. However, the effectiveness of immunotherapies can vary greatly between patients. Organoids derived from patient tumors provide a unique platform for testing the efficacy of different immunotherapies, such as immune checkpoint inhibitors, CAR-T cell therapies, and cytokine therapies. Cancer organoids can be co-cultured with immune cells to study how the immune system interacts with the tumor. This allows researchers to evaluate how immune cells infiltrate the tumor, recognize cancerous cells, and whether the tumor can evade immune detection. By using patient-derived organoids in immuno-oncology studies, it is possible to identify factors that predict responses to immunotherapy and improve the selection of patients who are most likely to benefit from these treatments.

3 Discussion

Organoids represent a transformative advancement in the field of disease modeling, bridging the gap between traditional 2D cell cultures and whole animal models. Their ability to mimic human tissues more accurately, both structurally and functionally, has significantly enhanced our understanding of complex diseases. As demonstrated throughout this article, organoids offer a more physiologically relevant model for studying a wide range of diseases, including genetic disorders, neurodegenerative diseases, infectious diseases, and cancer, among others. They allow for the replication of human tissue architecture, cellular diversity, and microenvironments, which are critical for understanding disease mechanisms that cannot be fully captured by animal models or traditional cell cultures.

Patient-derived organoids (PDOs) are particularly valuable in the context of personalized medicine. By using organoids derived from individual patients, researchers can create models that closely mimic the specific genetic, molecular, and environmental factors influencing disease development in that patient. This personalized approach allows for the evaluation of therapeutic strategies tailored to the patient's unique disease profile, potentially leading to more effective and targeted treatments. For example, organoid models of cancer have shown promise in identifying the most effective therapies for specific tumor types, enabling the testing of drug combinations in a patient-specific context. Similarly, organoids derived from patients with genetic diseases, such as cystic fibrosis or Duchenne muscular dystrophy, can be used to test potential gene therapies or drug candidates tailored to the patient’s specific mutation.

Despite their significant advantages, the use of organoids in disease modeling is not without its challenges.

One of the key limitations of organoid models is their inability to fully replicate the complexity of entire organs or the interactions between different organ systems. While organoids capture the cellular diversity and architectural features of individual tissues, they do not mimic the full range of physiological processes that occur in a whole organism [30].

Despite these limitations, organoids remain a powerful tool in disease modeling, offering a more accurate and relevant model for understanding human diseases. They provide a unique opportunity to study disease mechanisms in ways that were previously not possible, especially in the context of rare genetic disorders and complex multi-system diseases. Furthermore, organoids are being used to test drug candidates, identify biomarkers, and explore novel therapeutic strategies, contributing to the development of more effective treatments for a wide range of diseases.

4 Conclusion

This article provided a comprehensive review of organoids as innovative 3D biological models with significant applications in tissue engineering, disease modeling, and personalized medicine. It outlined the fundamental processes involved in organoid development—from stem cell selection and differentiation to maturation and functional validation. The article highlighted the diverse biomedical applications of organoids, including their roles in drug delivery studies, disease modeling for neurodegenerative and genetic disorders, and the development of personalized cancer therapies. Specific examples were discussed to demonstrate how organoid systems have been engineered to replicate organ-specific functions, improve drug testing accuracy, and reduce reliance on animal models. Challenges such as vascularization, scalability, and incomplete tissue maturation were acknowledged, alongside emerging solutions involving advanced bioinks, co-culture systems, and microfluidics. By compiling recent advancements and practical applications, this review underscores the transformative potential of organoid technology in advancing biomedical research and clinical therapies.

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