Frontiers in Dentistry

Potential Implications of Organoids in Dental Research

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A B S T R A C T

Organoids are among the most significant advancements in the past few years that have revolutionized the medical and dental research. These experimental organs have been used to study the developmental processes, pathophysiology, genetic mutations, and drug effects. The organoid technology is an important adjunct to two-dimensional culture methods and animal models. Stem cells are grown in specific environments to develop the organoids, thus, simulating the complexity of the in vivo environment. Oral organoids also recapitulate the architecture and functions of in vivo organs and tissues in the oral and maxillofacial region. Organoids are a promising tool to manipulate human dental stem cell biology for comprehending tooth-regenerative approaches, infectious diseases, genetic anomalies, oral cancer, and drug discovery.

Keywords: Organoids; Stem Cells; Regenerative Medicine; Molecular Targeted Therapy; Tissue Engineering

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INTRODUCTION

Over the decades, animal model systems, cell lines, two-dimensional tissue cultures, and patient-derived xenograft models have laid the foundation of biomedical research to understand the development process, disease pathogenesis, cellular interactions, signaling pathways, drug discovery, and targeted therapies. But these models could never completely simulate or substitute the in vivo environment [1]. A unique technology, named organoids, has slowly paved the way to revolutionize the 21st century research. Organoids refer to in vitro cells presented in a three- dimensional setup to form clusters of regenerative cells with the ability to recreate the architecture and physiology of human organs by differentiation and self-organization into various cell forms [2]. This research tool is a human in vitro three-dimensional cell culture resembling greater-extent actual human organs anatomically, physiologically, and histologically [3]. This technology has facilitated the understanding of development, course, and nature of disorders, targeting personalized treatment approaches, and has opened new avenues for human disease modeling, tissue engineering, drug development, diagnosis, and regenerative medicine [4]. This manuscript aimed to highlight the use of organoids in therapeutic sciences and regeneration, and its perspectives in dental research.

METHODS

Organoid formation: key aspects

This technology was highlighted first in 2009,

when self-organizing intestinal crypt-villus units were produced utilizing adult stem cells [3]. In the past few years, organoids have been developed for different organs including the brain, liver, colon, pancreas, stomach, retina, thyroid, and reproductive organs[5].Organoids better simulate the cellular environments, tissue structure, and development process in vivo than the conventional two-dimensional cell culture as these are derived from primary tissue or stem cells mainly from pluripotent stem cells (PSCs) or induced pluripotent cells (iPSCs) and adult stem cells; thus, mimicking human development or organ regeneration in vitro[6]. The quality and capacity of the foundation cells are the key for well-functioning complex and intact organoid models. They can also be generated from patient-derived iPSCs for building organoid replicas of infectious diseases, genetic disorders, degenerative diseases, and cancer, which can be used to create disease-specific research models to uncover intricate details of pathology [7].

Organoids can be derived from all three germ layers and simulate healthy as well as diseased tissues [6]. Stem cell-containing tissue samples are propagated in an appropriate extracellular matrix (Matrigel® is commonly used for this purpose). The cells are cultured in presence of cell culture media containing specific growth factors under controlled conditions that mimic the in vivo environment [8]. Cells further expand rapidly in culture while remaining genetically stable, and self-organize into 3D organoid structures incorporating cellular complexity of the modeled tissue. They can be passaged, and maintained indefinitely [9]. There are definite benefits for human organoid cultures over animal models such as faster and more robust outcomes, providing more quantity of material to work with than animal models, easy handling, feasibility of genetic manipulation, and personalization [1].

Organoids in the medical field:

Organoids can be generated through genetic engineering of human stem cells or from patient biopsy samples to study the disease pattern, and are becoming an asset in terms of modern medicine with their role in testing the drug efficacy in different controlled microculture environments [10]. Organoids are providing groundbreaking evidence in the study of diseases and development of effective treatments as follows:

-Human adult stem cell-derived organoids in the study of infection biology [11].

-Organoids have also been used to co-cultivate human epithelia with bacteria (for example, Helicobacter pylori) and with protozoan parasites (for example, Cryptosporidium) [1].

-Organoids for cystic fibrosis [12].

-Human brain development and Zika virus [13].

-Human organoids and severe acute respiratory syndrome-coronavirus [14].

Cancer biology has always been intriguing, and a lot of research is being done by the scientists all over the world. Organoids are revolutionizing the oncology field as well. Preclinical cancer models, animal experiments, and tissue cultures are essential to investigate tumor heterogeneity, genetics, epigenetics, and immunology [15]. Organoid culture models can be harnessed to study normal and neoplastic tissues using similar culture techniques, and are excellent tools to study tumorigenesis and cancer progression. Such samples can then be used to study cancer cell biology, their interactions with the environment, impacts of growth factors on cancer cells, signaling mechanisms, new drug molecules against potential targets, omics analysis, and genetic manipulation [16]. Various patient samples from colon, brain, liver, breast, bladder, prostate, pancreas, stomach, esophageal, endometrial, and lung cancers have readily been cultured as cancer organoid models [17]. Recently, an analysis of drug responses in patients and in their matched cancer organoids led to the conclusion that a drug with no anti-tumor activity in the organoids had the same efficacy and response in the matched patients. Moreover, pathogenic genes and mutations can be directly tested in organoids derived from cells isolated from healthy donors; thus, enabling human genetic studies in controlled genetic backgrounds [10].

Organoids in dentistry:

The organoid technology is being explored in dentistry to recapitulate the oral developmental

process, diseases, genetic disorders, and regeneration of dental tissues (Fig.1).

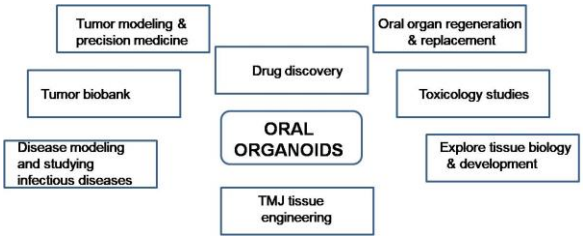

Fig 1. Applications of organoids in dentistry

Many experiments have been previously carried out combining biology and engineering principles using innovative biomaterials to achieve dental tissue regeneration, by impregnating and growing stem cells on a scaffold with the bioregulatory functions of odontogenic differentiation [18]. Organoids could be apathbreaking advancement towards regenerating the whole tooth structure and other oral tissues. Technological advancements have been made in development of organoids of the tooth, salivary glands, taste buds, tongue, pulp-dentin complex, and also oral cancer tissue [19-29] (Table1).

Table 1. Oral organoids and their applications in dentistry

Number	Organoid derived	Source	Function
1	Tooth germ organoids [19]	Adult human dental pulp cells	To study basic tooth developmental mechanisms
2	Epithelial organoids [20] (human tooth)	Stem cell from dental follicle of 3rd molar	To comprehend human tooth epithelial stem cell biology and epithelium–mesenchyme interaction.
3	Enamel organoid [21]	iPSC-derived ameloblasts	Attempt towards regenerative dentistry and treatment prospects for enamel disorders.
4	Tooth-bud organoids [18]	Human DPSCs, porcine dental epithelial cells	To understand tooth regeneration strategies
5	Pulp organoid[22]	Human dental pulp cells and endothelial cells	For toxicity screening of dental materials on dental pulp cells and tissue
6	Dentin-pulp organoids [23]	Human dental-pulp stem cells	For drug efficacy testing
7	Dental follicle cell organoid [24]	Human dental follicle cells	To comprehend functional PDL engineering
8	Salivary glands [25]	Adult human salivary gland stem/progenitor cells	For treating radiation-induced xerostomia As a novel therapeutic strategy to treat salivary gland dysfunction
9	Taste buds[26]	Source -Lgr5+ stem cells from the circumvallate papillae(murine)	To explore taste signaling mechanisms, disease modeling and taste tissue regeneration.
10	Lingual epithelium [27]	Bmi1-positive cells isolated from the basal layer of the lingual epithelium(mice)	To understand lingual epithelium, lingual regeneration and carcinogenesis.
11	Human mucosal organoids[28]	Primary oral squamous cell carcinoma cells Primary normal keratinocytes	To expand the repertoire of head and neck squamous cell carcinoma drugs and treatment personalization.
12	Esophageal head and neck and oral cancer organoid[29]	Tumoral tissue	Predicting drug sensitivity and potential therapy resistance mechanisms in a moderate-to-high through put manner, esophageal cancer patient-derived organoids (PDO) are highly translatable in personalized medicine.

Tooth is an easily accessible and non-invasive source of stem cells with self-renewal capabilities and the ability to differentiate into three different lineages. Different stem cell populations can be isolated from dental tissues such as dental pulp stem cells (DPSCs), periodontal ligament (PDL)stem cells, dental follicle progenitor stem cells, stem cells from human exfoliated deciduous teeth, and stem cells from apical papilla [30].

The experiments to characterize phenotype and biological function of human tooth epithelial stem cells are being conducted on the same ground as stem cells of mesenchymal origin so that epithelial-mesenchymal interactions leading to odontogenic differentiation can be simulated in vitro. Recent research has substantiated that the epithelial cell rests of Malassez, present in the dental follicle or PDL around the root can be the potential source of epithelial stem cells [31]. Thus, co-culturing of epithelial cell rests of Malassez-derived stem cells with DPSCs could induce ameloblast differentiation. Hence, dental organoid technology can be used to treat various dental infections, and developmental and genetic anomalies like amelogenesis / dentinogenesis imperfect [19]. Future research needs to emphasize on translating these in vitro findings to clinical practice, paving the way for realization of dental tissue regeneration and less reliance on dental restorations and prosthetics [32].

Organoids from dental pulp mesenchymal stem cells possess strong immunomodulatory properties, and the capacity for angiogenesis, growth factor expression, and formation of vascular pulp tissue [33].Also, regeneration of PDL with dental follicle cells using an organoid model has been reported, which can be useful to treat PDL defects and periodontitis[34].The underlying mechanism of taste bud genesis and taste function can be explored by taste bud organoids; thus, paving the way for taste bud regeneration, which can be helpful in oral cancer patients with taste dysfunction. Maxillofacial cartilage regeneration has also been attempted to develop cartilage organoids with superior chondrogenic activity and temporomandibular joint tissue engineering [35]. Lingual epithelial renewal and regeneration mechanisms have also been studied using organoid models as the incidence of tongue cancer is increasing with significant morbidity [26].

Research has reported the development of bioengineered tooth using an organoid tooth germ model. The three-dimensional salivary gland organoids have been successfully structured and have proven to be quite helpful in understanding the mechanisms to restore normal salivary gland function, treating salivary gland pathologies and xerostomia [25]. Lassche et al.[35] used drug screening organoids treated with tropomyosin receptor kinase-inhibitors to predict in vivo treatment response while preserving tumor genotype and phenotype in a case of ETV6-NTRK3 gene fusion-positive secretory carcinoma of the salivary glands; thus, illustrating the advances made in precision oncology and targeted therapy[36].Organoids have also revolutionized the investigations of infectious diseases as stem cell-derived organoids from oral mucosal tissue have been developed for viral infections caused by human papillomavirus, herpes simplex virus, etc. Many characteristics of in vivo diseases can be reduplicated by organoid models, providing new insights for disease pathogenesis and host-microbiome interactions [37].

Three-dimensional technology can also be harnessed to understand the influence of tumor microenvironment on oral carcinogenesis and tumor progression [37]. With regard to head and neck squamous cell carcinoma(HNSCC), there is a dire need to have reliable models to explore resistance-related mechanisms, guide treatment decisions, predict therapy outcome, and adopt personalized approaches [38]. Driehuis et al. [27] stated that HNSCC-derived organoids reconstructed the genetic, functional, and histological characteristics of original tumors; they could predict patient response, and widen the horizon of HNSCC drugs. Although the technology has its own specific limitations like lacking the holistic representation of tumor microenvironment, standardized protocols, and cost restraints, yet an

exponential surge has been observed in the recent years for utilizing organoids as models of biological processes and diverse pathophysiological states. A lot more can be explored in the field of oral oncology [39].

CONCLUSION

The promising role of organoid technology in strengthening the existing model systems, translational research, and drug discovery is widely appreciated. This technology has a lot of potential in dentistry but has to be judiciously explored considering its strengths and limitations.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

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