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REVIEW ARTICLE

Modeling Metabolic Diseases with Organoids: A Review

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INTRODUCTION

An organoid is a functional unit of any given organ capable of reproducing under culture, as well as a biological structure similar in both function and structure to its *in vivo* equivalent. They are miniature-sized functional versions of organs, formed by masses of cells which self-organize to form a three-dimensional structure.

An organoid originates from a fragment of a tissue; a stem cell located in an adult organ (ASC), or a Pluripotent Stem Cell (PSC) which can be an Embryonic Stem Cell (ESC) or an induced Pluripotent Stem Cell (iPSs). The use of iPSC will require an additional step compared to ESCs, as somatic cells will first have to be de-differentiated by expression of Oct4, Sox2, c-Myc and Klf4 genes [1].

There are some important differences between ESC and iPSC. ESC-derived organoid production requires genetic manipulation to induce a specific mutation, a process requiring specific technologies which can be difficult to obtain; their use being also limited due to religious and ethical concerns in some countries where the use of human embryos is forbidden. On the other hand, iPSC contain the specific mutation, making them easier to use, the problem being that all individuals are different and the specific mutation might or might not be helpful. The election between these two models has to be individualized as it depends on different factors. Choosing to use a combined model is a common practice between experts, e.g. in Fanconi anemia and QT syndrome [2].

In order to be called an organoid, a structure must meet specific requirements: (I) it must possess more than one representative cell type from the organ it represents; (II) it must possess at least one specific function from that organ; (III) its cellular organization must resemble that of the model organ [3].

Belda Moscardó [1] mentions that the first innovative experiments in the field of 3D culture were performed using Lgr5+ stem cells (Intestinal Stem Cells, ISC), which express the G protein-coupled receptor 5 and are located in the intestinal crypts [4,5]. This study demonstrated that ISC could be used to generate stable, near-physiological epithelia when supplied with growth factors and proteins similar to those present in the endogenous stem cell niche [6]. The breakthrough was a laminin-rich Matrigel which replaces the Extracellular Matrix (ECM), and culture media supplemented with growth factors intended to promote intestinal crypt growth and maintenance of ISC. The main growth factors are Noggin, Epidermal Growth Factor (EGF) and R-spondin. In addition to these growth factors, the Rho-

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kinase inhibitor Y-27632 is necessary for single cell culture, as it inhibits anoikis death in dissociated cells. Thus, this 3D culture method was able to reflect the cell diversity present in the intestinal tissue, as well as the crypt structures and villi characteristic of the intestinal epithelium.

Calvache Aguilar [7] emphasizes that the field of organoids has advanced prominently in recent years. As of today, a number of organs and tissues can be recreated *in vitro*, at least partially. He realized that researchers were using the terms "organoids," "spheroids," and "3D cultures" interchangeably. Thus they came to the consensus that organoid culture refers to 3D cell growth to generate cell units that resemble an organ in both function and structure. Hence the term organoid, with the suffix "-oid" meaning "resemblance" in latin [7].

However, the field of organoid research began many decades ago, when pioneers in cell culture began to wonder how organogenesis occurred. As early as 1900, researchers wanted to reproduce organogenesis in culture, initially by growing tissue fragments. Harrison in 1906 cultured nerve fibers by the "hanging drop tissue culture" technique. During the 1920s, research focused on embryology, which led to the development of tube cultures and the watch glass method [7].

By 1950, many other organs had been cultured *in vitro*, albeit with the limitation imposed by existing methods of the period, which only allowed the culture of thin organ slices. In this same decade, Moscona cultured cells in suspension and demonstrated that they were able to regroup and restore the structural pattern of their tissue of origin [3].

In 1971, Bissell and Tilles determined that adult and embryonic hepatocytes, as well as other cell types, grew better in collagen, but lost their differentiation functions after one or two days of culture. In 1975 Michalopoulos and Pitot discovered that it was possible to trigger the differentiation of epithelial cells such as hepatocytes by modifying the behavior of the substrate to which they were attached. They observed that when the gels were detached and floated on top of the medium, adult liver cells expressed tissue-specific differentiation markers [8].

In 1977, Engelbreth, Holm and Swarm isolated a gel with basement membrane characteristics and named it "EHS sarcoma", known today as Matrigel. In 1991, Streuli, et al. first showed that the ECM, through direct interaction with integrins, was regulating gene expression and differentiation. In the 2000s, a series of experiments demonstrated that 3D cultures were an excellent way to understand developmental mechanisms and the impact they have on disease development when these mechanisms go wrong.

The developmental process of the human body consists of a set of controlled processes that result in tissues differentiated from a zygote, a similar process occurs when teratomas are formed from PSC which can contain different types of tissues inside them. Calvache Aguilar (ob.cit.) emphasizes that organoids can be obtained from PSC thanks to a process similar to the formation of teratomas, but in a controlled manner and in the presence of an adequate 3D scaffold and the correct biochemical factors, which will allow the self-organization of the cells to take place [3].

Similarly, it is also possible to achieve the necessary homeostasis of each tissue thanks to the culture media and their specific conditions that guarantee cell differentiation and renewal. Thus, biochemical factors required for organoid formation include growth factors and small molecules whose purpose is to manipulate the most important signaling pathways in tissue-specific cellular homeostasis, which are added exogenously; and cell-derived niche components responsible for autocrine, paracrine or juxtacrine signaling.

As for scaffolding, there are different types of ECM which differ from one another because of the protein signature from the epithelial tissues, like omental adipose, lung ECM, rat mammary gland ECM, (Matrigel/Geltrex), among others. The ECM supports cell adhesion, among many other functions, and comprises over 300 proteins and 200 glycoproteins. For example, Matrigel® is a basement membrane, rich in ECM proteins, extracted from the Engelbreth-Holm-Swarm (EHS) 16 cell line very commonly used because it provides a good scaffold and also provides basement membrane ligands that contribute to cell survival and organoid formation [1,3,7,9,10].

Moreover, Torres Montoya [8] highlights that organoids are established as an exceptional avenue for the configuration of biological models that behave in a manner faithful to the organism. In general, the process of fabrication of an organoid begins with the intrinsic capacity that stem cells exhibit to assemble into complex structures; when these are placed inside a hydrogel (often matrigel) and in the presence of suitable exogenous factors they tend to form structures containing organized groups of cells.

The rise in the manufacture of stem cell-derived organoid systems provides 3D self-organizing tissue models that offer a new class of compelling biological models of tissues and organs. The organoids can recreate a myriad of biological parameters, including the spatial organization of tissue-specific heterogeneous cells, cell-cell interactions, cell-matrix interactions, and certain physiological functions generated by tissue-specific cells within the organoid. For this reason, organoids are bridging the gaps of existing model systems by providing a stable system that can be cultured and manipulated on a long-term basis, while being more representative of *in vivo* physiology [8].

The formation of each organoid requires specific factors for its formation. In the case of the intestinal epithelium, human PSC can be made to derive into an hindgut, the

Table 1: Advantage and Disadvantage of Organoids.

Advantages	Disadvantages
Highly malleable 3D structure [13]	Necrotic core development [13]
More precise disease study and identification [13]	Limited milieu growth [13]
Useful for the assessment of the tumoral transformation process [13]	
Allow the study of intestinal absorption drugs [14]	
Liver disease study [15]	
In-vitro test for the assessment of HBV and neoplastic origin [16]	

Table 2: Organoid-based liver disease models [13].

Disease	Species	Organoid source and derivation
Alpha-1 antitrypsin deficiency	Human	Adult tissue (surgical resection; liver transplantation; biopsy)
Wilson's disease	Dog	Adult tissue (surgical resection, needle biopsy, fine needle aspiration)
Primary liver cancer	Human	Adult tissue (needle biopsy) Adult tissue (chemical carcinogenesis)

caudal zone of the gastrointestinal tract, by applying activin A early in the process, a TGF-β family molecule related to cell differentiation, which is able to drive the cells to their conversion into mesoderm. Afterwards, the addition of Wnt3 and Fgf4 (downstream factors) are responsible for specifying the identity of the hindgut that will be the precursor to the intestine [3].

The formation of the human brain requires a high degree of coordination between Neural Stem Cells (NSC) and the dynamics of the niche within which they inhabit. Through the use of different morphogens such as BMP, Wnt, Shh, RA and FGF, PSC can be made to differentiate into various neural subtypes. There are also different protocols that allow giving rise to more complex brain structures such as the cortex or pituitary or organoids that present different interdependent brain regions [3].

On the other hand, liver organoids per se have not been successfully developed, however it has been possible to generate liver sprouts from the differentiation of PSC into endodermal cells. To accomplish this, three different cell populations were needed: liver-derived human PSC, human mesenchymal stem cells and human endothelial cells. It was observed that when mixed in a high-density Matrigel® layer, these cells spontaneously formed 3D aggregates [7].

To generate retinal organoids, it is necessary to give rise to 3D aggregates of PSC in a minimal medium to generate a neuroectoderm. In order to form firmer neuroepithelial tissues it is necessary to add Matrigel to the culture medium at the earliest stages of organoid formation. Thereby the formation of a pigmented epithelium is also achieved, which favors the formation of outgrowths of primordial retinal tissue similar to the optic vesicle. The sprouts are separated from the rest of the neuroepithelial tissue to be placed in a culture medium that ensures the identity of the retinal tissue, ultimately giving rise to optic cups quite similar to the retina at early stages of development [7,8].

The methods of generation and maintenance of patient-derived tumor organoids vary according to the type of tumor. Cavalheiro, et al. [3] report the need to develop a standard and robust technique for type-specific organoid generation and culture. The establishment and generation of organoids starts with a mechanical and enzymatic digestion of the tumor tissue, followed by immersion of the disaggregated cells in a biomimetic 3D matrix (mainly Matrigel). Later, the culture medium 10 is supplemented with growth factors and inhibitory molecules which simulate the natural niche of these cells in the in vivo tissue, and which are necessary for their correct generation.

Similarly, Cavalheiro et al. emphasize that organoids as a cancer model system represent an intermediate tool between cancer cell lines (*in vitro*) and xenografts (*in vivo*). An advantage to using this technology is the ability to generate patient-derived organoids from both tumor and normal tissue from patient biopsies, or from pluripotent stem cells. Furthermore, tumor organoids maintain the phenotype, genetic profile and functions of tumors, representing a promising model for understanding cancer biology [8].

The methods for generating and maintaining patient-derived tumor organoids vary according to the type of tumor. Therefore, there is a need to develop a standard and robust technique for type-specific organoid generation and culture. Generally speaking, organoid establishment and generation begins with mechanical and enzymatic digestion of tumor tissue, followed by immersion of the disintegrated cells in a biomimetic 3D matrix (mainly Matrigel). This is followed by the addition of culture medium 10 supplemented with growth factors and inhibitory molecules that simulate the natural niche of these cells in in vivo the tissue, and which are necessary for their correct generation. Nowadays, organoids have been successfully established for multiple types of cancer, including stomach, colorectal, liver, pancreatic, prostate and breast cancer [3,7,8].

TECHNIQUE

Extracellular scaffold method

It is one of the most popular methods for producing organoid and is relevant to this review as it has been used to generate both human and mouse hepatocyte organoids [11].

Initially, adult stem cells are extracted and plated on Matrigel, an extracellular matrix protein mix, and are maintained in culture conditions. If a specific cell type is desired, cells are stained with antibodies, sorted with a fluorescence-activated cell sorting system, and plated on different Matrigel dishes. This leads to genotypically and phenotypically similar organoids. This allows the monitoring of cell adhesion, migration or chemotaxis; however, the use of natural hydrogels, that have a low reproducibility between batches leads to a potentially altered formation of organoids [12].

ADVANTAGES AND DISADVANTAGES

Organoids mean a significant advance for science, technology and medicine, as they are made of highly malleable 3D structures which enable the differentiation and identiication of different tissues in a simpler form for further, more precise disease studies [13]. The Organoid Culture Techniques (OCT)´s main advantages are based on the molecular and physical similarities with its original tissue, enabling the assessment of healthy and tumoral cells, mimicking the milieu in which physiological and pathological processes occur.

Additionally, organoids are useful for pharmacological studies. Various studies have shown the organoids´ advantages for the research on the processes of gut absorption, distribution and clearance for drugs which have this kind of metabolism and pharmacokinetics [14].

Furthermore, the organogenesis research is based on the organoids´ intrinsical ability to interact and auto-assemble in an organ-like structure. Consequently, this research has been applied in recent years on the assessment of organs like the colon, stomach, prostate, liver, fallopian tubes, mammary gland, endometrium, placenta, pancreas and lungs. It has been used to evaluate in-vitro hepatocytes as well as liver toxicity, virology, metabolism and genetic diseases [15]. It has also allowed the study of hepatitis B-induced malignancy [16].

However, one of the main disadvantages of the OCT is the limited growth on the milieu and the development of the necrotic core [13].

ESC (EMBRYONIC STEM CELLS)

ESC are pluripotent cells with the capacity to generate tissues from the three germ layers. For a clinical and research application, using this type of cells has advantages such as: (I) the rate of tumors compared to the IPS cell line is much lower since there is minimal manipulation or genetic alteration of embryonic stem cells; and (II) due to its great capacity, being a pluripotent cell, it has also been used in treatment research for genetic diseases. Disadvantages of using this cell line include: (I) maintaining the ESC line in a differentiated state requires several specific and complicated culture criteria; (II) a follow-up control is essential to detect changes in the genetic state to determine if there is no phenotypic destabilization; and (III) the methods usually used require destruction of an embryo [17].

IPSC (INDUCED PLURIPOTENT STEM CELLS)

By using IPSC techniques, any nucleated somatic cell can be reprogrammed but several researchers have used adult bone marrow cells and adult neural stem cells through efficient reprogramming in order to generate pluripotent stem cells [18,19]. Advantages of using this cellular line are: (I) IPSC cells can be derived from the patient, making them less prone to immune rejection; (II) compared to the ESC line, the IPSC line fundamentally avoids requiring the destruction of an embryo to obtain the line of its cells. Disadvantages include: (I) they develop tumors in a more efficient and quicker way than ESC, and (II) they must also have a frequent control to determine if a genomic abnormality occurs [17].

GENERAL APPLICATIONS

As it was mentioned before, organoids are accurate representations of human tissue. Organoids are created from stem cells or organ specific progenitors. There have been a lot of applications to these techniques in the past few years, since 2009 when they were first introduced [20,21].

We would like to expose different applications for organoids in different tissues. We will go through lung organoids, retinal organoids, how they have been used in the studying of Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2) and what kind of biosecurity implications they have.

Lung epithelial tissue can be damaged because of various factors such as viruses, lifestyle habits etc. Organoids may help by recreating a whole picture of how the repair mechanism works. Different studies have shown that lung organoids helped to prove the presence of multiple stem cells during alveolar epithelial repair after the lung has been damaged, e.g. a population of lung distal progenitor cells have a strong organoid-forming capacity, which means they participate a lot in alveolar epithelial repair [20].

In addition, lung organoids also serve to understand how control mechanisms work in specific tissues of the respiratory system when the epithelial tissue has been

damaged, such as in the case of mesenchymal cells which stimulate the differentiation and proliferation of certain tissues. As well as the Axin2-Pa/PDGFR^{+} linkage which could promote renewing and differentiation of AT2 cells. [20].

As well as lung organoids, retinal organoids have been used in modeling different diseases, such as glaucoma. Retinal organoids are nowadays being used in various studies, like gene therapy, stem cells replacement therapy and small molecule therapy. Due to the complexity of therapeutic strategies involving the retina, organoids work just fine to model which method could work better [21].

On the other hand, organoids have also been used in the understanding of SARS COV-2. As animal models are way too far of being genetically similar to us humans, organoids are a more reliable way of studying the virus. Hence, we know that cells which express ACE2, TMPRSS2 or any kind of putative entry receptors and/or priming proteases, are more likely to get infected with the virus. There have been several studies in various target organs of the COVID-19, but the most important and studied is the lung.

Thanks to these investigations and assays in human pluripotent stem cells derived from the airway and alveolar organoids, it has been noticed that ACE2 will be expressed mainly in ciliated cells and in subpopulation of hAT-2 (alveolar epithelial type 2 cells). On the other hand, TMPRSS2 will express on the majority of cells [6].

Organoids have several applications, they are very helpful when it comes to understanding how diseases, and the mechanism to fight them, work within our bodies.

Nevertheless, there are some things that must be taken into account about organoids techniques. They might not represent any kind of harm for the patient nor for researcher, but there is concern about these techniques being used for harmful purposes such as bioterrorism. Even though, it is very unlikely for something like this to happen as special, sophisticated skills are needed in order to produce organoids accurately [22].

APPLICATION TO METABOLIC DISEASES

Liver diseases

Research in organoid models opens up endless new possibilities for the study of liver diseases, through the use of different sources and species of organoids such as ESC, genetically modified mouse models and IPSC, among many other. These type of resources provide us with the essential tools for the development of models of functionality, pathogenicity and targeted treatments in some metabolic diseases [23].

Below we present models of liver disease based on organoid culture:

Alpha 1 antitrypsin: A 1-Antitrypsin Deficiency (AATD) is an inherited metabolic disorder in which mutations in the coding sequence of the SERPINA1 gene prevent the secretion of α 1 -antitrypsin (α 1-AT) and cause predisposition to lung and liver diseases [4].

As the Z allele (Glu342LYS) induces AAT Protein to be in a misfolded state with a high incidence of accumulating in hepatocytes causing subsequent liver disease [5]. Gomez et al [5] concluded that organoids are an optimal model for disease research since they were able to reveal the fundamental characteristics of Z-AAT deficiency.

Wilson's disease: Wilson's disease is a hereditary disease due to mutations in the ATP7B gene, which generates an abnormal accumulation of copper in the body, thus producing alterations at the liver and neurological level [24].

Nantasanti, et al. [25] showed that a type of COMMD1 organoids dispensed with a large accumulation of copper compared to traditional organoids, similar to the defect of copper excretion in the in vivo case of Wilson's disease, which allows for setting the precedent of an organoid model that allows the investigation of this hereditary metabolic pathology, thus enhancing the future development of various interventions based on this approach to the disease based on the organoid COMMD1.

Liver cancer: An estimated 42,230 new cases and more than 30,000 deaths due to primary liver and intrahepatic bile duct cancer were registered in the United States population by 2021; we would like to highlight the importance of the use of organoids for future therapy development [26]

Notable Progress was established in the research of Wanlu Cao et al., by having organoids derived from primary tumors of the mouse liver, with the characteristic of being able to freeze, save and reuse a culture [27].

Pancreatic islet cells disease

Type 1 Diabetes is characterized by the damage in pancreatic islets cells, halting the normal production of insulin by the human organism. Intraportal islet transplantation could eventually be used in these patients, although peri-transplant period islet loss, due to inflammation, revascularization and immunocompetence poses a challenge. It has been shown that the use of organoids could make the islet transplant a very good treatment option [28] offering these patients the possibility of a curative treatment. Yoshihara et al. generated an organoid pancreatic islet, which produces insulin, using the IPSC model. In their study, they impaired the immune system functioning by applying interferon. This method induces epigenetic memory and in immunocompetent mice it maintains glucose control up to 50 days after transplantation [29].

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Kidney disease

Nowadays there are several organoid models and methods. This knowledge has stemmed from the study of the different types of human cells. Human pluripotent stem cells are attractive sources for regenerative medicine and disease modeling. Differential approaches are aimed at in vivo cell development rather than stoic cell differentiation. A variety of methods have been established to generate renal organoids from human pluripotent stem cells.

These organoids consist of cells with the characteristic of being able to differentiate into fundamental structures such as: podocytes, proximal tubules, Henle loops, and distal convoluted tubules in an adjoining arrangement that resembles nephrons in vivo, as well as interstitial cells.

There are also several bioprinting methods, biofabrication technologies, the most commonly used being: two-photon polymerization, light-assisted digital, light processing and extrusion. Each technique has its pros and cons with respect to materials, structural integrity, printing resolution and cell viability [30].

Currently, these applications are hampered by nephron immaturity, low performance-limited scale and organoid variability. Cellular extrusion technique, which might be the best option for kidney bioprinting, is based on dimensional cellular bioprinting of intermediate mesoderm to deliver a quick and high-perfomance generation of kidney organoids with highly reproducible cell number and viability [31].

Dimensional bioprinting enables precise manipulation of biophysical properties, including cell number conformation and organoid size with modification of organoid conformation, substantially increasing nephron yield per starting cell number. This facilitates the manufacture of uniformly patterned kidney tissue sheets with functional proximal tubular segments. Hence, automated extrusion-based bioprinting for kidney organoid production delivers improvements in performance, quality control, scale and structure, facilitating and in vivo applications of stem cell-derived human kidney tissue [31].

A standardized endothelialized vascular network within a bioengineered model is also important to provide a functional physiological microenvironment. There is important research such as the development of vascular structures from pluripotential cells found in the umbilical cord, which are used to design functional bioengineered artificial kidneys [32].

Furthermore, other methods involve the research and application in histological techniques, such as whole rat, pig, and human kidneys that have been decellularized with detergent perfusion, yielding acellular scaffolds with vascular, cortical and medullary tubules, as well as an intact collecting system architecture [32].

Current advances in directed differentiation protocols toward kidney-lineage cells have resulted in order to affront regenerative medicine and metabolic diseases associated with an inadequate nephron system.

Chronic kidney disease affects 15% of the adult population of all six regions of the world [33]; degeneration of the nephrons and the continuous fibrosis of the tubular and interstitial system allow the develop and progression of the disease, resulting in a disbalanced regulation of fluid electrolytes, accumulation of uremic toxins and an unsatisfied excretion of metabolic waste products [34].

The process of formation of new nephrons, which is called nephrogenesis, is limited to the period of embryonic development in humans. Kidney organoids and nephron progenitor cells, which can be designed from human pluripotent stem cells of patients with chronic kidney disease, could be a potential immunocompatible tissue for those patients with insufficient renal capacity to repair after injury [35,36].

There are currently more than 160 known inherited kidney diseases that affect mostly children, and about 10% of adults develop end-stage kidney disease [32-37]. Probably the most common of this group is the autosomal dominant polycystic kidney disease, which represents 7-10% of all patients on renal replacement therapy worldwide [32-38]. Therefore, it has been the target of recent studies on the use and application of organoids.

Autosomal dominant polycystic kidney disease might be a great challenge in the appliance of kidney organoids, considering late-onset stage disease where cysts can be noticed by ultrasound in approximately 65% in individuals aged 30 years and above, causing a considerable difficulty to encounter cystic phenotypes in that stage. Nevertheless, early phenotypes might be potentially detected in kidney organoids, essentially because the objective genes, PKD1/PKD2, encode ciliary proteins which are expressed in many cell types [32-39].

In summary, considerable advances have been made within the past decade to elaborate kidney organoids from human pluripotent stem cells. To improve this approach epigenetic variation, differentiation protocols and genetic background will need to be considered in depth when analyzing several types of phenotypes in kidney organoids [32].

The helpfulness of kidney organoids to examine inherited kidney diseases, the nephrotoxicity of drugs and the process of injury and repair, has been improving rapidly. Advances in genome editing with CRISPR/Cas9 are further promoting the use of kidney organoids to study inherited genetic kidney diseases [32].

SUMMARY

Organoids are a novel technology that has been studied in the last decade, created from ESC and IPSC models. Nowadays there are multiple studies which have shown their benefits in metabolic diseases such as diabetes mellitus, liver cancer and kidney diseases. It is a new technology which in the future could improve many chronic diseases without a definitive treatment and which should be implemented in further disease studies.

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