TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 14
Number 1 *Fall 2020*

59-66

2020

What is the Future of Organoids?

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Abstract

The term organoid refers to a miniature version of any organ of the body. An organoid is artificially produced in vitro from stem cells or tissue that possess the ability to recapitulate and form the three-dimensional structure of the organ they were once a part of. Scientists have learned to create a culture for the organoid that mimics its original micro cellular environment, allowing the 3-D structure to self-organize and develop into miniature organs. The purpose of this paper is to explore the many advancements of organoid technology, and how this progress has benefited the medical field. Organoid technology allows for the observation of human organ development and disease, while also providing scientists with the opportunity to test drug interactions with these "mini-organs" (Barbuzano, 2017). Organoids also shed light on the future of artificial transplantation, providing replacements for dysfunctional organs and tissue. The advancements of organoid technology can potentially revolutionize the field of medicine, contributing to the progress of modern biology.

Introduction

The human body is composed of a variety of tissue-specific adult stem cell populations. Adult stem cells of each organ in the body possess the ability to self-renew and generate all the different cell types present in that specific organ. Recent studies allow scientists to apply this knowledge of stem cells by culturing them in vitro. Through growing these cells under the right conditions, the cells can assemble miniature versions of the organs they were once a part of (Drost & Clevers, 2017). Through the development of new 3-D technologies and these ideas, scientists were successful in producing artificial organs like the liver, placenta, stomach, lymph nodes, and brain. (John D. Loike and Robert Pollack, 2019).

These miniaturized models that mimic real organs have been termed 'organoids' (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017). Cells of an organoid can be derived from tissue stem cells, embryonic stem cells or induced pluripotent stem cells (iPSCs). These cells possess the ability to regenerate, allowing the tissue to perform its original function (Prior, Inacio , & Huch, 2019).

The ability to create and develop human tissue in a lab offers a major breakthrough in modern biology. The advancement of organoid formation provides scientists with the ability to study human development and disease and test therapeutic medicine through a personal approach. Organoids also offer hope for transplantation of functioning organs, eliminating the need for organ donations (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017). Organoid research can also provide improvement when it comes to animal experimentation, bioethics, and gene therapy (Xinaris, 2019).

Method

This study was written by researching peer reviewed scholarly articles and medical journals to obtain the most accurate information on the advancements of organoid technology. The data was analyzed and evaluated from many different angles, using Touro College's access to online publications. Additional searches were done through Google Scholar, PubMed, and the Science Journal to accumulate relevant information for the study.

Discussion

In 1998, the first successful organoid culture system derived from adult stem cells was the small intestinal organoids of a mouse. This development in organoid research led to many discoveries, among them the knowledge that Wnt signaling is crucial for maintaining the stem cell compartment of the mouse small intestine. Further observation brought about the awareness that ectopic expression of R-spondin, which communicates with Wnt and acts as a Lgr5 ligand, is necessary to include in a culture of intestinal stem cells as well, for ultimate function of the organoid (Drost & Clevers, 2017).

Following these observations and through his own research, Toshiro Sato of Keio University confirmed that the artificial inclusion of growth factors present in the organ's original stem cell niche is crucial for optimum efficiency and function of the organoid. Sato too researched and studied intestine stem cells. He observed that the 3D organoid forms from single Lgr5-positive Intestine Stem Cells. He retained the architecture of the authentic intestine, and included Wnt/R-spondin, epidermal growth factor (EGF), noggin (BMP inhibitor) and an artificial laminin-rich extracellular matrix in his in vitro culture. (Drost & Clevers, 2017).

In the body, cells are exposed to intricate and complex surroundings where they are involved in many chemical interactions (Prior, Inacio, & Huch, 2019). When creating an organoid derived from adult stem cells in vitro, the stem cell niche of the specific tissue must be duplicated. Common niche factors necessary when dealing with healthy human tissue include, but are not limited to, Wnt, R-spondin, noggin and EGF (Drost & Clevers, 2017). Inclusion of the precise concentrations of growth factors within the culture, and maintaining identical micro-architecture, allows stem cells to mature into organized tissues, healthy or diseased (Dumont, Heremans, Jan et.al. 2019). Incorporating these factors in the culture will ensure natural interactions among stem cells. It is crucial to mimic these interactions when creating in vitro phenotypes to maintain the functions of the cells. This is a major advancement from 2D monolayer technology to 3D technology.

To begin creating an organoid, stem cells must be isolated from embryonic stages or adult tissues and placed into a media with these natural growth factors. Development begins from a totipotent cell undergoing rapid cell division. The divided cells become more restricted as they evolve. At the blastocyst stage, the outer cells mature into extraembryonic cells, while the inner cell mass of the blastocyst (ICM) is composed of pluripotent cells which possess the ability to evolve into tissue of the embryo proper. These pluripotent cells are isolated to form the embryonic stem cells. The next step in the developmental process is gastrulation. During this period, cells of the ICM mix together and perform morphogenetic movements that are controlled by signaling factors like Wnt, fibroblast growth factor (FGF) and transforming growth factor-beta ligands. These signaling factors activate transcription and differentiation into the three germ layers: endoderm, mesoderm and ectoderm. After forming the three germ layers, the progenitor cells become more specific and form the primitive structures of organs, thus developing into any tissues and organs of the body (Prior, Inacio, & Huch, 2019).

Transplantation and Xenotransplantation

The development of organ transplantation (OT) is "one of the most successful advances in modern medicine." For struggling patients with end stage disease, transplantation is usually their last hope to survive. One major problem we face today regarding OT is the lack of organ availability. We are unable to meet the exceptionally high organ demand (Bezinover & Saner, 2019). Arthur Caplan of NYU Langone Medical Center reports that the space between supply and demand of transplanted organs is "worse than it appears to be" (Caplan, 2014).

The phenomenon of creating human 3D cultures that duplicate authentic organs allows for extensive use of these organoids for many cell therapies, and as a potential substitute for whole-organ transplantation (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017). Organoids have been successfully transplanted both orthotopically, in the organs, in vivo location, and ectopically, outside of the organ's natural environment. Through both methods of transplantation, organoids were successful in undergoing cell maturation. These advancements show that organoid models can effectively mature and develop when in contact with natural signals provided by the in vivo environment, a crucial understanding for developing organoid transplantation. An abundance of research in the field of organoid transplantation is done to further advance our knowledge of its capabilities. The use of immunocompromised mice in many experiments has paved the way for great progress. When transplanting organoids into these mice for maturation, the organoids were positioned at highly vascularized sites, making it easier to control organoid engraftment and growth. This allows the organoid to develop for several months, without interfering with the mouse's required organ function. Some of these sites include epididymal fat pads and underneath kidney capsules (Holloway, Capeling, & Spence, 2019).

More recently, scientists were successful in orthotopically transplanting colonic epithelial organoids derived from human primary tissue into the murine colon. This study was supported by the Research Center Network for Realization of Regenerative Medicine project from the Japan Agency for Medical Research and Development. The experiment was done by removal of epithelial tissue from the mice. Results were most efficient when only one side of the colon mucosa was removed, to prevent obstruction of the murine colon. Following the removal of the epithelial cells, human colon organoids were transplanted. The xenografted organoids were observed by fluorescent endoscopic imaging. After many trials, long-term engraftment of the human colon organoids was eventually successful and was monitored and observed by endoscopy for over 6 months. Immunohistochemistry of human-specific cytokeratin (KRT8/7) confirmed the presence of the human donated epithelium in the colon of the mouse. This study broadened our understanding of transplantation through organoids in general, but also suggested that the location of the injury must be significantly large to successfully create a niche for the transplanted organoid. Small injuries requiring engrafted tissue, although also allowing for engraftment, proved to be more complicated. The tissue did not last as long as the engrafted tissue of the case of the larger injury, and eventually disappeared over time (Sugimoto, et al., 2017).

Personalized Medicine

Of the many exciting advancements brought about through organoid research, the ability to model diseases of specific patients in vitro can be of great benefit to medicine (Drost & Clevers, 2017). Scientists begin to predict a future in which organoid cultures derived from a patient can provide correct and effective therapeutic options for that particular patient. Induced pluripotent stem cells (iPSCs) are skin or blood cells that have been placed back into an embryonic-like pluripotent state. This allows the cells to mature and develop into any kind of human cell and is commonly used for therapeutic purposes. (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017).

In regard to oncological patients, these organoids could allow testing of drug response, minimizing the load of

therapy. Organoids created from tumor-derived cells are obtained from human tumor biopsies. Induced pluripotent stem cells or adult stem cells are taken from the biopsy and develop into organoids that mimic the cancerous organs. These organoids display identical tumor heterogeneity to their in vivo counterparts (Dumont, Heremans, Jan et.al. 2019).

Marc van de Wetering, a senior researcher dedicated to pediatric oncology, created a biobank of 20 tumor organoids derived from patients with colorectal cancer (CRC). He characterized the organoids by genes and performed drug testing to observe the correlation of specific mutations with drug responsiveness. For example, only one of the tumor organoid cultures reacted sensitively to LGK974, an inhibitor of Wnt secretion. The sensitivity toward this inhibitor was observed to be connected to a mutation that was found in the negative Wnt regulator. This study indicated that characteristics of tumors, histological and genetic, were mimicked precisely in the organoid. These findings can offer a promising future in understanding the correlation between tumor genetics and drug response (Drost & Clevers, 2017).

Additional studies have also been done to create organoid models from normal and neoplastic murine and human pancreas tissues. Pancreatic cancer is of the most fatal malignancies because of its lack of improvement from treatment and late diagnosis. Pancreatic organoids can develop quickly from cells derived from resected tumors and biopsies. These organoids display characteristics that are helpful in understanding drug and therapy response of the pancreas. Neoplastic organoids that are transplanted back into the body, reperform the whole tumor development. The organoids develop from early-grade neoplasms into "locally invasive and metastatic carcinomas." Organoids are an ideal model for genetic analysis because of their ability to be genetically duplicated. Close observation of murine pancreatic organoids presented altered genes and pathways during the onset and progression of the disease. After confirming these characteristics in human tissue, organoids have been deemed as an effective model system for discovering the nature of this deadly malignancy (Boj, et al., 2015).

Gene Therapy

Incorporating organoids into gene-editing through the use of tools like CRISPR/Cas9 technology offers the possibility of correcting gene mutations of patients. These repaired and healthy genes can then be transplanted into the patient (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017). CRISPR/Cas9 also allows for manipulation of genes in organoid cultures, causing drug testing for specific genes to be more definitive and reliable (Dumont, Heremans, Jan et.al. 2019). Comparing a variety of organoids that are all derived from the same iPSC line allows scientists to observe mutations in specific genes, and the effects on tissue specification and development in organs when the genes of a patient carry a specific congenital allele. The ability to create organoids from the diseased tissue offers various methods for clinicians to explore, like computerized drug screening tests, or mirroring antibiogram tests to determine antibiotic susceptibilities (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017).

Studies were done to prove the benefits that can be gained from adult stem cell-derived organoids with regard to hereditary diseases (Drost & Clevers, 2017). Recently, advancements in organoids have shown that CRISPR/Cas9 technology can repair cystic fibrosis gene mutations (Huch, Knoblich, Lutolf, & Martinez-Arias, 2017). Dr. J.M. Beekman of the Regenerative Medicine Center Utrecht, along with some colleagues, created a modeled cystic fibrosis (CF) in vitro culture. The model was composed of cells obtained from CF patients through rectal biopsies, creating intestinal organoids. The cystic fibrosis transmembrane conductance regulator (CFTR) gene is responsible for encoding an anion channel that is expressed on the surface of epithelial cells. CFTR maintains fluid and electrolyte homeostasis. Cystic fibrosis is the result of a mutation in the CFTR gene. As a result of this mutation, epithelial ion transport is weak, and a build-up of viscous fluid becomes present in the respiratory and gastrointestinal tract. CFTR is activated by forskolin, which increases intracellular cyclic AMP levels. In a healthy sample of intestinal organoids swelling was rapid. However, organoids derived from cystic fibrosis patients presented minimal swelling in comparison. It is now possible for researchers to test various drugs on different CF patient-derived organoids, depending on specific CFTR mutations. These findings shed light on a future of patient-specific treatment strategies (Drost & Clevers, 2017).

The Liver

There are many diseases associated with the liver, and over two million deaths a year worldwide are related to liver complications like cirrhosis, viral hepatitis and hepatocellular carcinoma (Asrani, Devarbhavi, Eaton, & Kamath, 2018). The amount of deaths associated with liver disease calls for the advancement of liver organoids as treatments for struggling patients. Researchers like Meritxell Huch of Gurdon Institute and Takanori Takebe from Yokohama City University present their progress in the field of liver organoids. They were successful in creating ductal structures from adult liver and went further

to activate these structures to differentiate into hepatocytes capable of producing bile acid and maintaining cytochrome activity (Muthuswamy, 2017).

The creation of the liver organoid has been further developed through the use of co-culture systems. Many studies reported that liver hepatocyte-like cells derived from human pluripotent stem cells (hPSCs) in 2D resulted in the cells developing immaturely and did not perform all functions of mature hepatocytes. Additionally, after implantation of these hPSC derived hepatocyte-like cells into immunocompromised mice, the cells operated with little effectiveness. Due to these poor results, research has been dedicated to creating more functional hPSC-derived hepatocytes, to produce a liver organoid model that will function more efficiently. The use of co-cultures is thought to be the answer to this progress. When observing mice, researchers found endothelial cells to be a crucial cell type in the process of

liver organogenesis. Due to this finding, a hypothesis was formed that placing endothelial cells and mesenchymal precursors with the hepatic endoderm in a co-culture will provide an environment that closely mimics in vivo development of the liver. This will give rise to efficient hepatocyte differentiation, ultimately generating a complex human liver bud organoid (Holloway, Capeling, & Spence, 2019).

The liver is made up of epithelial, stromal, endothelial and mesenchymal cells that all work together to carry out its functions. Hepatoblasts are the embryonic progenitor cells of the liver. At the time of organogenesis, these cells are set aside from the posterior foregut endoderm. Hepatoblasts communicate with surrounding signaling factors found within the mesenchyme, like FGF, BMP, hepatocyte growth factor (HGF) and Wnt. These communications cause the hepatoblasts to evolve and modify until they can migrate into the adjacent mesoderm to form the liver bud (Prior, Inacio, & Huch, 2019). After creation of the hPSC-liver buds, transplantation of the liver buds into immunocompromised mice tested the functionality of these artificial structures. The hepatocytes of the liver bud were proved to be functional due to the presence of high sustained levels of albumin within the liver bud (Holloway, Capeling, & Spence, 2019). After the liver bud is formed, the hepatoblasts expand and differentiate to form hepatocytes and biliary epithelium. Meanwhile, the mesenchyme generates liver fibroblasts and stellate cells. The structure of the liver is formed completely when the hepatocytes and cholangiocytes mature further and the endothelium and mesenchyme are integrated (Tremblay & Zaret , 2005).

Artificial Ovaries

Of all gynecological cancers, epithelial ovarian cancer (EOC) is the fifth largest cause of cancer-related deaths in European women. EOC patients frequently relapse, with an expanding resistance to chemotherapy and targeted therapy. Consequently, further research is crucial for the advancement of therapy in EOC patients, and organoid development seems promising. Models of EOC organoids can contribute a constructive platform for drug testing and screening, and can ultimately be utilized as a personalized in vitro prototype for an individual patient.

High-grade serous ovarian carcinoma (HGSOC) is a tumor that arises from the serous tubal intraepithelial carcinoma (Dumont, Heremans, Jan et.al. 2019). The fallopian tube epithelium (FTE) has been observed as the site where HGSOC originates (Yucer, et al., 2017). Therefore, observation of fallopian tube tissue can be very enlightening in discovering the nature of EOC. Mirjana Kessler of the Department of Infectious Diseases and Respiratory Medicine, through experimentation, created differentiated ovarian organoids from a single fallopian epithelial stem cell. These organoid models maintained their stability for over several months. This experiment uncovered the existence of fallopian tube stem cells for the first time. The creation of an ovarian organoid requires growth factors and microcellular substances, particularly Wnt and Notch pathways. The inclusion of Notch is especially important because it primarily regulates and maintains the stemness of these fallopian epithelial cells (Dumont, et al., 2019).

The urogenital system arises from the intermediate mesoderm (IM) of a developing embryo. The Müllerian duct within the urogenital system gives rise to the entire female reproductive tract (Yucer, et al., 2017). Following Kessler's research, Nur Yucer of the Regenerative Medicine Institute at Cedars-Sinai Medical Center was successful in constructing Fallopian tube organoids (Dumont et al., 2019). He created an in vitro culture of the Müllerian duct from induced pluripotent stem cells. Yucer then generated IM differentiation by adding pro-Mullerian growth factors, causing the fallopian tube epithelium to develop. The differentiation of the cells was monitored by the addition of cell-related markers such as PAX2, GATA3, OSR1, WT1, and OVGP1. A 3D growth platform was set up for further development and maturation of FTE, which successfully caused the tissue to self-organize into an FTE organoid structure. When forming the FTE organoid, the canonical WNT signaling pathway proved to be crucial. Sub- set of WNT gene family members were also included in the culture, like WNT3a and WNT4. These genes were necessary for generating the different phases of development and maturation of the Müllerian duct. WNT3a and WNT4

are also responsible for inhibiting male differentiation pathways. After three days of forming the culture, epithelial buds formed from the flat cell sheets. The buds then became spheroids, which were put in Matrigel beads with pro-mullerian growth factors. The intermediate mesoderm matured most at day 4, so spheroids were observed on days 3 to 6. Inclusion of a weak estrogen, phenol red, in Matrigel caused the complete organoid structure to form (Yucer, et al., 2017). This finding highlights the necessity of estrogen for the differentiating and maturing of the Fallopian tube. To maintain and stabilize fully developed organoids, both estrogen and progesterone must be present. (Dumont, et al., 2019) This is because estrogen alone did not maintain the organoids for long periods of time.

More progress has been made in regard to EOC organoid research. Dr. Oded Kopper of NewStem efficiently produced organoids with epithelial ovarian cancer characteristics. He obtained cells from primary tumors or metastatic lesions. The organoids he created successfully retained identical genomic landscapes as the tumors they were derived from. Histological aspects and heterogeneity of the tumors were also maintained. (Dumont, et al., 2019)

Ovarian cancer organoids can be utilized to observe various tumor responses to chemotherapy and for drug-screening assays. Xenografting OC organoids also allows clinicians to test drug susceptibility in vivo. These are some of the many advancements and applications of ovarian cancer organoids (Kopper, et al., 2019).

Another major benefit of an artificial ovary is to preserve fertility in patients suffering from cancer. An artificial ovary can allow women to fall pregnant after the damaging effects of chemotherapy. (University of Erlangen-Nuremberg, 2019) Ovarian tissue cryopreservation is the process of preserving reproductive potential in oncological patients after being exposed to gonadotoxic therapeutic agents. (Liverani, et al., 2019) Ovarian tissue cryopreservation involves the removal of a section or of the complete tissue of an ovary. This tissue is then preserved for use in the future. (Ben-Aharon, et al., 2016) Cryopreservation can be utilized by patients with aggressive malignancies who must receive instant gonadotoxic treatment. These women do not have the time to receive ovulation induction, and cryopreservation can be a great benefit. Although ovarian tissue cryopreservation can be of great assistance for many, cancer patients with moderate-to-high risk of ovarian metastasis are at too high of a risk. The process of cryopreservation introduces the possibility of malignant cells being reimplanted back into the patient.

A promising approach for these high-risk patients is the use of artificial ovaries. Isolating follicles from a patient's ovarian tissue and reimplanting the follicles into an artificial ovary can guarantee that no malignant cells will be reintroduced to the patient. (Liverani, et al., 2019) Because follicles are isolated in a basement membrane, there is no interaction between capillaries, follicular cells, white blood cells and nerves. Therefore, there is no threat that malignant cells will be introduced back to patients. Artificial ovaries make it possible to transplant primordial and primary follicles that were isolated to survive and could mature into follicles after transplantation. This permits sex hormones to be secreted, regulating oocyte maturation to the point where they are capable of fertilization. In the artificial ovary, it is essential for the follicles to be supplied with an environment that mimics the natural human ovary. In order for the follicles to survive and develop, interaction with the ovarian extracellular matrix (ECM), as well as surrounding ovarian cells must be present. For example, ovarian stromal cells are required to activate primordial follicles, while endothelial cells are necessary for vascularization, providing transportation of oxygen and nutrients, paracrine factors, and removal of metabolic waste. The presence of the ovarian ECM is responsible for maintaining 3D follicle structure, as well as other important roles. Therefore, all these factors must be present. (Dolmans & Amorim, 2019)

Drs. Teresa Woodruff and Ramille Shah of Northwestern University led a team of scientists in creating artificial ovary structures. The process utilized a 3D printer to create the structure that would hold the follicles. A stainless steel nozzle was used for the printer, which was around the width of a strand of hair. Five layers of gelatin filaments were printed at various angles. Tiny cylinders were punched through the sheets, creating pores to hold mice follicles. Nine mice were involved in the study, and all ovaries were removed. Seven of the mice received the structures with the follicles, and two received the artificial structures without follicles. Following the mating of these mice with male mice, three mice with artificial ovaries produced litters. The artificial ovaries also joined with the blood vessels of the mice, allowing for female hormones involved in milk production to be made. The hormones successfully traveled the mouse bloodstream to the breast tissue where it stimulated milk production (Piazza, 2018). The ability of an artificial ovary to restore endocrine function and provide an environment for follicular development can be extremely useful for oncological patients in the future (Cho, Kim, Noh, & Ku, 2019).

Virology

The coronavirus disease-19 (COVID-19), caused by the SARS-CoV-2 virus is responsible for over 250,000 deaths globally. (Han, et al., 2020) The COVID-19 pandemic

proved to the world just how threatening newly surfacing viruses can be. Understanding the nature of these viruses rests in the use of in vitro cultures capable of viral replication. The use of organoids is now demonstrating its practicality when experimenting the tendencies of these deadly viruses.

The novel coronavirus first infected humans in December of 2019. Various research groups have been experimenting with organoids to better understand the nature and tissue tropism of SARS-CoV-2. Josef Penninger of the Institute of Molecular Biotechnology, along with his colleagues, created capillary and kidney organoids, both derived from human iPSCs. Through this research, Penninger proved that SARS-CoV-2 can infect both sites in the body. These observations help explain the ability of the virus to spread throughout the body and the damaging effects on kidney function in infected individuals.

Multiple studies were done to establish whether the virus can infect the gastrointestinal tract. Intestinal organoids derived from adult stem cells were examined and presented high levels of angiotensin converting enzyme 2 (ACE2), a receptor for SARS. The studies displayed that enterocytes, the most common intestinal epithelium cell type, were infected with the virus. These findings verified that the intestine is a potential site for SARS-CoV-2 infection (Clevers, 2020).

Mart Lamers of Erasmus Medical Center, along with his colleagues, further investigated the ability of SARS-CoV-2 to infect the intestines. The human small intestine epithelium is composed of multiple cell types. The experiment consisted of 3D structures that displayed all cell types, grown in four separate cultures. Each culture displayed different amounts of ACE2, proving their ability to be infected with SARS-CoV-2. Through the use of electron microscopy, Lamers and his colleagues observed that the virus caused infection in mature and progenitor enterocytes alike. This study suggests that the use of human organoid models can provide researchers with beneficial resources for examining the nature of SARS-CoV-2 and other coronaviruses. (Aaas, 2020)

Since the primary infection site for SARS-CoV-2 is in the respiratory organs, research was done to create a lung organoid derived from human pluripotent stem cells (hPSCs). Development began with the differentiation of the hPSCs into definitive endoderm. The cells then further progressed into the anterior foregut endoderm (AFE) and formed AFE/lung progenitor cells. Further specification and maturation of these cells eventually formed the lung organoids. The ability of these lung organoids to provide a platform for modeling COVID-19 was then put to the test. The cultures were introduced to the SARS-CoV-2 virus, and after 24 hours viral RNA was detected. The use of immunostaining proved the presence of SARS-S protein in the lung organoids. Based on this research, scientists can utilize these organoids to observe the effects of various drugs on the coronavirus, by observing any decrease in the amount of markers present from the injected virus. (Han, et al., 2020)

Conclusion

Organoids possess the ability to model tissue structure and function with great accuracy, but more research is required to take full advantage of organoids. Organoids still lack vasculature, immune cells, and other cellular components that tissues communicate with and depend on in the body (Iakobachvili & Peters, 2017). Without all the essential cellular components of an organ, the use of organoid in human transplantation will be limited. Studying processes where these components are necessary is therefore limited. (Souza, 2018) Efforts to improve the vasculature of organoids will provide nutrient supply, excretion of toxins and signaling that is present in the body. This research is presently making progress, though it is demanding and yet to be fully incorporated into standard tissue culture facilities. (Iakobachvili & Peters, 2017) Organoid technology brings up many ethical questions as well. For example, what might happen if scientists can successfully create a brain organoid? Utilizing a brain organoid for drug testing would be helpful, but it may pose an ethical issue to transplant this organoid into a patient. These matters must be addressed in the future. However, we do know that organoid technology is adding a whole new dimension to the medical field.

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