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The Use of Stem Cell-Derived Organoids in Cancer Treatment Research

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Abstract

Cancer is one of the leading causes of death worldwide. While some forms of cancer are more manageable and nonfatal with treatments like chemotherapy and radiation, other forms are not as manageable and have high fatality rates, such as colorectal cancer. Colorectal cancer most commonly occurs in elderly adults but has the potential to occur at any age. Due to its sometimes-undetectable symptoms, it is often diagnosed at a very late stage. Once diagnosed, there are different levels of treatment. For example, surgical resection, chemotherapy, radiation, or any combination of the three can occur. When tumors are unresectable, patients are often left with little chance of survival, and receive only the extension of survival for a short period of time. While surgical resection, chemotherapy and radiation have had success in some patients, high recurrence rates and a lack of response to treatments have left patients and researchers looking for new treatments that will result in better survival rates for patients. Researchers have begun to answer the calls for new treatments with the discovery of patient-derived organoids. Patient-derived organoids are harvested from adult stem cells in the desired tissue, or from cancer cells in a patient's tumor. The cells taken from the patient are then grown *ex-vivo* in conditions that mimic the inside of the body. Organoids have grown to show both structural and physiological similarities to their parent organ. While organoids have not yet grown to be as large and highly vascularized as their parent organ, they have been useful in disease modeling and drug therapy testing. Patient-derived organoids that have been grown *ex-vivo* have shown to overlap almost completely with their parent organ in terms of genetic sequence and molecular makeup. Due to their high number of genetic similarities, patient-

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derived organoids have been shown to react the same way to certain drug treatments in a few studies, which allows researchers to provide combinations of different cancer drug treatments that are tailored to each individual patient, rather than using a standardized approach that only seems to work for some patients. Patient-derived organoids are still a rather new approach to cancer drug therapy testing, and they still present some limitations, such as their inability to grow as large and as highly vascularized as their parent organ. While these limitations may have the ability to hinder the effectiveness of patient-derived organoids, some organoids have shown success in colorectal cancer drug therapy trials, and their limitations are likely to be overcome as more information is known about patient-derived organoids. Organoids are a promising approach to the treatment of colorectal cancer and have the potential to help save more patients than previous approaches.

Keywords

Stem Cells; Organoids; Cancer Treatment

Abbreviations

ASCs: Adult Stem Cells; CRPM: Colorectal Peritoneal Metastases; DNA: Deoxyribonucleic Acid; ESCs: Embryonic Stem Cells; iPSCs: Induced Pluripotent Stem Cells; PSC: Pluripotent Stem Cells; RNA: Ribonucleic Acid; WHO: World Health Organization; 5 Fu: 5-Flourouracil

What is Cancer?

Cancer is a deadly genetic disease that kills people every day. The World Health Organization (WHO) names cancer as the leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 alone [1]. Approximately 35.9% of men and women will be diagnosed with cancer at some point during their lives. Although the highest incidence rates of cancer are found in older adults, an estimated 16,850 children and adolescents ages 0 to 19 will be diagnosed with cancer and 1,730 of them will die from the disease each year [2]. There are more than 100 types of cancer, with some forms being more aggressive than others; cancers are named by the name of the tissue where the cancers formed, and sometimes are classified by the cancerous cell type involved [3]. While anyone can get cancer, some genetic predispositions and lifestyle choices can increase the possibility of getting the disease. Some believe that genetic predispositions mean that an individual will get cancer regardless of lifestyle choices and environment, but only 5-10% of all cancer cases are due to genetics. Studies have shown that lifestyle choices play a very large role in an individual's possibility of developing cancer, with 25-30% of cancer deaths due to tobacco, as many as 30-35% are linked to diet, 15-20% due to

infections, and the remaining percent are due to other factors, such as radiation, stress, physical activity, environmental pollutants, etc. [4].

Cancer results from damage in a cell's DNA. Through normal and routine body processes, the body can remove cells with damaged DNA before they grow, eliminating the possibility of cancerous cells proliferating. However, the body's ability to rid itself of damaged cells decreases with age. The changes that cause the development of cancer affect three genes: protooncogenes, tumor suppressor genes and DNA repair genes. Protooncogenes are essential for normal cell growth and division. Protooncogenes that are altered can become oncogenes, which are cancer-causing cells [4]. Tumor suppressor genes are involved in controlling cell growth and division, by inhibiting proliferation and tumor development. When tumor suppressor genes are inactivated, certain negative regulatory proteins that prevent cancerous cells from forming are eliminated, which leads to the development of a tumor [4,5]. Sometimes cancers can spread to other parts of the body, also known as metastasis, which can cause damage to other tissues, organs, and important body functions and processes [4].

Current Treatment Options: Chemotherapy and Radiation Therapy

One of the most common treatment options is chemotherapy. In traditional chemotherapy, the agents mainly affect both macromolecular synthesis and function of cells by interfering with DNA, RNA or protein synthesis or affecting the functioning of the preformed molecule. When the disruption of macromolecule synthesis is adequate, programmed cell death, also known as apoptosis, occurs, effectively killing the harmful cells. While traditional chemotherapy can be effective, it may require repeated doses [6]. Combination chemotherapy consists of a combination of agents and has had adequate outcomes as well. Combination therapy can be beneficial in cancer treatment because cellular mechanisms that promote or suppress cell multiplication and differentiation are very complex. They involve several genes, receptors, and signal transduction. The use of multiple agents during chemotherapy is beneficial in selectively inhibiting growth rather than using a single agent, which makes it more difficult to selectively target cells. Chemotherapy can be delivered in neoadjuvant, adjuvant, combined and metastatic settings [6]. While chemotherapy is successful, it does have a few drawbacks. For example, traditional chemotherapy non-selectively targets actively proliferating cells, which leads to the death of cancerous and healthy cells [7]. Chemotherapy drugs not only inhibit the uncontrolled growth of malignant cancer cells, but the agents also suppress the action of normal cells with high proliferation rates, like hair follicles, gastrointestinal epithelium, and bone marrow stem cells. Weakening of bone marrow stem cells can compromise an individual's immune system and increase susceptibility to disease [7,8]. In addition, monotherapy treatment is more susceptible to drug resistance because repeated exposure to the same agent allows for cancer cells to recruit alternative salvage pathways [7]. While combination therapy generally has better patient outcomes than monotherapy, new cancer treatments are constantly being explored.

Another common cancer treatment is radiation therapy, which is the use of subatomic particles for cancer management. High-energy radiation damages DNA of cells, which prevents them from being able to divide and grow any further [9]. Radiation therapy can be delivered internally or externally, with external beam radiation, also known as teletherapy, being the most common. Teletherapy involves a radioactive source that is placed outside of the patient and is directed at an area of the body. Brachytherapy, or internal radiation therapy, involves placing naturally occurring radioactive sources inside the patient, which decay overtime and produce high doses of radiation [10]. The goal of radiation therapy is to maximize the radiation dose to abnormal cancer cells, while minimizing exposure to radiation of normal cells. Normal cells are usually less affected by radiation therapy than cancer cells because normal cells can repair themselves at a faster rate and achieve normal functioning status after exposure to radiation therapy much more easily than cancer cells [9]. While radiation therapy can be very effective in certain cases, it can lead to fibrosis, atrophy, necrosis, and vascular damage in tissues with slow turnover, such as the brain, kidney, liver, walls of the intestine, fatty tissue, and muscle [11]. Due to complications from radiation therapy, researchers are still looking for other approaches to cancer treatment and management and an innovation in cancer research, the use of patient-derived organoids, could be the answer.

What are Organoids?

An organoid is a 3-dimensional, multicellular *in-vitro* tissue that mimics its parent *in-vivo* organ and can be kept outside of the body. Since the organoid has the same genetic information and differentiating cells, it can be used to test a patient's reaction to various medical treatments [5]. Organoids can be formed from tissue-resident Adult Stem Cells (ASCs) that are gathered from biopsies, or Pluripotent Stem Cells (PSCs) such as Embryonic Stem Cells (ESCs) or induced Pluripotent Stem Cells (iPSCs). Organoids have currently been made from gut, stomach, kidney, liver, pancreas, mammary glands, prostate, upper and lower airways, thyroid, retina, and brain stem cells [12]. ASCs, also called somatic stem cells, are undifferentiated cells located in a differentiated organ. ASCs are housed in a structure within the organ called a niche, which aids in the maintenance of microenvironments that regulate growth of ASCs. The main role of ASCs is to maintain homeostasis within an organ. When needed, ASCs proliferate and differentiate to replace lost or injured cells when injury to the tissue occurs [13]. Tumor-derived organoids are another useful tool in the research of different cancer treatments for patients and are derived from ASCs. All tissues in the body arise from PSCs, which can self-renew when necessary. These self-renewed daughter cells have the same properties as the progenitor cell. ESCs are derived from the inner cell mass of preimplantation embryos and can be maintained for long periods of time *in-vitro*. PSCs can also be derived through a new *in-vitro* technology called reprogramming, which involves dedifferentiation of adult somatic cells [14]. We will only be discussing ASCs and tumor-derived organoids further (Fig. 1).

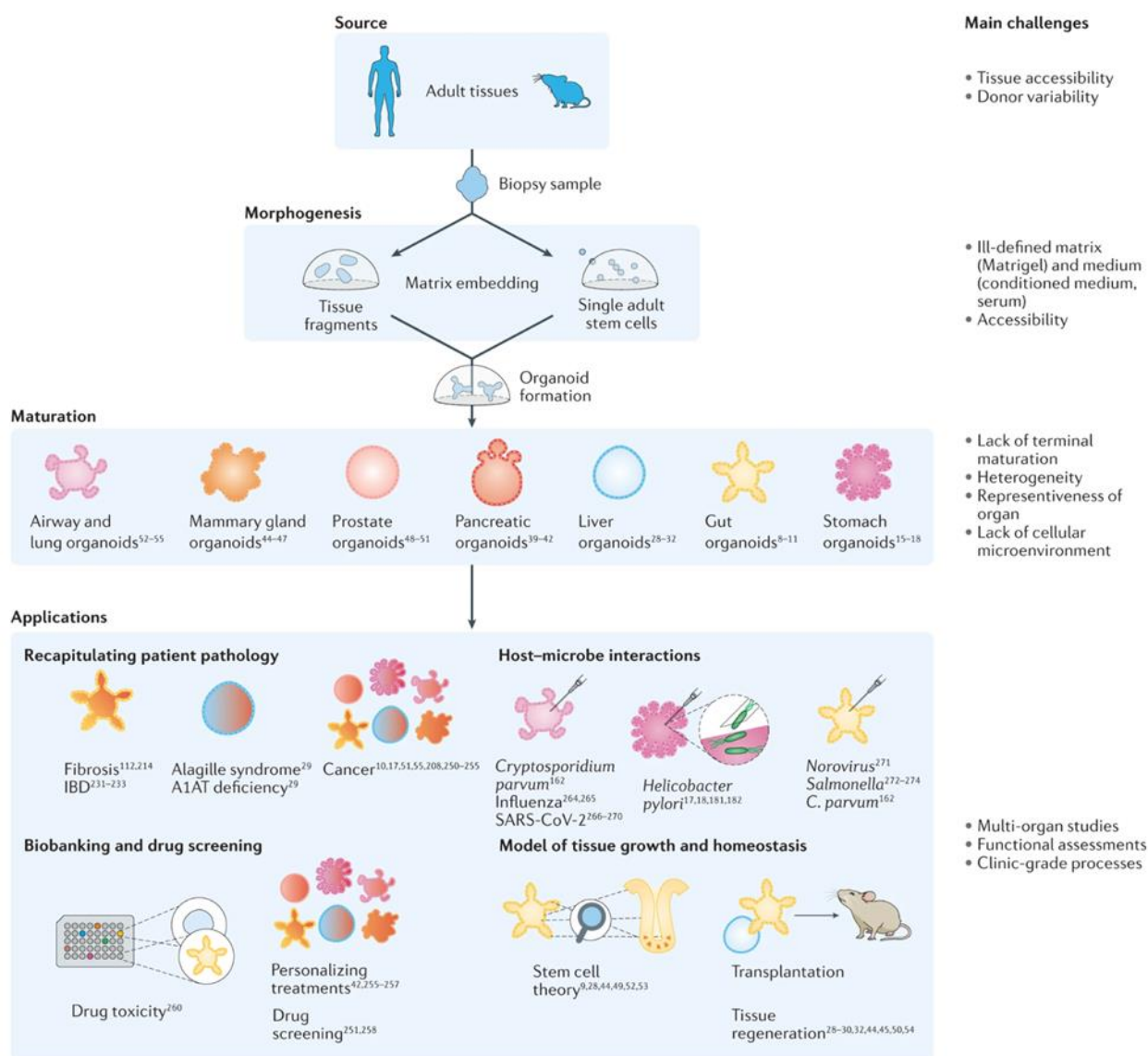


Figure 1: Tissue-derived organoids [12].

Tissue-derived organoids arise from ASCs and are collected through a biopsy. The tissue fragments are grown *in-vitro* in a matrix that mimics conditions of the niche where the ASCs reside. The ASCs undergo proliferation, differentiation, migration, and selection, and grow into structures that mirror the organization and cell type diversity of their *in-vivo* parent organ. Tissue-derived organoids start to grow and form a first layer of monolayered spheres. These spheres develop projections resembling the glandular epithelium of the parent tissue. Organoids continue to develop in homogenous control conditions and form 3-dimensional structures that structurally and functionally resemble their parent organ [12, Fig.1].

Colorectal Cancer

Colorectal cancer is the second most common cause of cancer death in the United States, according to the American Cancer Society, and more than 50% of cases and deaths are due to controllable risk factors, such as tobacco use, diet, alcohol consumption, physical activity, obesity, etc. As can be seen in Fig. 2, the highest prevalence of age at diagnosis 85 years or older (Fig. 2) [15].

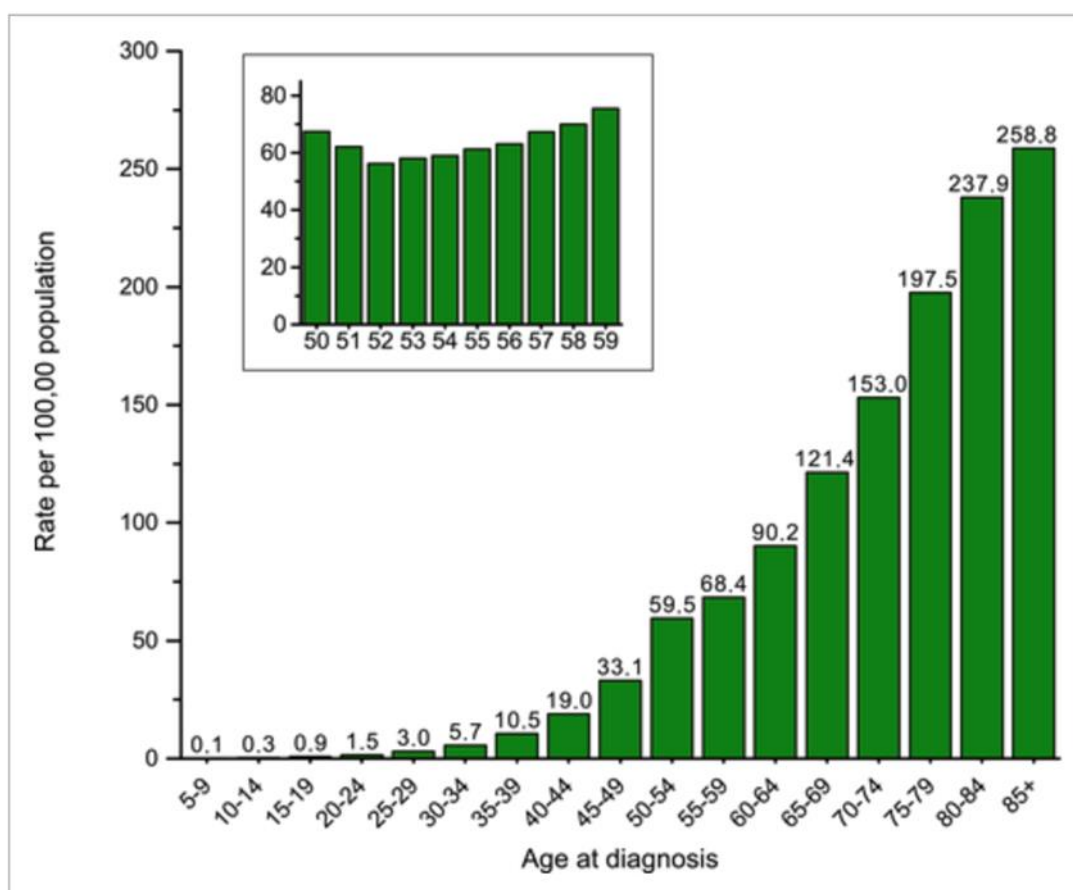


Figure 2: Colorectal cancer incidence rates by age in the United States from 2012-2016 [15].

Colorectal cancer results from the transformation from normal cells to malignant cells in the epithelium lining the external surface of the large intestine. These transformations are the result of genetic alterations and epigenetic modifications that are hypothesized to accumulate over decades. Most colorectal cancers display changes in protooncogenes and tumor suppressor genes, which leads to the deregulation of a few essential signaling pathways. While much has been learned about colorectal cancer overtime, the understanding of colorectal cancer by researchers at the genetic level has not been useful in achieving better outcomes for patients suffering from the disease [16]. Metastases commonly form in the peritoneum. A lot of

peritoneal metastases are not easily removed from patients. Therefore, patients with peritoneal metastases have a historically poor prognosis. Patients with Colorectal Peritoneal Metastases (CRPM) that cannot be resected have a median survival of 12-16 months after diagnosis. CRPM also has a low response rate to chemotherapy, with less than a third demonstrating any response to chemotherapy [17]. For patients with stages I-III colorectal cancer, the first course of treatment is resection of the tumor, followed by adjuvant chemotherapy, which usually consists of 5-Fluorouracil (5-Fu) and oxaliplatin. Although this approach can be successful short-term, patients have roughly a 40% chance of disease recurrence within 5 years [18].

Due to the ability to grow tumor-derived organoids from an *in-vivo* tumor using cancerous stem cells and compare them with patient-derived organoids taken from adult stem cells, organoids are an encouraging pre-clinical model of disease. The goal in using patient-derived organoids for cancer drug therapy research is to use the patient's genetic and molecular biology collected through their organoid to test different treatments before introducing the medication or combination of medications to the patient [17]. It can be very difficult to get a sample of normal intestinal cells from a biopsy using current technology, which is part of the reason that the prognosis for patients suffering from colorectal cancer continues to be poor [16]. Organoids have enough genetic similarity to their tumor or normal cell counterparts, making them a valuable tool in disease modeling and drug therapy testing.

Disease Modeling

Weeber, et al., obtained biopsies from 14 patients with metastatic colorectal cancer. Genetic analysis was performed sequencing for 1,977 cancer-relevant genes. Organoid cultures can be established from tumor biopsies of patients with metastatic colorectal cancer with a 71% success rate. Organoids matched the cell types of the original location of the cancer, and 90% of somatic mutations were shared between organoids and their corresponding biopsy [19]. Weeber's research provides the possibility of a promising outcome to this *ex-vivo* approach.

Yao, et al., obtained 18 biopsies from patients with rectal cancer. Results showed that patient-derived organoids had the same mutational spectrum observed in their biopsy counterparts in the most frequently mutated cancer genes. Patient-derived organoids and biopsies showed a 94.4% overlap [20].

Wetering, et al., created a living biobank using tumor-derived organoid cultures from 20 colorectal carcinoma patients, with some organoids also grown from normal tissue around the cancerous tissue. He found that organoids are very similar to their original *in-vitro* counterparts, and that most of the same molecular information was present in both organoids and biopsies [21].

Drug Therapy Testing

Yao, et al., created a living biobank with 80 locally advanced rectal cancer organoids taken from patients with no former treatment. The organoids grown had the same genetic information as the original tumors from which they were taken. Patients were then treated with medication based off their organoid's sensitivity results. 68 out of 80 patients had the same response as their organoid counterpart when treatment was complete [18,20].

Ganesh, et al., harvested 65 patient-derived rectal cancer tumor-derived organoids from patients with primary, metastatic, and recurrent rectal cancer [22]. The study found that the organoids grown had very similar molecular and genetic makeup to their parent tumor. The study evaluated patient response to treatment with radiation. 21 different tumor-derived organoids were separately treated with 5-FU and FOLFOX (combination chemotherapy consisting of 5-FU, leucovorin, and oxaliplatin). The data collected for both treatments correlated to the patient's clinical response [18, 22]. The study also evaluated 19 tumor-derived organoids that were radiated *ex-vivo*, which gave a response to radiation. To make sure that results of both chemotherapy and radiation combined were not shown, she used endoscopic tumor assessment before and immediately after radiation to get more accurate results of just radiation alone. Results showed that tumor-derived organoids have similar outcomes to their corresponding patient in a clinical setting [22].

Advantages and Limitations of Organoids

While organoids are a promising approach to possible cancer disease modeling and drug screening therapy, there are some limitations to this approach. Organoids are still very small, and there is still a small disconnect between organoid function compared to the function of their organ counterpart. For example, there is less vascularization in organoids, meaning the cells in the center tend to not be as healthy as cells around the outside due to the inability of nutritious substances necessary for growth to reach the inside. It is believed that an entire functional vascular system is not likely to be able to develop in organoids. Another limitation of organoids is that they are grown in immune environments, meaning that the organoid may not be able to survive inside an immunodeficient organism should it be placed inside the body of someone with an illness. Although there are limitations, there are still many promising uses for organoids, such as study of tumors, hereditary diseases, infectious diseases, and regenerative medicine [23].

Conclusion

Organoids have great potential to be the primary resource for disease modeling and drug therapy for cancer patients. Organoids are a rather new research tool, so there is still much more to be learned about them and much more that can be modified to ensure better

performance. The occurrence of animal trials is likely to come soon, which will be a valuable resource in learning more about organoids and their strengths, as well as different diseases. Organoids have already proven to be valuable in learning more about colorectal cancer, since they have made the study of colorectal tumors more easily available and have already proven to mimic patient responses to certain drug therapies. As more information is gathered about organoids and colorectal cancer itself, this new approach to treatment has the potential to save more patients than previous approaches.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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