International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

A Critical Review on the Role of Bioprinted Tumor Models in Cancer Research

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Abstract: ***Tumor modeling is a contemporary method of cancer research used to build tissues that are used to mimic the progression of metastasized cancerous cells. Bioprinting techniques are becoming a more common approach to generating tissues that can be used to study the course of different cancerous pathways. Recent developments in bioprinting technology have enabled improvements in research surrounding oncology, among other fields including regenerative medicine and pharmaceutical applications. This article summarizes some of the common techniques used in bioprinting and how they can be used for current and future medical applications, with a focus on its utilization in cancer research.***

Keywords: Bioprinting techniques, tumor modeling, oncology, regenerative medicine, and cancer research

1. Introduction

Cancer is a pressing global health issue with high mortality rates that affects millions of people across all demographics. Conventional cancer research models have contributed substantially to the development of treatment plans and understanding of the biology of cancer. The traditional cancer research models include two - dimensional (2D) cell cultures and animal models [1]. However, the traditional research models have many limitations, particularly in their inability to simulate the intricacies and complexities of three - dimensional (3D) cell cultures and microenvironments of tumor - fested human body parts. Due to these persisting limitations and difficulties using conventional research models, there has been a large number of therapeutic compounds showing promise that have failed in trials. This has caused a significant influx in the attrition rate of developing new drugs to tackle cancer.

Technological developments in bioprinting technologies have opened the areas of possibility for the production of biologically accurate 3D models of tumors for research purposes.3D models of tumors is an emerging technique that uses layer - by - layer deposition of bioinks containing living cells and biomaterials [2]. This allows for the creation of an environment where tissue - like structures can imitate the intricacies, complexities, and functionality of human tissues, including tumors [3]. This opens up an avenue of possibility where researchers are able to replicate the interplay between cancerous and non - cancerous cells and the microenvironment of the tumor for data collection and treatment production.

Bioprinted tumor models serve as a fundamental breakthrough technology that will help bridge the gap between traditional in vitro and in vivo models for cancer research. The models offer a more physiologically and realistic model for investigating cancer progression, invasion, and metastasis [4]. The models closely resemble the natural tumor microenvironment by mimicking the extracellular matrix, hypoxic conditions, and the extracellular matrix. Furthermore, these models show a promising future in personalized medicinal care by fielding the opportunity for targeting individualized cancer types and oncology.

Contemporary Bioprinting Technologies and Tumor Models used in Cancer Research:

Advanced Bioinks -

A critical advancement in 3D bioprinting is the production of complex bioinks that mimic the native extracellular matrix (ECM). The ECM plays an essential role in tumor progression, invasion, and metastasis [5]. Tissues receive structural support from the ECM, which also plays an important role in cell behavior influenced by biochemical and mechanical signals. The ECM is frequently altered in cancer, which promotes tumor growth and treatment resistance. Through close imitation of ECM functionality and complexity in ECM models, the realistic tumor microenvironments can be used to develop treatment plans.

Bioinks are usually composed of natural polymers, synthetic materials, or a combination of both. Natural polymers like collagen, alginate, and gelatin methacryloyl (GelMA) are often used [6]. This is because they closely resemble the ECM found in human tissues. The most prevalent protein in the human body, collagen, is often used to simulate the mechanical characteristics of tissues. Also, alginate and GelMA provide excellent biocompatibility and mechanical strength. Additionally, synthetic bioinks use polyethylene glycol (PEG) or polycaprolactone (PCL) to orchestrate greater control over mechanical and chemical properties [7]. The bioinks individually or in collaboration can be altered to include proteins, cytokines, and growth factors. This helps in imitation of the tumor's biochemical environment and produces a physiologically and realistic relevant cell environment to study and collect data on invasion, migration, and proliferation.

Nanomaterials have shown promising advancements in combination with bioinks to enhance their functionality in recent years. Bioinks can be enhanced with nanofibers, nanoparticles, and carbon - based materials [8]. This promotes the creation of tumor spheroids or cellular aggregates, which closely resemble the progression of tumor development in vivo environments. Nanomaterial incorporated bioinks have contributed significantly to the development of more dynamic and realistic models that capture the complexity of the ECM of tumors. This realistic and dynamic model mimics the

functionality of the ECM of tumors in promoting cell - cell interactions, drug resistance, and metastasis.

Tumor - Specific Microenvironments -

Advanced bioinks have opened up the possibility for bioprinted tumor models that can replicate tumor - specific microenvironments that are essential for cancer progression and proliferation. Each cancerous microenvironment consists of blood vessels, stromal cells, immune cells, cancer cells, and the ECM [9]. All these elements combine to create a supportive microenvironment in many tumors that promotes tumor development, immune evasion, and metastasis.

Another significant advancement of the production of tumor - specific microenvironments is the promising possibility of introducing immune cells into these models to study their interplay in the tumor. Incorporating immune cells such as B cells, T cells, macrophages, and natural killer cells into the bioprinted models helps researchers thoroughly study the efficacy of immunotherapies and how cancers evade the immune system [10]. An example of this is when bioprinted models can be used to test drugs such as checkpoint inhibitors. Checkpoint inhibitors block proteins that stop the immune system from attacking cancer cells. These drugs can be used on these bioprinted models to assess the effectiveness of the drug in different tumor microenvironments.

Advancements in creating heterogeneous tumor microenvironments have been critical in tackling the immense challenge in treating tumor heterogeneity. Tumor heterogeneity is where there is the existence of many cancer cell populations inside a single tumor [11]. Differential pharmacological responses result from the treatment of tumors that display heterogeneity. Some cancer cell populations display sensitivity and commit apoptosis to treatment, while others are resistant and continue to proliferate. With multi - material bioprinting, different bioinks can be utilized to print different tumor regions. Each different tumor region that is printed has its own collection of cell types and ECM components. This opens up an avenue of possibility where multi - zone tumor models can be produced that allow researchers to study and collect data on different regions of the tumor [12]. The researchers can thoroughly understand how different regions of the tumor interact with other regions, how cancer cells infiltrate adjacent tissues, and how medication resistance develops.

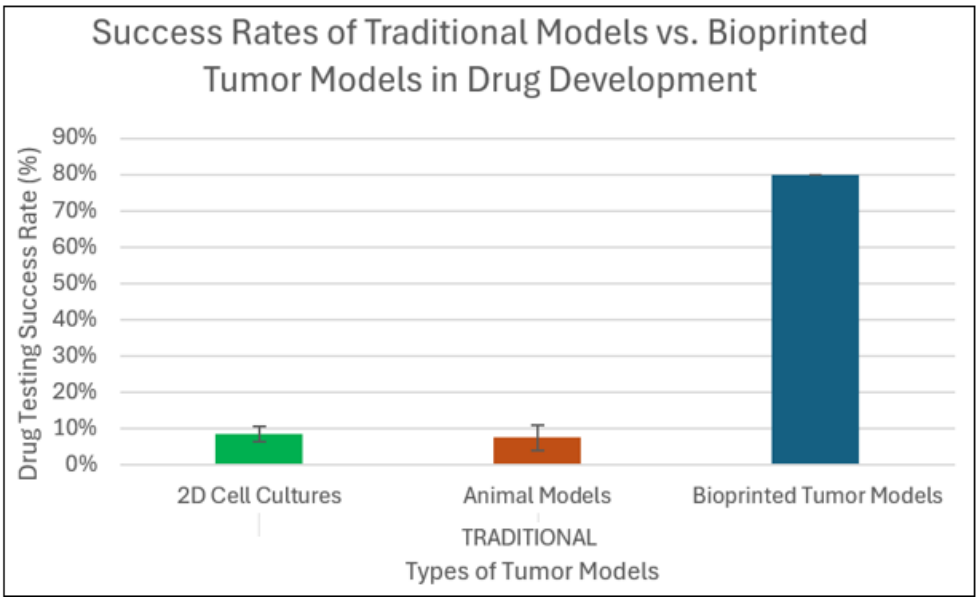
Vascular Bioprinting -

Conventional in vitro tumor models have been incapable of precisely mimicking the vascularization of actual tumors. Vascular networks play a crucial role in the growth, proliferation, and metastasis of cancer because they provide tumors with oxygen, nutrients, and a means to remove waste [13]. Traditional models fail to accurately replicate the dynamic interactions between cancer cells and blood arteries. This interplay between the cells and arteries is pivotal for researching tumor angiogenesis and testing anti - angiogenic treatments.

In recent years, vascular bioprinting has tackled the challenge of traditional methods inability to mimic proper vascularization of tumors. Researchers can now create complex and intricate blood artery networks within bioprinted tumor models [14]. Microfluidic bioprinting is one such method that involves creating small, interconnected blood vessel - like channels within the bioink [15]. This creates a pathway of potential to analyze how oxygen and nutrients are transported through the tumor. Additionally, it can help understand how medications and treatments are distributed across different areas of the tumor model by perfusing these channels with medium or blood - mimicking solutions.

Tumor metastasis is the process by which cancer cells leave the original tumor, enter the circulatory system, and colonize distant organs. By implementing vascular networks into bioprinted models, researchers are able to investigate how cancer cells enter blood arteries (a process known as intravasation), circulate through the bloodstream, and create a secondary tumor in distant tissues [16]. Anti - metastatic treatments that target cancer cell apoptosis and attempt to stop metastasis can also be tested and evaluated on these bioprinted vascularized models.

Angiogenesis inhibitors are drugs that target the blood arteries supporting the tumor and can be tested and studied by using bioprinted vascularized models. This treatment plan seeks to “starve” the tumor by cutting off the tumor’s blood supply [17]. The bioprinted vascularized models field a realistic and physiologically relevant apparatus for assessing the efficacy of such treatments. Researchers are able to collect data and study the effectiveness of these drugs in real time by observing how these medications affect tumor growth and vascular function in these bioprinted vascularized models and create more effective pharmaceutical compounds based off of the results collected.



The chart above displays the success rates of traditional models. This includes 2D Cell Cultures and Animal Models compared to Bioprinted Tumor Models [18]. The figure displays a projection for the Bioprinted Tumor Models based on ex vivo tests as bioprinting closely resembles organoids [19]. The chart suggests a significant increase in drug testing success with the Bioprinting Models compared to the Traditional Models [20].

2. Further Applications of Bioprinting Techniques

Bioprinting Applied to Regenerative Medicine -

While bioprinting exhibits great potential in assisting with the establishment of more effective treatments for cancer through the generation of tumor models, there are also other promising uses for the revolutionary technology. Another way that bioprinting technology can be applied to advance the medical field is in regenerative medicine. In the same way that bioprinting technology can be utilized for the creation of tumor models that allow for different cancer treatments to be observed and studied, those same tissues can be used to replace damaged or defective tissues in the body so that the body can continue to heal on its own. A practical example of this pertains to valvular heart disease, as it is common for people afflicted with this disease to require replacement of valves in the heart; bioprinting can be employed to recreate a functional aortic valve by combining hyaluronic acid, gelatin and alginate so that the heart can resume normal activity [21]. Other tissues such as nerves and skin can be structured using bioprinting techniques such as jettison - based bioprinting to combine components of the extracellular matrix including collagen, fibrin and soy agar into usable tissues. This application of bioprinting remains in its early stages, and there have been complications reported concerning the functionality of the recreated tissues. Examples of such complications include mechanical failure and calcification for the aortic valve; the prevalence of such complications suggest that future research should be done in the field to improve the quality of the bioprinted tissues. Despite the problems with the practical application of bioprinting in regenerative medicine, the utility of bioprinting technology has become apparent and it remains an area of research that could prove to be highly effective in improving the field.

The Significance of Bioprinting on Pharmaceutical Development -

Additionally, bioprinting technology could be considered for further study centers on the testing and development of drugs. While the development of tumor models and microenvironments through bioprinting can be useful for checkpoint and cancer - specific drug testing, the technique is not limited to such uses. Bioprinting has the potential for great advancement in the pharmaceutical field, as biological tissues can be created to then be used for testing prior to their implementation for human treatments. Bioprinting different human tissues has become a useful resource in developing more effective pharmaceuticals as it is representative of human tissue [22]. Bioprinting poses a legitimate alternative to animal testing of pharmaceutical products, and it could improve the rate at which products are tested and approved as human - like tissue would be more readily available. Tissue - specific testing would be easier to do and more practical as it would be possible to create models of different tissue that could be targeted by pharmaceutical drugs. Ultimately, if bioprinting becomes more effective in terms of creating consistently functional human tissue, it could drastically improve the speed at which drugs are produced as they could be tested and implemented much faster.

The Impact of Bioprinting on Mechanisms of Disease -

As bioprinting includes the fabrication of many types of biological tissues, its uses are not limited to cancer. One of the most promising fields of future research involving bioprinting includes focusing on how bioprinting can aid in the determination of disease mechanisms. Specific tissues can be generated using bioprinting techniques, which could then be introduced to different diseases so that the natural history and development of the disease can be studied; the investigation of such diseases is significant as it allows for the subsequent development of revolutionary treatment plans, or improving the efficacy of common drugs or treatments. Cardiovascular diseases, for example, involve interference in highly complex bodily functions and specialized cells that perform individual functions. Acute myocardial infarction involves complicated

pathophysiological interactions in the body that ultimately result in the dysfunction of myocardium due to disorganization of the tissue [23]. In cases like this, it is imperative that diseases continue to be studied so that effective treatments can be found; the production of complex tissues is made possible by biofabrication methods such as bioprinting, which is why it is a field that should be further researched, studied and improved upon. Through increasing the understanding of the mechanisms of complex diseases, bioprinting continues to be a field of research that yields significant potential to improve upon the medical field.

3. Conclusion

Bioprinting has started to become a useful tool in enhancing cancer research as it offers more physiologically accurate models compared to 2D cell cultures and animal models. Bioprinted tumors mimic complex microenvironments of tumors including extracellular matrices, immune cell interactions, and vascular networks; this allows in depth analysis on cancer progression by allowing for cancerous hallmarks such as drug resistance and metastasis to be studied. Vascular bioprinting enables tumor progression to be studied, as treatments can be developed to target the blood supply of the tumor, which is a requirement for the tumor to survive and grow. Utilizing the techniques of bioprinting to do effective tumor modeling and vascular bioprinting are two examples of how the technology can help with the development of cancer research; with improvements in such a way, bioprinting could play an increasingly crucial role in finding effective future treatments for cancer.

Right now, challenges such as optimizing bioinks and ensuring the reproducibility of bioprinted tissues remain; however, using bioprinting to simulate tumor environments similar to what is seen in humans remains a useful method of research and has the potential to significantly improve cancer research in the future. As bioprinting technology undergoes advancement, research in the oncology field could be significantly enhanced with the ultimate goal being to bridge the gap between preclinical studies and clinical applications.

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