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Review

3D Bioprinting as an Emerging Standard for Cancer Modeling and Drug Testing

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Abstract

Neoplastic diseases are a leading cause of death worldwide accounting for 10 million mortalities in 2020. Despite constantly revised and improved therapeutic regimens, the number of fatal cases increases annually. Therefore, better preclinical models are needed to study tumorigenesis and assess new drugs. Although 2D cell cultures significantly contributed to the understanding of tumor biology, they present high clinical trial failure rates. This is because 2D cannot reproduce the intricate tumor architecture and multiple cell interactions.

Nevertheless, novel 3D biofabrication technologies and 3D bioprinted tumor models successfully mirror the complexity of human tumors and are currently revolutionizing preclinical cancer research by using live cells encapsulated in a variety of biomaterials. Since bioinks possess excellent chemical and biophysical ECM-like characteristics, this allows for recreation of the intricate tumor-specific architecture with an unmatched level of control, accuracy, and reproducibility. The resulting cellular constructs approximate actual pathological microenvironment of the tumor and some key in vivo processes such as proliferation, differentiation, and metastasis. 3D bioprinted models of glioblastoma, cervical, ovarian, and breast cancer are already being successfully used to study tumorigenesis and cellular response to antitumor drugs. This success showcases the potential of these novel experimental platforms.

Keywords

3D biofabrication, 2D cell culture, 3D technology, drug screening, preclinical models, tumor models

INTRODUCTION

Three-dimensional (3D) bioprinting is an innovative method combining computer-generated design and printing technologies with biomaterials chemistry and tissue engineering in vitro. This novel type of biofabrication presents the opportunity to create models of organoids through the controlled deposition of live cells and supporting bioinks layer-by-layer. This way the printed cells are placed in conditions closely resembling key physiological aspects in vivo like cell-cell communication and interactions with the extracellular matrix (ECM). Bioprinting is therefore of intense interest to various fields of medicine such as oncology, regenerative medicine, plastic surgery, organ, and tissue transplantation. Because of its ability to mimic the complex tumor architecture and microenvironment, this method is superior to conventional monolayer (2D) cell cultures and 3D spheroids and may at least in part replace and reduce the use of animal studies. 3D models can also recreate the heterogeneity and pathophysiology of tumors and offer important advantages for studying the dynamics of the neoplastic process, mainly unrivaled control, flexibility, and reproducibility. Therefore, 3D bioprinted models are emerging as a new standard for in vitro disease modeling, present excellent platforms for drug screening, and can contribute greatly to personalized therapy.[1]

The aim of this review is to discuss 3D bioprinting as an innovative method for studying tumorigenesis, exploring drug resistance mechanisms, and testing new chemotherapeutics. We will first discuss existing cancer models like conventional monolayer cell cultures and 3D spheroids. Then, we will focus on the variety of 3D technologies like extrusion-based, inject (drip), and laser printing, and the most commonly used biomaterials. Lastly, examples of recent 3D bioprinted cancer models will be given in the context of the future implementation of this technology in the field of cancer research.

Tumor modeling in vitro

According to the World Health Organization, neoplastic diseases are among the leading causes of death. As an example, colorectal cancer (CRC) is a predominant malignancy in developed countries accounting for approximately 10% of deaths in Western countries. Despite constantly refined treatment regimens, the number of deaths is increasing every year, with a downward trend in the age group of diagnosed patients.

Over the past 100 years in vitro techniques like 2D monolayer and 3D cell cultures or animal in vivo studies have been used with very low translatability to the clinic. [2] Until a few years ago, these preclinical experimental systems were the most widely used ones for studying tumor cell behavior and for testing drugs. Although in vivo models have an advantage over in vitro platforms, both methods have major limitations[2] and result in false positive and false negative data. This contributes to the very low rates of new drugs passing through phase III trials. Despite early drug testing, 85% of new anticancer drugs fail. Moreover, half of the antitumor drugs reaching phase III clinical trials are unsuccessful.[3] Drug resistance results in treatment failure in 90% of patients with metastatic cancer. Thus, it is of utmost importance to accurately predict the effect of treatment. Three-dimensional systems like 3D bioprinted models hold great potential to facilitate the assessment of response or resistance to antitumor therapy[4] and can offer a solution to drug failure rates by providing reliable platforms to study cancer initiation, progression, and invasion in a more realistic microenvironment to the one in vivo[5].

Conventional 2D cell cultures

The use of traditional 2D cultures in recent decades has demonstrated poor success in translating the results in vivo and in the clinic. In 2D cultures, cells are grown in monolayers on standard polystyrene surfaces (flasks, plates, or dishes) and evaluated for viability, biomarkers, and drug efficacy and resistance. Although these models have contributed significantly to our current knowledge, they have severe limitations. Namely, conventional cell cultures fail to reproduce the complexity of cell-cell communications and the interactions with the ECM. Recapitulating the tumor microenvironment (TME) with all its components (signaling molecules, proteins, various types of tumors associated cells and mechanical elements of the ECM) is critical because it affects the initiation, propagation, and metastasis of the tumors and 2D cultures fail in this area too.[6] Alterations in some aspects of the TME can change the behavior of tumor cells as well as their response to chemotherapeutics resulting in false positive or negative data. These issues are partially addressed by 3D cell culture models.[7]

3D spheroids

Spheroids are groups of cells of up to 1 millimeter in size and represent the first attempt aimed at reproducing the three-dimensional cell architecture observed in tumors.[8] Two main strategies of 3D cell cultures exist. Scaffold-based (using artificial 3D structures) and scaffold-free (no exogenous biogels are used). In scaffold-based spheroids, cell growth takes place on artificial 3D structures via two methods: (A) cells are seeded on a prefabricated cell-free matrix, (B) cells are dispersed into a hydrogel. Cell laden biomaterials (gels or scaffolds) must allow proliferation; this leads to tissue formation, which mimics more readily cell-ECM interactions. This type of spheroid is mainly used for tissue engineering.[9] Successful examples include bone and skin.[10,11] In scaffold-free spheroids no exogenous biomaterials are used. The most common technique relies on coating of culturing vessels with substances that encourage cells to interact with each other rather than with the plastic surface. When spheroids are formed, cells generate ECM themselves.

3D cultures have significant advantages over 2D. For example, spheroids share characteristics with solid tumors. These include reduced oxygen supply, hypoxic core, nutrient gradient, and increased glucose metabolism. Of note, spheroid size has been shown to correlate to chemotherapeutic resistance with underlying mechanisms similar to those seen in patients.[9] Interestingly, Wartenberg et al. reported high expression of HIF-1α and P-gp (encoding P-glycoprotein) in prostate tumor spheroids contributes to multidrug resistance. Of note, response to therapeutics improved when glucose metabolism and expression of P-gp protein were reduced in this spheroid model.[12]

Spheroids exist in two different types: homotypic (built of a single type of cells) and heterotypic (made up of different cell types). In heterotypic 3D models, it is possible to observe interactions of different cell types and study the role of the stroma. Such relationships were investigated in a 3D spheroid model of CRC. The findings demonstrated that interaction between tumor cells and fibroblasts was essential for CRC invasion.[13] In another study conducted by de la Rosa et al. the comparison between the gold standard, 2D monolayers, with 3D spheroids showed that HCT-116 colorectal cancer cells in alginate capsules demonstrated better viability, increased stem cell populations (high

expression levels of CD44) and reduced area of hypoxia (low expression of HIF-1a) compared to regular spheroid cultures.[7] The effect of standard chemotherapeutics on homotypic and heterotypic spheroids has been studied as well. Compared to monotypic, heterotypic spheroids have been shown to exhibit elevated sensitivity to some standard combinations of inhibitors (5-fluorouracil and irinotecan) and increased resistance to others (5-fluorouracil and oxaliplatin). This observation reinforces the role of the stroma and the TME in the response to therapeutic agents.[14] Although better than 2D models, 3D spheroids in their varieties (homotypic, heterotypic) have weaknesses too. As an example, the lack of vasculature creates a perfusion gradient across the spheroid which interferes with nutrients and drug delivery to its center.[15]

Improving fabrication of in vitro models via 3D bioprinting

3D bioprinting is a novel approach combining the best of 2D cultures and 3D spheroids together with cutting edge additive manufacturing technologies and the latest biomimetic materials. This method holds great potential to improve preclinical in vitro models as it offers a highly reproducible controlled spatial configuration of cells in supporting materials (hydrogel bioinks) most closely resembling the ECM and recapitulating different aspects of the TME. In this way, the development and progression of the disease can be modeled.[14]

3D bioprinting components

Three-dimensional bioprinting techniques integrate a few components: (1) live cells; (2) 3D design for creating complex structures and for determining the spatial arrangement of more than one cell types; (3) bioinks providing ECM-like contacts and mechanical support to the cells. The type of cells used depends on the model needed to be recreated. As an example, to produce 3D CRC cancer models, established colorectal cell lines such as Caco-2 cells or primary cells can be used.

Bioinks are supportive and carry materials that are composed of biopolymer gel and live cells. The choice of bioink in 3D bioprinting is based on important characteristics like printability of bioink, which is determined by its viscosity. Bioinks must be able to withstand forces applied during the printing process and to possess structural integrity post-printing. Bioinks are classified as natural, synthetic and hybrid. The variety of the most commonly used bioinks is presented in **Fig. 1**.

Naturally obtained bioinks are derived from living organisms and are a better choice because of their high biocompatibility and close recapitulation of the ECM. Matrigel™ as an example is commonly used because it is ECM based. Additionally, collagen, gelatin, fibrin chitosan, and alginate are commonly used as 3D scaffolds.[15] Synthetically produced bioinks include artificial materials and genetically engineered protein polymers. They also possess some ECM characteristics. Synthetic bioinks include Pluronic® or polyethylene glycol (PEG), polycaprolactone (PCL). They are highly modifiable and can be easily manipulated by adding integrin binding sites like arginyl-glycyl-aspartic acid (RGD). RGD is a peptide motif found in natural polymers or matrix-metalloproteinase (MMP) sites and affects cell growth in the 3D microenvironment by promoting cell adhesion.[16] Hybrid or semi-synthetic bioinks chemically modify natural materials by adding synthetic components to create a biocompatible ink. The most frequently used ones are collagen/HA, alginate/gelatine, methylcellulose/alginate.

3D bioprinting modalities

Bioprinting modalities are classified into three main groups, depending on the principle of bioink deposition. Bioink

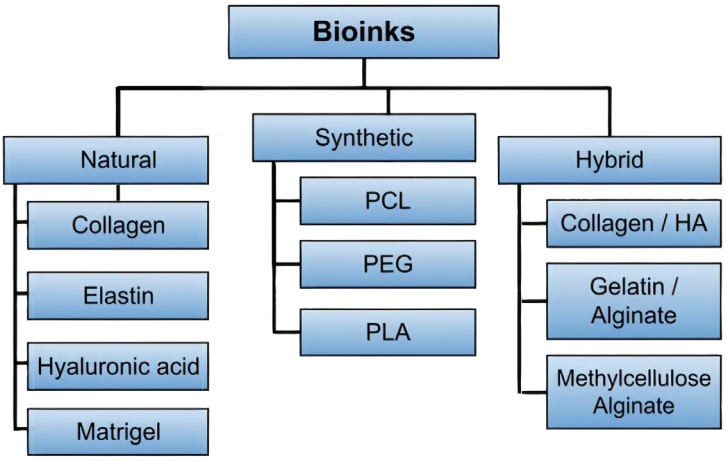

Figure 1. Types of the most commonly used bioinks.
HA: hyaluronic acid; PCL: polycaprolactone; PEG: polyethylene glycol; PLA: polylactic acid

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deposition is achieved by light-based (stereolithography (SLA), laser-assisted (LAB)), extrusion based (EBB) and droplet-based (DBB) approach. Each printing technique has its limitations. No single technique can be defined as better than others and therefore, in certain cases, combinations may be advantageous. All 3D bioprinting methods share an ability to create layer-by-layer complex 3D architectural models with a variety of medical applications.[17]

Stereolithography (SLA) is the first 3D method described. The 3D model is built layer by layer. Ultraviolet (UV) light is employed to crosslink UV sensitive fluid to build parts. The typical layer height is about 25-100 microns. The advantages of this technique are the high resolution of the fabricated model. Unfortunately, currently, only one type of material can be used when printing an item. Because of long printing time cell viability decreases.[18]

Laser assisted bioprinting (LAB) can position a single cell per droplet with great accuracy or can deploy multiple cell types. LAB can be characterized as a solid phase or as a liquid phase printing version. The advantages of LAB are high resolution and the ability to use biomaterials in different forms - solid or liquid. The drawbacks include thermal damage to the cells due to laser irritation and high cost.[19]

Extrusion based bioprinting (EBB), the most widely used type, relies on pneumatic or mechanical pressure to eject the bioink through a nozzle. EBB is an extremely flexible technique allowing for printing of various tissue structures, cells, and microfluidic chips. Like other techniques, EBB has distinct advantages including simplicity, speed, and reproducibility and printing with high cell density. Moreover, EBB ensures that up to 95% of printed cells remain viable. However, only viscous liquids can be used. The main challenge EBB is facing is how to avoid the effect that pressure upon extrusion has on cell morphology and function. This, however, can be addressed by manipulating nozzle diameter and viscosity of the bioinks.[19]

Inkjet-based bioprinting, also known as droplet printing, uses thermal or acoustic force to create droplets. Droplet spraying is performed thermally by heating or piezoelectric printing. Inkjet based bioprinting offers high fabrication speed, but low cell density and the generation of droplets can heat the print head to up to 300°C. Another challenge is to overcome unreliable cell encapsulation due to low ink concentration.[20]

3D bioprinted models for drug testing

The pharmaceutical industry faces many challenges in the process of developing and testing new drugs. The need for personalized models for individual patients and the development of precision therapy has already led to the generation of 3D bioprinted tissue models which are becoming promising tools for drug screening.[21,22] 3D bioprinted tumor models of cervical, ovarian, breast cancer, and glioblastoma have been used successfully to study tumorigenesis and cellular response to clinically relevant chemotherapeutics. It has been established that the TME affects the pharmacokinetics and dynamics of drugs. Therefore, it is not surprising that when 3D bioprinted organoids are compared to 2D cultures, these more complex models exhibit resistance to chemotherapeutics. One such example is observed in a glioma 3D bioprinted model where glioma stem cells were printed in an alginate/gelatin/fibrinogen bioink. In this experimental system, resistance to temozolomide was demonstrated compared to 2D cultures.[23] In another study, MRC-5 fibroblasts, and human ovarian tumor cells (OVCAR-5) were used in conjunction with Matrigel™ to create a co-cultured 3D model. The model was applied to study regulatory mechanisms between tumor and stromal cells, as well as to test drug sensitivity. Using their own system, the researchers followed the formation of acini and their kinetic ability up to 15 days after printing. The established 3D construct, qualitatively represents the micronodular future of ovarian cancer that exists in vivo.[24]

Using laser-based bioprinting with poly (ethylene glycol) (PEGDA) bioink together with HeLa cells and 10T1/2 (non-carcinogenic fibroblasts) a 3D model was designed, in which channels were created to study cell migration in the context of cancer metastasis. Two sets of data were obtained: cell area and cell speed in the channels. Interestingly, the cells were migrating at different speeds depending on channel width. As the width increased, the migration speed of HeLa cells decreased and with narrowing the diameter the cell speed increased. However, the migration speed of 10T1/2 cells was not changed. Thereby, the authors concluded using this complex 3D replica of capillary structure that blood vessel diameter affects the cancer cells' speed of migration.[25] Another interesting example of the possibilities that 3D bioprinting presents can be given with Organovo Inc. who developed an extrusion-based 3D bioprinted breast cancer model in which a mixture of fibroblasts, endothelial cells and adipocytes surrounded breast cancer cells. This model has been applied to test commonly used chemotherapeutics such as tamoxifen and cisplatin, as well as for testing some hormonal drugs.[26]

Stereolithography has been used to construct 3D bone matrices to study cellular relationships between breast cancer cells and bone stromal cells (osteoblasts or mesenchymal stem cells). Cells were embedded in GelMa bioinks and nanocrystalline hydroxyapatite (nHA). The interaction between breast cancer cells and stromal cells was observed and it was found that the presence of stroma could enhance the growth of breast cancer cells. Therefore, Zhou et al. developed and validated a novel model to study the mechanisms of metastasis in breast cancer.[27]

Paclitaxel is a clinically relevant chemotherapeutic agent, and its effect has been studied in a 3D in vitro model of cervical cancer. HeLa cells were used in conjunction with gelatin/alginate/fibrinogen bioink. In the developed model, cell proliferation, matrix metalloproteinase (MMP) and therapeutic response to Paclitaxel were investigated. Compared with 2D cultures, increased resistance to Paclitaxel,

high proliferation of HeLa cells with spheroid formation and augmented MMP activity were observed in this 3D bioprinted model **(Table 1)**.[28] In a scaffold-free tumor tissue with define architectural design, Langer et al. created a model using primary cells from patients with pancreatic cancer and other cell types and found that cell proliferation and migration within their model enhanced significantly, in response to the applied tumor growth factor beta (TGFβ).[26]

Table 1. Bioinks used in 3D bioprinting of cancer models

Bioink	Cells	Model	Ref.
Collagen	Glioma cell line U118	Glioblastoma	30, 31
Sodium alginate & gelatin	Human glioma stem cells U118	On-a-chip	
Matrigel	OVCAR-5 and MRC-5 fibroblast	Ovarian cancer	23
Gelatin - PEG	MCF-7 Cells	Breast cancer	24
Gelatin, alginate, and fibrinogen	HeLa cells	Cervical cancer	27
Alginate and gelatin	Stellate cells, endothelial cells	Pancreatic adenocarcinoma	28
Liver dECM	Human adult dermal fibroblasts Human perinatal fibroblasts	Hepatocarcinoma	29

Complex architecture and rich microenvironment were created in a 3D liver structure combining hexagonal lobular like structures with human iPSC-derived hepatic progenitor cells (HPCs) and supporting cells. The purpose of the study was to examine whether cell maturation and function can be promoted in the established model. Compared to 2D cell culture, the 3D model's high gene expression correlates with secretion of liver-specific proteins and corresponds to different stages of cellular maturation. By using induced human pluripotent stem cells derived from liver progenitors, the 3D bioprinted model can be refined and applied for both drug screening and follow-up of liver pathophysiology in vitro.[29]

CONCLUSIONS

Cancer diseases are associated with multifactorial pathology. The dysregulation of many genes and pathways plays a role in tumorigenesis and progression. Tumor heterogeneity creates difficulties in applying a unified therapy covering a wide range of mutations to all patients. Furthermore, the tumor stroma deserves special attention as it provides conditions favorable for growth and progression of malignant cells and can secrete growth factors which affect the outcome of chemotherapy. The role of the TME is, therefore, an important point in the development and use of anticancer drugs that must be considered when creating individual treatment regimens.

The innovative 3D bioprinted tumor models provide the possibility to control and mirror the cancer microenvironment with all its components including mechanical and flow forces. Despite the need for improvement, the superiority of 3D biomanufacturing over conventional monolayer cultures and spheroids is supported by a mounting body of evidence. The quickly evolving field of 3D bioprinting is emerging as a promising platform for studying diseases and testing new therapies and opens new horizons for personalized medicine to be exploited in the near future.

Author contributions

All authors have contributed equally.

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Conflict of Interest

The authors declare no conflict of interest.

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3D-биопринтинг как развивающийся стандарт моделирования рака и тестирования лекарств

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Резюме

Неопластические заболевания являются ведущей причиной смерти во всём мире, на их долю приходится 10 миллионов смертей в 2020 году. Несмотря на постоянно пересматриваемые и совершенствуемые схемы лечения, число смертельных случаев ежегодно увеличивается. Следовательно, необходимы лучшие доклинические модели для изучения онкогенеза и оценки новых лекарств. Хотя двумерные клеточные культуры внесли значительный вклад в понимание биологии опухолей, они демонстрируют высокий уровень неудач в клинических испытаниях. Это связано с тем, что 2D не может воспроизвести сложную архитектуру опухоли и взаимодействие нескольких клеток.

Тем не менее, новые технологии трёхмерного биопроизводства и трёхмерные биопечатные модели опухолей успешно отражают сложность опухолей человека и в настоящее время революционизируют доклинические исследования рака с использованием живых клеток, инкапсулированных в различные биоматериалы. Поскольку биочернила обладают превосходными химическими и биофизическими характеристиками, подобными внеклеточному матриксу, это позволяет воссоздать сложную специфичную для опухоли архитектуру с непревзойдённым уровнем контроля, точности и воспроизводимости. Полученные клеточные конструкции аппроксимируют реальное патологическое микроокружение опухоли и некоторые ключевые процессы *in vivo*, такие как пролиферация, дифференцировка и метастазирование. Трёхмерные биопечатные модели глиобластомы, рака шейки матки, яичников и молочной железы уже успешно используются для изучения онкогенеза и клеточного ответа на противоопухолевые препараты. Этот успех демонстрирует потенциал этих новых экспериментальных платформ.

Ключевые слова

3D-биофабрикация, 2D-культура клеток, 3D-технология, скрининг лекарств, доклинические модели, модели опухолей