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A comparative review on the resolution of 3D bioprinting over 2D cell cultures in cancer models

(Una revisión comparativa sobre la resolución de la bioimpresión 3D sobre cultivos celulares 2D en modelos de cáncer)

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Abstract(english)

The tumor microenvironment, composed of non-neoplastic cells and the extracellular matrix, plays a pivotal role in cancer progression. Traditional two-dimensional (2D) cell cultures fail to capture its complexity, resulting in disparities in drug responses compared to three-dimensional (3D) models. Recent research highlights the precision of 3D bioprinted cancer models, revolutionizing cancer research. 3D bioprinting offers diverse applications, including personalized tumor models for individualized drug testing. These models replicate physiological conditions, providing accurate drug screening for efficacy and toxicity. It also facilitates the study of metastasis mechanisms and therapeutic target identification. Moreover, 3D bioprinting aids in optimizing cancer treatments, such as gene and immunotherapies, and allows precise drug delivery to cancer cells. It supports medical education with realistic training tools and offers an ethical alternative to animal testing, potentially reducing its necessity in cancer research. In essence, 3D bioprinting is advancing cancer research by providing highly accurate models that closely mimic the tumor microenvironment, enhancing personalized medicine, drug screening, therapeutic development, and education. The present review delves into the multifaceted applications of 3D bioprinting in cancer research while exploring future directions and innovations in 3D bioprinting for Cancer Models.

Keywords(english)

3D bioprinting; Cancer; 2D methods; Animal models; Drug testing.

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Resumen(español)

El microambiente tumoral, compuesto por células no neoplásicas y la matriz extracelular, desempeña un papel fundamental en la progresión del cáncer. Los cultivos celulares bidimensionales (2D) tradicionales no logran captar su complejidad, lo que resulta en disparidades en la respuesta a los fármacos en comparación con los modelos tridimensionales (3D). Investigaciones recientes destacan la precisión de los modelos de cáncer bioimpresos en 3D, revolucionando la investigación oncológica. La bioimpresión 3D ofrece diversas aplicaciones, incluyendo modelos tumorales personalizados para el análisis individualizado de fármacos. Estos modelos replican las condiciones fisiológicas, proporcionando un cribado preciso de fármacos para su eficacia y toxicidad. También facilita el estudio de los mecanismos de metástasis y la identificación de dianas terapéuticas. Además, la bioimpresión 3D ayuda a optimizar los tratamientos contra el cáncer, como las terapias génicas y las inmunoterapias, y permite la administración precisa de fármacos a las células cancerosas. Apoya la formación médica con herramientas de formación realistas y ofrece una alternativa ética a la experimentación con animales, reduciendo potencialmente su necesidad en la investigación oncológica. En esencia, la bioimpresión 3D está impulsando la investigación oncológica al proporcionar modelos de alta precisión que imitan fielmente el microambiente tumoral, mejorando la medicina personalizada, el cribado de fármacos, el desarrollo terapéutico y la educación. La presente revisión profundiza en las aplicaciones multifacéticas de la bioimpresión 3D en la investigación del cáncer, al tiempo que explora futuras direcciones e innovaciones en la bioimpresión 3D para modelos de cáncer.

Palabras clave(español)

Bioimpresión 3D; Cáncer; Métodos 2D; Modelos animales; Pruebas de fármacos

Introduction

Cancer stands as a leading cause of human mortality, with oncology emerging as the pharmaceutical industry's most expansive therapeutic domain, marked by numerous projects, clinical trials, and substantial research investments (1). The intricate and resource-intensive journey to develop new anticancer agents is characterized by complexity, time constraints, and high costs, leading to a notable attrition rate. The standard developmental trajectory for anticancer drugs encompasses a preclinical phase followed by three clinical phases. Presently, regulatory preclinical studies, integral to translational cancer research, heavily rely on two-dimensional (2D) cell cultures and animal models, despite their inherent limitations in capturing the full complexity of cancer biology (2).The tumor stroma consists of abundant extra cellular matrix along with other supporting cells like cancer-associated fibroblasts (CAFs), endothelial cells, pericytes and immune cells. While these cells and matrix forms the major part, a less prevalent population of myeloid-derived suppressor cells (MDSCs), platelets and mesenchymal stromal cells (MSCs) also forms a part of the non-neoplastic part of the tumor microenvironment (3). The orchestrated interactions that occur between the tumor microenvironment and the surrounding stroma result in the poor clinical outcome and the aggressive nature of the tumor. Recent researches developed the evidence that the activated stroma plays a pivotal role in angiogenesis, metastasis, drug resistance, stem cell maintenance and immunosurveillance evasion (4).The loss of this pivotal cellular interaction within the 2D cell culture model not only affects the morphological characteristics but also impart differences in crucial biological events such as proliferation, gene/ protein expression and apoptosis when compared to that of 3D cell culture model (5). Considering the pitfalls associated with 2D cell culture and animal models, the present review is attempted to explore the wide applications of 3D bioprinting and its advantages over traditional cancer models.

Applications of 3D bioprinting

1. In tumor cell complexity: The conventional 2D cancer models inadequately capture the intricate and dynamic interplay between the tumor microenvironment and the surrounding stroma, falling short of replicating their complex interactions accurately (6). 3D bioprinting allows researchers to create highly complex and realistic tumor models. Unlike traditional 2D cell cultures, which are flat and lack the three-dimensional architecture found in the human body, 3D bioprinted models can mimic the complex structures of tumors, and the advantages of 3D model over 2D model is given in Figure 1. Langer et al created an in vitro cancer model, incorporating cancer cells along with a variety of stromal cell layers by using Organovo's Novogen MMX system. It was found that cancer cells within this model reacted to the signals from these stromal cells, forming extracellular matrix and organize themselves as the tissue matures. As this model replicated the heterogeneity of the tumor

microenvironment, the interaction of different cell populations within the tumor microenvironment was clearly elucidated (7).

Addressing the dynamic nature of the extracellular matrix (ECM) is a significant challenge in in vitro modeling. Customizing material properties to align with the physiological process is essential. For instance, in Digital Light Processing (DLP) based printed cardiac microtissues using methacrylated gelatin (GelMA) scaffolds, meticulous adjustment of crosslinking density synchronized scaffold degradation with ECM deposition by human cardiac fibroblasts (HCF). GelMA and other components in varying concentrations were added to form prepolymer solutions, tailored for specific mechanical and biological properties, aligning with each layer's function in 3D-printed constructs. This synchronization supported the maturation and contraction of the artificial tissue over a week (8). For enhanced mimicry, an artificial tissue can be combined with a dynamic culture system. In a study conducted by Fang et al., a microfluidic chip incorporating pressure channels was devised for culturing colon tumor organoids, replicating the peristaltic motion characteristic of their natural environment. This approach notably boosted organoid proliferation and size compared to static cultures, as media flowed through the pressure channels and provided mechanical stimulation. Peristaltic-stimulated organoids also exhibited reduced absorption and response to ellipticine-laden micelle dosing, suggesting that accurately mirroring extracellular matrix (ECM) dynamics can profoundly impact the in vitro model's reactions to drugs and toxins (9).

3D bioprinting involves the precise deposition of bioinks, which can include tissue spheroids, cell pellets, microcarriers, decellularized ECM components, and cell-laden hydrogels, layer by layer. This process follows a computer-designed structure to create living 3D constructs (10). To precisely regulate biochemical cues within scaffolds, researchers have engineered synthetic materials with customized biomolecules. In a collaborative study led by Taubenberger et al., they decorated PEG with various bioactive elements, including metalloproteinase-cleavable sites, ECM-mimicking cell adhesion peptides, and growth factors. This versatile platform enabled the creation of an in vitro bio-microenvironment with multiple controlled biochemical signals and matrix mechanical properties (11).Examining 3D tumoroids in biomimetic collagen I hydrogel, recent research delved into the unclear origin of early cancer invasion, revealing those fluctuations in invading protrusions and their interactions with the microenvironment correlate with tumor invasion. Notably, protrusion dynamics were identified as a novel

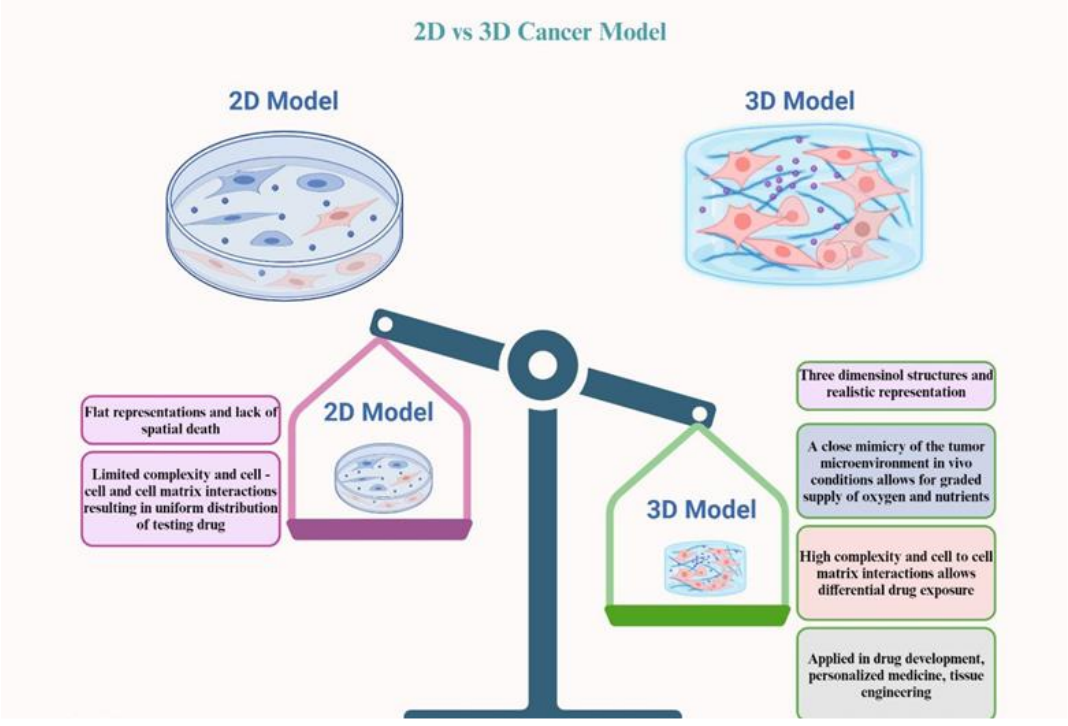

Figure 1. Advantages of 3D over 2D model

biophysical signature for tumors' metastatic potential (12). 3D cultures, in particular, offer greater precision in managing interactions among cells and between cells and their surrounding matrix. This includes the ability to fine-tune mechanical attributes like stiffness and fluid flow, modify the extracellular matrix (ECM) composition, introduce specific biochemical factors, and adjust tissue density. In sum, 3D cultures empower researchers to customize the microenvironment to closely mimic the characteristics of the target tissue or organ (13,14).

2. In drug screening: 3D bioprinted tumor models provide a more physiologically relevant environment for drug testing compared to traditional cell cultures. This can lead to more accurate predictions of how drugs will perform in the human body. In native tumor tissues, the interaction between tumor cells and endothelial cells (ECs) directly influences nutrient and metabolite transport. When ECs are co-cultured with cancer cells and stromal cells in a 3D system, they establish robust vascular networks and exhibit enhanced cellular functions compared to 2D cultures (15). In an effort to replicate the intricate liver tumor microenvironment, Fan et al., conducted a co-culture of human umbilical vein endothelial cells (HUVECs) and C3A (clonal derivative of HepG2 cells)cells to build an endothelialized liver cancer model. They successfully produced this constructs by combining GelMA and gelatin microbead printing. This combination offers structural stability as GelMA integrates well with gelatin, while providing ample cell attachment sites for HUVECs to adhere quickly during the sacrificial phase and promoting cell organization and network formation within the 3D structure. The developed models exhibited a notable increase in the effectiveness of Sorafenib when contrasted with either mono-cultured liver cancer constructs or 3D C3A spheroids. This improvement is likely attributed to the intact endothelial barrier structure hindering Sorafenib diffusion (16).

Researchers can assess not only the efficacy of potential cancer drugs but also their toxicity within these models. This information is crucial for drug development and clinical trial design. The complexity of native tissues, notably their high vascularity, is crucial for assessing toxicity. Massa et al, employed extrusion-based 3D printing to create a vascularized liver model with perfusable channels, featuring an endothelial barrier. This model was used to study the toxicity of acetaminophen, which harms liver sinusoid endothelial cells. It enabled testing the drug's effects on both the endothelial layer and the protected HepG2/C3A cells, offering a more realistic in vivo exposure simulation (17).Recent studies have demonstrated that cancer cells grown in 3D cell cultures are less sensitive to anti-cancer drugs when compared to that of their 2D counterparts. This difference in pharmacological responses may lead to higher rate of failure in drug discovery research as many of the drug screening analysis were conducted in 2D cell culture models. The complexity and microenvironmental factors of 3D cell cultures more closely resemble the in vivo conditions found in tumors, making them valuable for studying drug resistance mechanisms and for testing the effectiveness of anti-cancer drugs (18,19). The most frequently utilized 3D cancer models for drug testing include multicellular tumor spheroid model (MCTS), multilayered cell cultures, organotypic slices of cancer tissue, and cell seeded scaffolds (20).

The construction of in vitro tumor models necessitates a crucial requirement, a high level of cellular activity. Keeping this in mind, Duanet al., created a 3D bioprinted GelMA and polyethylene glycol diacrylate (PEGDA) scaffolds, with a 10/2.5% ratio, featured 10x10x1.2 mm dimensions, 0.8 mm spacing, and 6 layers, in their study. After printing, blue light shaped the scaffolds, followed by 24h UV sterilization. Deionized water rinses and storage prepared the scaffolds for cell experiments. The cell counting kit-8 (CCK8) assays were employed to assess cell proliferation in both 2D and 3D scaffold cultures. In the initial stages, cells tend to adhere and proliferate more readily on flat surfaces. However, with prolonged culture, 2D scaffolds exhibit faster cell contact inhibition as cells continue to multiply. In contrast, the three-dimensional structure of 3D scaffolds offers a greater surface area for cell growth, facilitating enhanced proliferation. In comparison to 2D scaffolds, 3D scaffolds prove to be more effective in promoting the aggregation and growth of tumor cells. Within the 3D culture system, A375 cells exhibited increased drug resistance, thus documenting that, the utilization of 3D-bioprinted cell mass models presents a novel avenue for constructing in vitro tumor models and conducting anticancer drug screening, showing significant promise for future advancements (21).

3. In Personalized Medicine: With 3D bioprinting, it's possible to create patient-specific-cancer models using a patient's own cancer cells. This enables the development of models that closely resemble the individual patient's cancer, allowing for personalized drug testing and treatment optimization. Exploration of multiple chemotherapeutic drugs through patient-specific bioprinted cancer models has

the potential to pinpoint the most effective combination of drug candidates tailored to individual patients. This approach takes into account not only the molecular subtype of the tumor, but also factors like age, gender, and ethnicity, enhancing the understanding of drug effectiveness and mechanisms. Furthermore, it facilitates the identification of optimal drug dosages, paving the way for more precise and patient-centric cancer treatments. Various cancer cell types, encompassing primary cancer cells, circulating tumor cells (CTCs), and stromal cells like fibroblasts, endothelial cells, and stem cells, can be employed for the fabrication of personalized tumor constructs (Figure 2). Wake et al., created urologic cancer models by converting the image segments of kidney and prostate cancer into surface mesh and exporting them in 3D PDF, standard tessellation language(.stl) and Alias/Wavefront(.obj) formats for direct visualization, multi-colored 3D printing and Augmented Reality(AR) programming and visualization respectively for patient education before and after their treatment procedures. They used Likert-scale survey to assess patient understanding of disease and procedure. Compared to the other two methods, patients demonstrated significantly improved comprehension and comfort when utilizing 3D printed models across various aspects, including understanding their disease, grasping cancer size, identifying cancer location, comprehending their treatment plan and level of comfort with the treatment plan. By testing potential treatments on patient-specific models, researchers can identify the most effective therapies while minimizing adverse effects, leading to more personalized and targeted cancer treatments (22).

4. Automated high-throughput assays: There is ample evidence to suggest that 2D cell cultures often fall short in accurately replicating the intricacies of complex diseases and tissue responses. Particularly in drug discovery and development, automated high-throughput assays for metabolism and toxicity are essential. Currently, 2D cell cultures in multi-well plates are used for high-throughput screening (HTS), but quantification techniques like absorbance and fluorescence measurements require extensive standardization. Therefore, the transition to 3D models is frequently considered pivotal. HTS has made notable strides, benefiting from advancements in molecular biology and genomics, leading to well-defined disease models and scalable bioreactors (23). Among various bioprinting methods, droplet-based bioprinting (DBB) is well-suited for HTS. It can deposit bioinks in a highly synchronized manner, maintaining high cell viability. Laser-based bioprinting (LBB) can achieve throughput rates of up to 20 Hz but may experience droplet instabilities at high frequencies. DBB shows significant potential for generating tumor tissue models for HTS, even in standard 384- and 1536-well plate sizes (24,25).

5. Metastasis Research: Metastasis is a critical aspect of cancer progression. 3D bioprinted models can be used to study how cancer cells invade nearby tissues, enter the bloodstream, and establish secondary tumors at distant sites. By understanding the mechanisms of metastasis within these models, researchers can identify potential targets for therapies aimed at preventing or treating metastatic cancer.3D cultures, in particular, offer greater precision in managing interactions among cells and between cells and their surrounding matrix. This includes the ability to fine-tune mechanical attributes like stiffness and fluid flow, modify the extracellular matrix (ECM) composition, introduce specific biochemical factors, and adjust tissue density. Overall, 3D cultures empower researchers to customize the microenvironment to closely mimic the characteristics of the target tissue or organ (13,14). A study conducted by Menget al., introduced a 3D bioprinted tumor model platform with functional vasculature and stromal elements, accompanied by programmable laser triggered EGF (Endothelial Growth Factor) release capsules. This innovative model system allows dynamic exploration of metastatic processes and drug screening. Notable advantages over traditional 2D cultures include matrix remodeling with fibroblasts, realistic vascular networks for drug testing and the collection of circulating tumor cells (CTCs) involved in metastasis. Unique features comprise a developed vasculature, spatially defined tumor sites, material flexibility, and temporal control through programmable capsules (26).

6. Therapeutic Development: Bioprinted models serve as valuable tools for optimizing cancer treatments, including immunotherapies and gene therapies. Scientists can fine-tune treatment protocols and delivery methods within these models. Immunotherapy has revolutionized cancer treatment with approaches like cancer vaccines, cytokine therapies, immune checkpoint inhibitors, and adoptive cell transfer. The latter involves extracting immune cells, such as macrophages, T cells, or natural killer (NK) cells, from peripheral blood and reintroducing them into the patient to enhance existing immune responses, marking significant progress in cancer care (27-29). NK cell-based immunotherapy is gaining interest due to its safety profile, minimal side effects like cytokine release syndrome, neurotoxicity, and low risk of graft-versus-host disease. Despite these benefits, challenges exist, which includes achieving a high expansion rate of

immune cells with viability, effective targeting, proper homing to the tumor site, and maintaining activity in the tumor microenvironment, impacting long-term anti-tumor efficacy (30-32). Various efforts have focused on enhancing the functions of immune cells using 3D culture systems and driving immune cells to the tumor site (33).

3D bioprinting is adept at creating 3D culture systems and clinical applications, including structures for insertion into tumor resection sites. Macropores formed through bioprinting facilitate the transport of oxygen, nutrients, and essential cytokines. The automatic processing of 3D bioprinting offers a faster alternative to traditional methods, making it a promising off-the-shelf product platform. Pore-forming hydrogels created through 3D bioprinting with NK cells enhance cell viability, proliferation, and activities, particularly in immunotherapy (32). While macropores formed through bioprinting facilitate the efficient transport of oxygen, nutrients, and essential cytokines, intentionally formed micropores can enhance NK cell aggregation, promoting improved cell viability, lysis activity, and cytokine release in a 3D bioprinted system (34). The extracellular matrix-like structure of hydrogels aids in enduring the harsh conditions of the tumor microenvironment, amplifying NK cell activities and preventing recurrence and metastasis post-tumor resection (35, 36).

Future perspective

In Precise Delivery: Anticancer drugs encounter challenges in reaching their target due to potential toxicity in noncancerous organs. Traditional delivery methods, like oral or intravenous administration, face solubility issues. 3D-printed scaffolds, utilizing polymers like PCL and PLGA, offer a solution, serving as patches with defined drug release over four weeks, improving patient acceptance (37). These models enable precise delivery of nanoparticles and nanomedicine to cancer cells and facilitate the evaluation of the therapeutic potential of these tiny particles. Maher et al.employed 3D printing for titanium implants with micro and nanosurface topography, promoting osseo-integration and localized delivery of doxorubicin and Apo2L/TRAIL for targeted chemotherapy in bone cancers, accompanied by the added benefit of fracture support(38).Chen and colleagues created a 3D-printed microfluidic chip with a multichannel helical structure, for the administration of combinational chemotherapeutics by swift mixing, which demonstrated a synergistic cytotoxic effect on

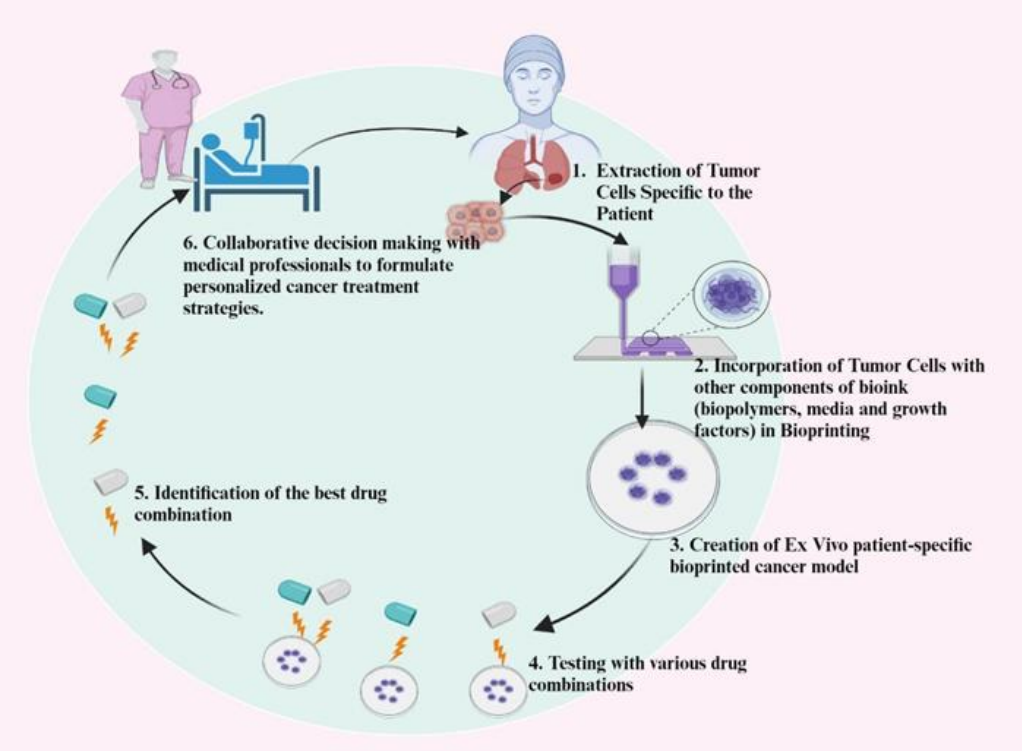

Figure2. Process of personalized drug testing and treatment optimization using 3D bioprinting

A459 cells(39). Utilizing 3D-printed templates for radioactive source placement proves more effective than conventional planning techniques. These templates improve the precision of dose distribution and notably reduce implementation time, underscoring their superior performance (40). Addressing the complexities of fatal diseases like cancer necessitates the development of a meticulously designed, personalized therapeutic system. The imminent fusion of 3D printing and nanotechnology holds promise for creating such intelligent and tailored solutions in the near future.

Education and Training: Medical students and healthcare professionals can use 3D bioprinted cancer models for hands-on training and practice. This can include simulating surgical procedures, radiation therapy, and other treatment modalities. Individual based (IB) models are extensively employed in mathematical oncology and various biomedical systems research due to the realistic simulations they provide, extending their applicability across diverse scientific domains. They focus on solid tumor growth, tumour-immune interactions, invasion and metastasis (41-44). Macnamara et al. using their computational IB Model illustrated the interaction between a growing solid tumor and pre-existing vasculature, examining the impact of oxygen diffusion from the blood vessel network on cancer cell growth (41). Chiu et al. demonstrated the utility of 3D printing in interstitial brachytherapy training programs by creating low-cost, reusable phantoms. These phantoms, with a material cost of approximately USD 23.98 and a preparation time of 1.5–2 hours each, offer a cost-effective means to acquire procedural skills in brachytherapy (45).While 3D postprocessed images surpass traditional 2D sets, they often lack adequate information for surgical simulation. Medical 3D printing offers advanced solutions for preoperative planning challenges (46). In preoperative planning, the versatility of viewing 3D models from any angle proves beneficial. These models aid in determining optimal endograft placement, minimizing surgical risks. Surgeons leverage the detailed anatomical insights offered by 3D models to address critical issues, such as accurately locating pseudoaneurysm lumens (47).

Ethical Alternatives: Genetically Engineered Mouse Model (GEMM), a pivotal asset in cancer research, outshines cancer cell inoculation models by developing authentic tumors within a natural, immune-proficient microenvironment. These tumors closely emulate histopathological and molecular characteristics of their human counterparts, exhibiting genetic diversity and the ability to progress spontaneously to metastatic disease (48). Patient - Derived Xenograft (PDX) models, comprising immunodeficient mice engrafted with patients' cancer cells or tissues, are developed under the assumption that they faithfully replicate the original tumors. These models ensure biological stability, accurately mirroring histopathology, gene expression, genetic mutations, inflammation, and therapeutic responses. Consequently, PDX models play a crucial role in assessing human tumor biology, identifying therapeutic targets, and conducting preclinical screening for diverse cancers (49). The creation and validation of Patient-Derived Xenograft (PDX) and Genetically Engineered Mouse Models (GEMMs) are costly, time-intensive, and resource-demanding. Additionally, they have a relatively low throughput and face growing ethical scrutiny due to the increasing emphasis on replacement solutions aligned with the principles of the 3Rs in animal experimentation (50). Bio printed models indeed hold significant promise as an ethical alternative to animal testing in various fields, including cancer research. The traditional use of animals in experimentation has raised ethical concerns regarding animal welfare, and there is a growing interest in developing alternative methods that can provide reliable data without causing harm to animals.

Conclusion

In summary, 3D bioprinting is a versatile technology that enables the creation of highly realistic and personalized cancer models. These models provide valuable insights into cancer biology, drug development, and treatment strategies, ultimately advancing our ability to understand and combat this complex disease. While these models often focus on isolated interactions between individual components of the tumor microenvironment (TME) and tumor cells, they do not fully replicate the intricate complexity of the tumor stroma in vitro. Nonetheless, ongoing developments in new models hold promise for enhancing drug discovery, serving as robust platforms for drug evaluation and facilitating the creation of personalized cancer treatment strategies, in an ethical and scientifically robust manner.

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Conflict of Interest

The authors declare that there is no conflict of interest in the content of this article.

Author's contribution

MPS drafted the manuscript
JA edited and reviewed the manuscript

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