Dean&Francis
ISSN 2959-409X

3D Bioprinting of Tumor Microenvironment (TME) Models: Advances, Applications, and Challenges

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Abstract:

This study examines the emerging role of three-dimensional (3D) bioprinting in constructing physiologically relevant tumor microenvironment (TME) models. By synthesizing recent advances in bioprinting strategies, bioink development, immune–tumor integration, and vascularization techniques, the analysis highlights how engineered spatial precision and controlled multicellular organization enhance the accuracy of cancer modeling. The findings indicate that 3D bioprinted TMEs provide improved platforms for studying tumor heterogeneity, therapy resistance, and drug response dynamics. Despite these strengths, challenges remain in achieving stable perfusion, standardizing bioink properties, and reproducing dynamic in vivo conditions. Future work should focus on integrating microfluidic systems, optimizing bioink formulations, and advancing interdisciplinary collaboration. Overall, this study underscores the value of 3D bioprinting as a transformative tool for oncology research and the development of more predictive preclinical models.

Keywords: 3D bioprinting; tumor microenvironment; bioinks; cancer modeling

1. Introduction

The tumor microenvironment (TME) plays a decisive role in cancer progression, metastasis, and therapeutic resistance. Conventional two-dimensional (2D) cell cultures fail to capture the intricate cellular architecture and biochemical interactions among cancer cells, stromal cells and the extracellular matrix (ECM) [1]. Although animal models provide some physiological relevance, they suffer from species differences, limited control over microenvironmental parameters and ethical considerations [2]. To overcome these challenges, three-dimensional (3D) bioprinting has emerged as a transformative approach: via computer-aided design (CAD) it fabricates complex tissue constructs layer by layer, permitting precise spatial deposition of cells, biomaterials ("bioinks") and growth factors [3]. This technology enables reconstruction of tissue-like structures with defined geometry and microenvironmental cues. Unlike random cell seeding methods, 3D bioprinting permits fine control over cell distribution, scaffold

ISSN 2959-409X

architecture, and heterotypic interactions, including tumor–stroma communication and cell–matrix crosstalk [4]. Such control has profound implications for modelling the TME, because it allows researchers to probe how cancer cells respond to microenvironmental gradients, mechanical cues and cell–cell signalling under physiologically relevant conditions. In sum, 3D bioprinting holds promise as an advanced platform to mimic the complexity of the TME and to advance research in tumour biology and drug screening.

2. Literature Review

2.1 Applications in TME Construction

Recent advances in three-dimensional (3D) bioprinting have demonstrated its powerful ability to reconstruct the complexity of the tumor microenvironment (TME), thereby providing more physiologically relevant platforms for disease modelling and drug discovery. For example, extrusion-based, multi-nozzle bioprinting has been used to spatially pattern triple-negative breast cancer cells, endothelial cells (ECs), and cancer-associated fibroblasts (CAFs) in biomimetic extracellular matrix (ECM) bioinks, faithfully reproducing the spatial heterogeneity of the tumour. In these models, regions of dense cancer cell clusters are embedded adjacent to stroma with microvessel-rich structure, enabling the study of angiogenesis, ECM remodelling, and spatially mediated drug resistance [5]. Another study used microextrusion bioprinting to generate breast cancer constructs with distinct cancer and stromal compartments, leading to hypoxic core formation, ECM deposition by CAFs, and increased stiffness over time; importantly, the presence of CAFs conferred radiotherapy resistance, recapitulating in vivo tumor-stroma interactions [6]. Furthermore, researchers have developed vascularized and immune-integrated bioprinted models, incorporating perfusable vasculature and immune cells such as T lymphocytes, to assess chemotherapeutic and immunotherapeutic responses. In one such platform, the model exhibited angiogenesis, cancer cell invasion, and even effective recruitment and infiltration of chimeric antigen receptor T (CAR-T) cells under flow, offering a dynamic system for personalized therapy testing [7]. These innovations illustrate how 3D bioprinting can simulate not only the physical architecture but also the functional interplay of the TME, improving the fidelity of preclinical drug evaluation.

2.2 Advances in Bioink Development

Bioinks are the cornerstone of bioprinting, critically determining structural fidelity, mechanical stability, and cellular functionality. Natural polymers—such as alginate, gelatin methacryloyl (GelMA), hyaluronic acid (HA), and collagen—provide excellent biocompatibility and cell adhesion sites, making them widely used in cancer-model bioprinting [8]. However, these materials often lack the mechanical robustness required for long-term stability. Synthetic materials, including polyethylene glycol (PEG) and polycaprolactone (PCL), offer superior printability and mechanical strength, but they typically lack biological signaling cues. To address these limitations, researchers increasingly develop hybrid bioinks that combine natural and synthetic components, aiming to balance biological performance with printability and stability [9].

Recent innovations include stimuli-responsive bioinks that dynamically modulate stiffness or porosity in response to external cues (e.g., pH, temperature, or ionic strength), thereby more closely mimicking the evolving characteristics of the tumour extracellular matrix (ECM) during cancer progression [9]. Such “smart” bioinks enable modelling of how changes in ECM stiffness or biochemical gradients influence tumour invasion, metastasis, and treatment response. Yet, a fundamental challenge remains: achieving a trade-off between biological activity and printability. Increasing mechanical strength or responsiveness often comes at the cost of cell viability or proper cross-linking. As a result, the field continues to refine hybrid formulations—tuning polymer ratios, crosslinking strategies, and filler materials—to optimize both the bioprinting performance and the capacity of bioinks to faithfully recreate the tumour microenvironment.

2.3 Immune–Tumor Integration and Vascularization Challenges

The integration of immune components into three-dimensional (3D) bioprinted tumor microenvironment (TME) models has become a critical frontier in cancer research. Incorporating immune cells such as macrophages, fibroblasts, and T lymphocytes (T cells) enables better simulation of the immunosuppressive and immunomodulatory landscape of real tumours, facilitating the study of mechanisms of immune evasion, cytokine signalling, and resistance to immunotherapy [10]. These multicellular systems more accurately reflect how tumor-stromal and tumor-immune interactions drive cancer progression and therapeutic outcomes.

However, one of the most persistent challenges in these

models is establishing functional and stable vasculature. Without well-developed microvascular networks, nutrient diffusion and oxygen transport are severely limited in larger constructs, leading to hypoxia and necrosis [11]. Current strategies attempt to address this by co-printing endothelial cells with proangiogenic growth factors or by integrating microfluidic channels to mimic perfusion or blood flow [12]. Despite these advances, achieving long-term vascular stability, proper lumen formation, hierarchical branching, and sustained perfusion remains difficult [11].

In addition to biological and engineering difficulties, another barrier is the lack of standardization across studies. Variability in bioprinting parameters — including printer resolution, bioink composition, crosslinking methods, and printing speed — impedes reproducibility between labs [10]. Without harmonized protocols and quality-control standards, it is challenging to compare results or translate 3D bioprinted TME models to more predictive preclinical platforms. Therefore, establishing universal guidelines and best practices for immune–vasculature integration will be essential for the future translational success of these models.

3. Discussion

3.1 Strengths and Current Capabilities of 3D Bioprinted TME Models

Three-dimensional (3D) bioprinting has emerged as a powerful tool that bridges engineering precision with biological relevance in cancer microenvironment research. Unlike traditional in vitro systems such as two-dimensional cultures or random spheroid formations, bioprinted constructs provide exceptional control over spatial arrangement, allowing researchers to dictate the exact positioning of cancer, stromal, endothelial, and immune cells. This spatial specificity enables the recreation of tumor heterogeneity, including gradients of hypoxia, nutrient availability, and extracellular matrix density. Such characteristics are essential for understanding how tumor cells adapt to microenvironmental pressures and develop therapeutic resistance.

In addition, 3D bioprinting allows precise modulation of mechanical cues and scaffold stiffness, which are known to influence cancer proliferation, invasion, and drug responsiveness. The ability to integrate multiple biomaterials offers further flexibility, enabling the construction of models that mimic tissue-specific extracellular matrix components. Bioprinted platforms also support the incorporation of biochemical gradients, which can approximate the signaling landscapes found in vivo and facilitate the study of tumor–stroma communication.

Another key advantage is the capacity to include diverse cell populations in a controlled manner. By incorporating stromal fibroblasts, vascular cells, and immune components, bioprinted tumor microenvironments can simulate complex interactions such as immune suppression, angiogenic signaling, and matrix remodeling. These advancements collectively make bioprinted models highly suitable for drug screening, therapeutic testing, and mechanistic studies. Although not yet perfect replicas of in vivo tumors, current capabilities demonstrate clear superiority over conventional approaches and highlight the transformative potential of bioprinting in oncology research.

3.2 Remaining Limitations and Future Development Directions

Despite substantial progress, significant challenges must be addressed before 3D bioprinted tumor microenvironments can become standardized and broadly accepted preclinical tools. One major limitation is the incomplete integration of functional vasculature and immune components. Current constructs often struggle to maintain stable perfusion, oxygen distribution, or long-term immune cell viability, resulting in microenvironments that only partially replicate the physiological conditions of real tumors. Without dynamic blood flow or continuous immune surveillance, the predictive accuracy of these models remains constrained.

Another challenge lies in the static nature of most bioprinted systems. Tumors in vivo experience constant mechanical changes—such as shear stress, interstitial flow, and tissue deformation—that influence signaling pathways and drug response. Present models infrequently replicate these dynamic elements, limiting their ability to simulate treatment scenarios or metastatic processes. Furthermore, inconsistencies in bioink composition, crosslinking conditions, and printing parameters create batch-to-batch variability that hampers reproducibility and slows clinical translation.

Looking ahead, interdisciplinary collaboration will be essential. Engineers can refine printing technologies to improve resolution and dynamic control, while materials scientists can design bioinks with more predictable behavior and enhanced biological functions. Oncologists can provide insights into clinical relevance and model validation. Emerging technologies, such as artificial intelligence-driven optimization of printing parameters or automated bioink formulation, may further enhance precision

ISSN 2959-409X

and scalability. In addition, coupling 3D bioprinting with organ-on-chip microfluidic systems could introduce perfusion and mechanical dynamics, producing more physiologically faithful tumor models. Establishing widely accepted validation metrics and quality-control standards will ultimately accelerate adoption and pave the way for clinical integration.

4. Conclusion

This study aimed to investigate the potential of three-dimensional (3D) bioprinting to construct tumor microenvironment (TME) models that better replicate in vivo biological complexity. The findings indicate that 3D bioprinting enables precise spatial control, multi-cellular integration, and microenvironmental customization beyond what conventional in vitro systems can achieve. The analysis revealed that advances in bioink development, immune–tumor co-culture, and vascularization strategies collectively enhance the physiological relevance of bioprinted constructs, which supports the initial hypothesis that 3D bioprinting can serve as a transformative platform for cancer modeling and therapeutic testing.

This research contributes to the existing body of knowledge by synthesizing recent developments across engineering, biomaterials, and cancer biology, thereby addressing gaps identified in earlier literature regarding model heterogeneity and reproducibility. The findings extend previous theories by providing evidence that engineered spatial organization, dynamic biophysical cues, and controlled cell composition significantly influence tumor behavior, offering clearer conceptual frameworks for understanding TME-driven therapy resistance. Practically, this study has important implications for oncology research and drug discovery, as more physiologically relevant tumor models can accelerate preclinical screening, improve prediction accuracy, and support personalized treatment strategies.

However, this study is limited by the variability of current bioprinting protocols, the incomplete vascularization achieved in existing models, and the scarcity of long-term dynamic simulations, which may affect the generalizability of the conclusions. Future studies could focus on integrating microfluidic perfusion, improving bioink standardization, and incorporating artificial intelligence to optimize printing parameters and automate validation. In the future, the author will also explore hybrid bioprinting–organ-on-chip platforms to enhance physiological fidelity.

Overall, this study provides new insights into the capabilities and challenges of 3D bioprinted TME models and highlights the importance of interdisciplinary approaches for advancing cancer research. By shedding light on the biological and engineering dimensions of bioprinting, this work paves the way for more robust, reproducible, and clinically meaningful tumor modeling systems.

References

[1] Datta, P., Dey, M., Ataie, Z., Unutmaz, D., & Ozbolat, I. T. (2020). 3D bioprinting for reconstituting the cancer microenvironment. Npj Precision Oncology, 4(1), 18. https://doi.org/10.1038/s41698-020-0121-2

[2] Dong, Y., Zhou, X., Ding, Y., Luo, Y., & Zhao, H. (2024). Advances in tumor microenvironment: Applications and challenges of 3D bioprinting. Biochemical and biophysical research communications, 730, 150339. https://doi.org/10.1016/j.bbrc.2024.150339

[3] Parodi, I., Di Lisa, D., Pastorino, L., Scaglione, S., & Fato, M. M. (2023). 3D Bioprinting as a Powerful Technique for Recreating the Tumor Microenvironment. Gels, 9(6), 482. https://doi.org/10.3390/gels9060482

[4] Zhang, Z., Chen, X., Gao, S., Fang, X., & Ren, S. (2024). 3D bioprinted tumor model: a prompt and convenient platform for overcoming immunotherapy resistance by recapitulating the tumor microenvironment. Cellular oncology (Dordrecht, Netherlands), 47(4), 1113–1126. https://doi.org/10.1007/s13402-024-00935-9

[5] Yuan, T., Fu, X., Hu, R., Zheng, X., Jiang, D., Jing, L., Kuang, X., Guo, Z., Luo, X., Liu, Y., Zou, X., Luker, G. D., Mi, S., Liu, C., & Sun, W. (2024). Bioprinted, spatially defined breast tumor microenvironment models of intratumoral heterogeneity and drug resistance. Trends in biotechnology, 42(11), 1523-1550. https://doi.org/10.1016/j.tibtech.2024.06.007

[6] Desigaux, T., Comperat, L., Dusserre, N., Stachowicz, M. L., Lea, M., Dupuy, J. W., Vial, A., Molinari, M., Fricain, J. C., Paris, F., & Oliveira, H. (2024). 3D bioprinted breast cancer model reveals stroma-mediated modulation of extracellular matrix and radiosensitivity. Bioactive materials, 42, 316–327. https://doi.org/10.1016/j.bioactmat.2024.08.037

[7] Dey, M., Kim, M. H., Dogan, M., Nagamine, M., Kozhaya, L., Celik, N., Unutmaz, D., & Ozbolat, I. T. (2022). Chemotherapeutics and CAR-T Cell-Based Immunotherapeutics Screening on a 3D Bioprinted Vascularized Breast Tumor Model. Advanced functional materials, 32(52), 2203966. https://doi.org/10.1002/adfm.202203966

[8] Germain, N., Dhayer, M., Dekiouk, S., & Marchetti, P. (2022). Current Advances in 3D Bioprinting for Cancer Modeling and Personalized Medicine. International journal of molecular sciences, 23(7), 3432. https://doi.org/10.3390/ijms23073432

[9] Rasouli, R., Sweeney, C. & Frampton, J.P. (2025).

Heterogeneous and Composite Bioinks for 3D-Bioprinting of Complex Tissue. Biomedical Materials & Devices. 3, 108–126. https://doi.org/10.1007/s44174-024-00171-7

[10] Visalakshan, R. M., Lowrey, M. K., Sousa, M. G. C., Helms, H. R., Samiea, A., Schutt, C. E., Moreau, J. M., & Bertassoni, L. E. (2023). Opportunities and challenges to engineer 3D models of tumor-adaptive immune interactions. Frontiers in immunology, 14, 1162905. https://doi.org/10.3389/fimmu.2023.1162905

[11] Mir, A., Lee, E., Shih, W., Koljaka, S., Wang, A., Jorgensen, C., Hurr, R., Dave, A., Sudheendra, K., & Hibino, N. (2023). 3D Bioprinting for Vascularization. Bioengineering (Basel, Switzerland), 10(5), 606. https://doi.org/10.3390/bioengineering10050606

[12] Shukla, A. K., Yoon, S., Oh, S. O., Lee, D., Ahn, M., & Kim, B. S. (2024). Advancement in Cancer Vasculogenesis Modeling through 3D Bioprinting Technology. Biomimetics (Basel, Switzerland), 9(5), 306. https://doi.org/10.3390/biomimetics9050306