

Converging Bioprinting and Organoids to Better Recapitulate the Tumor Microenvironment: A Review

Anusha Khan

Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow, India

Abstract—The convergence of bioprinting and organoid technology offers a promising approach for recreating the complex tumor microenvironment (TME) in vitro. The TME governs cancer progression and therapeutic response through its diverse cellular components, biochemical signalling and physical properties, features that conventional two-dimensional culture systems fail to capture. Bioprinting allows precise spatial control over cell placement and biomaterial deposition, enabling fabrication of multicellular constructs that resemble native tissue architecture, while organoids derived from patient-specific cells recapitulate organ-level structure and function. This review examines how integrating bioprinting with organoid culture can more faithfully reproduce key features of the TME, including cellular heterogeneity, extracellular matrix composition, physiological gradients and vascular networks. Such converged models hold considerable promise for advancing cancer biology research, drug discovery and personalized medicine, although challenges such as vascularization, standardization and immune cell integration remain to be resolved.

Index Terms—*Bioprinting; Organoids; Tumor microenvironment; Cancer models; Extracellular matrix; Personalized medicine*

I. INTRODUCTION

Accurately recreating the tumor microenvironment (TME) is central to understanding cancer progression and to developing effective treatments. The TME arises from a complex interplay of diverse cell types, extracellular matrix (ECM) components and biochemical signals that collectively shape tumor behaviour and treatment response. Traditional cell culture models generally fail to reproduce these interactions, underscoring the need for more sophisticated in vitro systems. Recent progress in bioprinting and organoid technology offers a route toward addressing this gap. Bioprinting enables the precise arrangement of different cell types within

customizable three-dimensional structures, while organoids, derived from patient-specific cells, mimic organ-like architecture and function. Combining these technologies allows researchers to reproduce the physiological complexity of the TME with greater fidelity, capturing realistic cellular diversity, ECM structure and oxygen and nutrient gradients that are essential for studying cancer biology and treatment response.

This review examines how combining bioprinting and organoids improves the accuracy of TME models, with implications for drug testing, personalized medicine and the broader understanding of cancer biology, while also considering the challenges that remain before these approaches can be translated into clinical use.

II. THE TUMOR MICROENVIRONMENT: COMPOSITION AND SIGNIFICANCE

The TME is central to cancer biology, influencing tumor initiation, progression, metastasis and response to treatment. It comprises an intricate network of interactions between cancer cells, stromal cells such as fibroblasts and immune cells, endothelial cells and the ECM, mediated by growth factors, cytokines, chemokines and mechanical cues. The TME is typically characterized by low oxygen tension (hypoxia), acidic pH, altered nutrient availability, elevated interstitial fluid pressure and ongoing remodelling of the ECM. Together, these features contribute to tumor heterogeneity, treatment resistance and immune evasion, all of which significantly affect clinical outcomes. Conventional two-dimensional culture systems, although convenient and inexpensive, cannot reproduce the spatial and physiological complexity of the TME, since they lack the three-dimensional architecture, cell-cell interactions and ECM dynamics required to accurately model tumor behaviour in vivo.

III. BIOPRINTING TECHNOLOGY

Bioprinting is a developing technology that enables precise placement of cells, biomaterials and bioactive substances to generate three-dimensional structures that mimic native tissue. It follows a layer-by-layer approach similar to conventional 3D printing but incorporates living cells and biological materials. The principal bioprinting modalities, inkjet, extrusion-based and laser-assisted bioprinting, each offer distinct advantages in resolution, speed and compatibility with different biomaterials.

Bioinks used in bioprinting consist of cells combined with biomaterials such as hydrogels or decellularized ECM, deposited in defined spatial arrangements guided by computer-aided design (CAD) models, allowing intricate tissue architectures with precisely defined microenvironments to be recreated. Advances in bioprinting have enabled increasingly complex tissue models, including vascularized tissues, organ-on-chip systems and disease-specific constructs, giving researchers fine control over the arrangement and composition of cells and ECM components and considerable potential for developing more physiologically relevant TME models.

IV. ORGANOID TECHNOLOGY

Organoids are three-dimensional cell cultures derived from stem cells or primary tissue that self-organize into structures mimicking small organs, replicating aspects of an organ's architecture, cellular diversity and function. They are of considerable value for studying organ development, disease modelling and personalized medicine. Organoids are typically generated by embedding cells in an ECM-like matrix such as Matrigel and supplying growth factors and nutrients that support self-assembly.

They can be derived from patient-specific pluripotent stem cells, adult stem cells or tumor tissue directly, enabling the development of personalized models that reflect individual genetic and molecular characteristics. Compared with conventional culture models, organoids offer improved preservation of tissue architecture, intercellular communication and physiological function, and have been used to model organs including the gut, liver, brain and kidney, with growing application in modelling cancer and TME dynamics.

V. CONVERGENCE OF BIOPRINTING AND ORGANOID TECHNOLOGIES FOR TME MODELLING

Combining bioprinting and organoid technologies offers a robust route to improving the accuracy and applicability of TME models in cancer research. By integrating the spatial control offered by bioprinting with the physiological complexity of organoids, researchers can generate more authentic and functional representations of the TME in vitro.

5.1 *Recapitulating Cellular Heterogeneity*

A key advantage of combining bioprinting and organoids is the ability to reproduce the cellular diversity characteristic of the TME. Tumors contain distinct cell populations, including cancer cells, stromal cells, endothelial cells and pericytes, each contributing differently to tumor progression and treatment response. Bioprinting allows precise positioning of these cell types within a three-dimensional framework that mirrors their spatial arrangement in vivo, supporting the study of interactions such as cancer-stromal communication, immune cell infiltration and endothelial angiogenesis. Organoids derived from patient-specific cells inherently display this cellular diversity and spontaneously form structures resembling the composition of the original tissue or tumor.

5.2 *Modelling ECM Composition and Dynamics*

The ECM plays a critical role in regulating cell behaviour, migration, invasion and communication within the TME, comprising proteins such as collagen and fibronectin along with glycosaminoglycans including hyaluronic acid. Bioprinting enables precise deposition of ECM components and biomaterials that mimic the mechanical and biochemical properties of native ECM, allowing fabrication of three-dimensional frameworks with tunable stiffness, permeability and composition that influence cell behaviour and replicate the physical barriers cells encounter within tumors. Organoids embedded in ECM-like gels such as Matrigel interact naturally with surrounding matrix components and undergo remodeling processes comparable to those observed in vivo.

5.3 *Establishing Physiological Gradients*

Spatial gradients of oxygen, nutrients, metabolic waste and signalling molecules strongly influence tumor cell behaviour and treatment response, and are important

determinants of tumor survival, growth and adaptation. Bioprinting techniques can generate three-dimensional structures with precisely defined gradients of biochemical factors such as growth factors, cytokines and oxygen, enabling investigation of how cells respond to microenvironmental cues in different regions of a tumor and providing insight into growth dynamics, metabolic change and mechanisms of therapy resistance. Owing to their three-dimensional nature, organoids also naturally develop gradients of oxygen, nutrients and signalling molecules shaped by diffusion limits and cellular metabolic activity, closely resembling the spatial variation seen in tumors.

5.4 Integrating Vasculature and Blood Flow

Functional vasculature is essential for supplying nutrients and oxygen, removing metabolic waste and enabling immune cell infiltration within tumors, but replicating vascular networks in vitro has proven challenging owing to the complexity of vessel formation and perfusion. Advances in bioprinting have enabled the creation of vascularized tissue constructs by incorporating endothelial cells into three-dimensional scaffolds and stimulating angiogenesis, producing perfusable vascular networks that mimic the structure and function of tumor blood vessels. Although organoids typically lack intrinsic vascularization, bioprinting can be used to vascularize them, and integrating endothelial and supportive cells such as pericytes and smooth muscle cells into organoid cultures allows researchers to induce angiogenesis and establish functional vascular networks supporting nutrient exchange, immune trafficking and drug delivery.

VI. APPLICATIONS OF BIOPRINTED ORGANOIDS IN CANCER RESEARCH

Combining bioprinting and organoids to model the TME holds considerable potential for cancer research, drug development and personalized medical treatment.

6.1 Drug Discovery and Screening

Current drug development pipelines rely heavily on preclinical animal models and two-dimensional culture systems, which often fail to accurately predict human responses owing to species-specific differences and the absence of TME complexity. By incorporating patient-derived cells into bioprinted organoids, researchers can establish personalized models that reflect individual

genetic and molecular profiles, enabling the discovery of patient-specific drug responses.

6.2 Mechanistic Studies and Disease Modelling

Bioprinted organoid models are valuable for examining the mechanisms underlying cancer progression, metastasis and treatment resistance. By replicating the interactions among cancer cells, stromal cells, immune cells and ECM components within the TME, researchers can better understand the signalling pathways, cellular activities and molecular drivers of disease. Organoids derived from patient-specific cells preserve the genetic and molecular characteristics of the original tumor, making them well suited to investigating disease progression and identifying biomarkers of aggressiveness and treatment response, while bioprinting adds the spatial organization needed to study how spatial diversity affects growth dynamics, invasion and metastatic potential.

6.3 Personalized Medicine and Patient-Specific Therapies

The ability to generate customized bioprinted organoid models from individual patients' cells has significant implications for personalized medicine, offering the potential to forecast individual treatment responses, identify optimal therapeutic approaches and inform clinical decision-making based on the distinct characteristics of each patient's tumor. Integrating genomic, transcriptomic and proteomic data from patient samples into bioprinted organoid models allows researchers to link molecular profiles with drug response, supporting the identification of markers of drug sensitivity or resistance and the development of therapies tailored to individual molecular profiles.

VII. CHALLENGES AND FUTURE DIRECTIONS

Despite significant advances, several challenges must be addressed before the potential of bioprinting and organoid technology for TME modelling in cancer research and therapy can be fully realized.

7.1 Vascularization and Perfusability

Creating functional vascular networks within bioprinted organoid models remains a significant challenge. While bioprinting has enabled the development of vascularized tissues in the laboratory, generating perfusable networks that mirror the complexity and function of natural tumor

blood vessels remains a major obstacle. Future work should focus on refining bioprinting approaches, including improved biomaterials and bioinks that support endothelial cell survival, promote angiogenesis and establish open vascular lumens for nutrient and oxygen exchange.

7.2 Complexity and Standardization

Bioprinted organoid models are inherently complex, incorporating multiple cell types, ECM components and biochemical gradients that influence tumor behaviour and treatment response. Standardizing bioprinting protocols, biomaterial formulations and culture conditions is essential to ensure reproducibility, scalability and comparability across studies and clinical applications. Establishing standardized protocols and quality control measures will support wider adoption of these technologies in cancer research and drug development.

7.3 Incorporation of Immune Cells and Immune Modulation

The immune microenvironment plays a vital role in tumor progression, immune evasion and response to immunotherapy, yet existing bioprinted organoid models do not fully represent the intricate interactions of immune cells within the TME, limiting their usefulness for studying immune modulation and therapeutic approaches.

Future progress should focus on integrating immune cells such as T cells, macrophages and dendritic cells into tumor models to replicate immune cell infiltration, activation and function, which will require refining culture conditions to sustain the viability and interactions of immune cells with tumor and stromal cells.

7.4 Computational Modelling and Predictive Analytics

Advances in computational modelling and predictive analytics have the potential to complement experimental approaches in bioprinting and organoid technology. Computational models can simulate complex biological processes within the TME, forecast cellular behaviour, refine experimental design and guide hypothesis-driven research. Integrating bioprinting data with computational models of the TME will allow researchers to simulate tumor growth dynamics, predict drug responses and optimize treatment strategies in silico before experimental validation.

VIII. CONCLUSION

The convergence of bioprinting and organoids represents a novel and promising approach for better recapitulating the complexity and diversity of the TME in vitro. By combining the precise spatial control offered by bioprinting with the physiological relevance of organoids, researchers can construct more authentic models that capture key features of tumor biology, including cellular diversity, ECM dynamics, physiological gradients and immune interactions. These advanced models have the potential to deepen understanding of cancer biology, improve drug discovery and testing, and support the development of personalized medicine tailored to individual patient tumors. Despite persistent challenges around vascularization, immune cell integration and standardization, continued research and interdisciplinary collaboration are likely to drive substantial progress in bioprinted organoid technology. Sustained investment in research, technology development and collaborative partnerships will be essential to fully realize the potential of bioprinting and organoids for TME modelling and to translate these advances into clinical benefit for cancer patients.

ACKNOWLEDGEMENTS

The authors thank the Department of Biotechnology, Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow, for institutional support during the preparation of this review.

REFERENCES

- [1] B. W. Stewart and C. P. Wild, Eds., *World Cancer Report 2014*. Lyon, France: International Agency for Research on Cancer, World Health Organization, 2014.
- [2] A. L. Harris, "Hypoxia, a key regulatory factor in tumour growth," *Nature Reviews Cancer*, vol. 2, pp. 38–47, 2002.
- [3] N. C. Denko, "Hypoxia, HIF1 and glucose metabolism in the solid tumour," *Nature Reviews Cancer*, vol. 8, pp. 705–713, 2008.
- [4] J. M. Brown and W. R. Wilson, "Exploiting tumour hypoxia in cancer treatment," *Nature Reviews Cancer*, vol. 4, pp. 437–447, 2004.

- [5] D. Hanahan and R. A. Weinberg, "Hallmarks of cancer: The next generation," *Cell*, vol. 144, pp. 646–674, 2011.
- [6] T. P. Calmels, V. Mattot, N. Wernert, B. Vandenbunder, and D. Stehelin, "Invasive tumors induce c-ets1 transcription factor expression in adjacent stroma," *Biology of the Cell*, vol. 84, pp. 53–61, 1995.
- [7] N. A. Bhowmick, E. G. Neilson, and H. L. Moses, "Stromal fibroblasts in cancer initiation and progression," *Nature*, vol. 432, pp. 332–337, 2004.
- [8] B. De Craene and G. Berx, "Regulatory networks defining EMT during cancer initiation and progression," *Nature Reviews Cancer*, vol. 13, pp. 97–110, 2013.
- [9] J. A. Joyce and J. W. Pollard, "Microenvironmental regulation of metastasis," *Nature Reviews Cancer*, vol. 9, pp. 239–252, 2009.
- [10] S. J. Turley, V. Cremasco, and J. L. Astarita, "Immunological hallmarks of stromal cells in the tumour microenvironment," *Nature Reviews Immunology*, vol. 15, p. 669, 2015.
- [11] Y. Cao, "Tumor angiogenesis and therapy," *Biomedicine & Pharmacotherapy*, vol. 59, pp. S340–S343, 2005.
- [12] D. Fukumura and R. K. Jain, "Tumor microenvironment abnormalities: Causes, consequences, and strategies to normalize," *Journal of Cellular Biochemistry*, vol. 101, pp. 937–949, 2007.
- [13] C. Swanton, "Intratumor heterogeneity: Evolution through space and time," *Cancer Research*, vol. 72, pp. 4875–4882, 2012.
- [14] A. Marusyk, V. Almendro, and K. Polyak, "Intra-tumour heterogeneity: A looking glass for cancer?" *Nature Reviews Cancer*, vol. 12, pp. 323–334, 2012.
- [15] J. N. Weinstein, E. A. Collisson, G. B. Mills, K. R. M. Shaw, B. A. Ozenberger, J. Ellrott, et al., "The Cancer Genome Atlas Pan-Cancer analysis project," *Nature Genetics*, vol. 45, pp. 1113–1120, 2013.
- [16] T. Walter, D. W. Shattuck, R. Baldock, M. E. Bastin, A. E. Carpenter, S. Duce, et al., "Visualization of image data from cells to organisms," *Nature Methods*, vol. 7, pp. S26–S41, 2010.
- [17] D. L. Longo, "Tumor heterogeneity and personalized medicine," *New England Journal of Medicine*, vol. 366, pp. 956–957, 2012.
- [18] L. Thibaudau, A. V. Taubenberger, B. M. Holzapfel, V. M. Quent, T. Fuehrmann, P. Hesami, et al., "A tissue-engineered humanized xenograft model of human breast cancer metastasis to bone," *Disease Models & Mechanisms*, vol. 7, pp. 299–309, 2014.
- [19] S. Y. C. Choi, D. Lin, P. W. Gout, C. C. Collins, Y. Xu, and Y. Wang, "Lessons from patient-derived xenografts for better in vitro modeling of human cancer," *Advanced Drug Delivery Reviews*, vols. 79–80, pp. 222–237, 2014.
- [20] S. Aparicio, M. Hidalgo, and A. L. Kung, "Examining the utility of patient-derived xenograft mouse models," *Nature Reviews Cancer*, vol. 15, pp. 311–316, 2015.