MULTIDIMENSIONAL ATTENTION IN ONCOLOGY: CONTRIBUTIONS OF THREE-DIMENSIONAL MODELS TO THE STUDY OF THE TUMOR MICROENVIRONMENT AND THE DEVELOPMENT OF THERAPIES

ATENÇÃO MULTIDIMENSIONAL EM ONCOLOGIA: CONTRIBUIÇÕES DOS MODELOS TRIDIMENSIONAIS PARA O ESTUDO DO MICROAMBIENTE TUMORAL E O DESENVOLVIMENTO DE TERAPIAS

ATENCIÓN MULTIDIMENSIONAL EN ONCOLOGÍA: CONTRIBUCIONES DE LOS MODELOS TRIDIMENSIONALES AL ESTUDIO DEL MICROAMBIENTE TUMORAL Y AL DESARROLLO DE TERAPIAS

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ABSTRACT

Introduction: Cancer constitutes one of the main challenges in global public health due to its high morbidity and mortality and the biological complexity associated with the tumor microenvironment. Traditional experimental models, such as two-dimensional cell cultures and animal models, present important limitations in reproducing cellular interactions and the three-dimensional architecture of tumors.

Objective: To analyze the role of three-dimensional platforms in cancer modeling, discussing their biological foundations, technologies used, and applications in tumor investigation and therapy development.

Methodology: A literature review was conducted through searches in international scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Studies published between 2014 and 2025 were considered, using descriptors related to three-dimensional cell culture, organoids, tumor spheroids, 3D bioprinting, and organ-on-a-chip systems.

Results: Three-dimensional platforms demonstrate a greater capacity to reproduce tumor heterogeneity, metabolic gradients, and cellular interactions present in the tumor microenvironment. Models such as spheroids, organoids, and three-dimensional bioprinting enable more realistic investigations of tumor progression and present higher predictive value in the screening of antineoplastic drugs.

Conclusion: Three-dimensional models represent promising tools for oncological research and for the development of innovative therapeutic strategies, contributing to advances in translational oncology and personalized medicine.

Keywords: Cancer. Three-Dimensional Models. Tumor Microenvironment. Organoids. 3D Bioprinting.

RESUMO

Introdução: O câncer constitui um dos principais desafios da saúde pública global devido à sua elevada morbimortalidade e à complexidade biológica associada ao microambiente tumoral. Modelos experimentais tradicionais, como culturas celulares bidimensionais e modelos animais, apresentam limitações importantes na reprodução das interações celulares e da arquitetura tridimensional dos tumores.

Objetivo: Analisar o papel das plataformas tridimensionais na modelagem do câncer, discutindo seus fundamentos biológicos, tecnologias utilizadas e aplicações na investigação tumoral e no desenvolvimento de terapias.

Metodologia: Realizou-se uma revisão da literatura com busca em bases de dados científicas internacionais, incluindo PubMed/MEDLINE, Scopus, Web of Science e Google Scholar. Foram considerados estudos publicados entre 2014 e 2025, utilizando descritores relacionados à cultura celular tridimensional, organoides, esferoides tumorais, bioimpressão 3D e sistemas organ-on-a-chip.

Resultados: As plataformas tridimensionais demonstram maior capacidade de reproduzir a heterogeneidade tumoral, gradientes metabólicos e interações celulares presentes no microambiente tumoral. Modelos como esferoides, organoides e bioimpressão tridimensional possibilitam investigações mais realistas da progressão tumoral e apresentam maior valor preditivo na triagem de fármacos antineoplásicos.

Conclusão: Os modelos tridimensionais representam ferramentas promissoras para a pesquisa oncológica e para o desenvolvimento de estratégias terapêuticas inovadoras, contribuindo para avanços na oncologia translacional e na medicina personalizada.

Palavras-chave: Câncer. Modelos Tridimensionais. Microambiente Tumoral. Organoides. Bioimpressão 3D.

RESUMEN

Introducción: El cáncer constituye uno de los principales desafíos de la salud pública global debido a su elevada morbimortalidad y a la complejidad biológica asociada al microambiente tumoral. Los modelos experimentales tradicionales, como los cultivos celulares bidimensionales y los modelos animales, presentan importantes limitaciones para reproducir las interacciones celulares y la arquitectura tridimensional de los tumores.

Objetivo: Analizar el papel de las plataformas tridimensionales en la modelización del cáncer, discutiendo sus fundamentos biológicos, las tecnologías utilizadas y sus aplicaciones en la investigación tumoral y el desarrollo de terapias.

Metodología: Se realizó una revisión de la literatura mediante búsquedas en bases de datos científicas internacionales, incluyendo PubMed/MEDLINE, Scopus, Web of Science y Google Scholar. Se consideraron estudios publicados entre 2014 y 2025, utilizando descriptores relacionados con cultivo celular tridimensional, organoides, esferoides tumorales, bioimpresión 3D y sistemas organ-on-a-chip.

Resultados: Las plataformas tridimensionales demuestran una mayor capacidad para reproducir la heterogeneidad tumoral, los gradientes metabólicos y las interacciones celulares presentes en el microambiente tumoral. Modelos como esferoides, organoides y

bioimpresión tridimensional permiten investigaciones más realistas de la progresión tumoral y presentan mayor valor predictivo en el cribado de fármacos antineoplásicos.

Conclusión: Los modelos tridimensionales representan herramientas prometedoras para la investigación oncológica y el desarrollo de estrategias terapéuticas innovadoras, contribuyendo a avances en la oncología traslacional y la medicina personalizada.

Palabras clave: Cáncer. Modelos Tridimensionales. Microambiente Tumoral. Organoides. Bioimpresión 3D.

1 INTRODUCTION

Cancer represents one of the main challenges of global public health, being responsible for high morbidity and mortality and significant socioeconomic impact. The biological complexity of tumors involves dynamic interactions between cancer cells, extracellular matrix, immune system cells, and vascular components that constitute the so-called tumor microenvironment, which plays a central role in tumor progression, cell invasion, and response to antineoplastic therapies (Rodrigues; Kings; Pirraco, 2024).

Traditionally, experimental studies in oncology have used two-dimensional (2D) cell culture models or animal models. Although these approaches have contributed significantly to the advancement of scientific knowledge, they have important limitations. Two-dimensional models do not adequately reproduce the three-dimensional architecture of tumor tissues or the complex interactions between cells and extracellular matrix. Animal models, on the other hand, may present physiological and metabolic differences in relation to the human body, which compromises the prediction of the efficacy of pharmacological treatments (Sharma et al., 2023; Rodrigues; Kings; Pirraco, 2024).

In this context, three-dimensional tumor modeling (3D) platforms emerge as innovative tools capable of reproducing with greater fidelity the physiological conditions found in human tumors. These platforms include systems such as tumor spheroids, organoids, biomaterial-based models, microfluidics (*organ-on-a-chip*), and three-dimensional bioprinting. These models allow the simulation of oxygen, nutrient, and metabolite gradients, in addition to favoring complex cellular interactions similar to those observed in tumors in vivo (Cordeiro et al., 2024).

Three-dimensional cancer modeling has been widely used to understand mechanisms of tumor progression, study invasion and metastasis processes, and evaluate the efficacy of new antineoplastic therapies. In addition, these technologies contribute to the development of personalized medicine, allowing treatments to be tested in cultures derived directly from patients' tumor cells (Lv et al., 2024).

Three-dimensional platforms allow for a more precise investigation of cellular processes associated with tumor heterogeneity. In 3D models, tumor cells organize themselves into structures that reproduce important features of the solid tumor, including peripheral proliferative zones, intermediate hypoxic regions, and central necrotic areas. This spatial organization reflects the limitation of oxygen and nutrient diffusion within the tumor mass. In this way, three-dimensional models provide a more physiologically relevant experimental environment for the study of tumor progression and metabolic adaptation of cancer cells (Zanoni et al., 2020; Rodrigues; Kings; Pirraco, 2024).

Another relevant aspect of these platforms is the possibility of incorporating different cell types present in the tumor microenvironment, such as cancer-associated fibroblasts, endothelial cells, and immune system cells. The inclusion of these components makes it possible to reproduce complex cellular interactions that influence processes such as angiogenesis, tumor inflammation, and therapeutic resistance. Studies have shown that three-dimensional models based on cell co-culture allow a more realistic analysis of the communication between tumor cells and stromal cells, contributing to the understanding of the molecular mechanisms involved in cancer (Flörkemeier et al., 2024; Cauli et al., 2023).

Unlike two-dimensional models, which often overestimate the efficacy of certain compounds, 3D cultures reproduce physical barriers and chemical gradients that influence the penetration and distribution of drugs within the tumor. As a result, these models allow obtaining pharmacological responses closer to those observed in human tumors, increasing the reliability of preclinical tests and contributing to reducing the failure rate of new drugs in clinical trials (Cordeiro et al., 2024).

In this scenario, there is a growing integration between different technologies for the development of more complex three-dimensional platforms, including systems based on biomaterials, microfluidics and 3D bioprinting. These approaches allow controlling physical and biochemical properties of the tumor microenvironment, such as extracellular matrix stiffness, fluid flow, and growth factor distribution. The combination of these technologies has driven the advancement of experimental oncology, enabling the construction of highly biomimetic tumor models (Rodrigues; Kings; Pirraco, 2024; Sharma et al., 2023).

These platforms have stood out for allowing a more faithful reproduction of tumor architecture, overcoming the limitations of traditional models and offering experimental systems closer to *in vivo* conditions. Thus, three-dimensional models emerge as relevant tools for the investigation of tumor biology and the advancement of personalized medicine strategies.

The present study aims to analyze the role of three-dimensional platforms in cancer modeling, discussing their biological foundations, main technologies used and applications in tumor investigation, drug development and translational oncology.

2 METHODOLOGY

This chapter was prepared through a narrative review of the updated literature, aiming to synthesize updated knowledge and allowing the discussion of conceptual and methodological advances and emerging applications in different areas of science.

The bibliographic search was carried out between January and March 2026, including publications available in the period from 2014 to 2025, with the inclusion of previous classical studies when considered relevant to the understanding of the historical development of three-dimensional culture technologies. Scientific databases used in the biomedical field, including PubMed/MEDLINE, *Scopus, Web of Science, and Google Scholar,* were consulted due to their scope and relevance in the indexing of international scientific literature.

To identify the studies, descriptors in Portuguese and English were used, combined by Boolean operators (AND and OR). Among the main terms used are *3D cancer models*, *tumor spheroids*, *organoids*, *3D cell culture*, *tumor microenvironment*, *3D bioprinting*, *organ-on-a-chip* and *cancer modeling*. These keywords were selected based on terminology widely used in studies on three-dimensional cell culture and tumor modeling. The search prioritized studies that addressed experimental applications of these technologies in the investigation of tumor biology, drug development, and personalized medicine.

The inclusion criteria included peer-reviewed scientific articles that directly addressed the use of three-dimensional platforms in the study of cancer, including systematic reviews, narrative reviews, in *vitro experimental studies,* and translational research. Studies that addressed: (1) three-dimensional cell culture techniques applied to the study of cancer were included; (2) development of three-dimensional platforms for modeling the tumor microenvironment; and (3) applications of these technologies in drug screening, therapeutic development, and personalized medicine. Studies that did not have a direct relationship with three-dimensional tumor modeling and duplicate publications or those with restricted access to full content were excluded.

After the initial search, the identified studies were submitted to a screening process by reading titles and abstracts, followed by the complete analysis of the selected articles. From this stage, the studies considered most relevant were included in the qualitative analysis. The synthesis of the information was organized in a thematic way, allowing the discussion of the main scientific advances related to three-dimensional platforms, including tumor spheroids, organoids, models based on biomaterials, microfluidic systems and three-dimensional bioprinting.

The qualitative analysis of the studies considered aspects such as methodologies employed, experimental applications, advantages, limitations and future perspectives of three-dimensional platforms. In this way, the review made it possible to integrate recent scientific evidence on the potential of these technologies in biomedical research and in the development of new therapeutic strategies against cancer.

3 THEORETICAL FRAMEWORK

Three-dimensional cancer modeling represents a significant advance in biomedical research, as it allows reproducing structural and functional characteristics of human tumors with greater fidelity compared to traditional models. These systems enable the investigation of complex cellular processes, including tumor growth, cell invasion, and interaction with the tumor microenvironment.

Among the three-dimensional models most used in oncological research, tumor spheroids stand out, which can be considered the gold standard in vitro model due to their high translational predictive value (Zhu et al., 2022). They consist of multicellular aggregates formed spontaneously under culture conditions that prevent cell adhesion to the substrate. These aggregates reproduce important features of the solid tumor, including cell heterogeneity, metabolic gradients, and hypoxia regions (Cordeiro et al., 2024).

In spheroids, cells located in the outer layers have a higher proliferation rate due to greater availability of nutrients and oxygen. On the other hand, the cells present in the central regions encounter conditions of hypoxia and low nutritional availability, simulating the conditions found in solid tumors in the human body (Rodrigues; Kings; Pirraco, 2024). This organization makes spheroids particularly useful for drug resistance studies, as the diffusion of drugs through the three-dimensional structure occurs in a similar way to that observed in real tumor tissues.

Confocal microscopy has already been used to observe glioma cell invasion, for example, in neural tissue spheroids derived from rodent neural progenitor cells (Datta et al., 2020). As metabolic products such as lactate accumulate, tumor microenvironments can become acidic, which contributes to pharmacological resistance. 3D spheroids are able to exhibit low pH in deeper regions, which amplifies their potential as a screening platform. These models have also been applied in the study of the role of amino acids (such as leucine and glutamine) in melanoma growth (Zhu et al., 2022).

Another important approach in three-dimensional cancer modeling involves tumor organoids, which are three-dimensional structures derived from stem cells or tumor cells obtained directly from patients. These models have high genetic and phenotypic fidelity in relation to the original tumor, preserving specific characteristics of the disease (LV et al., 2024).

Organoids allow the study of complex processes related to tumor progression and therapeutic response, and are widely used in personalized medicine research (Li et al, 2024). Therefore, it is possible to evaluate different treatments directly in cultures derived from the patient's tumor, allowing the identification of more effective therapeutic strategies and

reducing adverse effects associated with inappropriate treatments. It is also noteworthy that organoids enable the investigation of interactions between tumor cells and tumor microenvironment, including immune system cells and fibroblasts associated with the tumor (Li et al, 2024). Although patient-derived spheroids are less commonly used than patient-derived organoids, they are more cost-effective and easier to manipulate, as they do not simulate the extracellular matrix (Zhu et al., 2022).

Among the most advanced technologies in the field of cancer modeling, three-dimensional bioprinting (3D *bioprinting) stands out*. This technology makes it possible to position cells and biomaterials precisely, forming complex structures that reproduce the architecture of tumor tissue. 3D bioprinting makes it possible to create models that include different cell types and components of the extracellular matrix. In addition, this technology allows you to control structural parameters such as cell density, spatial organization, and tissue composition (Shukla et al., 2024). These models have been used to investigate processes such as tumor angiogenesis, cell invasion, and metastasis.

Three-dimensional platforms have been widely used in the discovery and development of new antineoplastic drugs because they are not able to use the tumor.

The *organ-on-a-chip* system, in turn, requires lower consumption of reagents, in addition to ensuring continuous perfusion and control of pressure and shear stress in the cells (Ryu; Lee; Park, 2019). The glioblastoma model on a chip, for example, uses patient-derived glioblastoma cells grown with endothelial cells. In this model, a concentric tumor stromal ring was developed and demonstrated relevance in reproducing patient resistance to chemoradiation concomitant with temozolomide (Datta et al., 2020).

Microfluidic cell culture also made it possible to analyze the infiltration of T cells between breast cancer cells with monocytes (Zhu et al., 2022). There are also reports of successful use of other multicellular models with prostate and lung cancer cells (Zhu et al., 2022). By reproducing metabolic gradients, cellular interactions, and physical barriers similar to those seen in human tumors, three-dimensional models offer more realistic experimental platforms. In addition, the use of these technologies can contribute to reducing dependence on animal models, aligning with ethical guidelines that encourage the use of alternative methods in biomedical research.

Despite significant advances, three-dimensional cancer modeling still faces important technical challenges. Among the main limitations, the difficulty in the reproduction of complex vascular systems stands out, which are fundamental for the adequate diffusion of oxygen, nutrients and drugs within the tumor tissue, since many three-dimensional models are still unable to replicate functional vascular networks similar to those observed *in vivo* (Bova; Billi;

Cimetta, 2020; Shukla et al., 2022). In the case of spheroids, the lack of control over the structure can still lead to the formation of heterospheroids, which have an architecture contrary to that of the solid tumor (Heinrich et al., 2021).

It is observed that limitations related to the standardization of experimental protocols persist, which can compromise the reproducibility of the results and make it difficult to compare studies developed in different laboratories (Visalakshan et al., 2023; Sharma et al., 2023). Also noteworthy is the high cost associated with the technologies employed, especially those related to three-dimensional bioprinting and the use of specialized biomaterials and advanced equipment, which may limit the wide application of these platforms in different biomedical research contexts (Visalakshan et al., 2023; Wang et al., 2024). However, the continuous advancement of tissue engineering, biotechnology, and bioprinting technologies tends to overcome these limitations, expanding the potential of three-dimensional platforms in oncology research.

Table 1

Comparison of 2D × 3D models in cancer research

Criteria	**2D models (monolayer crops)**	**3D models (spheroids, organoids, bioprinting)**
Cell organization	Cells grow on a flat surface	Cells grow in three-dimensional structure similar to tissue
Representation of the tumor microenvironment	Limited; does not reproduce tumor architecture	Reproduces oxygen, nutrient and cell interaction gradients
Cell–cell and cell–matrix interaction	Reduced or absent	Present and similar to the in vivo environment
Cell growth	Rapid and homogeneous proliferation	Heterogeneous growth with proliferative and hypoxic zones
Drug sensitivity	Usually higher, and may overestimate therapeutic efficacy	More realistic and close responses to tumor behavior in vivo
Metabolic gradients	Uniforms	Presence of hypoxic regions and central necrosis
Application in drug screening	Wide use, low cost	More predictive for clinical response
Experimental complexity	Low	Moderate to high
Cost and trial time	Lower cost and easy replication	Increased cost and need for specialized protocols
Biological relevance	Limited	Elevated for translational studies

Source: Adapted from Abuwatfa et al. (2024); Lovitt et al. (2014).

Three-dimensional cultures can better reproduce the dynamics of solid tumors because they include heterogeneous cell populations, including proliferative and quiescent cells.

4 FINAL CONSIDERATIONS

Three-dimensional tumor modeling platforms represent a significant advance in cancer research, offering experimental systems capable of more realistically reproducing the structural and functional complexity of human tumors. Technologies such as spheroids, organoids and three-dimensional bioprinting significantly expand the possibilities of scientific research, contributing to the development of innovative therapies and personalized medicine strategies.

Despite the technical limitations that still exist, the continued development of these technologies points to a future in which three-dimensional platforms will become central tools in oncology research and the development of new cancer treatments. These approaches emerge as strategic tools for translational oncology. Although technical challenges still persist, the advancement of the areas of tissue engineering, biotechnology, and biofabrication tends to consolidate three-dimensional platforms as central components in contemporary oncology research.

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