Editorial Commentary

Revolutionizing preclinical research for pancreatic cancer: the potential of 3D bioprinting technology for personalized therapy

Hang Sun[#], Yan Wang[#], Huayu Yang

Department of Liver Surgery, Peking Union Medical College (PUMC) Hospital, PUMC & Chinese Academy of Medical Sciences (CAMS), Beijing, China

[#]These authors contributed equally to this work.

Correspondence to: Huayu Yang, PhD. Department of Liver Surgery, Peking Union Medical College (PUMC) Hospital, PUMC & Chinese Academy of Medical Sciences, 1# Shuai-Fu-Yuan, Wang-Fu-Jing, Beijing 100730, China. Email: dolphinyahy@hotmail.com.

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Pancreatic cancer (PC) is a prevalent digestive malignancy worldwide and ranks as the fourth leading cause of cancer-related deaths globally. The incidence and mortality rates have been increasing annually, and due to its insidious onset and high malignancy, most patients are diagnosed at an advanced stage, with a 5-year survival rate of less than 8% (1). PC can be classified into endocrine and exocrine tumors, with over 95% of pancreatic malignant tumors originating from the exocrine portion of the pancreas. Among them, pancreatic ductal adenocarcinoma (PDAC) accounts for 85–90% of all pancreatic tumors and is the most common type of PC. Owing to its highly malignant biological characteristics, PDAC has been the focus of extensive research.

Surgical resection remains the only curative method in the treatment of PC. However, only a small number of cases can undergo surgical resection at the initial diagnosis due to its difficulty in early detection and treatment (2). Furthermore, even after complete resection, the prognosis is poor, and the development of effective treatment methods for PDAC is limited compared to other gastrointestinal cancers with various molecular targeted drugs currently being developed. The standard chemotherapy for PDAC is a combination therapy consisting of cytotoxic anticancer drugs (3), such as the FOLFIRINOX regimen (chemotherapy regimen of Irinotecan, Oxaliplatin and 5-fluorouracil) and gemcitabine plus albumin-bound paclitaxel. Therefore, a comprehensive treatment strategy for PC that includes combination chemotherapy is becoming increasingly important in the future of PC treatment. The focus of comprehensive treatment is on individualized treatment. Currently, the selection of chemotherapy regimens is usually based on the patient's physical condition, comorbidities, and the doctor's experience. However, due to the heterogeneity of tumors and the complexity of the tumor microenvironment (TME), different patients respond differently to the same drugs, and neoadjuvant and adjuvant chemotherapy performed before and after surgical resection has limited effectiveness in improving survival. Hence, the reliable application of preclinical models to predict drug treatment response and assist in formulating individualized chemotherapy regimens is a pressing issue in the treatment of PC.

Traditional preclinical models of PC, such as immortalized cell lines cultured in two-dimensional (2D), have provided valuable insights into cancer biology. However, due to the lack of tumor heterogeneity and the absence of a complex microenvironment, these models cannot fully preserve the original characteristics of the parental tumor, making them unsuitable for individualized treatment. In contrast, human-derived animal models are designed to mimic the TME and preserve parental tumor characteristics. Patient-derived xenograft (PDX) models are well-established examples of this approach and have demonstrated their applicability for predicting individualized treatment response in PDAC (4). Despite their effectiveness, PDX models suffer from low success rates, high cost, and time-consuming requirements, which limit their widespread adoption.

Currently, an increasing number of three-dimensional

(3D) *in vitro* models of humanoid microenvironments are being developed with the aim of recreating the biological and physical complexity of the TME. Undoubtedly, 3D models far surpass the limitations of 2D single-layer cell cultures and expensive, low-throughput animal models. The available toolbox for engineering 3D *in vitro* models of human microenvironments includes randomly assembled 3D spheres, patient-derived organoids, cell-laden hydrogel platforms, microfluidic tumor chip platforms, and 3D bioprinting (5).

Organoids are currently the most widely used and promising 3D preclinical models for PDAC. They have the potential to assist in individualized treatment of patients in clinical settings. Organoid-derived pathways for PDAC include using fine-needle biopsy to obtain small tumor samples and, for patients who have undergone surgery, using large numbers of surgical specimens to establish a PC organoid bank that can be used to test possible follow-up treatment options to make the best treatment choice (6). The PDAC organoid model is a promising alternative to the time-consuming and expensive PDX model to a certain extent. However, its low success rate, lack of standardized methods, and poor reproducibility cannot be ignored (7).

Over the past 15 years, 3D bioprinting technology has emerged as an interdisciplinary frontier offering a range of strategies for the development of functional tissues (8). This technology has been applied to the reconstruction of *in vitro* tissues, and it offers a unique advantage in its ability to deposit various types of co-cultured cells in a single spatial arrangement that matches the natural architecture of native tissue. The adaptability of 3D bioprinting to various types of cells is enabled by the use of different bioinks, which are mainly composed of non-toxic and biocompatible materials such as natural polymers (e.g., alginate, gelatin, collagen, chitosan, and hyaluronic acid) or synthetic molecules (e.g., polyethylene glycol). Cell-containing bioinks can be digitized and modeled using computed tomography, magnetic resonance imaging, computer-aided design, computer-aided manufacturing tools, and mathematical modeling to generate simulated 3D structures. The digital images are then used to print tissues and organs using techniques such as laser-assisted printing, microextrusion, and inkjet with polymer interconnects activated by light or heat.

The advent of 3D bioprinting technology has opened up new avenues for studying tumor models of clinical significance (9). One of the key advantages of 3D bioprinting cancer cells is the use of computer-assisted technology, which provides benefits such as high precision, efficiency, and consistency, thereby overcoming the limitations of traditional organoid techniques. Moreover, this technology has natural advantages in constructing *in vitro* multicellular microenvironments that closely resemble native tissue architecture, leading to better representation of tumor formation, progression, and response to anticancer drugs. Numerous studies have highlighted the role of microenvironmental components in conferring chemoresistance (10). Therefore, the utilization of 3D bioprinting technology is well suited for the development of personalized drug screening programs in PC.

Hakobyan *et al.* (11) utilized laser-assisted bioprinting to fabricate 3D arrays of pancreatic cell spheroids and examined their phenotypic changes over time through image analysis and phenotypic characterization. The findings suggest that this bioprinting-based miniaturized spheroid array model can facilitate the investigation of intrinsic and extrinsic factors that promote precursor lesion formation and cancer progression in PDAC, which may provide insights into future therapeutic strategies for PDAC. Langer *et al.* (12) printed OPTR3099C, a human PC cell line derived from PDX tumor tissue, on a matrix containing human umbilical vein endothelial cells (HUVECs) and normal human primary pancreatic stellate cells (PSCs). The co-cultured cancer and stromal cells responded to microenvironmental signals in bioprinted tumors and closely resembled the parental tumor morphology, indicating that bioprinting allows for primary patient or patient-derived bioprinting in complex microenvironments. These studies highlight the potential application of 3D bioprinting in both basic and clinical research of PDAC.

Additionally, there have been limited studies integrating patient-derived PDAC tumor cells into 3D bioprinting platforms to validate its potential for personalized therapy. Our research group has previously established successful 3D-printed models of liver cancer cell lines, *in vitro* microenvironment models of cholangiocarcinoma cell lines, and patient-derived 3D bioprinting models of liver cancer cells, highlighting the reliable value of 3D bioprinting in tumor drug screening (13-15). These results demonstrate that 3D bioprinting technology holds significant potential for clinical applications in preclinical tumor model research. However, standardization of protocols in PDAC for this technology is highly necessary to optimize disease modeling accuracy in future work. In summary, 3D bioprinting technology holds immense promise as an innovative clinical tool for individualized treatment in PDAC, and further research is needed to explore its full potential.

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Footnote

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