3D Bioprinting Tumor Models and their Application Progress

Huaixu Li[1#], Yang Qiao[1#], Xingliang Dai[1,2*], Haotian Tian[1], Zhenyu Han[3], Sheng Cheng[3], Peng Gao[1,4*], Hongwei Cheng[1*]

1. Department of Neurosurgery, the First Affiliated Hospital of Anhui Medical University, Hefei 230001, China;
2. Department of Research & Development, East China Institute of Digital Medical Engineering, Shangrao 334000, China.
3. Department of Medical Imaging Technology, the First Clinical College of Anhui Medical University, Hefei 230032, China;
4. Department of Neurosurgery, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China;

[#] Contributed equally to this work
[*]Author to whom any correspondence should be addressed:
E-mail: hongwei.cheng@ahmu.edu.cn (H. Cheng); gaopeng@ahmu.edu.cn (P. Gao); daixingliang@ahmu.edu.cn (X. Dai)

Abstract

The most common cause of mortality in people is cancer, which has turned into an unbridgeable health gap because of its unrestrained aberrant proliferation, quick growth, metastasis, and high heterogeneity. Conventional two-dimensional cell culture models along with animal models for tumor diagnostic and therapeutic studies have extremely low clinical translation rates due to their intrinsic limitations. Appropriate tumor models are required for cancer research. Engineered human 3D cancer models are better able to replicate the spatial organization, cellular resources, and tumor microenvironment features (hypoxia, necrosis, and delayed proliferation) of the actual human tumor microenvironment. Emerging technology known as 3D bioprinting makes it possible to fabricate live structures by precisely regulating the spatial distribution of cells, biomolecules, and matrix components. The aim of this paper is to review the current technology and bioink of 3D bioprinted cancer models, including glioma, breast, liver, intestinal, cervical, ovarian, and neuroblastoma models, as well as the advances in their applications in the fields of tumor microenvironment, tumor vascularization, tumor stem cells, tumor resistance and drug screening, tumor immunotherapy, and precision medicine.

Keywords: Bioprinting; TME; Cancer model; Application

Introduction

An innovative new technique called 3D bioprinting enables the rapid, precise, and quantitative deposition of biologically active components, including living cells, biomaterials, drugs, growth hormones, and genomes, for creating active tissues with extremely complex spatial structures(1-4). Bioprinting fabricated scaffold material-containing and scaffold material-free tissue/organ-like structures(5), microtissues(3), and organ cores(6-9) have gained much progress and even demonstrated alternative human organ functions, including cardiac, hepatic, and renal tissues, demonstrating the potential for application as in *vitro* organ-like organs(1). Nevertheless, due to difficulties with internal vascularization of tissues, complex heterogeneity, simulation of cell-cell and cell-tissue microenvironments, histological structure and function, biomaterials that can be bioprinted and encourage cell growth and proliferation, along with their decay and biomimetic degree, the real large-scale and complete replacement of human organs by these bioprinted tissues/organs is still not feasible(2). Despite additional challenges, 3D bioprinting has started to gain widespread acceptance and applications. For example, 3D printed tissue models are beginning to replace 2D models and animal models for drug testing, because 2D cell culture models cannot replicate 3D tissue microenvironments(10-13) and animal models do not reliably predict toxicological and pathophysiological responses in humans(14). To aid in the healing and recovery of skeletal muscle injuries, biological engineering, and regenerative healthcare have employed bioprinted bone and cartilage(2, 3, 15, 16), and in-situ bioprinting technology has been used to enable direct printing in the surgical site and the regeneration of complex larger tissues through body-driven cardiovascular regeneration(4, 17, 18). Due to the rise of artificial intelligence, some studies have proposed 3D printing combined with artificial intelligence to print tissue organs(19). Bioprinted tumor models exhibit vastly different molecular features, gene expression, and drug sensitivity than conventional 2D models and have great potential for both basic and applied oncology research. In contrast to 2D models, they can mimic complicated 3D cell-cell and cell-matrix connections that have been crucial to physiopathology(20).

Tumor models are important tools necessary for studying various aspects of tumorigenesis, diagnosis and treatment(21). The traditional use of flat dish cultured cell models and xenogeneic animal models have unavoidable natural inherent defects that make the clinical translation of research results low(22), severely limiting the pace of human attack on tumors, and the task of developing new and appropriate tumor models to be applied in tumor research has become imminent. The in *vitro* reconstruction of human tumors faces numerous challenges, including in *vitro* construction methods, support material systems, culture systems for nutrition and oxygen maintenance and metabolic waste elimination, in *vitro* reconstruction of 3D tumors replicating the in *vivo* tumor microenvironment is moving in a more promising path thanks to the advancement of 3D bioprinting technology. Common methods used for 3D bioprinting of tumor models include extrusion bioprinting(23), inkjet bioprinting(24), light-curing bioprinting(25), and laser-assisted bioprinting(26), etc. Materials used for

bioprintability include synthetic and natural hydrogels like polyethylene glycol (PEG), Planitronic F-127, sodium alginate, gelatin and its derivatives, and hyaluronic acid and its derivatives(27-29). The research direction and content of the applications include the construction of the tumor microenvironment, tumor stem cells, tumor vascularization, tumor therapy tolerance and drug screening, tumor immunotherapy, and precision medicine. 3D bioprinting has been used to create a variety of tumor models, including neurological tumors, breast cancer tumors, reproductive system tumors, digestive system tumors, bone tumors, and skin tumors, among others.

In order to apply 3D bioprinting in oncology applications, it is essential to have a general grasp of how 3D bioprinted tumor models work today. For readers interested in fundamental and translational research on 3D bioprinted tumor models, it also offers a critical analysis of those models and their drawbacks.

3D bioprinting technology

Currently, there are four main 3D bioprinting technologies for tumor models, including droplet bioprinting (DBB)(30)(Fig. 1a), extrusion bioprinting (EBB)(23) (Fig. 1b), laser-assisted bioprinting (LAB)(31)(Fig. 1c), and stereolithography bioprinting (SLB/DLB)(32)(Fig. 1d). Each bioprinting method has already been thoroughly explained. As a result, we will list below the benefits and drawbacks of the four bioprinting methods.

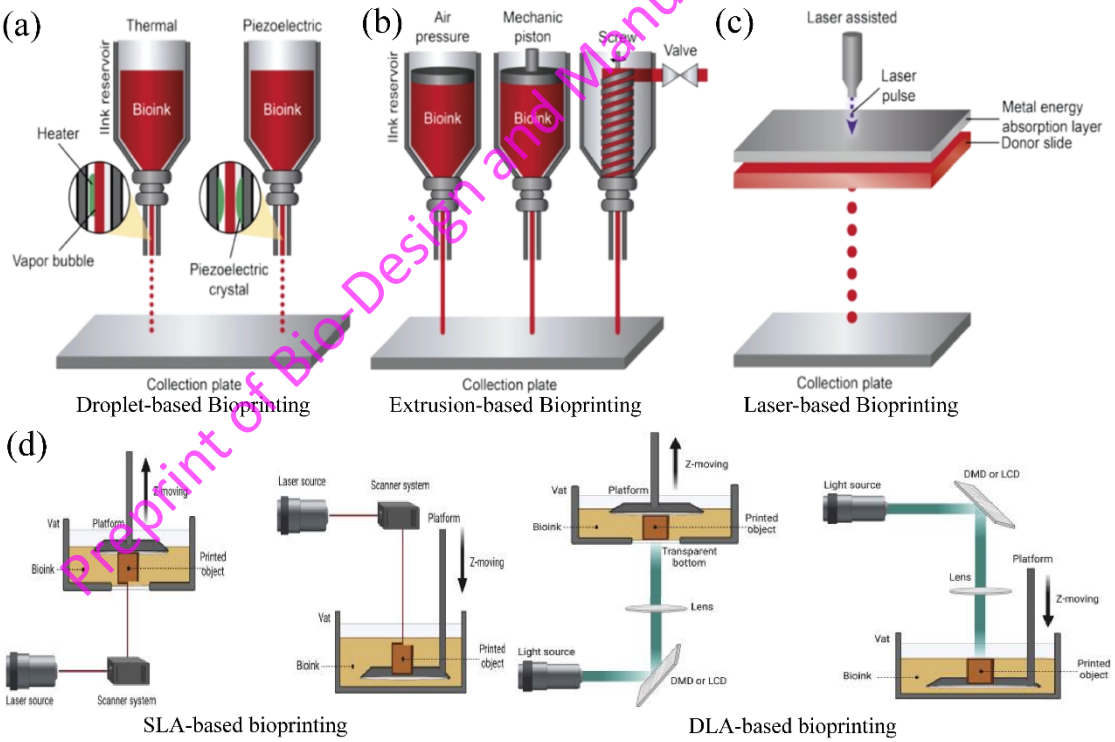

Fig. 1 Five methods of bioprinting. **a** Droplet-based Bioprinting; **b** Extrusion-based Bioprinting; **c** Laser-based Bioprinting (adapted and modified from Ref. (33), Copyright 2023, with permission from The Royal Society of Chemistry); **d** SLA/DLA-based Bioprinting. (adapted and modified from Ref. (34), Copyright 2023, with permission from the author(s).)

Droplet bioprinting (DBB)(30), also known as "drop-by-drop" printing, is a non-contact printing technology that can be categorized as inkjet, piezoelectric, acoustic and microwave bioprinting(35-37). Currently, droplet bioprinting has been successfully applied to many different types of tumors, including breast, colorectal, and liver cancers (38-40). Because of the deposition pattern's comprehensive control, rapidity, flexibility, and ease of usage, it offers several benefits. Regulating the quantity of bioink deposited at a preset area makes it possible to print living cells and makes it easier to localize cells clearly(3). The method currently encounters difficulties like the limited selection of bioink materials that can be used for printing, non-homogeneous droplet sizes and nozzle clogging, a substantial amount of bioprinting-induced cell death, a bioprinted constructions lacking integrity and mechanical strength, and a lack of vascularization and porousness that restricts the size of printed structures(35, 41). Extrusion bioprinting, also known as "layer-by-layer" printing, is an extremely popular and inexpensive 3D printer for both biological and non-biological materials, whereby the desired 3D spatial structure is created by extruding a fluid ink from a specific ID needle through layer-by-layer stacking of 2D structures by pneumatic, piston or screw power(23, 42). Currently, EBB technology has been successfully used in the study of a variety of tumors, including breast, liver, and colorectal cancers (43-45). It can create tissue at extremely high cell densities while vertically printing hyper-viscosity biological inks like clay substrates, and complicated polymers, along cell spheroids(46, 47). However, it can lead to cellular structure deformation and viability loss and is only ideal for printing thick liquids(46, 47). DBB is analogous to laser-assisted bioprinting (LAB), an indirect manufacturing technology that utilizes laser-induced transfer of energy(31, 48-50). In recent years, LAB technology has been used in the construction and study of a variety of tumors, including breast cancer, glioblastoma, and pancreatic cancer (51-53). In terms of bioprinting, LAB does away with the need for printheads and provides the benefits of high throughput, high resolution, and high speed(54, 55). This not only eliminates the issue of printhead failure or clogging but also enhances the compatibility of printed materials while extending the range of viscosities of printable material applications(56). However, during laser transfer, live cells may be subjected to thermal and/or mechanical stressors. If these stresses exceed the ability of the cell to withstand them, irreparable damage may result(57-59). SLB /DLB is a bioprinting method that in the existence of cells utilizes micromirror arrays to photopolymerize polymer resins(32). Since it is not prone to alignment problems that single-nozzle extruders are prone to, it allows for rapid printing of biological cells with high resolution and without the need for additional support materials, and the cells have extremely high viability (>85% viability)(60-62). SLB/DLB technology has been applied in the research of multiple types of tumors, such as breast cancer, liver cancer, glioma, and so on (63-65). SLB/DLB, however, has numerous drawbacks, including the absence of biodegradable and biocompatible polymers, the adverse impacts of harmful light-curing components on the cells, being unable to completely remove the framework, and the lack of ability to generate horizontal variations in the designs(46, 66). These problems need to be addressed using this technique.

A single bioprinting approach has not yet been able to produce synthetic tissues and

organs that are perfect in every way. The many approaches to bioprinting desired tissues differ owing to considerations of their particular guidelines, material needs, and benefits and drawbacks(67). The development of 3D bioprinting in the medical industry has had a considerable impact on both the production of medical equipment and the therapeutic industry. We may combine these techniques to produce the necessary tissues since 3D bioprinting has been divided into several categories based on its functions.

Bioinks

Bioink is a key material in 3D bioprinting technology, which consists of cells, matrices, and other biomaterials, and can be used to 3D print a variety of biological tissues that require complex structures and specific functions(68). Bioinks can be categorized into natural bioinks and synthetic bioinks based on their source, and currently used bioinks can be collected in Table 1. Since different 3D bioprinting technologies have different requirements, the selection of bioinks must take into account characteristics such as biocompatibility, mechanical properties, hydrophilicity, porosity, acid-base neutralization, and biodegradability(69-71). In the larger literature, many kinds of bioinks and their appropriate printing techniques have been detailed in depth(72, 73). This review will focus on an overview of natural and synthetic bioinks and their applications in tumor models.

Most natural bioinks were applied for tumor models, including gelatin, hyaluronic acid, fibronectin, filipin, dextran, sodium alginate, chitosan, collagen, cellulose, decellularized extracellular matrix (dECM), matrix gels, junction cold gels, cellular aggregates, and konjac gum(74). Using glial cells embedded in hyaluronic acid hydrogels as bioinks, for instance, Ma created a trustworthy experimental model for the investigation of aggressive glioma migration(75). In order to create durable and shape-retaining 3D-printed tumor models that imitate tumor micro-environment (TME) for chemotherapeutic drug screening of triple-negative breast cancer and lung adenocarcinoma, Gebeyehu and colleagues created polysaccharide-based bioinks(76). The extracellular matrix microenvironment of the tumor is more accurately represented by the dECM made from tissues. For the 3D bioprinting of tumor models, a variety of dECM bioinks have been employed. These include glioblastoma microarray bioprinting utilizing dECM bioinks produced from healthy pig skin or brain and bioprinting of hepatic cancer utilizing hepatic dECM bioinks(64, 77, 78). Although dECM has the benefit of closely resembling the original tumor stroma, it may lose certain crucial elements, including glycosaminoglycans(79), and has poor mechanical properties(64). Because stromal gels' complexity is equivalent to the make-up of in *vivo* cells, they are frequently employed as the foundation for 3D carcinoma modeling. The repeatability and exact regulation of the chemical and mechanical characteristics of organic bioinks to bioprinting, however, are sometimes hampered by matrix gels' batch-to-batch fluctuation and poorly specified compositions(80). Compared to natural bioinks, synthetic bioinks are tunable, simple to prepare, have higher mechanical properties and immunogenicity, and easily meet different printing requirements(81). Polyethylene glycol, polycaprolactone, polyvinylpyrrolidone, poly(l-lactic) acid, and poly(lactic-go-

glycolic) acid are a few examples of synthetic bioinks that are often utilized(82). Multi-arm PEG was used by Anseth's team to model the interaction between stromal cells and melanoma cells(83). It has been demonstrated that lung adenocarcinoma tumor growth may be mimicked using acrylate-modified PEG hydrogels(84, 85). Shi et al. used poly(lactic-co-glycolic acid) (PLGA) hydrogels to print drug-loaded scaffolds, and they showed that doing so dramatically reduced breast cancer development and recurrence(86). However, synthetic bioinks continue to face some difficulties, such as the use of harmful solvents or radiation that damages cells, and their limited cell compatibility, such as the lack of adhesion sites embedded in the cells, are significant issues(82), which have limited their use in some tumor models.

In order to guarantee that bioprinted tissues and organs operate properly, it is vital to use bioinks that have the required arbitrary, rheological, and physiological features of the specific tissue(87). Therefore, there is an urgent need for standardized bioink formulations that can be used for different bioprinting applications.

Table 1. Natural and synthetic bioinks currently in use and their advantages and disadvantages

		Advantages	Disadvantages
Natural Bioinks	agarose	good biocompatibility; forms gentle gels; degradable	lower plasticity
	alginate	easy to prepare; chemically and biocompatible; high plasticity	fairly biocompatible; not precise enough
	dextran	good biocompatibility; can form static gels; easy to process and modify	not very malleable; faster solidification
	hyaluronic acid	extremely cytocompatible and biocompatible; good water absorption and water retention; aids in cell migration and proliferation	expensive; not suitable for trauma
	silk	biological structure similar to human tissue; good biocompatibility and plasticity; can be customized through genetic engineering	expensive; requires chemical modification
	fibrin	biocompatible; promotes growth and regeneration; can form strong gels	easily degradable; requires the addition of blood during use
	collagen	biologically similar to human tissue; promotes cell attachment and	easily degradable

		growth; can be customized through genetic engineering	
	dECM	wide range of sources; natural fiber arrangement suitable for application to muscle, bone and other tissues	easy to pollute; high production costs
	matrigel	variety of substances such as collagen, ovalbumin and whey proteins that contribute to a complex three-dimensional environment; compatible with a wide range of cell types	significantly reduces the size of the cell patch, making it difficult to use for large tissue repairs
	cellulose	soluble cellulose is easy to process and modify; non-toxic; biodegradable; assimilable in the human body	plasticity is generally low
	gelatin	easy to handle and 3D print; good biocompatibility	possible adverse reactions
	chitosan	good biocompatibility and bioactivity; easy to process and modify	fragile, breakable; slow to solidify
	natural gums	biodegradable; can be modified to produce many different bioinks	less precise; more variable plasticity
Synthetic Bioinks	Polyethylene Glycol	biocompatible; forms highly controllable carriers; prevents protein inactivation	possible effect on growth factors
	Poly-Glycolic Acid	biodegradable; biocompatible; can form strong templates	rapid dissolution; susceptible to heat and free acid during dissolution, leading to protein inactivation
	Polycaprolactone	biodegradable; good plasticity; biocompatible	slower degradation; low expansion
	Polyvinylpyrrolidone	easy to prepare; good biocompatibility; properties can be adjusted by controlling the molecular weight	unstable and easily affected by light, heat, etc.
	Poly(L-Lactic) Acid	biodegradable; good biocompatibility; good bioabsorbability	slower degradation; potential for tissue irritation

	Polylactic-Co-Glycolic Acid	biodegradable; high strength; good biocompatibility; its degradation rate can be adjusted by controlling the ratio	insufficiently precise degradation rate; potential for tissue irritation
	Pluronic Acid	easy to prepare and process; forms stable gels; good biocompatibility	low gel strength; susceptible to temperature, pH, etc.
	Polydimethylsiloxane	good plasticity; good biocompatibility	reacts easily with other substances and loses stability
	Acrylonitrile Butadiene Styrene	strong, wear-resistant; organ structures can be fabricated by 3D printing	may cause tissue irritation; not degradable
	Polyether Ether Ketone	excellent biocompatibility; high stability and plasticity; biodegradable via	high production costs
	Polyvinyl Alcohol	Easy to prepare and process; good biocompatibility	low solubility and difficult to degrade
	Polyurethane	High plasticity; generally good biocompatibility; high strength; various organ structures can be fabricated by 3D printing	may cause tissue irritation; not degradable

3D bioprinting tumor models

Due to ethical and safety constraints and limitations, research on tumors and antitumor drugs is not allowed to directly conduct clinical studies. Compared with 2D models and animal xenograft tumor models, 3D tumor models have become the most promising tumor models for application due to their ability to simulate the microenvironment of human tumor tissues better(88, 89). Through precise colonization, various types of cells embedded in hydrogel materials to simulate the tumor microenvironment can be used to study the characteristics of tumorigenesis, tumor heterogeneity, invasion and migration, and anticancer drug sensitivity(90). Currently, 3D bioprinting has been carried out in a variety of tumors including glioma, breast cancer, liver cancer, colorectal cancer, cervical cancer, ovarian cancer, pancreatic cancer, intestinal cancer, pituitary tumor, neuroblastoma, and lung cancer, which lays the foundation for the fundamental and practical use of bioprinted tumor models for precision medicine(11, 22, 91-93).

Glioma

Glioma remain the greatest prevalent carcinomas located in the adolescent nerve system, with a high degree of malignancy, extremely high rates of recurrence and mortality, an average prognosis period of even less than one year, and a very low 5-year survival rate. Because there are currently very few effective treatments for glioma, it is

urgently necessary to develop new medications and therapies for use in the clinic(94-97). The biological tumor model serves as a useful tool for researching carcinogenesis and evaluating the impact of radiation treatment. It is predicted that the creation of 3D glioma models that are capable of simulating the in *vivo* milieu would present an opportunity to explore the process of glioma genesis and enhance the sensitivity and prognosis of radiation for glioma. The absence of appropriate tumor models has impeded research into brain malignant glioma.

Our team created an in *vitro* 3D model of glioma using 3D bioprinting technology to overcome the aforementioned issues, and discovered glioma stem cell enrichment effect and transdifferentiated vascular endothelial potential(98-100), as well as fusion of glioma stem cells with bone marrow mesenchymal stem cells(101, 102), which confirms that the 3D glioma model has stronger invasive and temozolomide-resistant characteristics(103)(Fig. 2a). Furthermore, studies have demonstrated that three-dimensional bioprinted glioma models more faithfully replicate in the human being tumor microenvironment(65, 104). For the biomanufacturing of micro-physiological brain structures over pharmaceutical evaluation and disease simulation applications, in addition to artificial neural organs and tissues for regenerative medicine, Haring et al. proposed a biomimetic hydrogel with Herschel-Bulkley fluid rheological properties(105) (Fig. 2b). Through a thorough examination of glioblastoma (GBM), DePalma offered a method for creating complex, multi-component in *vitro* cancer modeling, promising the creation of a tumor model that more precisely resembles in the *vivo* microenvironment of the tumor(106) (Fig. 2c). Most chemotherapeutic drugs have difficulty acting across the blood-brain barrier, Tang et al. proposed a bioprinting strategy that mimics relevant biomaterials from natural tissues as well as enabling model fabrication for more reliable mechanistic studies and preclinical drug screening, which may ultimately accelerate the drug development process for GBM(107). Heinrich, in 3D bioprinted glioblastoma models, added a macrophage component to study the interaction between macrophages and GBM(108) (Fig. 2d) and found that glioblastoma cells actively recruit macrophages and polarize them into glioblastoma-associated macrophages (GAMs)-specific phenotype and that macrophages have a role in inducing the development and intrusiveness of brain tumors. It has been discovered that patient-derived tumor stereo models more accurately capture the biological, biochemical, along bodily characteristics of real tumors(109), which may make cancer treatment plans more effective. It was possible to demonstrate parallels between the gene expression of cells cultivated in *vivo* and those in the 3D bioprinting system by the simultaneous generation of perfusive blood arteries employing sacrificial bioinks comprising pericytes and endothelial cells(110) (Fig. 2e). In order to study the interactions between cancer stem cells (CSCs) in proliferation and hypoxia, a new ex *vivo* model called patient-derived glioblastoma-like organs has been developed(111). These organs have the potential to be used in the future for things like individualized assay drug screening.

The 3D bioprinting of glioma models holds tremendous potential for the advancement of glioma research and treatment. However, I believe there are currently some challenges that need to be overcome. For instance, the complexity and cost of

bioprinting tumor models may limit their widespread clinical application. Additionally, the biological similarity and sustainability of the models still need further improvement in order to better reflect the characteristics of real tumors. Overall, I think that 3D bioprinting of glioma models is an exciting field with great potential. Through continued research and technological advancements, we can further develop these models and drive progress in glioma research and treatment, ultimately providing more effective personalized medicine for patients.

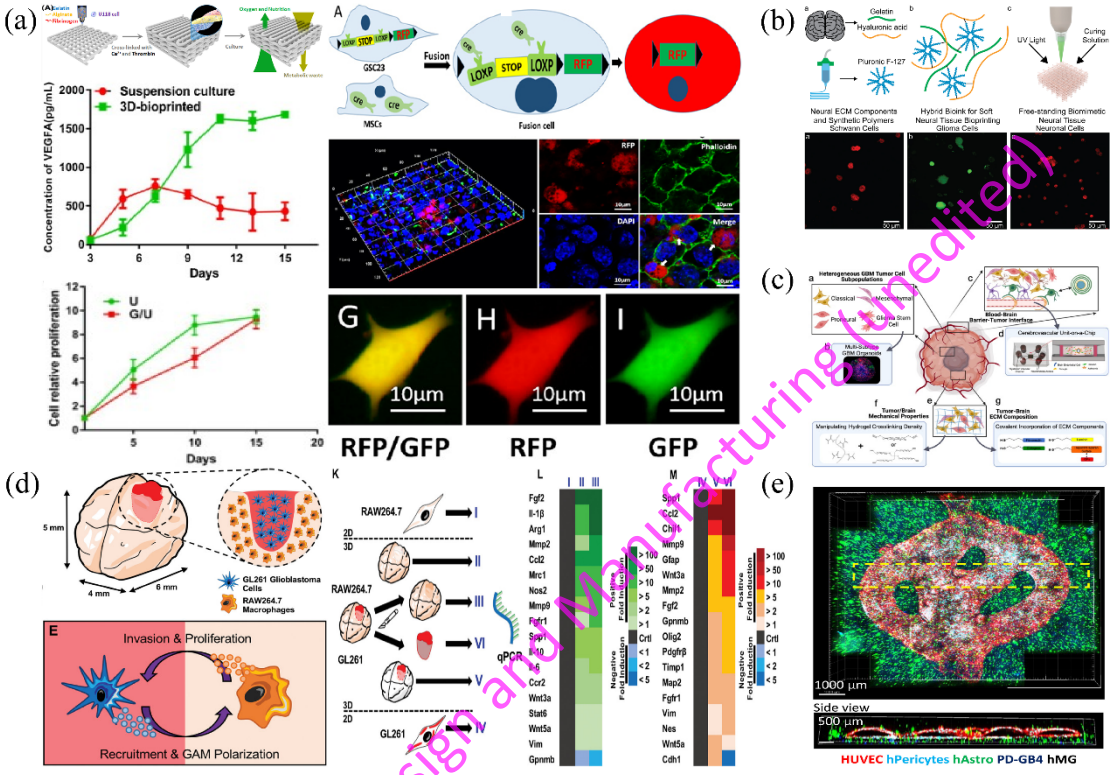

Fig. 2 3D bioprinting of brain glioma models. **a** 3D bioprinting technology to create in *vitro* 3D models of gliomas and further study of glioma stem cell properties and applications;(adapted and modified from Ref. (98), Copyright 2018, with permission from Elsevier B.V.; adapted and modified from Ref. (99), Copyright 2018, with permission from Wiley Periodicals, Inc.; adapted and modified from Ref. (101), Copyright 2017, with permission from the author(s); adapted and modified from Ref. (102), Copyright 2022, with permission from American Chemical Society; adapted and modified from Ref. (103), Copyright 2018, with permission from Elsevier B.V.) **b** A biomimetic hydrogel bioprinted glioma model with Herschel-Bulkley fluid rheological properties; (adapted and modified from Ref. (105), Copyright 2019, with permission from IOP Publishing Ltd) **c** A strategy for developing complex multicomponent in *vitro* glioma models;(adapted and modified from Ref. (106), Copyright 2021, with permission from Elsevier B.V.) **d** Macrophage-GBM interactions in a 3D bioprinted glioblastoma model; (adapted and modified from Ref. (108), Copyright 2019, with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.) **e** Creating perfusable blood vessels using sacrificial bioinks containing pericytes and endothelial cells to study the relationship between cellular gene expression; (adapted and modified from Ref. (110), Copyright 2021, with permission from the authors)

Breast cancer

The latest statistics from the World Health Organization (WHO) show that for the first time, breast cancer cases surpassed lung cancer as the dreaded killer of human health(112). One of the best ways to treat clinical malignancies systemically is chemotherapy, but few of these treatments have received Food and Drug Administration (FDA) approval for clinical trials since there aren't enough bionic tumor models for drug testing(113, 114). In addition to the large number of cancer cells that make up breast cancer, a key factor in regulating the cellular activity of the malignancy's microenvironment is the extracellular matrix (ECM) of the tumor (115-117). In order to boost their biocompatibility and heterogeneity and to produce better realistic in *vitro* tumor models, efforts are being made to add tumor stromal components into bioinks that mimic the tumor stromal milieu(118).

Epithelial-adipose interaction is an indispensable step in the development of lethal metastasis of breast cancer cells, and Chaji et al(119) investigated adipocyte-breast cancer cell interactions by simulating breast cancer tumors through 3D bioprinted breast cancer tumor models(Fig. 3a). Vinson(120) used laser direct-write bioprinting to incorporate a hydrogel matrix containing differentiated adipocytes loaded with breast cancer cells in a microbeads biofabricated simulation models of breast cancer cell invasion into adipose tissue, which allowed tracking of MCF-7 and MDA-MB-231 breast cancer cell invasion for more than 2 weeks in an optically transparent hydrogel scaffold(Fig. 3b). Blanco-Fernandez et al(121) (Fig. 3c) developed a decellularized tissues and organ-derived matrices (TDM) bioink based on decellularized porcine breast tissue combined with type I collagen, which was able to tightly reconstruct breast tumors in *vitro*, promote breast cancer cell proliferation to form cell clusters and spheroids, and increase the model resistance, which is a good biomaterial for creating breast carcinoma models, and the decellularized human or rat mammary tissues were also used to make hydrogels(122). These ECM hydrogels are able to retain unique structures and signaling profiles to construct breast cancer-like organs with tissue-specific matrices. In addition, there are hydrogel-based models of hydrogel-encapsulated breast cancer shell and core structures printed by laser direct writing(123), scaffold-free 3D breast cancer tumors(124), as well as 3D vascularized breast cancer structures and mimicked breast duct-like structures and filled with breast cancer cells(125, 126). It is shown that 3D tumor models are important for studying the interaction between tissue-specific ECM and cancer cells as well as cancer treatment. Burks et al used laser direct-write bioprinting of breast cancer cells onto ex *vivo* microvascular networks containing vasculature, lymphatic vessels, and mesenchymal cell populations for the purpose of quantifying cancer cell migration and the effects on angiogenesis and lymphangiogenesis in an intact network that needs to resemble the complicated makeup of the tumor's microenvironment(127) (Fig. 3d).

Breast cancer metastasis will lead to fatal consequences, and the currently existing 3D bionic models are insufficient to similarize this procedure in *vitro*. In order to study the interactions among breast cancer (BrCa) cells and bone tissue cells, Zhou et al(128) developed a hydrogel with a bionic bone matrix using stereolithography 3D bioprinting (Fig. 3e). They discovered that BrCa cells had been improved through the existence of bone marrow and mesenchymal stem cells (MSCs), while bone marrow and mesenchymal stem cell (MSC) proliferation were blocked because of BrCa cells. 3D bioprinted BrCa cells and bone stromal metastatic cancer models provide an

opportunity to study the mechanisms and the mechanisms of cancer of breast bone metastases and MSCs. It was discovered that the presence of osteoblasts and MSCs boosted BrCa cells while inhibiting the proliferation of these cells. A useful technique for researching the mechanism of breast cancer's bone metastasis and developing targeted treatments is the 3D bioprinting of BrCa cells and skeletal tissue metastatic cancer models.

The intimate tumor milieu is more closely resembled by 3D cancer models than by traditional 2D cultures, and 3D bioprinting allows for fast duplication of a cancer microenvironment allowing high-throughput screening of drugs(129). In an in *vitro* breast tumor model, Jiang et al.(130) reported using an engineered composite hydrogel made of gelatin and alginate components to create multicellular tumor spheroids from 3D bioprinted breast cancer cells (Fig. 3f). To produce tumor tissue models that are able to be employed right away, Swaminathan et al(131) also investigated the bioprinting of pre-formed 3D spheres of breast cancer directly in alginate-based bioinks. Individuals' breast epithelial cell lineages got bioprinted as single cells or as spheres that had already been produced and retained their viability, structure, and function (Fig. 3g). The anti-tumor medications camptothecin and paclitaxel did not have the same effect on the independently printed breast cells as they did on the bioprinted breast spheroids(132). Nam(133) built 3D complex tissue structures containing processed gels obtained from porcine skin and human decellularized adipose tissue by bioprinting and demonstrated their potential in breast tumor therapy using plasma photothermal therapy (PPTT) with gold nanoparticles (AuNPs) (Fig. 3h). In recent years, there has been an upsurge in nanomedicine research for tumor therapy, The conventional methods for evaluating nanoparticles (NPs) have mainly relied on two-dimensional cultures of cells and models of animals. These models, however, cannot comprehensively explore the complicated movement of NPs and have difficulty adequately simulating the human tumor microenvironment, which restricts the application of nanomedicine formulations in clinical research. Chen (134) used fat-dECM-enhanced hybrid bioinks to fabricate tumor models via 3D bioprinting, which not only more closely resembled real tumors in terms of tumor proteins, gene expression, and tumorigenicity, demonstrating ECM reconstruction and transition from epithelial to mesenchymal features, but also observed higher nanomedicine resistance, suggesting that the model is expected to provide greater precision platforms for pharmaceutical development and design prior to entry into animal and clinical trials (Fig. 3i).

I believe that 3D bioprinting of breast cancer models is an important technology in the field of breast cancer research and treatment. By having more realistic, comparable, and user-friendly breast cancer models, we can better understand the mechanisms of breast cancer development, evaluate the effectiveness of different treatment strategies, and conduct drug screening. However, there are still some challenges that need to be overcome. For instance, bioprinting breast cancer models require high-precision techniques and complex equipment, which can be costly and time-consuming. Furthermore, there is still room for improvement in terms of the biological similarity and reproducibility of bioprinted models, particularly in simulating the interactions between cancer cells and normal cells in a 3D environment. In summary, I believe that 3D bioprinting of breast cancer models is a promising field that can bring significant advancements to breast cancer research and treatment. By continuously improving the technology and conducting further research, we can enhance the clinical applications of bioprinted models and provide better medical services for patients.

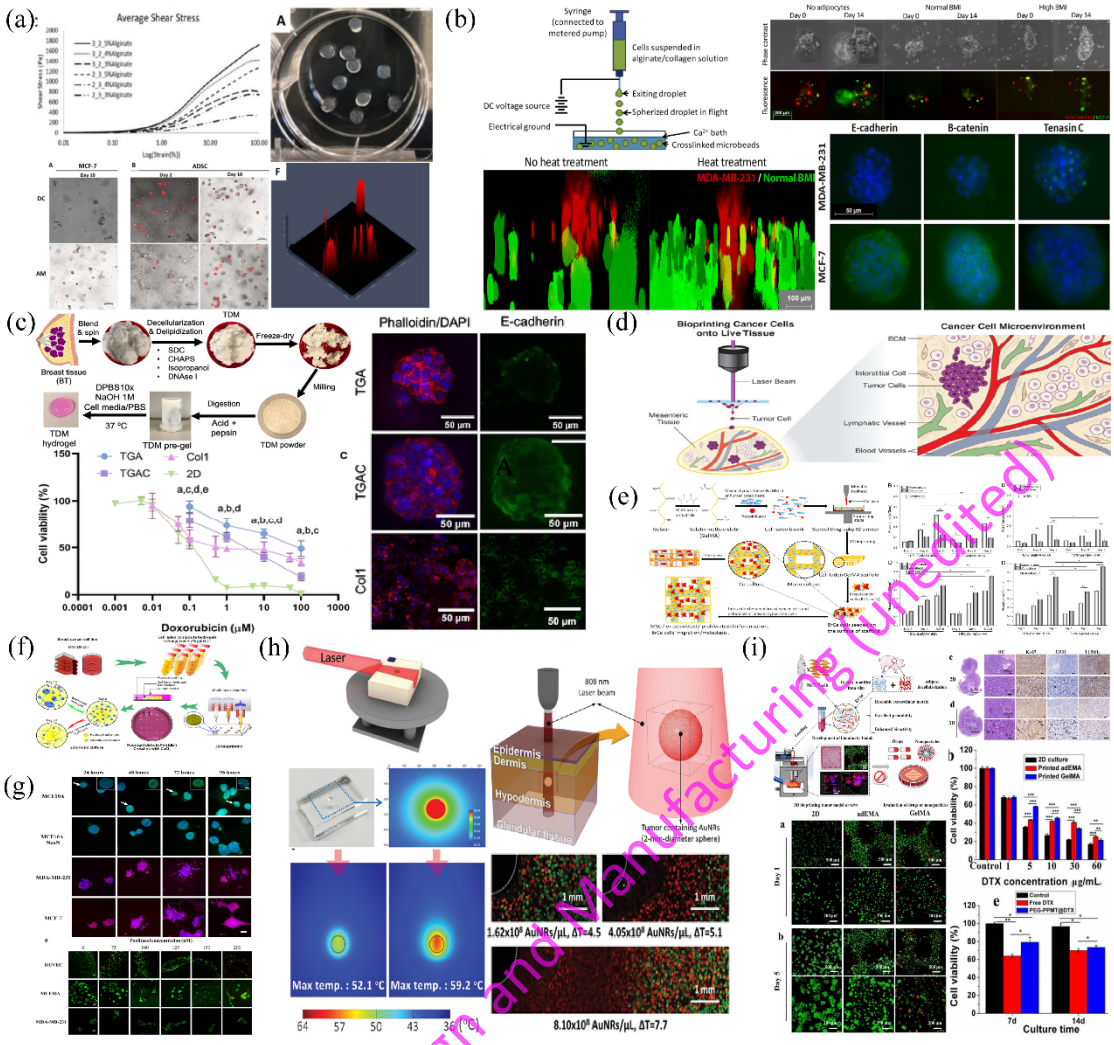

Fig. 3 3D bioprinting of breast cancer tumor models. **a** 3D bioprinted breast cancer tumor model to study adipocyte-breast cancer cell interactions;(adapted and modified from Ref. (119), Copyright 2020, with permission from the authors.) **b** Laser direct writing bioprinted breast cancer models to study tumor invasiveness and drug resistance; (adapted and modified from Ref. (120), Copyright 2017, with permission from IOP Publishing Ltd) **c** Development of TDM bioink based on decellularized porcine udder tissue combined with type I collagen and cell viability study;(adapted and modified from Ref. (121), Copyright 2022, with permission from the authors.) **d** Bioprinting cancer cells onto live tissue as an ex *vivo* model to study cell migration;(adapted and modified from Ref. (127), Copyright 2016, with permission from Wiley Periodicals, Inc.) **e** Schematic diagram of direct, 3D bioprinted, cell-laden bone matrix as a biomimetic model for breast cancer metastasis study; (adapted and modified from Ref. (128), Copyright 2016, with permission from American Chemical Society) **f** Schematic depicting the generation of the composite gels, bioprinting process, and subsequent generation of MCTS of breast cancer cells in bioprinted alginate/gelatin hydrogels;(adapted and modified from Ref. (130), Copyright 2019, with permission from IOP Publishing Ltd) **g** Bioprinted 3D breast epithelial spheroids maintained typical spheroid morphology for 96 h in collagen/alginate bioink and Representative Live/Dead images from co-culture experiments showing HUVEC, MCF10A, or MDA-

MB-231 bioprinted grid areas;(adapted and modified from Ref. (131), Copyright 2019, with permission from IOP Publishing Ltd) **h** Quantitative Photothermal Characterization with Bioprinted 3D Complex Tissue Constructs for Early-Stage Breast Cancer Therapy Using Gold Nanorods;(adapted and modified from Ref. (133), Copyright 2021, with permission from the authors.) **i** 3D bioprinted tumor model with extracellular matrix enhanced bioinks for nanoparticle evaluation;(adapted and modified from Ref. (134), Copyright 2022, with permission from IOP Publishing Ltd.)

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the second-greatest contributor to the number of cancer-related deaths globally and is ranked fifth among the most numerous malignancies(135). The stiffness of the hepatic extracellular matrix has a significant impact on the onset and progression of HCC and is correlated with greater stiffness values in healthy liver parenchyma(136, 137). Additionally, HCC progression includes invasion of the fibrous septum by tumor tissue(138). The traditional approach to studying HCC progression involves simply adjusting the 2D substrate stiffness; yet this model lacks an accurate representation of the 3D mechanical environment seen in the natural liver, which might cause the results to differ from those obtained using 3D methods(139-142).

Ma(64) developed a photocrosslinkable liver dECM and a quick 3D bioprinting process based on light curing as a platform for the study of the progression of HCC occurrence (Fig. 4a). Cirrhotic liver tissue's mechanical characteristics might be securely encapsulated in 3D bioprinted liver dECM scaffolds. HepG2 cells showed decreased proliferation and an increase in invasive markers when enclosed in dECM scaffolds with cirrhotic stiffness as opposed to unaffected controls. Li et al.(143) integrated 3D bioprinting, co-culture and microfluidics to build a 3D co-culture microfluidic model of a controllable hepatocellular carcinoma-like histosome and applied it to the pharmacodynamic test of a novel anti-CD147 monoclonal antibody, metoclizumab, and found that hepatocellular carcinoma cells in the new model had a faster proliferation rate and less impact on migration performance and proliferation than the common *in vitro* 3D model fabricated only by cell printing(Fig. 4b). The findings are in line with those of comparable animal studies and anti-CD147 clinical trials, and they offer an invaluable frame of reference for the investigation of intricate in *vitro* liver cancer models. Sun et al(44) created 3D models with HepG2 cells using extruded 3D bioprinting, revealing a dramatic difference in gene transcription across 3D models and 2D cell cultures, particularly mutations associated with hepatocyte function. They also compared antitumor drug sensitivity, and hypothesized that this difference may lead to differences in drug pharmacodynamics (Fig. 4c). Hwang(144) first proposed a DLP-based integrated 3D bioprinting platform to print liver cancer cell models in conventional porous cell culture plates to rapidly generate in *vitro* 3D tissue models for high-throughput preclinical drug screening and disease modeling. The choice of bioink is equally important to the printing technique (Fig. 4d). Ying(145) developed a novel bioink formulation based on an aqueous two-phase emulsion of gelatin methacryloyl (GelMA) solution and polyethylene oxide (PEO) solution, and printed tumor cells

showed enhanced cell viability, spreading, and proliferation (Fig. 4e). Polez(146) proposed for the first time to use a hydrogel of plant origin as a bioink for printing hepatocellular carcinoma tumor models and showed that the scaffold promoted the proliferation of hepatocellular carcinoma HepG2 cells by in *vitro* cell viability testing (Fig. 4f). Recently, Zhang et al(147) constructed an injectable cellular hydrogel consisting of 2,2,6,6-tetramethylpiperidine 1-aryloxy oxidized cellulose nanofibers (TOCNF) and chitosan nanofibers (CsNF), to better mimic the cellular microenvironment and offer the potential of biologically-adaptive 3D cell culture for biomedical applications (Fig. 4g). Mao(148) bioprinted intrahepatic cholangiocarcinoma cells isolated from patients into pre-designed grid structures using a gelatin-alginate-Matrigel TM composite hydrogel system. The colony-forming ability of intrahepatic cholangiocarcinoma cells with high viability and active proliferation was observed. The tumor microenvironment of the aggressive and metastatic phenotype of intrahepatic cholangiocarcinoma cells was confirmed by the expression levels of tumor markers, cancer stem cell markers, matrix metalloproteinase proteins, tumor fibrosis index, liver function index, and epithelial-mesenchymal transition regulatory proteins in 3D prints. Further, the team used clinical specimens from hepatocellular carcinoma patients for bioprinting to successfully construct 3D models of patient-derived hepatocellular carcinoma tissues and achieve a longer-term culture in *vitro*, which retained the characteristics of parental hepatocellular carcinomas, including stable biomarker expression, genetic alterations, and stable maintenance of expression profiles, and are expected to be able to predict patient-specific medications for personalized therapy(149).

3D bioprinting of liver cancer models is an important technology in the field of liver cancer research and treatment. However, similar to breast cancer models, 3D bioprinting of liver cancer models also faces some challenges. For example, it requires high-precision printing techniques and complex equipment, and there is still room for improvement in terms of biological similarity and reproducibility of the models. Additionally, considering the complex structure and function of the liver, completeness and authenticity of the models are also crucial factors to consider. In conclusion, I believe that 3D bioprinting of liver cancer models is a promising field that can bring significant advancements to liver cancer research and treatment. By continuously improving the technology and conducting further research, we can enhance the clinical applications of liver cancer models and provide better treatment options for liver cancer patients.

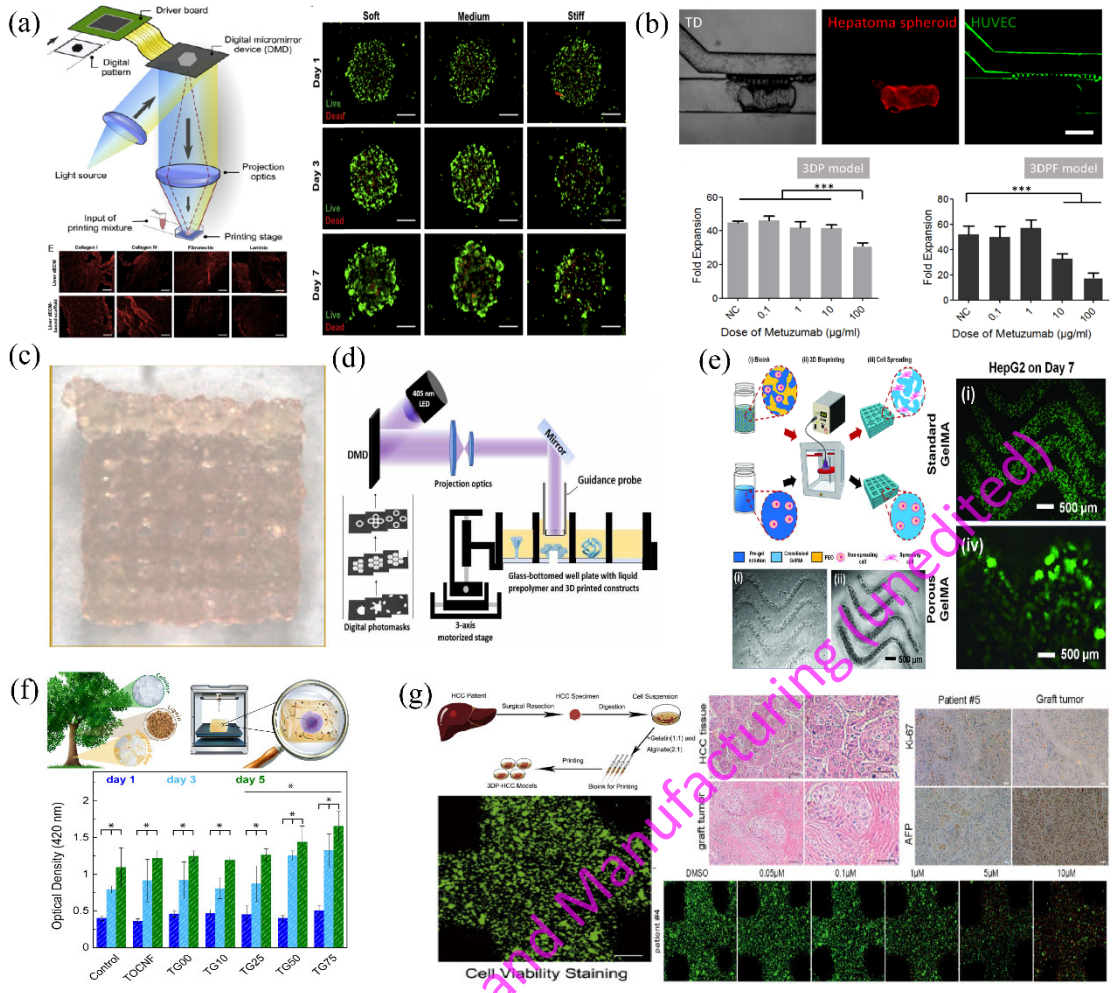

Fig. 4 3D bioprinting of hepatocellular carcinoma tumor models. **a** Schematic diagram showing the bioprinting of the dECM-based hexagonal scaffolds and Characterization of HCC growth and invasion potential in dECM-based scaffolds with varied stiffness; (adapted and modified from Ref. (64), Copyright 2018, with permission from Elsevier Ltd.) **b** 3D bioprinting of hepatocellular carcinoma cells and its microfluidic application in pharmacodynamic testing of Metuzumab; (adapted and modified from Ref. (143), Copyright 2019, with permission from IOP Publishing Ltd.) **c** 3D bioprinting of hepatocellular carcinoma cell models in antitumor drug research; (adapted and modified from Ref. (44), Copyright 2020, with permission from the authors.) **d** DLP-based integrated 3D bioprinting platform prints liver cancer cell models for high-throughput preclinical drug screening and disease modeling;(adapted and modified from Ref. (144), Copyright 2021, with permission from IOP Publishing Ltd.) **e** Novel bioink formulation based on gelatin methacryloyl solution and polyethylene oxide solution for printing tumor cells and studying their cell viability, spreading, and proliferative capacity;(adapted and modified from Ref. (145), Copyright 2018, with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.) **f** Printing hepatocellular carcinoma tumor models using plant-derived hydrogels;(adapted and modified from Ref. (146), Copyright 2022, with permission from the authors.) **g** Patient-derived three-dimensional bioprinted HCC (3DP-HCC) model and its study;(adapted and modified from Ref. (147), Copyright 2020, with permission from

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Colorectal cancer

Currently, the cancer of the colorectal is recognized as a serious disease that may affect human beings(112, 150). Fibroblasts and endothelial cells that have been enlisted from neighboring tissues make up the complicated mesenchymal extracellular matrix that makes up the solid tumor microenvironment(151-153). Tumor-associated endothelial cells (TECs) are associated with tumor malignancy and metastasis(154) and affect not only the metabolism of tumors(155) but also their resistance to drugs(156). Co-culturing cancerous cells with TME-related cells is a unique method for analyzing different TME characteristics. TME-associated cells produced from normal cells can evolve into tumor-specific stromal cells under the control of tumor signaling and can be used to create in *vitro* 3D tumor models due to their innate flexibility. Chen et al(157) developed a method for obtaining tumor-associated stromal cells and constructed a reproducible 3D colon cancer tissue model (3DT) using 3D printing, which allowed for direct cell-to-cell straightforward interactions and the formation of tissue network structures (Fig. 5a). Similar results were obtained with a coaxial bioprinted intestinal-like tissue body constructed by Han(158) (Fig. 5b). Cadamuro developed a protocol for 3D bioprinting of colorectal cancer (CRC) models based on hyaluronic acid and signaling glycans, and the results demonstrated that glycosylated hydrogels showed good 3D printability, biocompatibility and long-term stability(159) (Fig. 5c). A three-dimensional multicellular model consisting of SW480 cells, tumor-associated macrophages, and endothelial cells was constructed by 3D bioprinting, and the biological activity of the model was evaluated by immunofluorescence, hematoxylin and eosin staining of frozen pathological sections, and transcriptome sequencing, which was further implemented in the antitumor drug screening experiments, and it was found that the 3D printed-M group was significantly more resistant to chemotherapy as compared with the 3D printed-S group(160) (Fig. 5d). Sbirkov built an affordable, flexible and highly replicable 3D bioprinted CRC model that can be used for disease modeling and drug testing, and tested the experimental platform with three of the most commonly used chemotherapeutic drugs (5-fluorouracil, oxaliplatin, and irinotecan), providing innovative opportunities for personalized treatment screening (45) (Fig. 5e). The 3D tumor model also exhibited a physiological state similar to that in *vivo*, with a high degree of drug resistance, with continuous long-term culture for monitoring and functional assessment. Andrew(161) used hybrid nano-inks composed of alginate, gelatin methacryloyl (GelMA), and cellulose nanocrystals (CNCs) with superior rheological and mechanical properties characteristics to apply multicellularity to fabricate complex in *vitro* intestinal cancer tumor models(Fig. 5f). Bowel cancer stem cells are the root cause of tumor recurrence and metastasis, and therapies targeting tumor stem cells are of the highest priority. However, in *vitro* expansion and stemness maintenance of bowel cancer stem cells are still relatively limited. Zhang(162) found that gelatin methacryloyl (GelMA)-nanoclay hybrid hydrogels were capable of inducing and enriching colorectal cancer stem cells in 3D bioprintable materials (Fig. 5g). However, it is still believed that in *vitro* rebuilding of organoids from patient-

derived tumor tissues is the most effective method for simulating the genuine tumor microenvironment. Chen(163) used patient-derived colorectal tumors and healthy organoids precisely aligned by acoustic bioprinting methods to re-encapsulate the structure of primary tissues (Fig. 5h). These tumor-like organs can be efficiently generated and can present histological, genomic, and phenotypic primary tumor features allowing physiologically relevant in *vitro* drug (5-fluorouracil) screening and thus prediction of response to patient-matched chemotherapy, establishing 3D bioprinting of colorectal cancer for precise and personalized medicine in bowel cancer tumor models. This study allows acoustic bioprinting of patient-derived colorectal cancer tumors to accurately reconstruct the primary tumor microenvironment and serve as an adjunctive diagnostic tool to guide clinical practice.

The 3D bioprinting of colorectal cancer models is an important technology in the field of colorectal cancer research and treatment. This model can provide a more realistic and accurate environment for colorectal cancer cells, helping us to better understand the disease's mechanisms and evaluate the effectiveness of different treatment strategies. However, this technology also faces several challenges. Firstly, it requires high-precision printing techniques and complex equipment to create colorectal cancer models. Secondly, to improve the biological similarity and reproducibility of the models, further improvements in printing materials and processes are needed. Additionally, the heterogeneity and individual differences of colorectal cancer increase the complexity of model design. Despite these challenges, I believe that 3D bioprinting of colorectal cancer models still holds tremendous potential. Through continuous research and technological advancements, we can gain a better understanding of the development process of colorectal cancer and provide more accurate and personalized treatment options. This will lead to improved treatment outcomes and survival rates for patients with colorectal cancer.

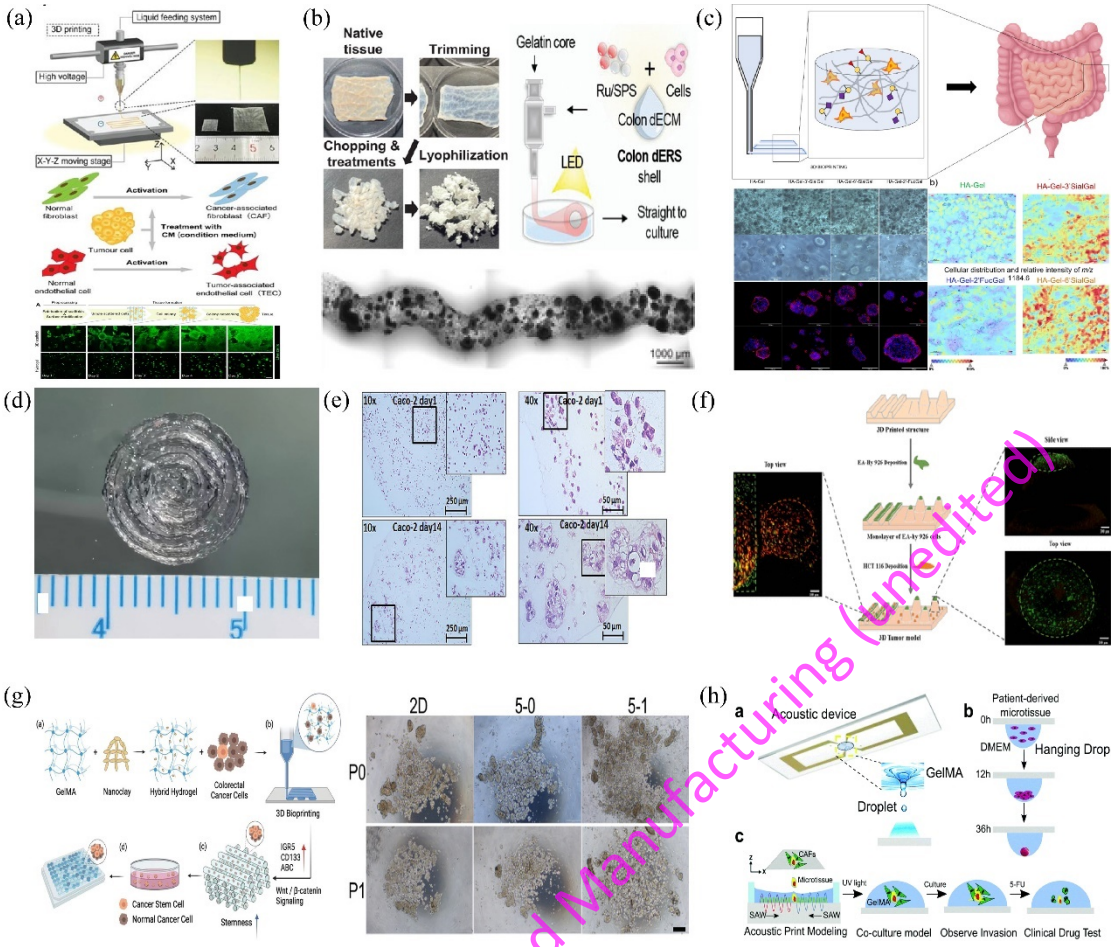

Fig. 5 3D bioprinting of colorectal cancer tumor models. **a** Flowchart of 3D printed colon cancer model and mechanism of promoting cell function network formation;(adapted and modified from Ref. (157), Copyright 2023, with permission from Ivyspring International Publisher.) **b** Bioprinted tubular bowel model using colon specific extracellular matrix bioinks;(adapted and modified from Ref. (158), Copyright 2021, with permission from Wiley-VCH GmbH) **c** A 3D bioprinted colorectal cancer model based on hyaluronic acid and signaling glycans;(adapted and modified from Ref. (159), Copyright 2022, with permission from the authors.) **d** Experimental results of antitumor drug screening in a three-dimensional multicellular model; (adapted and modified from Ref. (160), Copyright 2023, with permission from the authors.) **e** Three of the most commonly used chemotherapeutic drugs were subjected to drug testing results in a 3D bioprinted CRC model;(adapted and modified from Ref. (45), Copyright 2021, with permission from the authors.) **f** An illustration of hybrid nano-inks for multi-nozzle micro-extrusion 3D printing of tumor models;(adapted and modified from Ref. (161), Copyright 2022, with permission from American Chemical Society.) **g** Methacryloyl (GelMA)-nanoclay hybridized hydrogels induce and enrich colorectal cancer stem cells;(adapted and modified from Ref. (162), Copyright 2022, with permission from Wiley-VCH GmbH.) **h** Acoustic bioprinting of patient-derived colorectal tumors and healthy organoids;(adapted and modified from Ref. (163), Copyright 2022, with permission from the Royal Society of Chemistry.)

Cervical cancer

The 3D bioprinted cervical cancer model is one of the earlier three-dimensional bioprinted tumor models studied. Professor Sun Wei's team at Tsinghua University(164) reported an extruded 3D bioprinted Hela cells and gelatin/alginate/fibrinogen hydrogel for constructing an in *vitro* model of cervical cancer in 2014. The 3D bioprinted model of cervical cancer showed a high cell viability of up to 90%, maintained high proliferative activity, tended to form cell spheroids, and found that the secretion of matrix metalloproteinase (MMP)-2 and MMP-9 matrix metalloproteinases, which are associated with tumor invasive migration, was significantly increased compared with 2D (Fig. 6a). In addition, after treatment with paclitaxel chemotherapeutic drug, a large number of apoptotic cells, irregular cell morphology, loose cytoskeleton pattern, a significant decrease in the average diameter of cell spheroids, and significantly lower metabolic activity than that of the 2D control group could be observed in the 3D tumors. This result was similarly validated in Gospodinova et al.'s model of Hela biofabricated by extruded 3D bioprinting of a highly viscous and thixotropic hydroxyethyl cellulose-based hydrogel mixed with sodium alginate(165) (Fig. 6b). Professor Sun Wei's team in 2018(166) again reported that a 3D bioprinted tumor sphere model based on gelatin, sodium alginate, matrix gel, and cervical cancer cells successfully induced the epithelial mesenchymal transition (EMT) process in Hela cells by TGF-β (Fig. 6c). It was found that Smad2/3 was activated by TGF-β treatment pathway and promotes the expression of the transcription factor Snail, which inhibits the expression of E-cadherin and induces the expression of Vimentin and N-cadherin, whereas the use of disulfiram (DSF) and the EMT pathway inhibitor C19 to enclose TGF-β can successfully inhibit the EMT of 3D bioprinted cervical cancer cells. The EMT outcomes of 2D cultivated cells have been demonstrated to differ from those of 3D bioprinting-based cervical cancer models, which are anticipated to be a novel model for assessing the efficacy of chemotherapeutic drugs for cervical cancer. Recently, Becconi(167) used platinum nano-electrodes and scanning electrochemical microscopy to characterize oxygen concentration, a crucial aspect of the cellular microenvironment, at high spatial resolution in a tumor model (Fig. 6d). He also quantitatively measured drug molecule diffusion over time in a tumor model, which can be used in the future to evaluate the penetration and distribution of drugs in the body.

I believe that 3D bioprinting of cervical cancer models also holds great potential in terms of application. Compared to traditional 2D cell culture models, 3D bioprinted models can better simulate the three-dimensional morphology and microenvironment of tumors, presenting more realistic biological characteristics. As a result, they can effectively evaluate the efficacy of different treatment strategies. Similar to 3D bioprinting of colorectal cancer models, creating 3D bioprinted cervical cancer models also requires high-precision printing techniques and complex equipment. Suitable printing materials and processes are necessary to simulate the in *vivo* environment of cervical cancer cells, thereby enhancing the biological similarity and reproducibility of the models. Additionally, cervical cancer exhibits heterogeneity and individual differences, which need to be considered for more detailed and personalized model designs. Overall, the research and application of 3D bioprinted cervical cancer models

have broad prospects. They can help us better understand the development mechanisms of the disease and evaluate the effectiveness of different treatment strategies, ultimately providing more accurate and personalized treatment plans for patients.

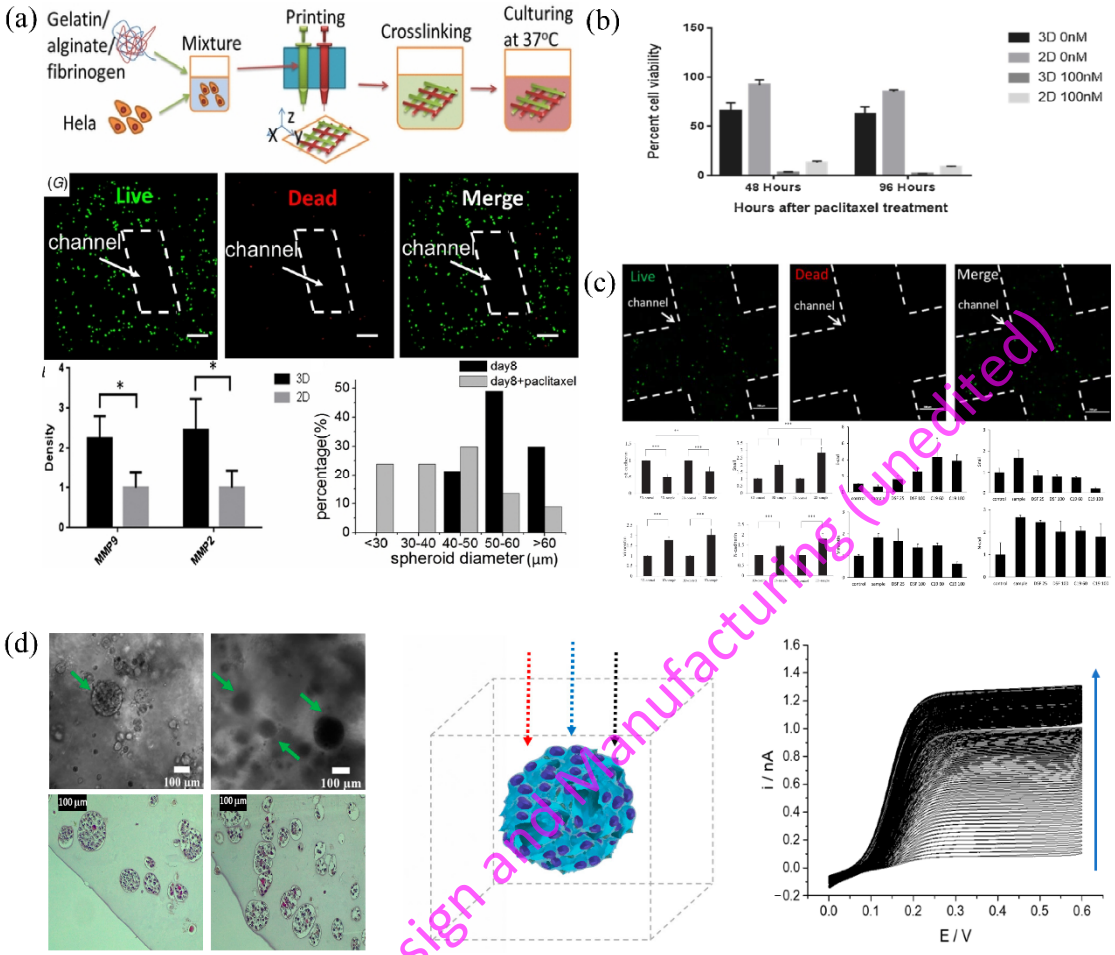

Fig. 6 A study of 3D bioprinted cervical cancer models. **a** 3D printing of Hela cells and gelatin/sodium alginate/fibrinogen hydrogels to construct an in *vitro* cervical cancer tumor model and to study cell proliferation, matrix metalloproteinase protein (MMP) expression and chemotherapy resistance;(adapted and modified from Ref. (164), Copyright 2014, with permission from IOP Publishing Ltd.) **b** Cell viability determined after 48 and 96 h of Paclitaxel treatment;(adapted and modified from Ref. (165), Copyright 2021, with permission from Elsevier Ltd.) **c** 3D bioprinted in *vitro* model of cervical cancer to study epithelial-mesenchymal transition (EMT) during cervical cancer metastasis;(adapted and modified from Ref. (166), Copyright 2018, with permission from IOP Publishing Ltd.) **d** Determination of Oxygen Concentration in HeLa Spheres Using Micron Spatially Resolved Scanning Electrochemical Microscopy for the Construction of Drug Diffusion Studies;(adapted and modified from Ref. (167), Copyright 2023, with permission from the authors.)

Ovarian cancer

High-throughput automated 3D ovarian cancer model production is made possible by combining extracellular matrix and ovarian cancer cells with 3D bioprinting. The biofabrication of ovarian cancer has been accomplished using droplet bioprinting

techniques. Xu et al(168) used a droplet-based system to print OVCAR-5 (an epithelial human ovarian cancer cell line) ovarian cancer cells and MRC-5 (normal human fibroblast cell line) normal fibroblasts in a controlled spatial distribution on Matrigel gel scaffolds to construct ovarian cancer micro-organisms in order to study the feedback mechanism between tumor and stromal cells and provide a high-throughput drug screening Tools (Fig. 7a). Wu(169) used an extrusion bioprinting platform to biofabricate 3D ovaries (Fig. 7b). While the focus of this study was on isolated oocyte maturation, ovarian cancer cell lines were used in the process of optimizing the biocompatibility of the bioinks, which showed high cell viability during and after the extrusion process. Baka et al. optimized the bioinks while investigating a variety of biological characterizations of ovarian cancer, including viability and proliferation assays, histology, and immunological staining, which laid the groundwork for studies such as drug screening(170) (Fig. 7c). Lucà et al(171) demonstrated by extrusion bioprinting that murine double minute 4 (MDM4) was able to reduce the ability of ovarian cancer cells to migrate and disseminate, while also impairing intravascular infiltration (Fig. 7d). Recently, Estermann proposed the creation of a 3D multicellular tissue model, which offers a cutting-edge platform for researching how ovarian cancer cells spread and may be crucial to the precise management of malignancies(172) (Fig. 7e). As an emerging biofabrication technology, 3D bioprinting in ovarian cancer models has been reported less frequently, and although ovarian cancer cells have not been investigated using techniques including inkjet bioprinting, laser-assisted bioprinting, or stereolithography to date, these are promising techniques that, in combination with synthetic bioinks with even more printable properties, could allow for the creation of high-throughput 3D cancerous ovarian cell models and high-throughput drug screening(173, 174).

Compared to traditional 2D cell culture models, 3D bioprinted ovarian cancer models have the advantage of better simulating the three-dimensional morphology and microenvironment of tumors, presenting more realistic biological characteristics, and thus can better evaluate the effectiveness of different treatment strategies. However, when creating 3D bioprinted ovarian cancer models, it is necessary to carefully select appropriate printing materials, processes, and equipment to simulate the complex biological environment of ovarian cancer cells in the body. In addition, ovarian cancer exhibits heterogeneity and individual differences, requiring more detailed and personalized designs to create accurate models. To address these issues, researchers need to continuously explore and improve the technology to enhance the biological similarity and repeatability of 3D bioprinted ovarian cancer models. In summary, the research and application of 3D bioprinted ovarian cancer models have broad prospects. They can provide more accurate and reliable models for early detection of ovarian cancer, formulation of treatment plans, and development of new drugs. However, further exploration and improvement in technology and research are still needed in order to fully realize its potential and bring greater benefits to patients.

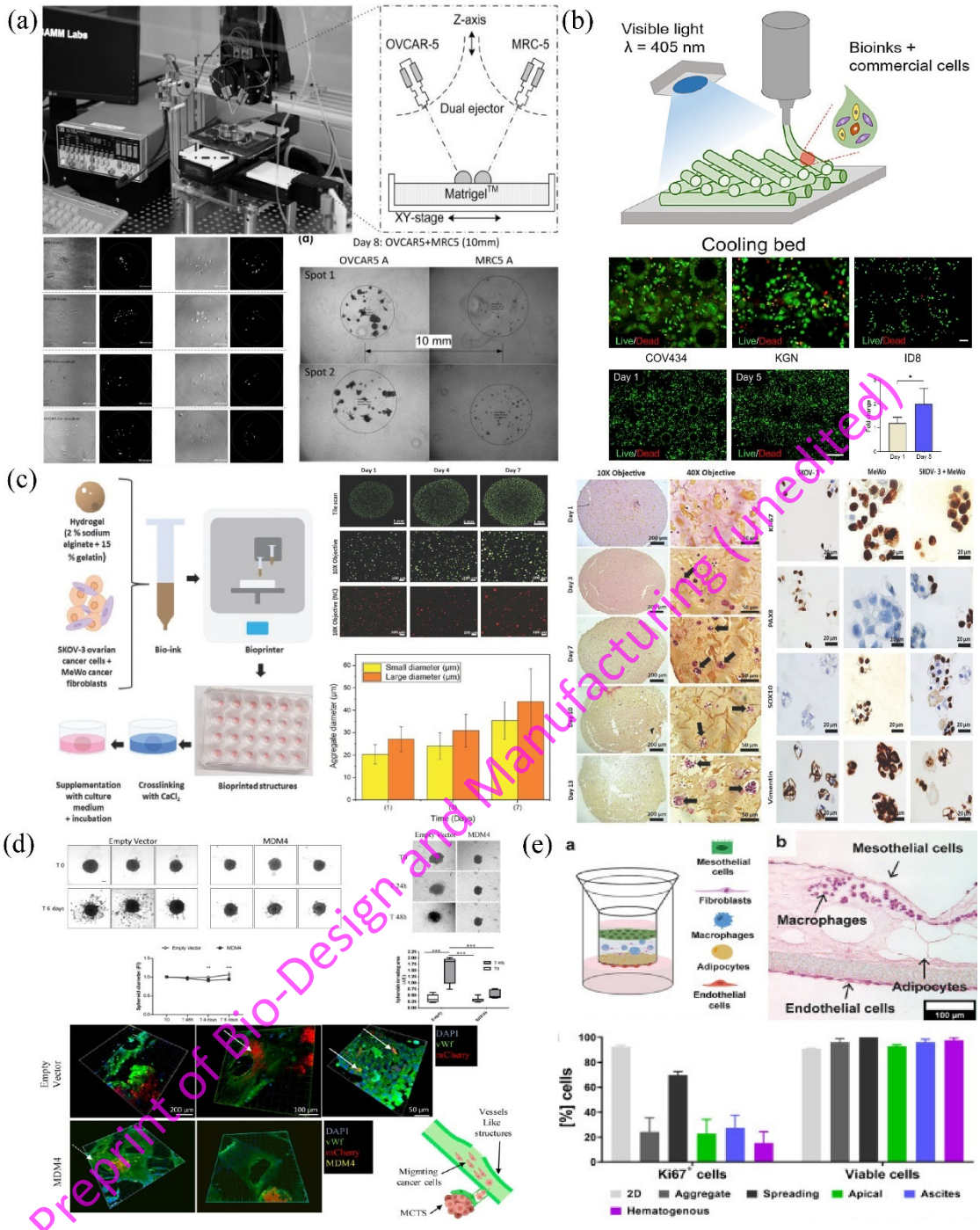

Fig. 7 A study of 3D bioprinted ovarian cancer models. **a** 3D printing of an in *vitro* co-culture model of ovarian cancer based on a high-throughput cellular patterning platform to study the feedback mechanism between tumor and stromal cells;(adapted and modified from Ref. (168), Copyright 2011, with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.) **b** Validation of GelMA-Sodium Alginate Printing Suitability by Shape and Integrity of Gel Fibers Printed with Bioinks;(adapted and modified from Ref. (169), Copyright 2021, with permission from the authors.) **c** 3D bioprinted ovarian cancer model to study tumor viability and proliferation as well as histological and immunological staining;(adapted and modified from Ref. (170), Copyright 2023, with permission from Wiley-VCH GmbH.) **d** Extruded bioprinted

tumor model confirms MDM4's ability to reduce ovarian cancer cell migration and propagation;(adapted and modified from Ref. (171), Copyright 2021, The Authors.) **e** A 3D multicellular tissue model;(adapted and modified from Ref. (172), Copyright 2023, with permission from the authors.)

Neuroblastoma

Early childhood neuroblastoma is an extracranial solid tumor with a poor prognosis. Finding patient-specific medication responses in tissue models that replicate the interaction between a patient's cancer cells and the tumor environment is one method for increasing cure rates.

Wu et al(175) demonstrated the value of using 3D tumor models in humans for the study of anticancer drugs by using pneumatic extrusion bioprinting to fabricate a renal neuroblastoma model and evaluate the efficacy of two chemotherapeutic drugs (Fig. 8a). Nothdurfter(176) developed a perfused and microvascularized tumor microenvironment model, which was constructed as a bioprinted, microvascularized neuroblastoma-tumor-environment model by direct printing into a microfluidic fluidic chip providing a novel medium-throughput biofabrication platform for future precision medicine research on cancer angiogenesis along with migration (Fig. 8b). Monferrer(177) used methacrylated alginate to study the relationship between the physicochemical signals of SK-N-BE (2) neuroblastoma cells and the hardness of the printable hydrogel, and to extrapolate the potential of how the spatial hardness of the hydrogel could drive aspects of clinical behavior relevant to neuroblastoma patients through 3D in *vitro* cellular models (Fig. 8c). Similarly, López-Carrasco investigated the effect of extracellular matrix stiffness on genomic heterogeneity of neuroblastoma cells(178). Bordoni et al(179) prepared bioinks based on cellulose nanofibers (CNF), alginate, and single-walled carbon nanotubes (SWCNT) for 3D bioprinting of conductive scaffolds in free-form reversibly embedded hydrogels (FRESH) (Fig. 8d). The findings show that conductivity, with or without differentiation stimulation, enhances the division of human neuroblastoma carcinoma cells (SH-SY5Y cell line). This study helps to a better understanding of the pathogenic processes behind neurodegenerative illnesses and offers a novel method for building simulated 3D brain models in *vitro*.

The 3D bioprinting of neuroblastoma models is a highly promising research field. Creating a 3D bioprinted neuroblastoma model requires careful selection of suitable printing materials, processes, and equipment to accurately simulate the tissue structure and cellular interactions of neuroblastoma. Additionally, the heterogeneity and individual differences of neuroblastoma need to be considered in the design of the model to make it more representative and reliable. Although research on 3D bioprinted neuroblastoma models is still in its early stages, its prospects are promising. This technology has the potential to provide more accurate and reliable models, aiding in a deeper understanding of neuroblastoma and the development of more effective treatment methods. However, continuous exploration and improvement in both technology and research are needed to overcome current challenges and advance this technology further. In brief, 3D bioprinting of neuroblastoma models is an exciting field

with tremendous potential. Through ongoing research and innovation, we hope to pave new pathways for the understanding and treatment of neuroblastoma, ultimately bringing better clinical outcomes for patients.

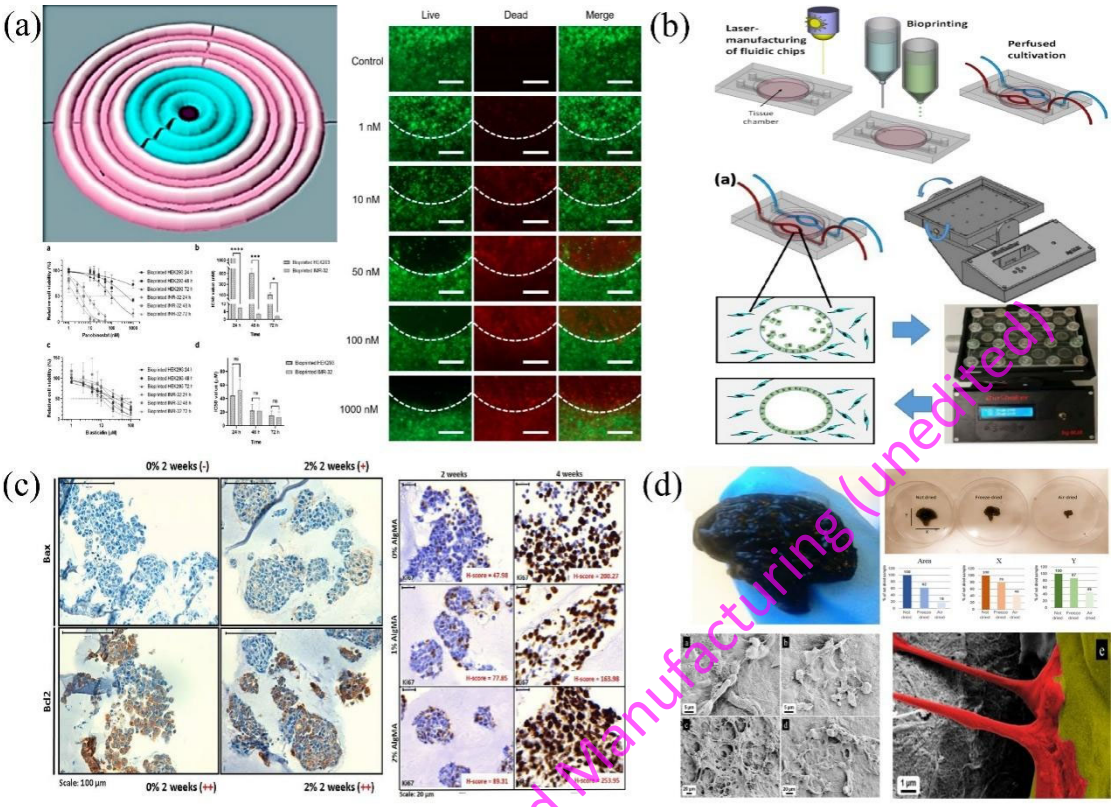

Fig. 8 A study of 3D bioprinted neuroblastoma models. **a** Pneumatic extrusion bioprinting creates a renal neuroblastoma model to assess the effects of two chemotherapeutic agents;(adapted and modified from Ref. (175), Copyright 2021, with permission from the authors.) **b** A tumor microenvironment model for perfusion and microvascularization;(adapted and modified from Ref. (176), Copyright 2022, with permission from the authors.) **c** 3D bioprinted model to assess the effect of hardness on neuroblastoma cell cluster dynamics and behavior;(adapted and modified from Ref. (177), Copyright 2022, with permission from the authors.) **d** Free reversible embedded hydrogel (FRESH) 3D bioprinted conductive scaffolds based on cellulose nanofibers (CNF), alginate and single walled carbon nanotubes (SWCNT);(adapted and modified from Ref. (179), Copyright 2020, with permission from the authors.)

Other tumor models

In addition to the above tumors, 3D bioprinted tumor models have been studied in other human tumors, including pancreatic cancer, lung cancer, kidney cancer, bone cancer, osteosarcoma, skin cancer, pituitary tumors, and leukemia. The most frequent malignant pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC). Hakobyan et al(180) used laser-assisted bioprinting to create arrays of 3D pancreatic cell spheroids and characterized their phenotypic evolution over time through image analysis and phenotypic characterization due to the inability of existing 2D cell culture models to

mimic the three-dimensional complexity of pancreatic tissues (Fig. 9a). These bioprinted spheres made of follicular and ductal cells may be able to mimic the early phases of PDAC development, according to the data. This model could offer fresh perspectives for potential PDAC therapy approaches in the future. The findings imply that these bioprinted spheres made of ductal and alveolar cells are capable of simulating the early phases of PDAC development. This model could offer fresh perspectives on potential PDAC therapy approaches in the future. Wang(181) used cryo-molded 3D bioprinting to construct a 3D tumor model of pulmonary carcinoma, that could maintain activity for up to 28 days in *vitro* and confirmed at the molecular level that lung cancer cells demonstrated enhanced invasiveness and migration (Fig. 9b). Herrada-Manchón used a similar approach to bioprint a 3D model of renal cancer that survived for at least 15 days in *vitro* and self-assembled within hydrogels to build similar functionalized tunneling nanotube-like structures(182) (Fig. 9c). Based on alginate/gelatin hydrogels, the addition of bioglass increases the proliferation and mineralization of bioprinted SaOS-2 cells(183), but these osteoblast-like cells cultured in *vitro* can be directly transformed into osteosarcoma-like models(184).In addition, bone microenvironment-based models of metastatic cancer are not infrequently reported, such as breast cancer bone metastasis models(185, 186) and prostate cancer bone metastasis(187, 188). Wu used coaxial bioprinting to construct a 3D model of multiple myeloma in *vitro*, which can release interleukin 6 (IL-6), and attempted to explore related targeted sensitizing drugs in trials(189) (Fig. 9d). In order to create an in *vitro* melanoma micro-model, Duan(190) used 3D printing to create gelatin methacryloyl(GelMA)/ Polyethylene (glycol) diacrylate(PEGDA) scaffolds made of composites, which resembled the environmental conditions associated with human malignancy in melanoma cell (A375) growth (Fig. 9e). Based on this model, it was discovered that lignocaine's effects on melanoma cells were time- and dose-dependent and that tumor cells in the 3D culture system became increasingly insensitive towards the drug. Diao et al(191) constructed a growth hormone pituitary adenoma model using extrusion bioprinting, and comparisons revealed that pituitary adenoma cells in the 3D environment exhibited more active cell cycle progression, secretion, proliferation, invasion, and tumorigenesis, which could help to study the etiology and treatment of pituitary adenomas in depth (Fig. 9f). In addition, by combining hydrogel with leukemia cells to create cell-containing scaffolds, Sbrana et al(192) were able to 3D bioprint leukemia cells effectively, improve their in *vitro* viability, which could be maintained for up to 28 days, and create reproducible models of long-term 3D culture. The result was an in *vitro* model of chronic lymphocytic leukemia. We discovered changes in the gene expression patterns between 2D and 3D samples by RNA sequencing (RNAseq) research, demonstrating that cells behave differently in two distinct culturing settings. This will make it possible to conduct more trustworthy investigations of the molecular and cellular interactions that take place in *vivo* under both normal and malignant circumstances. It may also be applied clinically to assess how each person reacts to various medications.

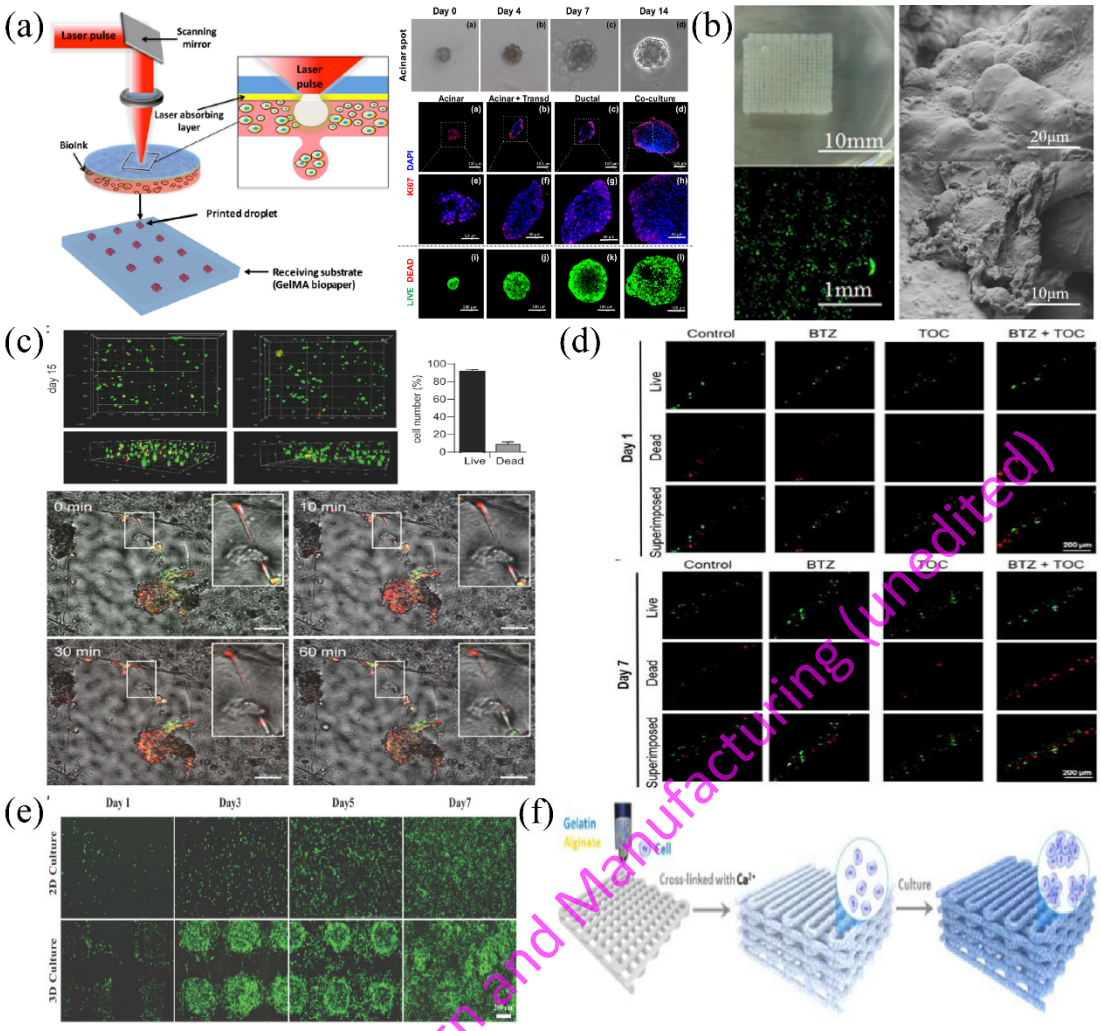

Fig. 9 Three-dimensional bioprinting of multiple cellular tumor models. **a** Laser-assisted bioprinting to fabricate 3D pancreatic cell sphere arrays;(adapted and modified from Ref. (180), Copyright 2020, with permission from IOP Publishing Ltd.) **b** Cryomolding 3D bioprinting to construct 3D tumor models of lung cancer to study the invasiveness and migration of lung cancer cells;(adapted and modified from Ref. (181), Copyright 2018, with permission from Springer-Verlag GmbH Germany, part of Springer Nature.) **c** 3D bioprinting to construct kidney cancer models and self-assembly within hydrogels to build functionalized tunneling nanotube-like structures;(adapted and modified from Ref. (182), Copyright 2021, with permission from Elsevier B.V.) **d** Coaxial bioprinting to construct 3D models of multiple myeloma in *vitro* and explore related targeted sensitizing drug trials;(adapted and modified from Ref. (189), Copyright 2021, with permission from Wiley-VCH GmbH.) **e** In *vitro* construction of a micromodel of melanoma to study its drug resistance;(adapted and modified from Ref. (190), Copyright 2022, with permission from the authors.) **f** Extrusion bioprinting to construct a growth hormone pituitary adenoma model to study its intrinsic characteristics; (adapted and modified from Ref. (191), Copyright 2019, with permission from IOP Publishing Ltd.)

The development of 3D bioprinting of tumor models is widely regarded as a

significant advancement in medical research. By creating more realistic and reliable tumor models, researchers can better understand the biological characteristics, progression, and treatment responses of tumors. This helps accelerate drug screening and development, and improves the personalization and precision of treatments. On the other hand, some people have concerns about the ethical and legal issues that 3D bioprinting of tumor models may raise. Furthermore, the development of 3D bioprinting of tumor models also faces technical challenges and cost issues. The current technology is still in its early stages and requires constant improvement and innovation to enhance the accuracy and reliability of the models. Additionally, the high cost of equipment and materials also limits the widespread application of this technology. Overall, most people believe that 3D bioprinting of tumor models is a promising and prospective research field. It provides scientists with better tools to study tumors and lays the foundation for the future development of personalized treatments. However, while advancing this technology, we also need to carefully consider the ethical and legal aspects and continuously strive to overcome technical challenges.

3D bioprinted tumor models applied research

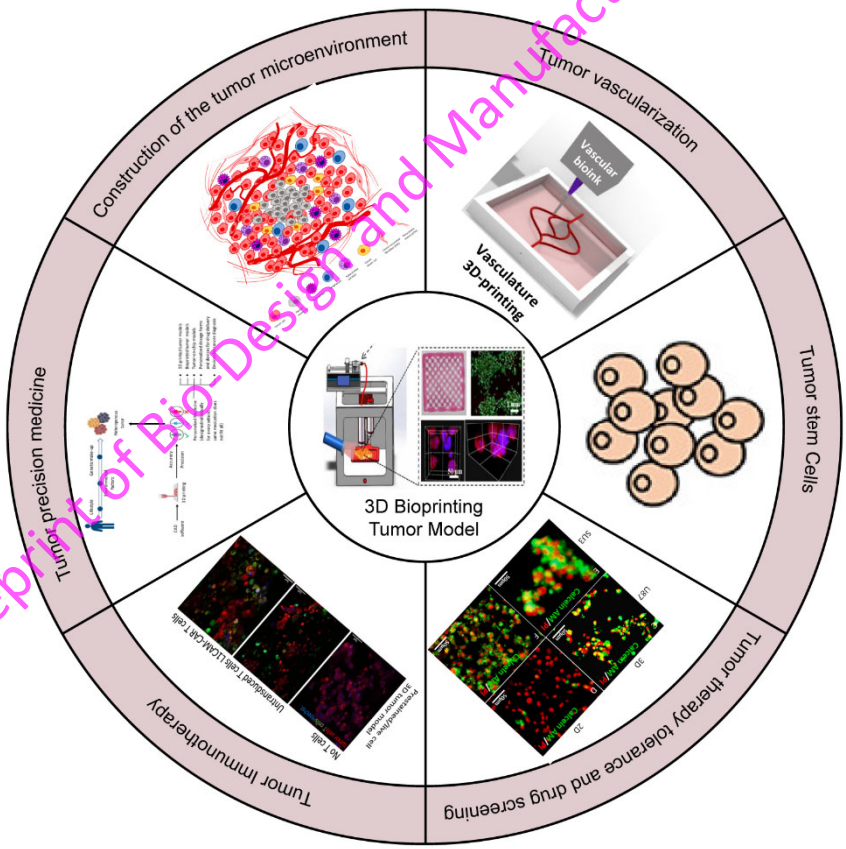

Fig. 10 Schematic of 3D bioprinted tumor model application study. Construction of the tumor microenvironment(adapted and modified from Ref. (193), Copyright 2021, with permission from the author.); Tumor vascularization (adapted and modified from Ref. (110), Copyright 2021, with permission from the authors.); Tumor stem cell (adapted and modified from Ref. (102), Copyright 2022, with permission from American

Chemical Society); Tumor therapy tolerance and drug screening (adapted and modified from Ref. (100), Copyright 2016, with permission from IOP Publishing Ltd.); Tumor immunotherapy (adapted and modified from Ref. (194), Copyright 2021, with permission from the author.); Tumor precision medicine(adapted and modified from Ref. (195), Copyright 2018, with permission from Elsevier Ltd.); 3D bioprinted tumor model (adapted and modified from Ref. (134), Copyright 2022, with permission from IOP Publishing Ltd.)

Construction of the tumor microenvironment

The milieu in which tumor cells thrive is known as the tumor microenvironment and is intimately connected to carcinogenesis, development, invasion, and metastasis. It typically consists of tumor cells, malignant vessels, stromal parts and host immune cells. Constructing a simulated 3D tumor microenvironment can be better used for basic tumor research and anticancer drug screening. Conventional 2D models are unable to simulate the tumor microenvironment, especially when it comes to oxygen and nutrient availability, and thus are so restricted as bionic models for fundamental tumor biology research or evaluating anticancer drugs(196, 197). In a computer-controlled layer-by-layer process, 3D bioprinting enables precise localisation of cells and biomaterials and preserves cell viability(3). As a result, it is viewed as a viable route for developing tissue architectures that capture the complicated nature of the tumor microenvironment's composition and geometry(198). For instance, multicellular spheroids developed in hydrogel grids uniformly loaded with HeLa cells, a cervical cancer cell line, in less than five days of culture, and tumor cells in this 3D environment were more resistant to the anti-tumor chemotherapeutic drug paclitaxel than in a 2D environment(164). Additionally, 3D bioprinted microarray tumor models replicated the specificity and diversity of patient response to radiation seen in the clinic and described the biochemical and biophysical features of glioblastoma(78). Using 3D printing, breast cancer cells, peripheral blood mononuclear cells, and fibroblasts were created in the same hydrogel milieu to study the self-assembly and co-culture of various cell types(199). Despite neither of the model tissues created thus far can exactly duplicate every aspect of the tumor microenvironment, the majority of them offer insightful information on tumor biology.

Tumor vascularization

Compared with traditional methods for studying tumor angiogenesis (including 2D culture and animal models), 3D culture provides tumor cells with the geometry and microenvironment required for cell growth in *vivo*, promotes cell-cell and extracellular matrix interactions, and is closer to in *vivo* tissues in terms of cell proliferation, migration, invasion, cell signaling, and gene expression, which lays the foundation for studying the mechanisms of tumor angiogenesis and development(107, 200-203).

Numerous 3D models have been created recently by researchers to explore malignant angiogenesis. Wang(204) developed a 3D hydrogel co-culture model containing glioma cells and endothelial cells. The use of a porogenic agent caused endothelial cells to form

vascular-like structures in the 3D hydrogel. The findings demonstrated that the 3D model dramatically boosted glioma cell proliferation while considerably reducing the expression of endothelial cell adhesion proteins. Meng et al(205) constructed a 3D model containing tumor cells, human umbilical vein endothelial cells (HUVEC), and fibroblasts using gelatin-methacrylic acid bioinks and studied tumor vascularization by laser-induced loading of vascular endothelial growth factor (VEGF)/EGF capsules for slow release of vascular growth factors to form a chemical concentration gradient. Understanding endothelial cell vascularization in the constructed 3D tumor angiogenesis model requires better utilization of the biological functions of tumor cells in the co-culture system. This is because tumor cells can participate in tumor angiogenesis by means other than direct transdifferentiation into endothelial cells(206). Furthermore, by secreting vascular growth factors on their own, tumor cells can attract and persuade peripheral endothelial cells to take part in tumor neovascularization(207). Hence, the key to understanding tumor angiogenesis is to build a model that optimizes the fundamental biological characteristics of tumor cells. Chen's(208) model of a perfusable vascular network was created using a 3D bioprinting platform. In the research, mouse fibroblasts and human umbilical vein endothelial cells were co-cultured, and both single and multicellular sprouts were shown to move from the created vascular network into the matrix gel. Sousa(209) simulated vascular basement membranes by combining 3D printing with layered assembly techniques to embed biologically active 3D multilayered microchannels in light-cured hydrogels and planted endothelial cells in them to construct tissue vascularization networks. However, these attempts have mainly focused on the use of 3D printing technology to create geometries that resemble vascular systems, and the relevance and function of 3D bioprinted tumor cells, particularly printed tumor cells, in tumor angiogenesis have not received much attention. Tao Xu(99) constructed gelatin/sodium alginate/fibrinogen hydrogel scaffolds loaded with glioma cells U118 using 3D bioprinting technology, and found that the content of VEGF in the cultured glioma cells was increased in the 3D bioprinted tumor model, which suggests that the tumor model created by 3D bioprinting might deserve to be investigated for the vascularization of tumors. The 3D bioprinted tumor model could better mimic the in *vivo* tumor microenvironment than the traditional 2D culture. In further studies, Tao Xu's team constructed a 3D bioprinted tumor model of glioma stem cells and found that the microenvironment provided by the 3D printed tumor model not only promoted the growth and proliferation of stem cells, but also the ability of glioma stem cells to secrete VEGF, the expression of genes related to tumor angiogenesis, and the ability of vascularization in *vitro* were all improved(98). In addition, current research indicates that 3D bioprinted glioma cells may be able to transdifferentiate into endothelial cells(210).

Tumor stem cells

The capacity to renew themselves and create diverse tumor cells is possessed by tumor stem cells, which are crucial for the survival, growth, metastasis, and recurrence of cancers(211). For the purpose of researching the biological activity of tumor stem cells, building an accurate 3D model of tumor stem cells is crucial. Investigations have

demonstrated that 3D bioprinted glioma stem cells are more stable in their proliferation than typical suspension cultured glioma stem cells, with more numerous mitochondria and rough endoplasmic reticulum in the stem cells as well as a significant number of long microvilli on the cell surface. Not only that, in *vitro* 3D bioprinted glioma stem cells had higher cell stemness, expression of tumor angiogenesis-related genes, and angiogenic potential than suspension culture conditions(98). Using a 3D printing platform, Herreros-Pomares(212) created a model of lung cancer that is not small-cell carcinoma. It was discovered that the proliferation profile of tumor stem cells was enhanced on rigid scaffolds compared to culture on hydrogel scaffolds or tumor spheroids. However, tumor stem cells grew better in hydrogel scaffold or tumorsphere culture. The majority of the stemness and invasion promoters evaluated were strongly expressed by tumor stem cells in 3D hydrogel scaffolds compared to control cells in 2D culture, according to gene expression analyses. The findings demonstrate that, in comparison to in *vivo* 2D culture models, 3D printed hydrogel scaffolds may more accurately replicate the complexity of tumors and control the biological activities of tumor stem cells. Tao Xu's team constructed a glioma model by 3D bioprinting using gelatin/sodium alginate/fibrinogen as biomaterials to enrich glioma stem cell-like cells. Compared with the traditional 2D culture model, the proportion of stem cell-like cells, expression of stem cell biomarkers and epithelial-mesenchymal transition-related genes in glioma cells cultured in 3D bioprinted hydrogel scaffolds were significantly increased. Glioma cells on 3D bioprinted scaffolds made of hydrogel also exhibited increased tumorigenicity and stronger treatment resistance in *vitro*. The hypoxic environment and the activation of epithelial-mesenchymal transition together promoted the enriching of glioma stem cell-like cells, and it was shown that the hydrogel microenvironment constructed by 3D bioprinting provided a new platform for glioma stem cell enrichment studies(99).

Tumor therapy tolerance and drug screening

Surgical excision along with postoperative radiation, chemotherapy, and additional complete therapies is the primary form of treatment for the majority of cancers. Nevertheless, some malignant tumors, such as glioblastoma, are not ideally treated with post-surgical radiotherapy, and the recurrence of malignant tumors is mostly due to the tumor cells' resistance to chemotherapeutic treatments. Since the 2D culture model of traditional methods for studying tumors has many defects, the creation of an optimal in *vitro* model is required to investigate the drug resistance and invasiveness of tumor cells.

Compared with traditional 2D cell culture, 3D tumor models could more realistically emulate the tumor microenvironment by 3D bioprinting technology, which can help to further elucidate the basic mechanisms of tumorigenesis and development, study the behavior of tumor cells, screen drugs and develop effective clinical treatments. Basic research on 3D bioprinted tumor models is expected to be a bridge to actual clinical diagnosis and treatment. In the future, we may create customized tumor models for patients using 3D bioprinting technology, evaluate the effects of drug therapy in *vitro*, offer details on the best medication kind and dose, and create customized tumor therapies for patients. By reproducibly producing 3D cell-hydrogel structures,

bioprinting technology has been able to address these criteria and produce intricate, high-throughput disease models. These models incorporate extracellular stressors and component regulation, pharmacological therapy, and studies of illness development, all of which might be helpful in better comprehending and eventually treating disease. A high-throughput bioprinted spherical system for disease modeling has been developed by Nano3D Bioscience. Their commercial equipment can create spheres for up to 384-well plates using magnetic 3D bioprinting. Publications based on their 3D bioprinting system technology include, among other things, cancer disease models and toxicity screening. Organovo is a publicly traded company in the pharmaceutical industry that produces a wide variety of tissue-engineered, bioprinted high-throughput models for drug screening, and they also create cancer disease modeling and screening models that use a variety of cell types and associated ECM components to bioprint tumor models and form microcapillaries, which are then subjected to chemotherapy testing and high-throughput drug screening.

Tumor immunotherapy

One of the characteristics of cancer and a frequent occurrence in the tumor microenvironment is tumor immune escape(213). Therefore, targeted therapy focusing on immune cells has become the most promising anti-tumor therapy(214). Compared with traditional cell culture technology, 3D bioprinting platform from technology can achieve the model construction of the multicellular complex tumor immune microenvironment, so its use for in *vitro* immune-targeted therapy for tumor research and development is highly expected.

The most promising treatment option for autoimmune disorders, cancer, and infections is now T-cell immunotherapy. T-cell therapies cannot, however, be widely used due to the ineffective growth, functional flaws of isolated cells, and high cost of these treatments. The key lies in the development of an affordable, easily expandable and accessible method to maintain a population of T cells that maintains good cancer-targeting function of immune cells. Delalat et al(215) used 3D-printed highly-organized micrometer lattice structures functionalized by plasma polymerization to bind monoclonal antibodies that cause cell proliferation to facilitate the expansion of therapeutic human T cell subsets, including regulatory, effector, and cytotoxic T cells, while maintaining the correct phenotype. The cell expansion platform is easy to use, accelerates cell recovery and expansion, and promises to be an ideal way to move T-cell therapies from the lab to the clinic. Chimeric antigen receptor (CAR) T cells are the current hotspot for tumor immunotherapy, but CAR-T therapy also faces the validity of 2D cell therapy in *vitro*, while animal and clinical trials are often unsatisfactory, and the validity of CAR-T therapy in 3D solid tumors is only more convincing. A 3D neuroblastoma tumor model was created via bioprinting by Grunewald et al(194) for the preclinical validation of CAR T cell effector function targeting L1 cell adhesion molecule (L1CAM). According to the findings, the 3D model exhibits a greater activation of L1CAM-specific CAR T cells by neuroblastoma cells than the 2D co-culture. Bioprinted 3D neuroblastoma models are a superior in *vitro* analytical tool for preclinical CAR T cell characterization, and they may even be better at selecting CAR

T cells that can better exert their effects in *vivo* than in 2D culture. They are suitable for detecting and quantifying CAR T cells infiltrating in tumors, speeding up preclinical testing and reducing cost and animal use.

Kim(216) developed a bladder cancer microarray including tumor cells, vascular endothelial cells, and immune cells to mimic the tumor microenvironment using 3D bioprinting and microfluidics, and assessed the immune response of the tumor model to different concentrations of Bacillus Calmette-Guerin (BCG) vaccine by THP-1 monocyte migration and the concentration of growth factors and cytokines. The use of 3D bioprinted bladder cancer for BCG immunotherapy applications is expected to be an effective tool for analyzing drug responses, opening up new directions for the development of precision medicine for tumor immunotherapy as well as for the utilization of patient-derived cancer cells for tailored therapeutic applications.

Tumor precision medicine

Precision medicine in oncology is a therapeutic approach based on genetic information that is intimately tied to the tumor disease's pathogenesis and is a tool that clinicians can use to determine the treatment of a patient's tumor. There may be specific mutations directly associated with tumorigenesis. However, not all mutations are therapeutically relevant, but they can provide information on disease characterization as they are major drivers of pathology. In this context, the use of in *vitro* simulated 3D tumor culture models allows tumor tissue to be extracted from patients for culture and extended to in *vitro* 3D tumor models for study, while still maintaining parental genotype characteristics in *vivo*(174, 217). A significant variety of patient-specific tumor disease models may be produced using 3D bioprinting and human-derived tumor tissue or cells. These models can be used independently or in conjunction with clinical trials through precision medicine initiatives. Precision medicine not only helps patients in the short term, but also collects large amounts of data for long-term studies of disease progression and response to drug therapy. Thus, precision medicine, defined as individualized diagnosis and treatment using strategies that target patient- or disease-specific genetic, proteomic, and phenotypic traits(218), is critical to the success of patient-directed diagnosis and treatment. The behavior, progression, and response to pharmacological therapy of patient cell populations have been cultured and expanded using 3D cell culture models. These models can be used to predict how primary cultured cells and patients will respond to treatment since they use fewer cells to replicate the in *vivo* milieu. Additionally, patient cells can be used to make customized models that are better suited to a patient's particular ailment than cell lines that are readily available commercially. These studies are superior to disease models using cell lines because each patient has a unique mutation, and they offer insight into genetic variants, cell type mixtures, and patient-specific variants. This allows investigators and sufferers to have additional personalized knowledge of their specific illness state.

Precision medicine's present use of 3D bioprinted tumor models is still in its early stages(219). In *vitro* 3D cell culture involves the isolation of tissue directly from the patient, followed by further single-cell isolation and ECM reconstruction. In order to obtain whole lineage cell types and ECM components from patient-diseased tissue or

biopsies, cells can be isolated and expanded in 2D culture. Additionally, patient cell expansion is necessary for high-throughput 3D bioprinting precision medicine applications because it enables the simultaneous fabrication of numerous replicable 3D culture systems(220). It is difficult to expand patient cells from tissues, particularly when dealing with cell numbers, the tumor microenvironment, whole cell lineages, and stromal components. Culture expansion using human induced pluripotent stem cells (hiPSCs) before differentiation to produce millions of cells that differentiate into the desired diseased cell type may be an alternative. Although current methods have limitations, as expansion takes time and may produce tumor models that lose parental characteristics, it is still currently the best option. Precision medicine is an emerging field of extreme interest to clinicians, patients, and researchers. A huge number of clinical oncology patients should be able to receive precision medicine thanks to the application of 3D bioprinting in tumor disease prediction models and high-throughput drug screening(22, 221).

Challenges and perspectives

The initial bioprinted tumor models were relatively simple, typically involving the arrangement and assembly of tumor cells or other relevant cell types using bioprinting technology to form a basic tumor structure. However, these models lacked the complex reconstruction of the tumor microenvironment. In contrast, current 3D bioprinted tumors offer several advantages in terms of complexity, biological similarity, controllability, and application prospects. They can more accurately simulate the tumor microenvironment by adjusting printing parameters and cell assembly, thereby achieving consistent and comparable tumor models. Bioprinted tumors have been widely used in areas such as drug screening, personalized medicine, and surgical simulation, playing a crucial role in advancing tumor research and treatment. Therefore, further research and application of bioprinted tumor models are imperative.

Precision therapy helps physicians make more informed medical decisions while providing customized treatments for patients and improving the service level of personalized care for patients or groups of patients. In the future, 3D bioprinting for precision therapy can first obtain tumor cells from the patient's body to build a tumor model in *vitro* for screening out sensitive chemotherapeutic drugs, and then print normal tissues in the residual cavity of the patient's resected tumor after obtaining the patient's normal cell expansion combined with the sensitive chemotherapeutic drugs as bio-ink to promote the repair and regeneration of the tissues and to prevent the recurrence of the tumor. Owing to the complexity involved in designing precisely tailored tumor models and products, their production and delivery remain challenging. Therefore, in-depth knowledge and detailed research are still needed for the future development of a unique state-of-the-art model that will ultimately lead to precision therapy.

The development of 3D bioprinted replicas of tumors may significantly alter how healthcare professionals approach cancer prevention, diagnosis, and therapy. Future 3D bioprinting technology, which may be combined with gene editing technology, artificial intelligence technology and biochip technology, can establish more accurate tumor

model prediction models and achieve high-throughput tumor drug screening, thus improving screening efficiency and saving the cost of tumor drug development, and further promoting the development of precision treatment of tumors. Combined with in *vitro* organ culture and tissue engineering technology, 3D bioprinted cancer models can simulate the environment of real human organs and better evaluate the safety and effectiveness of tumor therapy drugs. In conclusion, in the future, 3D bioprinting technology can be combined with a variety of new technologies to continuously advance the development of tumor models and provide more accurate, rapid and safe solutions for precision tumor therapy.

Declaration of Competing Interest

There are no conflicts to declare.

Acknowledgments

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