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TOPICAL REVIEW

# Decellularized tumor matrices as biomimetic cancer niche: a new perspective on cancer research and therapy

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## Abstract

Cancer is among the major causes of mortality, responsible for approximately 15% of all deaths worldwide. Despite remarkable progress in modern medicine, it remains a significant global health challenge. Nevertheless, conventional therapies such as chemotherapy and radiotherapy target healthy and malignant tissues, leading to adverse side effects, including hair loss, fatigue, and nausea, which significantly reduce patients' quality of life. Even more critically, the therapeutic response varies from patient to patient, which reduces the effectiveness of treatment. Therefore, cancer tissue engineering has evolved as a novel interdisciplinary field, aiming to develop structures that mimic the tumor microenvironment to elucidate cancer development mechanisms and devise effective treatment methods. However, producing a fully synthetic biosimilar matrix by assembling all individual ECM components remains unfeasible due to the heterogeneity and complex structure of tumor tissues, as well as the necessity of highly advanced micro- and nanoengineering techniques. Consequently, decellularization techniques have recently been applied to cancer tissues to produce biomimetic tumor models. In this review, we provided a comprehensive overview of the extracellular matrix (ECM) architecture and its role in tumor progression. We also discussed the structural differences between normal and malignant tissues. We briefly reviewed decellularization techniques and analytical approaches for ECM characterization. Emphasizing the cutting-edge research, we categorized developments into three groups: decellularized tumor-derived ECM (dT-ECM), hydrogels, and bioinks. Subsequently, we critically assessed the benefits, limitations, and potential future developments of dT-ECM-based strategies. Finally, we envision that tumor tissue engineering will provide preventive treatment approaches by developing patient-specific predictive and personalized cancer models through integrating advanced biomaterials with artificial intelligence and machine learning.

## 1. Introduction

Cancer, an atypical form of cell proliferation, is a complicated systemic disorder that emerges from the combination of genetic-environmental factors and involves dynamic interactions between tumor cells and tissue microenvironment, such as stromal components, immune cells, and extracellular matrix (ECM) [1]. Based on the World Health Organization's 2020 report, cancer remains one of the main global health challenges of the 21st century, with 19.3 million new cases and 10 million related deaths worldwide. The International Agency for Research on Cancer (IARC) projects that by 2040, the number of new cancer cases will increase by 47%, reaching 28.4 million globally [2]. As an economic perspective, the total cost of cancer between 2020 and 2050 was estimated to reach $25.2 trillion [3]. Tumor development is initially triggered by cellular damage and DNA injury, leading to genomic instability and the loss of tumor suppressor genes, resulting in uncontrolled cell proliferation [4]. However, beyond this sequence of events lies a far more intricate and multifaceted biological landscape. The majority of solid tumors consist

of cancer-associated fibroblasts (CAFs), fat cells, endothelial cells, ECM molecules (including collagen, fibronectin, laminin, hyaluronan, etc), pericytes, and microglia, as well as immune cells like macrophages, platelets, and lymphocytes [5, 6]. The ECM of neoplastic tissues has been observed to exhibit increased stiffness compared to that of healthy tissues. This increased stiffness has been demonstrated to promote cancer cell proliferation and survival, as well as induce immunosuppression [7]. Although significant financial resources and considerable scientific efforts have been devoted to the development of innovative diagnostic techniques and therapeutic interventions, the fundamental etiology of cancer remains mostly elusive. Therefore, current treatment methods only rely on limited standardized protocols, rather than being personalized to patient characteristics [8]. Furthermore, the variability in patient responses to these conventional cancer therapies often decreases the effectiveness of existing treatment options, resulting in a reduction in patients' quality of life and increased economic burden on national healthcare systems [9].

Tissue engineering is a multidisciplinary field that integrates bioengineering, cell biology, and materials science to repair, regenerate, or fully replace damaged or diseased tissues [10]. To achieve this, it employs a combination of human/animal-derived tissues, hybrid constructs composed of biological and synthetic components, or completely synthetic scaffolds, along with autologous cells and molecular cues [11, 12]. Tumor tissue engineering also uses similar tools to simulate the cancer niche. Nevertheless, cancer models generated with the ECM of healthy tissues [13, 14] or synthetic polymers [15, 16] and cancer cells (2D) [17] are insufficient to mimic native tumor tissue. Because tumor ECM is highly heterogeneous and exhibits structural and chemical differences from typical ECM [18]. Over the past decade, a novel approach, biomimetic 3D cancer models using tissue-specific decellularized tumor matrices (dT-ECMs) derived from target organs or tissues, to comprehend the mechanisms of cancer has evolved as the tumor microenvironment's (TMEs) role in cancer cell migration, invasion, metastasis, hypoxia, metabolic stress, mechanotransduction, and drug infiltration processes has been illuminated. Accordingly, decellularization is the removal of cellular components from tissues while preserving the essential elements and mechanical properties of the ECM. Consequently, the decellularized matrices retain the native tissue's bioactivity and dynamic architecture by maintaining vital elements like collagen, elastin, sulfated glycosaminoglycans (sGAG), growth factors, and cytokines [19, 20].

Since their emergence, decellularization technologies and decellularized matrices have undergone continuous development, progressively expanding the applications of these technologies in the biomedical field. Specifically, the application of decellularization to cancer tissues has emerged only in the past decade. Figure 1 indicates the chronological overview of key milestones in tissue and tumor decellularization research from 1948 to the present [17, 21–24]. To date, although only a limited number of studies have reported the impact of tumor ECM on tumorigenesis, research in this area has been steadily increasing. Nonetheless, there is a significant lack of comprehensive review articles comparing and analyzing these outcomes. In this review, we introduce the structural and functional differences between normal and cancerous extracellular matrices, highlighting the vital effect of the ECM in tumor progression. Next, the decellularization of cancer tissues is discussed as a method for engineering biomimetic environments. Subsequently, we explore up-to-date methodologies and recent advancements in the application of dT-ECMs in cancer research. Finally, the advantages, limitations, and future prospects of these 3D tumor tissue models are revealed.

## 2. Architect or architecture?: The ECM

ECM is a 3D dynamic micro-ecosystem composed of bioactive molecules such as collagen, elastin, glycoproteins, proteoglycans (PGs), matrix-reconstructing proteases, inhibitors, crosslinkers, chemokines, and growth factors. The ECM is responsible for providing structural support and organization to tissues, thereby serving as their architecture. Concurrently, by modulating cell adhesion, communication, and differentiation, it functions as an architect that directs cellular behavior and tissue homeostasis. The host cells secrete the ECM, which supervises cell adhesion, cell-to-cell communication, proliferation, and differentiation, providing crucial chemical, physical, and mechanical signals. Indeed, cells and the ECM are in a dynamic interaction to maintain tissue homeostasis [25]. The ECM in mammals is comprised of approximately 300 proteins, including 43 collagen subunits, 36 PGs, and around 200 complex glycoproteins [26]. Among these, collagen is the predominant fibrous protein (∼90%) within the ECM, accounting for ∼30% of the entire human proteome [27]. Collagens are classified as homotrimers or heterotrimers of three polypeptide chains ($\alpha$ chains), with repetitive Gly-*X*-*Y* sequences, where *X* and *Y* are generally proline and 4-hydroxyproline, respectively. Glycine enables structural flexibility, whereas proline confers rigidity [28]. Type I collagen is the most prevalent subtype in the human body, with high concentrations in dermal and tendon tissue. Conversely, other collagen types are more locally restricted; for instance, type II collagen is primarily found in cartilage and the cornea, while type III collagen is mainly associated

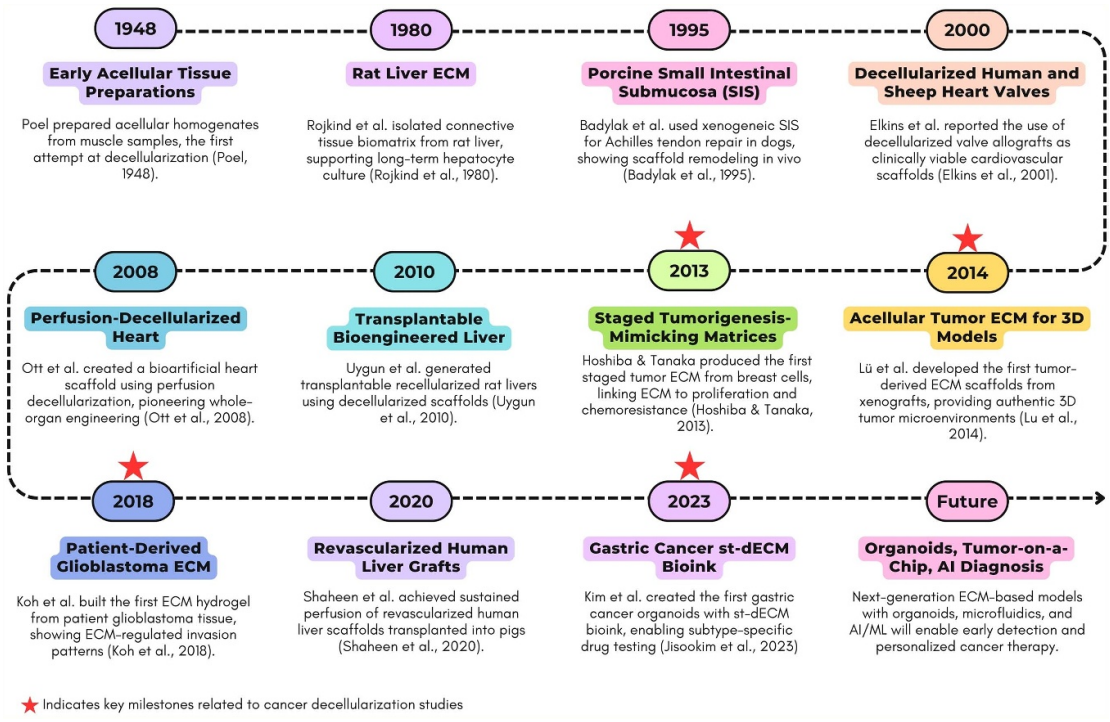


**Figure 1.** Timeline of key milestones in tissue and tumor decellularization.

with the structural framework of vascular arteries. Besides, fibroblasts are the primary source of collagen biosynthesis; endothelial and epithelial cells also contribute significantly to collagen fabrication [29]. PGs are formed from a specific protein core (e.g. aggrecan, syndecan, glycan, decorin, perlecan, and versican, etc) and repeating disaccharides called glycosaminoglycans (GAGs). GAGs contribute to the ECM's unique viscoelastic, mechanical buffering, and selective permeability properties by filling the majority of the extracellular space with a hydrated gel form, thanks to retaining water molecules within their polysaccharide chains [30]. There are various types of GAGs, including chondroitin sulfate, heparan sulfate, keratan sulfate, dermatan sulfate, and hyaluronic acid (HA). Unlike other GAGs, HA is devoid of a sulfate group and is not covalently linked to the core protein [31]. Glycoproteins are another ECM molecule in which an oligosaccharide and a polypeptide are covalently attached. In one respect, they are similar to PGs but differ from them in that they do not contain a repeating disaccharide unit [32, 33]. Glycoproteins (e.g. laminins, fibronectins, thrombospondins, tenascins, and nidogens) incorporate into the ECM structure, promote cell adhesion through specific regions and patterns, and also behave as ligands for cell surface receptors such as integrins, thereby influencing ECM–cell signaling. Furthermore, glycoproteins function as reservoirs for growth factors bound to the ECM, which can be released following proteolysis [34]. One of the primary factors contributing to the dynamic structure of the ECM is the degradation of collagen by matrix metalloproteinases (MMPs). This process leads to the release of signaling molecules, such as endostatin and tumstatin, which in turn affect the mechanical properties and cellular signaling pathways in the microenvironment [35–37].

As expected, in pathological conditions such as cancer, ECM remodeling is irregular. Thereof, there are distinct structural and proteomic differences between healthy and cancerous ECMs (figure 2). In the initial phases of tumor development, stromal cells proliferate and synthesize substantial amounts of ECM protein, thereby safeguarding normal tissue from the infiltration of tumor cells. Indeed, researchers discovered the upregulation of fibronectin, tenascin-C, and specific collagens (particularly types I and III), accompanied by an increase in ECM remodeling enzymes in the proteomic analysis of cancer tissues [39]. The increased synthesis of collagen types (1–12, 15, 16, 18, 19, 22, 24) in tumor tissue increases tissue stiffness by aligning and highly cross-linking fibers. Consequently, tumor ECM is typically denser, more fibrotic, and stiffer than its healthy counterpart. These mechanical changes both promote cell migration and invasion and may negatively affect drug penetration, decreasing treatment response [40]. On the other hand, some glycoproteins, such as laminin subunits $\alpha 4$, $\beta 1$, $\beta 2$, and $\gamma 2$, are associated with disruption of basement membrane integrity [41]. Moreover, the overexpression of fibronectin is critical

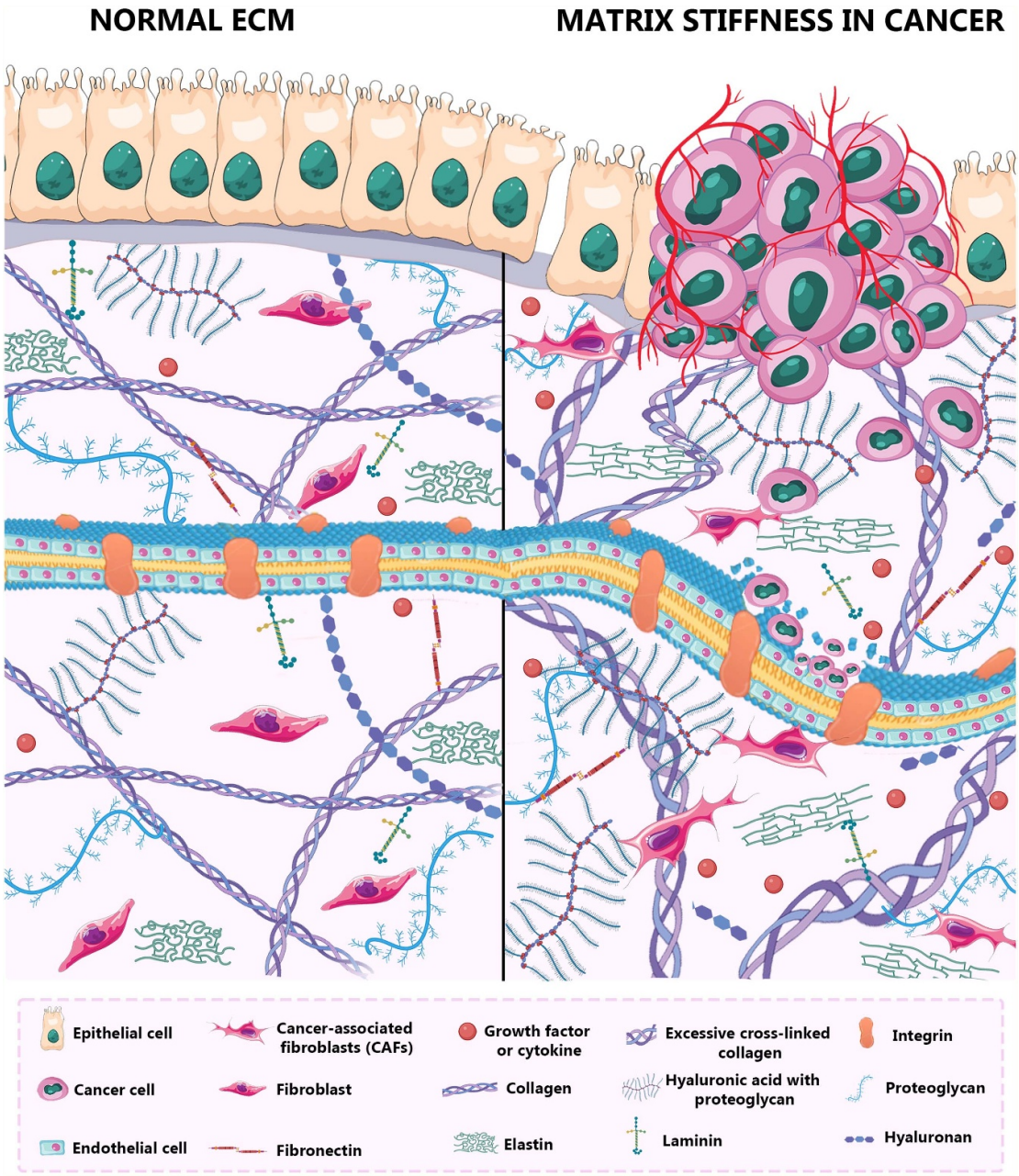


**Figure 2.** Schematic comparison of the ECM composition and organization in normal and cancerous tissues. Created in BioRender [38].

for collagen organization and integrin-mediated cell-ECM interactions, contributing to invasion, poor prognosis, and the development of resistance [42]. The overexpression of HA also contributes to poor prognosis and enhanced malignancy by promoting epithelial–mesenchymal transition (EMT) [43]. Similarly, the expression of molecules such as decorin from PGs is generally increased in cancer cells; however, expression levels vary depending on the type of cancer [44].

TME is a specialized niche defined by various cell types located within a reorganized ECM [28]. In cancer tissues, anomalous cross-linking of ECM proteins by enzymes such as the lysyl oxidase family (LOX, LOXL2, 4) promotes enhanced tissue stiffness by increasing collagen deposition [45]. This phenomenon, referred to as desmoplasia, is an indicator of TME [29]. Mechanical stiffening increases integrin-mediated adhesion and cytoskeletal tension and also activates tumor-promoting signaling pathways by inducing the nuclear translocation of transcriptional mediators such as YAP/TAZ [30, 31]. In addition, tumor cells are capable of sensing and migrating toward stiffer ECM regions (durotaxis), thus contributing to metastasis (figure 3). Subsequently, CAFs secrete MMPs that disrupt the structure of the ECM, thereby unveiling the ECM-located mediators (e.g. GFs, chemokines, cytokines, and extracellular vesicles) [32]. The release of such mediators, particularly vascular endothelial growth

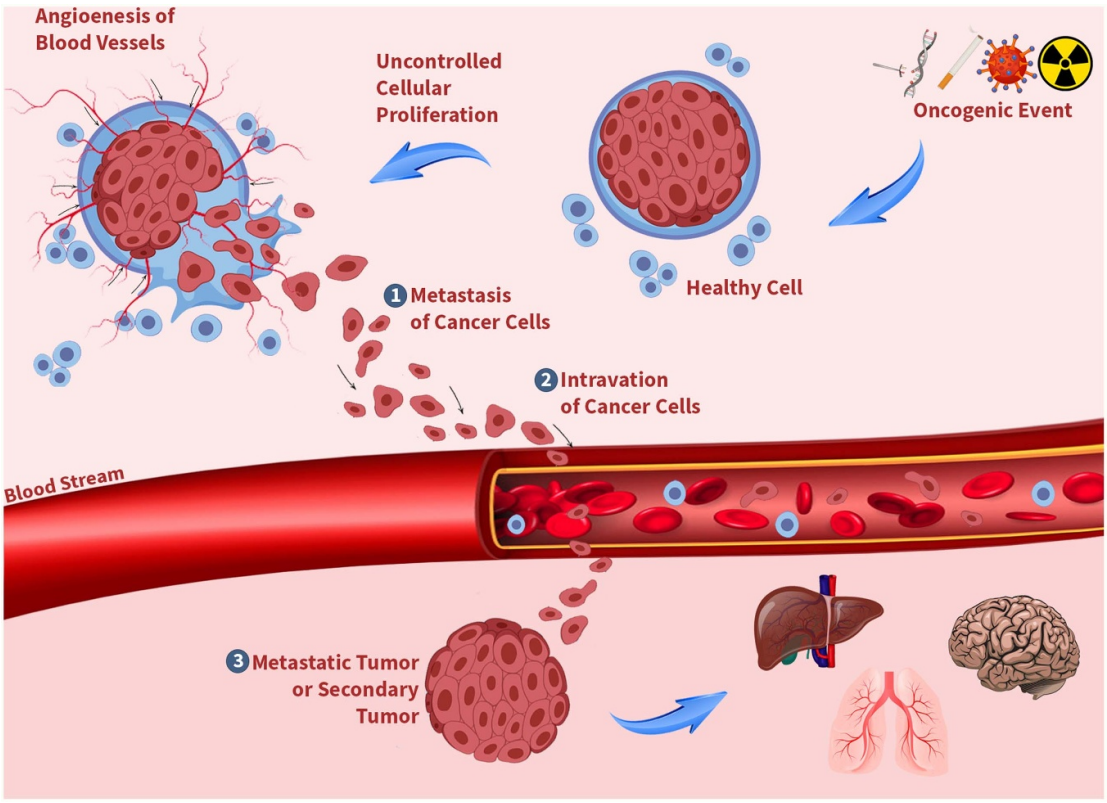


**Figure 3.** Overview of the metastatic cascade in cancer progression.

factor (VEGF), increases vascular permeability and promotes neovascularization [30]. TGF-$\beta$2, on the other hand, inhibits tumor growth at an early stage of cancer; however, it promotes tumor cell invasiveness and metastasis at later stages of tumorigenesis [46]. Additionally, modifications in ECM properties such as porosity, stiffness, and viscoelasticity create a microenvironment that favors tumor progression. These changes not only facilitate tumor invasion and the formation of secondary tumors but also enhance angiogenesis, suppress immune cell infiltration, and contribute to therapy resistance [30, 47].

## 3. Decellularization: a paradigm shift in biomimetic ECM engineering

As of today, the fabrication of a fully synthetic biosimilar matrix by combining all the individual components of the ECM is impracticable due to its extremely complex structure and the requirement for ultra-precise micro/nanoengineering. Hence, decellularization is considered the most effective technique to achieve biomimetic ECM. This procedure encompasses the removal of host cells, cellular and genetic materials (e.g. DNA, RNA, lipids, mitochondria, and cytoplasmic proteins), which are sources of the immune response, from the tissue while preserving the unique native ECM structure and composition. To obtain decellularized matrices, a series of processes is required. First, cell membranes must be disrupted and cell components removed from the ECM, then cytoplasmic/nuclear components must be solubilized, and finally, cell debris must be removed [48]. The following table 1 presents a detailed comparison of the various decellularization methodologies, along with a comprehensive analysis of their respective advantages and disadvantages [7, 21, 49, 50]. Briefly, they are classified into three categories, dependent upon the characteristics of the agent employed: physical (freeze-thawing, hydrostatic pressure, shaking, and sonication), chemical such as detergents (e.g. sodium dodecyl sulfate, sodium deoxycholate, Triton X-100, Tween-20, and CHAPS), acids, bases, and hypertonic or hypotonic solutions, and enzymatic (trypsin, pepsin, collagenase, DNase, and RNase) [51]. However, the optimum decellularization process generally involves a combination of physical, chemical, and enzymatic methods. Moreover, supercritical carbon dioxide ($scCO_2$) has recently emerged as an environmentally sustainable alternative to conventional chemical decellularization protocols, aligning with green chemistry concepts. $scCO_2$, with its unique properties such as low surface tension, high diffusivity, and non-toxicity, is a prominent method for decellularization. Exhibiting both liquid and gas-like behavior, $scCO_2$ easily penetrates tissues, removing cellular components while causing minimal damage to the ECM structure. Furthermore, the strong

**Table 1.** Comprehensive comparison of decellularization strategies.

| Decellularization method | Principal mechanism | Advantages | Limitations |
|---|---|---|---|
| Physical | | | |
| Freeze-thaw cycles | Formation of intracellular ice crystals disrupts cell membranes and induces cell lysis | Simple and inexpensive; avoids chemical residues; partially preserves ECM architecture | Can severely damage ECM proteins; mechanical properties compromised; incomplete DNA removal |
| Hydrostatic pressure | Application of high pressure causes cell rupture while attempting to preserve the ECM | No chemical agents; effective for large tissue volumes; maintains gross architecture | Alters ECM mechanics; potential protein denaturation; uneven efficiency in thick tissues |
| Non-thermal irreversible electroporation | Electric pulses create permanent pores in cell membranes, leading to cell death | Minimally invasive; preserves ECM components; no chemical contamination | High energy may damage structural proteins; incomplete removal of nuclear material |
| Supercritical $CO_2$ | Supercritical $CO_2$ penetrates tissues, removing cellular and nuclear materials | Maintains ECM structure and mechanical strength; avoids toxic remnants | Limited penetration in dense tissues; specialized equipment required; costly |
| Chemical | | | |
| Ionic detergents (e.g. SDS) | Solubilize cellular membranes and denature proteins | Highly effective at removing cellular content; scalable for large samples | Causes significant ECM protein loss; damages GAGs and growth factors; disrupts ultrastructure |
| Non-ionic detergents (e.g. triton X-100) | Disrupt lipid-lipid and protein-protein interactions without extensive denaturation | Gently on ECM proteins compared to ionic detergents; useful for soft tissues | Less efficient for nuclear material removal; may leave cellular remnants |
| Zwitterionic detergents (e.g. CHAPS) | Combine properties of ionic and non-ionic detergents; disrupt lipid-protein and protein-protein interactions | Balance between efficiency and ECM preservation; useful for soft tissues; less denaturing | Less effective than SDS for complete decellularization; may require combination with other agents |
| Acids and bases | Hydrolyze cellular components and solubilize nucleic acids | Effective DNA removal; rapid and inexpensive | Severe damage to collagen and GAGs; compromises ECM bioactivity |
| Hypertonic/hypotonic solutions | Induce osmotic stress leading to cell swelling and lysis | Mild approach; preserves many ECM components; easily combined with enzymes | Incomplete decellularization; persistent cell debris in the ECM |
| Enzymatic | | | |
| Trypsin | Digests cell adhesion proteins and membrane components | Specific targeting of cell proteins; useful for dense tissues | May excessively degrade ECM proteins (collagen, laminin); residual enzyme activity alters biofunctionality |
| Collagenase | Breaks down collagen fibers within the ECM | Effective for removing dense collagen-rich regions; facilitates cell infiltration | Can excessively degrade ECM structural integrity; loss of biomechanical strength |
| Pepsin | Cleaves peptide bonds in collagen and other ECM proteins at acidic pH | Useful for partial digestion of ECM to expose binding sites; aids solubilization of ECM | May disrupt collagen triple helix; reduce tensile strength; require precise pH control |
| Nucleases (DNase, RNase) | Degrade DNA and RNA into small fragments | Effective nucleic acid removal improves biocompatibility | Do not remove cytoplasmic proteins; residuals may induce an immune response |
| Combined approaches | Sequential or simultaneous integration of physical, chemical, and enzymatic techniques | Maximizes efficiency; balances cell removal with ECM preservation | Requires optimization; higher cost and longer processing time; potential ECM heterogeneity |

solvent properties and the very low critical temperature (31.06 °C) increase the suitability of this method for physiological conditions. Consequently, the use of $scCO_2$ reduces the need for additional purification and processing steps, thus enhancing the process's efficiency and environmental sustainability [19].

The characterization of decellularized ECM (dECM) is critical to ascertain the adequate elimination of cells and cellular components, as well as for assessing the structural and biochemical integrity of the ECM. Correspondingly, the presence of residual DNA in the ECM can be evaluated by staining the sample with DAPI or Hoechst fluorescent dyes that bind to AT-rich regions in the DNA. Additionally, quantitative methods employing propidium iodide and PicoGreen have been developed to detect residual DNA content [7]. Researchers have proposed a set of standards that define the hallmarks of successful decellularization. According to these standards, the double-stranded DNA (dsDNA) in decellularized tissues must be less than 50 ng per mg of ECM dry weight. Nevertheless, the dsDNA content is not the only factor influencing the host response to ECM scaffolds. Furthermore, DNA fragments must be shorter than 200 base pairs, and no visible nuclear material must be present in tissue sections stained with DAPI (4′,6-diamidino-2-phenylindole) or hematoxylin and eosin (H&E) [52]. These standards are quite rigorous and, in some cases, may be considered overly restrictive for particular tissues or applications. Notably, numerous ECM-based scaffolds that are already on the market do not fully comply with these benchmarks, yet they continue to demonstrate favorable clinical results [53]. To confirm the preservation of ECM components, key molecules such as adhesion proteins (e.g. fibronectin and laminin), GAGs, elastic fibers, and various collagens must also be verified using alternative histological stains, including Masson's Trichrome, Movat's Pentachrome, Alcian Blue, Toluidine Blue, Sirius Red, or Safranin O. Beyond the aforementioned histochemical methods, immunochemical methods are also available to detect specific ECM proteins using specific antibodies. Specifically, certain GAGs can be identified using lectins [48]. In addition, mass spectrometry and proteomic analysis have been extensively utilized to elucidate the dECM composition. Architectural investigations of dECM can be conducted through the utilization of scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Complementarily, mechanical tests and rheological analyses provide valuable insights into the material's tensile strength, elastic modulus, hardness, yield strength, and viscoelastic properties [54]. In current medical practice, tumor decellularization is commonly carried out via physical, chemical, and enzymatic methods, similar to those employed in the decellularization of normal tissues and organs. For instance, SDS efficiently removed cellular constituents from both normal and cancerous colon specimens [55, 56], whereas Triton X-100 produced comparable decellularization in both healthy and tumor liver samples [57, 58]. Different agents and techniques are used depending on the type of cancer. Notwithstanding, innovative and detergent-free methods, such as high hydrostatic pressure or supercritical $CO_2$, which yield commendable outcomes in normal tissues, have yet to be applied in the decellularization of tumors.

## 4. Applications of decellularized matrices in cancer research

Although the limited number of studies in literature has significantly contributed to understanding the role of the ECM in cancer development, extensive research is still needed to identify potential therapeutic targets and to elucidate the mechanisms underlying chemosensitivity, chemoresistance, angiogenesis, and metastasis. In the forthcoming subsections, the origins of tumor tissues, the sources of these tissues, the decellularization techniques, and their applications (figure 4) are systematically discussed under thematic categories based on the form in which dT-ECM is employed.

### 4.1. Decellularized tumor matrices

dT-ECMs can be obtained from a variety of sources, including human, animal, or cell culture origins [7]. They are gaining prominence as biomimetic platforms for tumor microsimulation, offering insightful perspectives into the mechanisms of cancer progression and therapeutic response. **Colorectal cancer** (CRC), which originates in the colon and rectum, is a highly lethal malignancy marked by its high therapeutic resistance, frequent recurrence, and distant metastasis, ranking as the second leading cause of cancer-related mortality on a global scale. Marques–Magalhães and colleagues [55] **decellularized human CRC tissue** using physical (agitation), chemical (hypotonic solution and 0.2% SDS), and enzymatic (50 U $ml^{-1}$ DNase solution) methods. H&E (figure 5(A)) and Masson's trichrome staining (figure 5(B)) validated that the ECM network was preserved while cellular material was effectively removed. Afterward, authors used dT-ECMs as biomimetic 3D platforms to model the effects of ECM on cancer stem cell (CSC) markers ($\alpha$-Tubulin and F-actin) in the TME by recellularizing HT-29 and HCT-15, CRC cell lines (figure 5(C)). Gene expression analysis of HT-29 cells cultured on dT-ECM demonstrated a significant upregulation of key pluripotency-associated markers, including NANOG, SOX2, OCT4, and SNAI1, indicating a

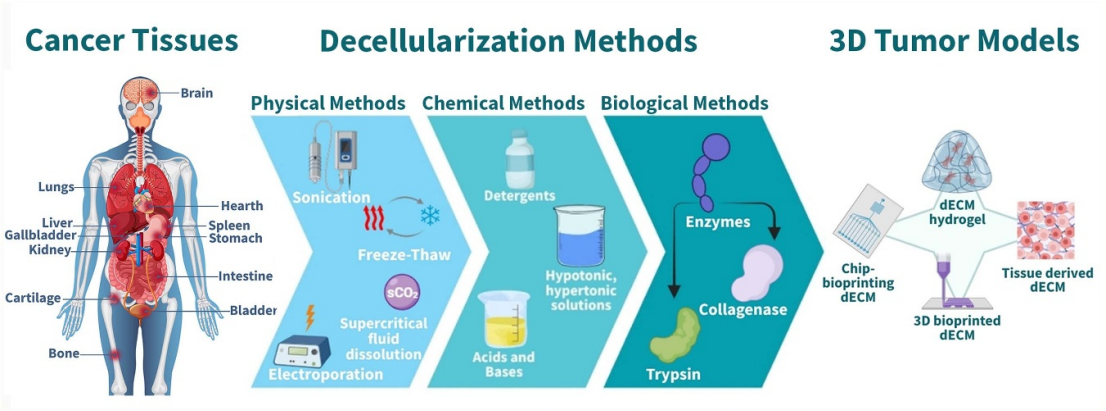


**Figure 4.** Illustrative representation of decellularization techniques applied to tumor tissues and their applications in 3D cancer modeling. Created in BioRender [59].

potential shift toward a CSC or stem-like subpopulation (stemness) phenotype. The cell surface markers $CD44^+/CD133^+/CD166^+$ are commonly associated with stemness. The simultaneous expression of these markers is strongly correlated with enhanced tumorigenic capacity, therapeutic resistance, invasive behavior, and adverse clinical outcomes [40]. Surface markers $CD44^+$, $CD133^+$, and $CD166^+$, commonly associated with stemness, were also notably increased, indicating enhanced tumorigenic potential, therapeutic resistance, and invasiveness. Moreover, the study showed increased levels of transforming growth factor-beta (TGF-$\beta$), a critical factor in driving late-stage tumor progression, EMT, invasion, and metastasis, and elevated activities of MMP-2 and MMP-9, both of which are essential for ECM remodeling. In conclusion, these findings indicate that dT-ECM actively supports tumor cell phenotype (stemness, invasion, treatment resistance) beyond being merely a passive structure providing a strong rationale for developing biomarkers targeting the ECM and for clinical investigation of ECM-modulating therapeutic strategies.

In another study conducted in 2025, Lee and co-workers [47] performed a comprehensive proteomic analysis to investigate differences in the ECM between tumor and adjacent normal tissues in **CRC** patients. They aimed to elucidate the mechanisms by which the TME is remodeled and to identify the cellular origins of these changes. Tissue samples were decellularized using a detergent-based method containing 1% Triton X-100 and 0.1% ammonium hydroxide. The dECM samples were analyzed via liquid chromatography-tandem mass spectrometry (LC-MS/MS) to identify protein-level variations. Additionally, integrative analyses were performed using single-cell RNA sequencing (scRNA-seq) and bulk RNA-seq data. The results illustrated that 110 ECM proteins were significantly enriched in normal tissues, indicating their higher abundance compared to tumor equivalents. In contrast, 28 ECM proteins were found to be significantly overexpressed in tumor tissues relative to their levels in normal counterparts. Researchers have established that the majority of ECM proteins characteristic of normal tissues are derived from $PI16^+$ (immune modulator) and $ADAMDEC1^+$ (pro-inflammatory and ECM remodeler) fibroblasts. Notably, in **CRC** samples classified as the mesenchymal subtype CMS4, high expression levels of THBS2, CTHRC1, and BGN (markers of desmoplastic fibroblasts), as well as SFRP2, PRELP, OGN, and SRPX, which are associated with PI16+ fibroblasts, were observed. This expression pattern was found to correlate with poor prognosis. Ultimately, this study highlights that ECM components are not only closely associated with tumor biology but also with the stromal cell compositions of diverse tumor subtypes, providing strong evidence for the potential use of ECM proteins as prognostic biomarkers in **CRC**.

**Breast cancer** (**BC**) is the most commonly diagnosed malignancy among women, affecting over two million individuals worldwide each year. Despite advancements in preventive strategies, early detection programs, and the development of innovative and personalized therapies, **BC** remains the primary reason for cancer-related mortality in women globally [60]. Triulzi *et al* [61] have developed dT-ECM models to reconstruct the TME specific to **BC**. To this end, **human BC** samples were initially decellularized using a hypotonic Tris-HCl solution, followed by a 4% SD solution. The authors reported a significant enrichment of proteins implicated in tumor ECM relation through shotgun proteomic analysis of decellularized human **BCs**. CLEC3A (a member of the secreted C-type lectin domain family 3), a mechanosensor protein, was determined to be overexpressed in tumor tissues by immunohistochemical analysis. In

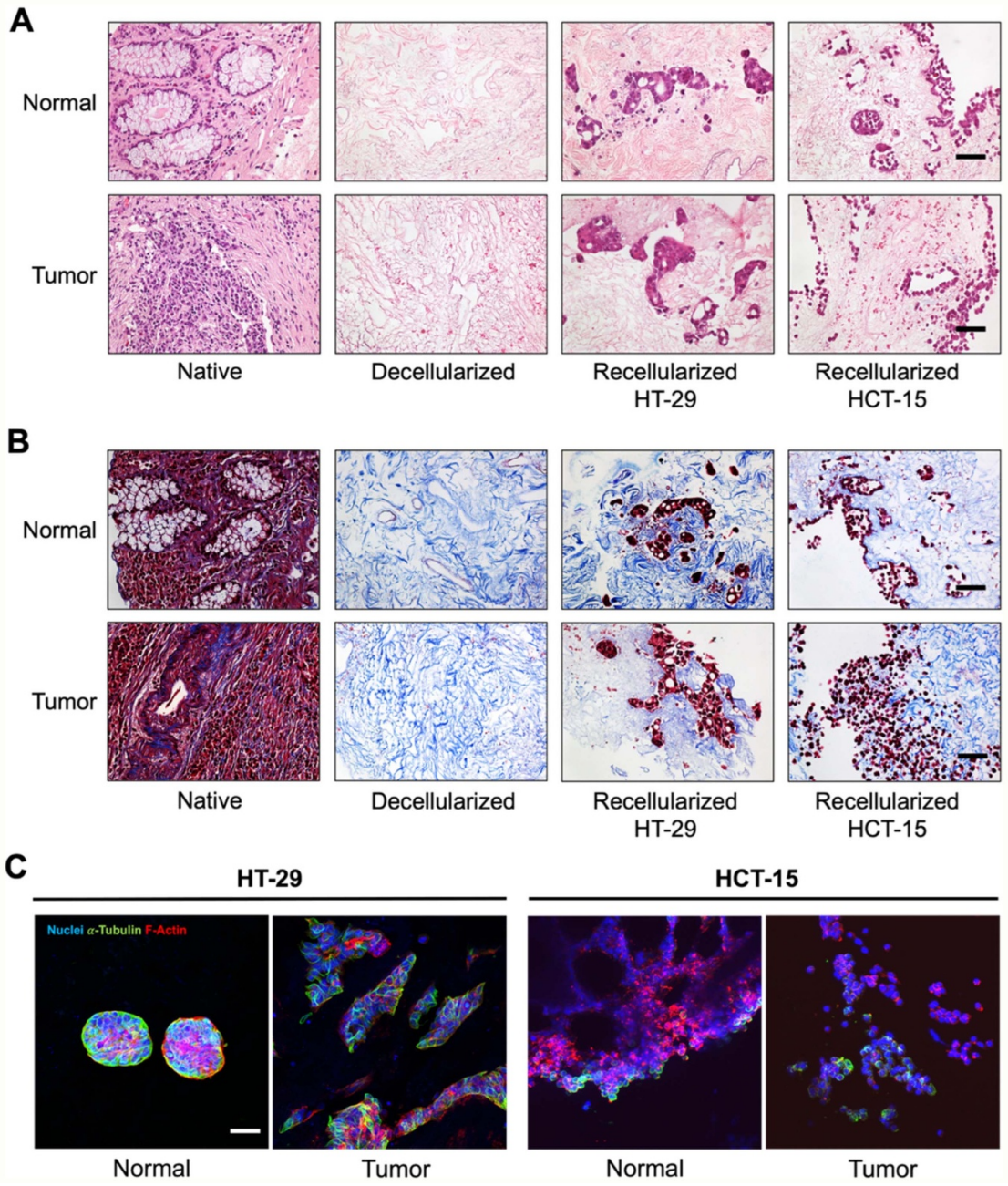


**Figure 5.** Colorectal tumor and non-tumorous mucosal matrices, decellularized from surgical samples of CRC patients, were recellularized using HT-29 or HCT-15 colon cancer cell lines. (A) Hematoxylin and eosin, and (B) Masson's trichrome staining display morphological changes across native, decellularized, and recellularized scaffolds (scale bar: 20 μm). (C) Confocal microscopy of recellularized matrices shows cytoskeletal F-actin (red) visualized with Alexa Fluor 568-phalloidin, microtubules (green) stained using $\alpha$-tubulin monoclonal antibody and Alexa Fluor 488-conjugated secondary antibody, and nuclei stained with DAPI (blue). Scale bar: 50 μm.

addition, overexpression of CLEC3A in BC cells was found to enhance intracellular regulators involved in tumor adhesion to the ECM, organization of actin stress fibers, activation of YAP signaling, and promotion of cell migration. In accordance, an elevated expression of the YAP/TAZ gene marker was observed in CLEC3A-positive neoplasms, and a direct correlation was identified between the levels of this marker and the degree of tumor stiffness. These outcomes suggest that CLEC3A facilitates tumor progression by enabling BCs to detect signals in the surrounding ECM. CLEC3A-positive dT-ECM findings offer realistic translational potential for prognostic stratification, patient-specific *ex vivo* drug testing, and ECM-directed therapeutic strategies in BC.

**Liver cancer** poses a significant burden on global health, with estimates that the number of cases will exceed one million by 2025. **Hepatocellular carcinoma (HCC)**, representing approximately 90% of all liver cancer cases, is the predominant histological subtype. Chronic infections with the hepatitis B virus and the hepatitis C virus are the primary

etiological factors contributing to **HCC** pathogenesis [62]. In the study by Wang *et al* [57], a novel *in vitro* model was developed to evaluate the efficacy of trans arterial chemoembolization (TACE), which is widely used in the treatment of **liver cancer**. This method targets and blocks blood flow to the tumor and provides localized therapy. An *in vitro* liver model was developed by decellularization of rat livers with diethylnitrosamine (DEN)-induced HCC via 4% Triton X-100 and 1% SDS. The integrity of abnormal vascular structures and specialized ECM components, key elements of the TME, was confirmed through H&E staining, immunohistochemical analysis, and SEM. The obtained dT-ECM exhibited a denser ECM structure and significantly disrupted vascular networks compared to the healthy liver matrix. Immunohistochemistry and proteomic analyses disclosed increased expression of type I, IV, and VI collagens in HCC. The release of a clinically used chemoembolization agent, doxorubicin-loaded lipiodol emulsion, was evaluated using a biomimetic liver dT-ECM model. The results demonstrated prolonged drug retention within tumor regions, whereas rapid release was observed in healthy liver tissue. The authors concluded that the abnormal vascular architecture and fibrotic nature of the TME significantly influence the distribution of drugs. As a preclinical platform, this model holds promise for embolic materials and elucidating the effects of embolization on the TME.

### 4.2. Hydrogels

Hydrogels are preferred in clinical practices due to their advantageous features, such as the ability to fill irregularly shaped wound areas, their 3D structure, bioactivity similar to that of the native matrix, high liquid content, and adjustable physical properties [63]. **Glioblastoma multiforme (GBM)**, the most prevalent form of brain tumor, is characterized by an aggressive and infiltrative nature. To develop an innovative 3D *in vitro* tumor model as a hydrogel, Koh and colleagues [22] **decellularized patient-derived glioblastoma tissue**. This hydrogel served as a platform to investigate cell–ECM interactions and the invasive phenotype of glioblastoma cells. This hydrogel was used to investigate cell-ECM interaction and the invasion phenotype of glioblastoma cells. For this purpose, glioblastomas were treated with 0.1% ammonium hydroxide and 1% Triton X-100 to remove cellular components. Subsequently, the DNA content in the tissue decreased to 8.9%, while the ECM components (collagen IV, fibronectin, laminin, HA, and GAGs) were preserved. After validation, dT-ECMs were lyophilized, and lyophilized dT-ECMs were digested with a 1 mg ml $^{-1}$ pepsin-HCl (0.01 M) acid solution to obtain a pre-hydrogel. Thereafter, the pre-hydrogel was neutralized with 10x PBS at 37 °C for 1 h. Concurrently, the dT-ECM hydrogel demonstrated a low elastic modulus (78.09 $\pm$ 29.22 Pa), which is similar to that of brain tissue. The patient-derived primary **GBM** cells cultured in dT-ECM displayed a heterogeneous morphology, consisting of elongated and round shapes, and indicated a high invasive potential. In addition, the migration rate of cells in dT-ECM (0.97 $\pm$ 0.06 μm min$^{-1}$) was found to be significantly higher than that in the collagen matrix (0.33 $\pm$ 0.02 μm min$^{-1}$). Furthermore, the inhibition of enzymes associated with ECM remodeling (MMP2/9 and HAS2) resulted in a modification of the invasive behavior of cells. MMP inhibitor SB-3CT increased amoeboid-type invasion by reducing the proportion of elongated cells, while HAS inhibitor 4-MU activated an alternative invasion pathway by directing cells to elongated morphology. These findings suggest that **GBM** cells can employ diverse invasion strategies as a means of adapting to the microenvironment, with these strategies potentially varying based on enzymatic activity. The present study demonstrated that patient-derived dT-ECM is an effective tool for modeling the invasive dynamics of **GBM**.

In another study, 3D hydrogels were fabricated from colon tumor tissue to examine the aggressive behavior of **colon cancer** and the effects of the TME [64]. These hydrogels were used to model the growth, invasion, and metabolic adaptation of tumor cells, angiogenesis dynamics, and the impact of ECM components on cell behavior. First of all, Romero-Lopez and colleagues **decellularized colon tumor tissue** with 1% SDS and 1% Triton X-100 detergents and then with 100 U of DNase. These processes facilitate the effective removal of nuclear material and cytoplasmic debris while preserving the main structural and functional components of the ECM, such as collagen, elastin, and GAGs. The structural integrity of the ECM obtained post-decellularization was confirmed through histological staining (H&E, DAPI) and GAG content quantification. Proteomic analysis showed that tumor aggressiveness-related proteins such as fibronectin, tenascin-C, and periostin were significantly increased in dT-ECM. Additionally, structural proteins such as collagen IV, collagen VI, fibrillin, emilin, vitronectin, and laminin were also substantially increased in dT-ECM. In parallel with these compositional differences, the mechanical properties of dT-ECM were found to be 3 times stiffer compared to healthy ECM. Angiogenesis studies have revealed that dT-ECM significantly affects vessel formation. The vascular networks developing within dT-ECM exhibited a wider diameter, excessive branching, and irregular morphology, reflecting the typical pathological characteristics of tumor vessels. In contrast, the vessels formed in healthy ECM showed a more regular and stable structure. In studies on tumor cell behavior, SW620 colon cancer cells were observed

to proliferate significantly faster in dT-ECM than in healthy ECM. Besides, metabolic analyses performed using fluorescence lifetime imaging microscopy revealed an increase in the free NADH ratio in cells cultured in dT-ECM, indicating that the cells had shifted to glycolytic metabolism. This discovery is confirmed by an increase in the expression of glycolysis-related genes, including HK1, GLUT1, and PDK1, in dT-ECM. Finally, *in vivo* studies in mouse models have corroborated *in vitro* findings by demonstrating that tumor cells exhibit higher vascular density in dT-ECM. In essence, this 3D tumor model is critical for the development of targeted therapies and the design of personalized treatment strategies. Especially, the inhibition of ECM components (e.g. tenascin, periostin) or the modulation of metabolic pathways (glycolysis) are emerging as new therapeutic targets.

### 4.3. Bioinks and organoids

Bioinks are a combination of living cells and printable hydrogels that possess favorable physicochemical and rheological properties for cell growth and differentiation. In particular, dECM-based bioinks contain additional cell adhesion proteins and bioactive molecules [49]. Also, organoids are self-organizing 3D stem cell structures that imitate the physicochemical environment of native tissue, such as tissue boundaries, cell-tissue and cell-cell interactions [65]. Tavlak [66] developed **BC** organoids by decellularizing cell-derived ECM to fabricate a biomimetic 3D **BC** tumor model. To achieve this, MCF-7 **breast adenocarcinoma cells** were initially cultured in Dulbecco's Modified Eagle's Medium-High Glucose supplemented with 10% fetal bovine serum (FBS) at 37 °C with 5% $CO_2$ for 48 h. Then, the ECM derived from MCF-7 cells was decellularized using 0.5% Triton X-100 and 20 mM $NH_4OH$, followed by enzymatic treatment with DNase and RNase to remove residual nucleic acids. The matrix was lyophilized and digested in a pepsin solution (1 mg $ml^{-1}$ pepsin in 0.01 M HCl) to obtain **BC** dT-ECM hydrogels. **BC** organoids were produced from the conventional hanging drop culture method, and the impact of dT-ECMs in varying concentrations on organoid formation was assessed. The analysis results demonstrated that **BC** dT-ECM-enriched media enhanced cell proliferation, decreased apoptosis and necrosis, and ensured balanced distribution of nutrients and oxygen. Furthermore, morphological assessments indicated that **BC** dT-ECM influenced the structural organization of organoids, promoting heterogeneity and characteristics similar to the TME. In conclusion, this study indicates that **BC** dT-ECM provides a robust biomimetic platform for organoid development. Serving as an alternative to conventional matrices such as Matrigel, this strategy enables a highly accurate model of the TME and represents a notable advancement for personalized medicine and preclinical cancer research.

In another study, Kim and colleagues [24] developed a bio-printed vascularized organoid model (VOM) from patient-derived gastric tissue to overcome the clinical challenges encountered in the treatment of **gastric cancer (GC)**, such as genetic heterogeneity, the complexity of the TME, and the inadequacy of existing models. This model combines patient-derived GC organoids (PDOs), perfusable endothelial cells, and gastric-specific decellularized ECM (st-dECM) to highly mimic the *in vivo* TME. Firstly, **GC** tissue was decellularized in a 1% SDS solution prepared in PBS for 48 h, followed by exposure to 1% Triton X-100 for 30 min. The decellularized **GC** tissue was subsequently rinsed thoroughly with PBS for a minimum of three days to ensure the removal of residual reagents. Kim *et al* developed a customized bioprinting system (MtoBS) equipped with six syringe holders, thereby enabling the simultaneous dispensing of multiple materials. In their approach, polycaprolactone (PCL) was heated to 80 °C and extruded under pneumatic pressure (400–650 kPa) to form the supporting scaffold, while cell-encapsulated dECM pre-gel was maintained below 15 °C and delivered through a piston-based low-dosage system. During the process, the molten PCL rapidly cooled in air before deposition, which facilitated structural stability of the printed constructs. The mechanical stiffness of st-dECM was found to have a significant impact on various biological processes, including cell proliferation and drug resistance. Nuclear translocation of the YAP/TAZ signaling pathways and the expression of target genes (ANKRD1, CTGF, CYR61) exhibited a direct correlation with the stiffness of st-dECM. Notwithstanding, the VOM model was conceived with the intention of encompassing not only stromal and tumor cells, but also the vasculature. In this system, created with bioprinting technology, spontaneous angiogenesis was observed between PDOs and vascular structures, and it was determined that this angiogenic behavior varied between GC subtypes. Furthermore, the clinical applicability of the model was confirmed by its successful prediction of patient responses to the VEGFR2 inhibitor ramucirumab. In tests conducted with PDOs obtained from patients with ramucirumab-sensitive and ramucirumab-insensitive tumors, treatment responses in the VOM model showed high concordance with patient clinical outputs. In conclusion, this study demonstrates that the development of patient-specific vascularized tumor models offers the potential to optimize personalized treatment strategies and effectively model tumor heterogeneity. The developed VOM system is considered a powerful framework for the identification of novel therapeutic targets and the prediction of treatment responses, particularly in cancer types where standard treatment protocols are unavailable or ineffective.

In a final study, Zhou and collaborators [67] developed a hybrid bioink that simulates the TME by combining **decellularized HCC** matrix with gelatin methacrylate (GelMA) hydrogels to study chemoresistance in **HCC** treatment. In this study, **HCC** tumors were generated in nude mice using the Huh7 cell line (a human-derived **HCC** line was originated from a Japanese patient). Subsequently, the tumor tissues were decellularized with 3% Triton X-100 detergent in a hypotonic solution (10 mM Tris-HCl). Afterward, dT-ECM/GelMA, a photocrosslinkable composite hydrogel, enabled the encapsulation of **HCC** cells using microfluidic-based 3D printing technology. For this, a new droplet-based microfluidic 3D printing system was used. The mechanism components were listed as follows: (i) syringe pump, (ii) bioprinting machine arm, (iii) operating system, (iv) superhydrophobic surface, and (v) UV crosslinking equipment. Initially, hydrogel precursor solutions containing Huh7 cells at a concentration of $1 \times 10^6$ cells $ml^{-1}$ were loaded into syringe-pump assemblies and injected, producing droplets through Plateau-Rayleigh instability; stabilization was provided by polydimethylsiloxane surfaces microfabricated with pillar arrays to mimic lotus-leaf super-hydrophobicity. The results showed that the dT-ECM bioink supported the viability and proliferation of **HCC** cells. In chemoresistance assays, bioink provided higher resistance in **HCC** cells compared to the control group (GelMA). This was attributed to the activation of the mTOR pathway by increasing Aquaporin 3 expression, ultimately providing a protective effect against chemotherapy via autophagy. This innovative strategy represents a powerful platform for advanced liver cancer drug resistance research, the identification of new therapeutic interventions, and potential regulatory targets.

## 5. Conclusions

Over the past decade, dT-ECMs have emerged as an innovative model in cancer research thanks to the biochemical heritage from tumor-derived tissue. In this regard, dT-ECMs present a promising approach for simulating tumor-specific heterogeneity, invasion patterns, cell behavior, chemotherapy resistance mechanisms, and metastatic processes that are challenging to imitate in conventional 2D culture systems or synthetic biomaterials [7]. These dT-ECM environments, which mimic 3D cancer tissue, enable the elucidation of properties such as invasion, cancer cell differentiation, and metastatic behavior [68]. Besides, these models provide more accurate results than classical 2D cell culture systems in drug sensitivity and chemotherapy resistance evaluations [67]. Furthermore, dECM derived from patient-derived tumor tissues provides the creation of personalized 3D tumor models. This facilitates the development of individualized and preventive treatment strategies [69].

Despite these prominent advantages, decellularized tumor matrices face several critical technical and biological limitations. A significant challenge is the absence of standardization in the decellularization process. Different tissue types and decellularization protocols can lead to variability in the structural and biochemical integrity of the dT-ECMs. Moreover, patient-specific variations and biological heterogeneity in cancerous tissues complicate the reproducibility and standardization of the tumor model [55]. Moreover, patient consent and ethical approval are required for human patients' tumors. In addition, the limited availability of patient-derived tissue sources poses a significant challenge for large-scale *in vitro* studies [7]. A further challenge is the potential structural deterioration of dT-ECMs during long-term storage, which can lead to a decrease in biological functionality [70–73]. The potential immunogenic response of ECM components, even after decellularization, is another factor that limits their application in clinical practices [74, 75].

Tumor-on-a-chip (ToC) is a flow- and velocity-controlled microfluidic cell culture system that mimics the microenvironmental behaviors of tissues, such as the multicellular structure, chemical gradients, inter-tissue interfaces, mechanical signals, and vascular perfusion [76]. In this context, the integration of dT-ECM-based models with organoid and organ-on-a-chip systems has the potential to address the lack of knowledge in studies of cancer development, chemoresistance, and personalized treatment. Beyond physical integration, the processing of data obtained from dT-ECM-based models with omics technologies, including transcriptomics, proteomics, and metabolomics, is expected to provide an advanced comprehension of the molecular-level mechanisms guiding tumor-ECM interactions. In conjunction, machine learning (ML) and artificial intelligence (AI)-driven tools can assist in predicting novel therapeutic targets and optimizing treatment strategies, thanks to the increasing volume of complex dT-ECM data, which encompasses proteomic, genomic, and mechanical characteristics. Because ML and AI are two such innovative approaches that are becoming increasingly important in the field of tissue engineering. These technologies find application in a wide range of areas, including scaffold design, prediction of biological responses, optimization of drug delivery, support for image analysis, and modeling *in vivo* performance. The utilization of ML-supported methodologies, particularly in areas such as the optimization of bioprinting processes, cell imaging analysis, and the modeling of scaffold performance, provides significant advancements over conventional techniques [77, 78]. This is evident as preclinical studies have indicated the benefits of these models in the prediction of tumor behavior and

the evaluation of treatment options. For instance, histopathological tumor data (WSI) can be analyzed using deep learning models such as CNN, U-Net, and ResNet, thereby enabling the digital scaling of dT-ECM data obtained from limited biological samples. Furthermore, AI algorithms such as Random Forests, ANN, and Reinforcement Learning have been successfully applied to predict biomaterial properties, design scaffolds for 3D bioprinting, and simulate ECM-cell interactions. The integration of such algorithms with extensive bioinformatics databases, such as PubChem, NanoMine, and Reaxys, facilitates the virtual design of biomimetic alternatives to dT-ECM, thereby reducing the experimental demands [79, 80]. However, additional research is necessary to assess their capacity to predict clinical outcomes. The translation of dT-ECM into clinical practice is limited by two factors. Firstly, there is a paucity of large-scale validation cohorts. Secondly, there is a lack of standardized criteria to assess dT-ECM performance. To address this knowledge gap, meticulous clinical studies are necessary to establish a correlation between dT-ECM-based findings and patient outcomes.

In this review, we focused on the decellularization of cancerous tissues and their applications. In line with this, we briefly highlighted the ECM structure, its role in tumorigenesis, the differences in ECM composition between healthy and cancerous tissues, decellularization, and characterization methods. Especially, we discussed the most recent studies in detail according to their forms as dT-ECM, hydrogel, and bioink. We also criticized the advantages, disadvantages, and future perspectives of dT-ECMs. In conclusion, tumor decellularization represents a promising up-to-date era, as evidenced by the aforementioned advantages. Hence, there is a necessity for further research to be conducted on the integration of dT-ECMs with state-of-the-art technologies to illuminate the dark secrets of cancer.

## Data availability statement

No new data were created or analysed in this study.

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