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Extracellular matrix dynamics in tumor immunoregulation: from tumor microenvironment to immunotherapy

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Abstract

The extracellular matrix (ECM), closely linked to the dynamic changes in the tumor microenvironment (TME), plays a critical role in modulating tumor immunity. The dual role of the ECM in tumor progression, encompassing both promotion and inhibition, is attributed to its components influencing immune cell activation, migration, and infiltration. This mechanism is intricately connected with the efficacy of immunotherapies. Currently, there is limited understanding of how ECM remodeling spatially and temporally coordinates with immune checkpoint inhibitors (ICIs) or adoptive cell therapies. Furthermore, strategies to selectively target pathological ECM components while preserving their homeostatic functions urgently require systematic investigation. In this review, we summarize current findings on the interplay between ECM and tumor immune regulation, with a particular focus on how key ECM components contribute to immune modulation. Furthermore, we discuss emerging strategies targeting ECM-related mechanisms to enhance the efficacy of immunotherapies, including approaches that remodel the ECM to improve immune infiltration and strategies that synergize with existing immunotherapies. By integrating these insights, we provide a perspective on leveraging ECM-targeted interventions to overcome immune evasion and optimize cancer immunotherapy outcomes.

Introduction

Recently, significant breakthroughs have been made in the cancer diagnosis and treatment with the clinical application of immune checkpoint inhibitors (ICIs). It has been found that within the context of the tumor microenvironment (TME), tumor cells alter immune homeostasis by regulating T cells, allowing them to escape immune surveillance [1]. ICIs restore and maintain the immune system's ability to target tumor cells by blocking specific signaling pathways. Despite the fact that some patients show significant responses to immunotherapy, a significant percentage of patients still have poor or even ineffective treatment. This variability in treatment response is closely related to the high complexity of the TME.

TME, consisting of tumor cells, diverse cell components surrounding the tumor cells, and the extracellular matrix (ECM), plays an important role in tumor occurrence, development and metastasis [2]. The TME influences the function of immune cells through various mechanisms, such as altering immune cell phenotypes, and regulates tumor cell growth, invasion, and

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metastasis, all of which are crucial for tumor progression and therapeutic outcomes.

This dynamic regulation not only affects the recruitment and function of immune cells, but may also lead to immunotherapy resistance. During the process, TME showed both the heterogeneity of spatial distribution and characteristics of dynamic changes over time. Additionally, cancer cells interact with surrounding non-cancerous host cells mainly through intercellular interactions and paracrine signaling, facilitated by the ECM. As a key component of the TME, the ECM serves as a reservoir for nutrients, enzymes, and growth factors. During its dynamic remodeling, the ECM plays critical roles in providing mechanical support, transmitting biochemical signals, and maintaining microenvironmental homeostasis.

The ECM is a complex, dynamic network of macromolecules that provides structural and biochemical support to cells within tissues. Several reviews have investigated how ECM influences the cancer invasion. However, ECM, as an essential component of the TME, plays a role far beyond its role in structural support and cancer invasion. The ECM not only serves as a physical barrier to immune cell infiltration but also modulates immune cell behavior through biochemical cues, affecting the recruitment, activation, and functionality of immune cells. Moreover, ECM components contribute to the architectural and mechanical properties of the TME, thereby influencing tumor cell behavior and immune cell responses. Additionally, ECM remodeling mediated by cancer-associated fibroblasts (CAFs), including ECM degradation, deposition and cross-linking, enhances ECM stiffness, altering the TME and potentially facilitating immune escape mechanisms. Although ICIs have demonstrated clinical success, their efficacy remains limited in solid tumors due to the dual barriers of ECM-mediated immune exclusion and active immunosuppression mediated by mechanochemical signaling and dynamic ECM-TME crosstalk [3]. Current strategies to target ECM often fail due to indiscriminate disruption of physiological ECM functions. A critical gap remains in understanding spatiotemporal ECM dynamics, such as how ECM stiffening during therapy narrows the treatment window. Furthermore, the process of continuous deposition of ECM which is associated with fibrosis in multiple organs can be exacerbated by mitochondrial activity through various signaling pathways. Consequently, the ECM-mitochondria communication mechanism can enhance immune responses. Therefore, this review not only further explores the heterogeneity and functional roles of ECM components within the TME, but also summarizes the complex crosstalk among ECM and immune cells, which may affect the efficacy of immunotherapy. In addition, we discuss the potential for targeting ECM and the feasibility of these strategies in clinical settings (Fig. 1) (Table 1).

The ECM–TME crosstalk

The complexity of ECM and TME

Solid tumors represent a highly heterogeneous form of cancer, characterized by a complex ecosystem shaped by interactions among malignant cells, non-malignant cells, and the ECM [45]. The local environment surrounding the tumor constitutes the TME, which includes tumor cells, diverse immune cell types, stromal cells, the ECM, blood and lymphatic vessels, and nerve endings [46] (Fig. 2). This intricate interplay between the ECM and TME is crucial for understanding tumor behavior and progression, which is associated with the efficacy of immunotherapy.

TME is a dynamic and complex system, characterized by variations in its cellular composition and functional states influenced by factors such as tumor type, stage of progression, and organ specificity [47]. For example, in the advanced or metastatic stages of breast cancer, the proportion of immunosuppressive cells, such as immunosuppressive or anti-inflammatory macrophages and regulatory T (Treg) cells, gradually increases, facilitating immune evasion and promoting tumor growth. This shift in immune cell composition is often accompanied by changes in the ECM, which can alter the physical and biochemical properties of the TME. Moreover, these immune cells exhibit distinct activity patterns at different metastatic sites, such as the bone and lung [48].

The ECM is a complex and dynamic three-dimensional network, primarily composed of the basement membrane and the stromal connective tissue matrix. The basement membrane acts as a barrier while supporting cell adhesion, migration, proliferation, and differentiation. The stromal matrix regulates the TME through both physical support and biochemical signaling. The ECM consists chiefly of structural proteins, glycosaminoglycans (GAGs), proteoglycans, growth factors and cytokines, remodeling-associated proteases, small molecules and metabolites, as well as extracellular vesicles and microvesicles [49–51]. The structural proteins constituting the ECM include COL, elastin, fibronectin, and laminin, which form a proteinaceous network that provides mechanical support [52]. GAGs mainly include HA, chondroitin sulfate, dermatan sulfate, and heparan sulfate. Proteases mediating ECM remodeling consist of matrix metalloproteinases (MMPs), cathepsins, A Disintegrin and Metalloproteinase (ADAM) and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) family proteases, as well as serine proteases, which disrupt the structural integrity and stability of the ECM, thereby facilitating cancer cell invasion and

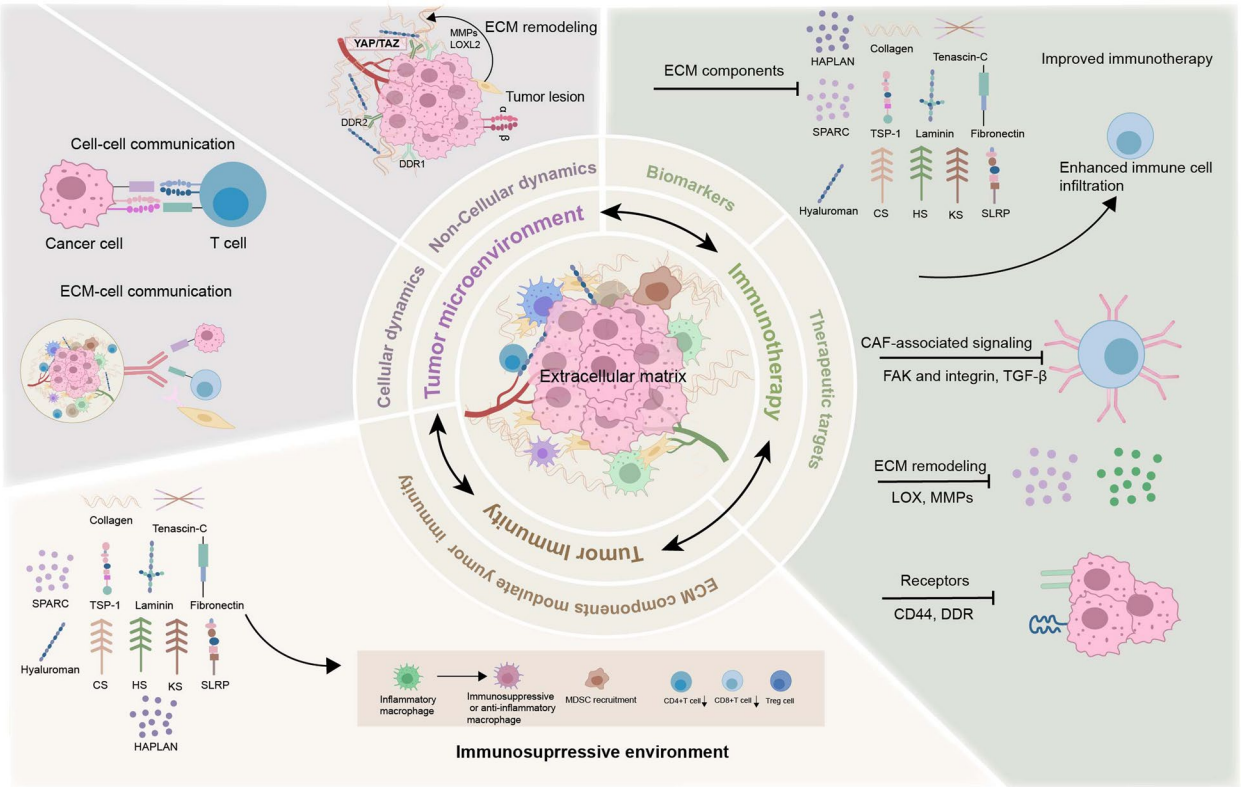

Fig. 1 Overview of the extracellular matrix dynamics in tumor immunoregulation: from tumor microenvironment to immunotherapy. Though significant breakthroughs have been made in the cancer diagnosis and treatment with the clinical application of immune checkpoint inhibitors (ICIs), the benefit of which is limited to a minority of patients. This variability in treatment response is closely related to the high complexity of the extracellular matrix (ECM) in the tumor microenvironment (TME). Therefore, this review not only further explores the heterogeneity and functional roles of ECM components within the TME, but also summarizes the complex crosstalk among ECM and immune cells, which may affect the efficacy of immunotherapy

metastasis [53, 54]. This remodeling of the ECM not only supports tumor progression but also alters the TME in ways that can enhance or inhibit immune cell infiltration and activity. Thus, ECM-TME crosstalk holds the key to understanding tumor biology and developing effective therapeutic strategies.

Cellular dynamics in ECM-TME crosstalk

Cell–cell communications in the TME

The interaction between cancer cells and surrounding non-cancerous host cells, along with the dynamic process of vascular and ECM remodeling, is regulated through intercellular interactions and paracrine signaling. Modes of cell–cell contact primarily include adhesion molecule-mediated interactions, membrane protein-receptor interactions, and local nanotube-mediated communication. Adhesion molecules include cadherins, integrins, selectins, and members of the immunoglobulin superfamily. E-cadherin mediates calcium-dependent adhesion, forming tight connections with adjacent cells to maintain epithelial integrity and mediate signal transduction [55]. The functional loss of E-cadherin is central to epithelial-mesenchymal transition (EMT), enabling reduced cell–cell adhesion and enhanced mesenchymal motility during cancer progression. Additionally, the intracellular portion of E-cadherin binds to β-catenin at the cell membrane, inhibiting its translocation to the nucleus, where it would otherwise promote the expression of genes associated with EMT and facilitate cancer metastasis [56]. The downregulation of E-cadherin in tumor cells was previously thought to promote tumor metastasis and invasion [57, 58]. However, recent studies suggest that in invasive ductal breast carcinoma metastasis, E-cadherin helps metastatic tumor cells withstand environmental stresses induced by molecules such as transforming growth factor-β (TGF-β) and reactive oxygen species (ROS), the absence of which affects cell viability. In addition, a soluble fragment of E-cadherin (sE-cad) facilitates tumor progression by enhancing cellular invasiveness and metastatic potential through disruption of intercellular adhesion and activation of pro-migratory signaling pathways, which serve as a prognostic marker for solid tumors [59].

Table 1 The dual-opposing roles of extracellular matrix in the tumor microenvironment

Cancer types	Tumor stages	Specific ECM components	Functional roles	Immune modulation types	Potential therapeutic interventions	Refs
Pancreatic Cancer	III, IV	COL I, Fibronectin	Promotes tumor cell invasion and metastasis, and forms a fibrotic TME	Inhibits T cell activity by binding to immune cell surface receptors, promoting tumor immune evasion	Drugs targeting ECM components, such as collagenase inhibitors; ICIs combined with ECM modulators	[4–7]
	I, II	Fibrin	Forms a pro-fibrotic matrix via coagulation pathways, supporting micro-metastases	Activates platelets releasing TGF-β, inhibiting DC maturation	Anticoagulants or TGF-β receptor inhibitors	[8]
Breast Cancer	II, III	Laminin, COL IV, COL XII	Promotes tumor angiogenesis, providing nutrients and oxygen for tumor growth	Interacts with tumor-associated macrophages, inhibiting anti-tumor immune response	Drugs targeting tumor angiogenesis, such as anti-VEGF monoclonal antibodies; drugs modulating tumor-associated macrophages	[9, 10]
	I	COL IV	Disruption of basement membrane integrity, promoting local invasion and angiogenesis	Recruitment of immunosuppressive or anti-inflammatory macrophages	Targeting α3β1 integrin antibody for MMP inhibitors	[11]
	Chemotherapy Resistant	Fibronectin	Activation of PI3K/AKT pathway via α5β1 integrin, enhancing resistance	Recruitment of MDSCs, secretion of TGF-β inhibiting NK cell function	Anti-α5β1 integrin monoclonal antibody (Volociximab) combined with Paclitaxel	[12]
Lung Cancer	I-IV	Proteoglycans,Hyaluronic Acid	Promotes tumor cell proliferation and invasion, and regulates interactions between tumor cells and the matrix	Inhibits immune cell activation by affecting dendritic cell maturation and function	Drugs targeting proteoglycans, such as heparan sulfatease inhibitors; immune modulators like interferons	[13]
Glioblastoma	IV	Fibronectin, Laminin	Promotes tumor cell invasion into brain tissue, forming an invasive tumor boundary	Interacts with immune cells in the brain, inhibiting their anti-tumor activity, promoting tumor immune evasion	Drugs targeting ECM components, such as fibronectin antagonists; tumor-treating fields combined with immunotherapy	[6, 14]
	Recurrent	CSPG	Forms physical barriers obstructing T cell infiltration; activates Notch pathway promoting stem cell properties	Inhibits microglial phagocytic function, promoting IDO expression	Chondroitinase ABC combined with IDO inhibitors (Epacadostat)	[15]
Colorectal Cancer	II, III	COL I, COL III, Elastin	Promotes tumor cell invasion into surrounding tissues, forming fibrotic tumor stroma	Modulates the activity of tumor-associated fibroblasts, affecting immune cell infiltration and function	Modulates the activity of tumor-associated fibroblasts, affecting immune cell infiltration and function	[7, 16]
	In Situ Cancer	HS, Proteoglycan	Binds growth factors to promote angiogenesis	Promotes TAM polarization via HSPG-TLR4 signaling	Heparanase inhibitors	[12]
Liver Cancer	II, IV	Laminin, COL IV	Promotes tumor angiogenesis and lymphangiogenesis, providing conditions for tumor growth and metastasis	Interacts with liver immune cells, inhibiting their anti-tumor activity, promoting tumor immune evasion	Drugs targeting tumor angiogenesis, such as Sorafenib; ICIs combined with anti-angiogenic drugs	[17, 18]

Table 1 (continued)

Cancer types	Tumor stages	Specific ECM components	Functional roles	Immune modulation types	Potential therapeutic interventions	Refs
Gastric Cancer	III, IV	COL I, Fibronectin	Promotes tumor cell invasion into the gastric wall, forming a fibrotic TME	Interacts with tumor-infiltrating immune cells, inhibiting their activity, promoting tumor immune evasion	Drugs targeting ECM components, such as collagenase inhibitors; ICIs combined with chemotherapy	[19, 20]
Prostate Cancer	II-IV	Laminin, COL IV	Promotes tumor cell invasion into surrounding tissues and blood vessels, forming tumor invasion fronts	Modulates immune cells in the tumor microenvironment, promoting tumor immune evasion	Androgen deprivation therapy combined with ICIs; drugs targeting ECM components, such as fibronectin antagonists	[21]
Ovarian Cancer	III, IV	COL, HA	Promotes tumor cell implantation and metastasis in the abdominal cavity, forming tumor-associated fibrosis	Interacts with immune cells in the abdominal cavity, inhibiting their anti-tumor activity, promoting tumor immune evasion	Drugs targeting HA, such as hyaluronidase inhibitors; ICIs combined with chemotherapy	[22, 23]
Melanoma	II-IV	Fibronectin, Laminin	Promotes tumor cell invasion into surrounding tissues and blood vessels, forming tumor invasion boundaries	Modulates immune cells in the tumor microenvironment, promoting tumor immune evasion	ICIs; drugs targeting B-Raf proto-oncogene, serine/threonine kinase mutations combined with immunotherapy	[24, 25]
	Immunotherapy Resistant	HSPG	Captures CXCL12, promoting tumor cell escape to vasculature	Blocks $CXCR4^+$ T cell migration to tumor	CXCR4 antagonists (Plerixafor) combined with anti-PD-1 therapy	[26]
Cholangiocarcinoma	II-IV	COL I, Fibronectin	Promotes tumor cell invasion into surrounding tissues, forming a fibrotic tumor microenvironment	Interacts with TAMs, inhibiting their anti-tumor activity, promoting tumor immune evasion	Drugs targeting ECM components, such as collagenase inhibitors; immune checkpoint inhibitors combined with chemotherapy	[27, 28]
Esophageal Cancer	III, IV	Laminin, COL IV	Facilitates esophageal wall invasion	Modulates tumor microenvironment immune cells for immune escape	ICIs; fibronectin antagonists	[29]
Meningioma	I-III	Fibronectin, Laminin	Drives brain tissue invasion and tumor margins	Suppresses brain immune cell activity	Fibronectin antagonists; surgery + radiotherapy	[30]
Renal Cancer	II-IV	COL IV, HA	Promotes invasion of tissues/vasculature	Interacts with tumor microenvironment immune cells	Hyaluronidase inhibitors; ICIs + anti-angiogenics	[31, 32]
Bladder Cancer	II-IV	Laminin, COL IV	Facilitates bladder wall invasion	Modulates tumor microenvironment immune cells	ICIs; fibronectin antagonists	[33, 34]
Nasopharyngeal Cancer	III, IV	COL I, Fibronectin	Promotes tissue invasion and fibrotic microenvironment	Inhibits tumor-infiltrating immune cells	Collagenase inhibitors; ICIs + radiotherapy	[35]
Head and Neck Cancer	II-IV	Laminin, COL IV	Drives tissue or vascular invasion	Modulates tumor microenvironment immune cells	ICIs; fibronectin antagonists	[36]
Soft Tissue Sarcoma	II-IV	COL I, Elastin	Promotes tissue invasion and stromal fibrosis	Modulates CAFs to impair immune cell activity	TGF-β inhibitors; ICIs	[37, 38]
Osteosarcoma	II-IV	Laminin, COL IV	Facilitates bone tissue invasion	Suppresses bone immune cell activity	Fibronectin antagonists; ICIs + chemotherapy	[39, 40]
Hepatoblastoma	II-IV	COL IV, HA	Drives tissue/vascular invasion	Interacts with tumor microenvironment immune cells	Hyaluronidase inhibitors; ICIs + chemotherapy	[41]

Table 1 (continued)

Cancer types	Tumor stages	Specific ECM components	Functional roles	Immune modulation types	Potential therapeutic interventions	Refs
Neuroblastoma	III, IV	Laminin, COL IV	Promotes tissue invasion	Modulates tumor microenvironment immune cells	ICIs; fibronectin antagonists	[42]
Retinoblastoma	III, IV	COL I, Fibronectin	Facilitates retinal tissue invasion	Suppresses intraocular immune cell activity	Collagenase inhibitors; ICIs + radiotherapy	[43, 44]

* *Abbreviations*: *Refs* References, *COL* Collagen, *HS* Heparan Sulfate, *CSPG* Chondroitin Sulfate Proteoglycan, *HSPG* Heparan Sulfate Proteoglycan, *HA* Hyaluronic Acid, *TME* Tumor Microenvironment, *DC* Dendritic Cell, *CAFs* Cancer-associated Fibroblasts, *TAM* Tumor-associated Macrophage, *TLR* Toll-like Receptor, *PD-1* Programmed Cell death-1, *MDSCs* Myeloid-derived Suppressor Cells, *MMPs* Matrix Metalloproteinases, *ICIs* Immune Checkpoint Inhibitors, *TGF-β* Transforming Growth Factor-β, *ECM* Extracellular Matrix

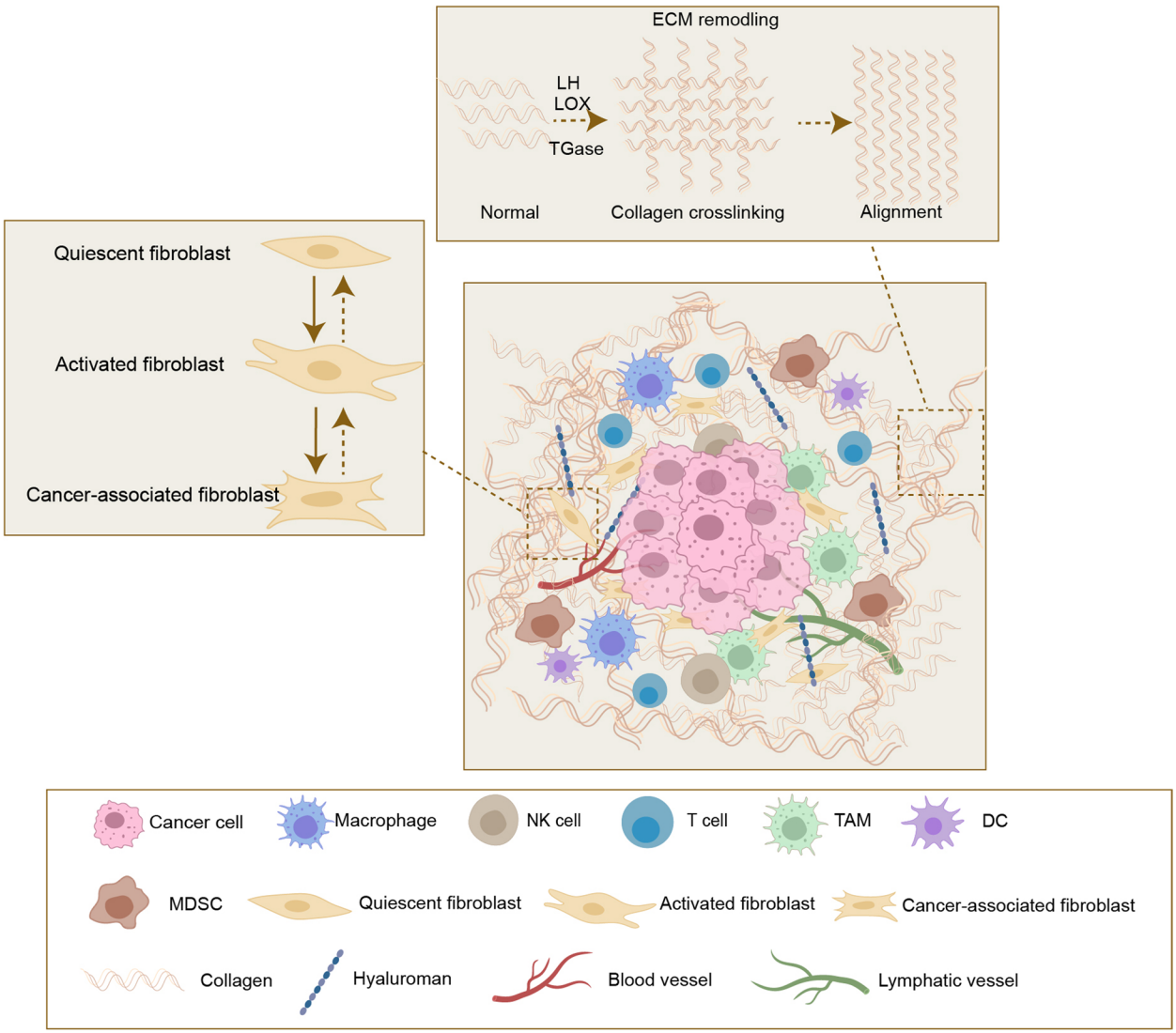

Fig. 2 The extracellular matrix (ECM) in the tumor microenvironment (TME). The local environment surrounding the tumor constitutes the tumor microenvironment (TME), which includes tumor cells, diverse immune cell types, stromal cells, the extracellular matrix (ECM), blood and lymphatic vessels, and nerve endings. ECM, as a key component of the TME, plays critical roles in providing mechanical support, transmitting biochemical signals, and maintaining microenvironmental homeostasis during its dynamic remodeling. Collagen-dominated protein molecules within the ECM are cross-linked by lysyl oxidase (LOX), transglutaminase (TGase), and prolyl hydroxylase (PHD), enzymes secreted by cancer-associated fibroblasts (CAFs), which reinforce the matrix's structural stability and mechanical properties

The dual functions of E-cadherin could be linked to the presence of interacting partners on the cell surface that associate with intact E-cadherin, along with the regulation of soluble E-cadherin production. One research found that the modulator, TMEM52B, may explain this phenomenon [60]. Therefore, the presence of E-cadherin may be more conducive to tumor survival [61].

Communication between cancer and non-cancer cells in the TME involves not only cell adhesion and migration but also complex autocrine and paracrine signaling, facilitated by the ECM. As a key component of the TME, the ECM serves as a reservoir for nutrients, enzymes, and growth factors. During its dynamic remodeling, the ECM plays critical roles in providing mechanical support, transmitting biochemical signals, and maintaining microenvironmental homeostasis.

ECM-cell communications in the TME

The interaction between ECM and cells, such as cancer cells, immune cells, and stromal cells in the TME plays a vital role in tumorigenesis and development [62]. This intricate communication is particularly evident in the

behavior of tumor-associated macrophages (TAMs), which secret matrix-modulating enzymes like MMPs in the process of ECM remodeling, facilitating tumor progression and metastasis. The altered ECM also influences TAM behavior, enhancing their pro-tumorigenic functions and creating a feedback loop that further supports the TME [63]. Moreover, ECM components and arrangement can affect the migration and activation of immune cells, limiting the effectiveness of immunotherapy. For instance, the normal function of T cells can be impaired by ECM remodeling, underscoring the importance of ECM-cell interactions in shaping immune responses. ECM remodeling can alter the physical and biochemical properties of the extracellular environment, affecting T cell migration, activation, and differentiation. Mechanisms include changes in ECM composition, stiffness, and the availability of signaling molecules, which can disrupt T cell receptor signaling and hinder effective immune responses. Consequently, impaired T cell function may lead to inadequate immune surveillance and diminished responses to infections or tumors [64]. Therefore, targeting the ECM represents a promising emerging strategy to enhance the efficacy of immunotherapy. In the context of cancer, the metabolic reprogramming of Endothelial cells (ECs) not only restricts the infiltration and activity of T lymphocytes but also attracts pro-angiogenic immune cells. Under conditions of nutrient deprivation, cells can utilize the ECM as a source of amino acids, altering their interaction with the ECM. This change can affect the composition and mechanical properties of the ECM, potentially influencing the cellular mechanotransduction pathways and resulting in phenotypic changes. Additionally, Metabolic reprogramming reshapes the ECM through the metabolic activities of CAFs and TAMs. CAFs enhance amino acid metabolism to supply essential nutrients like glutamine, while TAMs alter the ECM composition through fatty acid oxidation and lipid metabolism, further promoting tumor progression [65]. Loss of ECM-cell adhesion in spherical aggregates enhances cell–cell adhesion, resulting in localized hypoxia and metabolic reprogramming that relies on glutamine to sustain lactate and adenosine triphosphate production. This condition also induces autophagy to delay cell death and may activate mitophagy, with varying effects on reactive oxygen species levels influenced by the soft ECM and its interactions with the actin cytoskeleton [66]. This metabolic shift, driven by ECM cues, can attract pro-angiogenic immune cells and contribute to an immunosuppressive TME. The interplay between ECs, the ECM, and tumor cells creates an immunosuppressive TME that can promote cancer progression and therapeutic resistance [67].

The physical barrier formed by ECM remodeling is a mesh structure of 20–500 nm size, which limits the infiltration of cancer cells [68]. Additionally, the pore size is more commonly 50–200 nm in solid tumors. Therefore, nanoparticles smaller than 50 nm can penetrate the matrix pores and are widely utilized in drug delivery systems due to their ability to navigate the ECM barriers in tumor tissues [69]. Both cell motility and drug delivery is regulated by the pore size in the ECM. When ECM pore sizes exceed cellular nuclear size, cells can navigate through pre-existing structural pathways without requiring enzymatic degradation, with migration patterns governed by intrinsic mechanical traits such as integrin-mediated adhesion and cytoskeletal contractility [70]. For example, the glycocalyx consisting of glycoproteins and proteoglycans can affect the efficacy of ICIs and other drugs by acting as a diffusion barrier. Dense ECM components, such as COL deposition, restrict T cell migration toward the tumor core by reducing pore size, and synergize with the glycocalyx to establish an immune-excluded phenotype [71].

Stromal cells, one of the main sources of ECM, provide not only structural support and nutrients to tumor cells but also regulate tumor growth and metastasis through the secretion of various cytokines and ECM components. Within the TME, CAFs, which exhibit diverse subtypes with distinct functions and phenotypes, can actively participate in the cross-talk with cancer cells. Among the various phenotypes of CAFs, myCAF is the primary cell type regulating ECM deposition. Excessive ECM deposition increases tumor stiffness, affecting the permeability of drugs. MyCAFs, characterized by α-SMA, enhance ECM secretion and remodeling. They promote ECM stiffness through a series of crosslinking enzymes. The deposited ECM hinders immune cell infiltration into the tumor core, suppresses and isolates $CD8^+$T cells and other immune cells, thereby aiding tumor immune evasion. Meanwhile, the rigid ECM maintains the activated state of fibroblasts through mechanical signaling stimulation, further exacerbating matrix deposition and stiffness [72–74]. In pancreatic ductal adenocarcinoma (PDAC), CAFs are closely associated with the metastatic and invasive characteristics of the tumor by being responsible for ECM deposition [75]. The pro-tumorigenic role of myCAF in clear cell renal cell carcinoma (ccRCC) [76], breast cancer [77] and cholangiocarcinoma [78] has been reported in several studies. Col I is a critical component of ECM deposition in PDAC [73], and its crosslinking accelerates tumor metastasis [79]. In the mouse models of PDAC, epidermal growth factor receptor (EGFR)-activated myCAFs promote the metastasis of PDAC [80]. Kalluri and colleagues were the first to propose that $aSMA^+$ myCAFs suppress the recruitment of CXCL5 to

myeloid-derived suppressor cells (MDSCs) in pancreatic cancer, the depletion of which accelerates tumor progression [81]. Karin and colleagues demonstrated that the cleavage forms of COL I determine its function in PDAC. The COL-cleaved form and the uncleaved form exhibit opposing roles, with the uncleaved form (iCol I) suppressing pancreatic tumor growth by downregulating the DDR1/NFκB/p62/NRF2 pathway [82]. This further underscores the heterogeneity of ECM components and CAF subtypes within the TME, suggesting that other ECM components and matricellular proteins may exhibit similarly complex dynamics. Our review will further explore the heterogeneity and functional roles of ECM components within the TME.

Non-cellular dynamics in ECM-TME crosstalk

ECM crosslinking and mechanosignaling in tumor invasion and proliferation

ECM dynamics play a crucial role in the TME, where COL-dominated protein molecules are cross-linked by lysyl oxidase (LOX), transglutaminase (TGase), and prolyl hydroxylase (LH), enzymes secreted by CAFs, which reinforce the matrix's structural stability and mechanical properties [83, 84]. Col cross-linking mediated by Procollagen-Lysine, 2-Oxoglutarate 5-Dioxygenase 2 (PLOD2) expressed by CAFs enhances tumor invasiveness in a mouse model of lung adenocarcinoma [85].

The increased stiffness of the ECM influences cellular mechanotransduction by activating pathways including TGFβ, PI3K/AKT, and insulin-like growth factor (IGF), which promote tumor cell growth [86–88]. For example, changes in ECM stiffness affect the activation of EGFR signaling in breast and pancreatic cancer models, which in turn regulates cell proliferation and survival [89]. Additionally, it also triggers the Yes-Associated Protein/Transcriptional Coactivator with PDZ-Binding Motif (YAP/TAZ) pathway, enhancing the self-renewal capacity and pluripotency of tumor stem cells [90]. Cellular responses to mechanical stress exhibit heterogeneity, with those expressing high levels of YAP being more capable of surviving and proliferating under such stress. YAP/TAZ pathway acts as mechanosensors, transducing mechanical stress into biochemical signals that orchestrate cytoskeletal reorganization and adaptive cellular responses, which are crucial for tumor cell migration [91, 92]. However, one research found that YAP and TAZ can inhibit tumor growth by promoting the activation of surrounding normal hepatocytes, which highlights the dynamic changes in the cellular competition mechanism of YAP and TAZ in bidirectional regulation [93]. Additionally, integrins, in conjunction with various adhesion molecules such as cadherins, also take part in the composition and dynamics of the cytoskeleton, facilitating the mechanical coupling. By modulating the actin cytoskeleton, integrins like α5β1 and αvβ3 drive cellular migration and invasion, crucial for tumor progression [94]. For example, stromal stiffness promotes cell migration and invasion through integrin activation of the FAK-SRC signaling pathway [95]. Therefore, targeting integrins enables precise control of cancer cell migration, offering innovative strategies for the design of anti-cancer biomaterials and advancing therapeutic approaches for tumor metastasis [96]. Several reviews have analyzed in detail the role of matrix biomechanics in tumor migration and proliferation [97, 98]. In brief, matrix-derived mechanical stress drives tumor metastasis by activating mechano-immunomodulatory pathways that reshape both cancer cells and the immune microenvironment. Key downstream mediators involved in mechanotransduction include the YAP-TAZ, MEK-ERK, FAK-SRC, and ROCK signaling pathways. These mechanobiological insights compel us to rethink the dynamic changes between ECM and TME, where physical forces and biochemical signals co-evolve. We reasonably surmise that targeting the mechanical memory of the TME, while preserving immunosurveillance, may unlock more durable therapeutic synergies against metastatic adaptation.

Metabolic reprogramming and ECM-mitochondria crosstalk

Mitochondria, as the central hub for energy metabolism and signal transduction, play a crucial role in the exchange of metabolic substances between cancer cells, immune cells, and CAFs in the TME. Dysfunction of mitochondria impacts various aspects of cancer cell metabolism, proliferation, invasion, and more. A substantial body of literature has reviewed the impact of mitochondrial homeostasis on tumor progression and metastasis, however, few studies were carried out to explore the exact mechanisms through which ECM regulates it.

Studies have shown that ECM stiffness can transmit mechanical signals by regulating mitochondrial fission through the phosphorylation of MIEF1 and the recruitment of dynamin-related protein 1 (DRP1). This process can influence cell proliferation by modulating transcription factors such as YAP/TAZ, SREBP1/2, and NRF2 [99]. YAP, as a mechanosensor, activates ECM stiffness through multiple signaling pathways. For example, YAP enhances mitochondrial OXPHOS and immunosuppressive functions in TI-Tregs by promoting the transcriptional upregulation of Lars2, which is dependent on the amino acid leucine as a substrate [100]. Moreover, ECM stiffness can regulate mitochondrial translocation through the RhoA/ROCK1 pathway, which was found in a single-cell sequencing in gastric cancer, resulting in oxaliplatin resistance in gastric cancer cells.

The increased drug resistance may be due to mechanical signaling prompting mitochondrial translocation in gastric cancer cells and decreasing mitochondrial autophagy [101]. At the same time, the soft tumor stroma, proved to be a double-edged sword for cancer, increases mitochondrial division via actin, leading to an increase in mitochondrial reactive oxygen species (mtROS) and enhancing chemotherapy resistance [102]. During this process, actin regulates mitochondrial fission by facilitating the recruitment of DRP1 to the mitochondria, which is essential for the division process. This mechanotransduction pathway highlights the interplay between the tumor microenvironment and mitochondrial metabolism in cancer cells.

Tumor progression is slowed in soft three-dimensional ECM where autophagy-lysosome-histone protease axis mediates YAP1 degradation via CTSL to make cancer cells dormant [103]. The increase in stiffness during ECM remodeling generates external forces activating integrins to promote actin polymerization and regulate mitochondrial function and dynamics. The recruitment of DRP1, which relies on the cytoskeleton, participates in mitochondrial function and dynamics by regulating the localization of DRP1 to mitochondria. The endoplasmic reticulum-associated INF2 protein interacts with Spire1C to promote actin polymerization, and induces mitochondrial contraction by driving the recruitment of myosin II, thereby facilitating DRP1 binding and mitochondrial fission [104–106].

Continuous ECM deposition disrupts tissue architecture, which is associated with fibrosis in multiple organs, including the kidneys, heart, and lungs. Mitochondrial damage drives and exacerbates this process [107–109]. Studies have shown that TMEM2-mediated ECM remodeling affects mitochondrial function, triggers the TGF-β response, and induces mitochondrial fission and the unfolded protein response. Consequently, the ECM-mitochondria communication mechanism can enhance immune responses [110]. The intact ECM suppresses hypoxia, thereby reducing aberrant collagen cross-linking and inhibiting the formation of pre-metastatic niches that facilitate tumor dissemination [111].

Bidirectional regulation of hypoxic microenvironment

In the TME, hypoxia induces a series of biological changes in stromal cells, promoting cancer initiation and progression. It also affects the efficacy of immunotherapy, targeted therapy, radiotherapy, and other anticancer treatments [112]. The formation of the hypoxic microenvironment in cancer is due to a variety of factors, among which the activation and proliferation of stromal cells and the increase of stromal components are crucial. This process leads to remodeling of the cancerous form, such as compression of blood vessels, which further leads to thrombosis and increased tissue hypoxia. The hypoxic TME serves as a dynamic niche that orchestrates bidirectional crosstalk between ECM remodeling, immunosuppression, and therapeutic resistance, primarily through hypoxia-inducible factor-1α (HIF-1α)-driven signaling [113]. HIF-1α transcriptionally activates genes that enhance collagen deposition and ECM crosslinking, thereby increasing tissue stiffness and fostering a fibrotic TME. ECM stiffness not only promotes tumor invasion by mechanically activating integrin-ROCK-YAP/TAZ pathways but also recruits immunosuppressive cells, including Tregs and MDSCs. On one hand, ECM crosslinking and elevated interstitial fluid pressure (IFP) impede oxygen diffusion, creating a distance-dependent hypoxic gradient [114]. On the other hand, excessive deposition of COL I and IV activates an invasive tumor cell phenotype via the integrin β1-FAK signaling pathway while compression of the vasculature limits oxygen delivery [112]. Moreover, mesenchymal hypertension also activates the YAP/TAZ pathway through mechanical stress and promotes the maintenance of tumor stem cell properties [115]. Therefore, targeting mechanosignaling may become an important direction for future intervention in TME hypoxia.

Hypoxia-driven suppression of DNA repair mechanisms fosters genomic instability, amplifying tumor mutational burden and immunogenicity, which paradoxically sensitizes tumors to ICIs by enhancing neoantigen presentation and T cell recognition. For instance, hypoxia-induced mismatch repair deficiency via MutL Homolog 1/MutS Homolog 2 downregulation creates a "hot" immune microenvironment, while breast cancer gene-mutated cancers under hypoxia exhibit synthetic lethality with poly ADP-ribose polymerase inhibitors, revealing a therapeutic window for combinatorial immunotherapy [116]. This suggests that hypoxia-induced genomic instability may not only drive tumor progression but also create an opportunity for combined "hypoxia-immunotherapy" strategies to improve treatment outcomes.

In conclusion, the mechanisms of TME hypoxia formation are complex, multidimensional, and dynamic. Not only can abnormal vascular structures with insufficient pericyte coverage lead to inefficient oxygen delivery, but also high metabolic demand of tumor cells and mesenchymal hyperpressure further exacerbate oxygen depletion and diffusion impairment [117]. TME hypoxia drivers tumor evolution by inducing genomic instability, remodeling the immunosuppressive microenvironment and promoting treatment resistance. Clinically, the dynamic interplay between anti-angiogenic therapies and the hypoxic TME presents both challenges and

opportunities. Anti-angiogenic treatments may inadvertently exacerbate hypoxia in some cases, leading to increased HIF-1α activity and further ECM remodeling. Therefore, targeting hypoxic pathways, such as HIF inhibitors, may represent a promising strategy to enhance the effectiveness of existing therapies. By disrupting the hypoxic signaling cascade, it may be possible to reduce ECM stiffness, diminish Treg recruitment, and ultimately improve the response to radiotherapy and immunotherapy.

ECM-driven physical barriers and therapeutic resistance

Our review has discussed the effect of ECM stiffness before, including establishing physical barriers, influencing metabolic reprogramming and causing TME hypoxia, which all obstruct the smooth delivery of drugs. For example, the viscoelasticity and mechanical plasticity of the ECM further regulate cancer cell migration [118]. In the process of ECM remodeling, IFP was elevated within the tumor, thus sustaining tumour cell proliferation, and promoting migration and invasion [119]. Compared to normal tissues, elevated IFP in the tumor can enhance cancer migration and provide nutrients to the tumor, thereby exacerbating volume expansion. IFP results in the collapse of blood vessels in the tumor, which not only results in inadequate perfusion of the tumor tissue, but also further inhibits the infiltration of immune cells, as well as impedes drug delivery and distribution. One research targeted IFP in tumors, which enhanced drug delivery efficacy, as demonstrated by the improved therapeutic outcomes of GNP-docetaxel/quercetin/imatinib nanoparticles in metastatic breast cancer treatment [120]. However, since transient reduction of IFP may trigger compensatory ECM remodeling, spatiotemporal regulation of dynamic barriers is difficult.

Excessive ECM accumulation not only imposes steric hindrance to molecular transport, thereby significantly diminishing therapeutic agent accumulation, but also fosters biomechanically immunosuppressive niches via elevated interstitial stress, which spatially excludes tumor-infiltrating lymphocytes (TILs) and desensitizes immunotherapies. For instance, the stiffened ECM binds to β1-integrin, activating the ILK/PI3K/AKT pathway, which induces stem cell-like characteristics in cancer cells, thereby enhancing their resistance to treatment [121]. Although it has been demonstrated in preclinical models that integrin inhibitors may reverse radiation or chemotherapy resistance, it has not been approved for clinical use due to its lack of clinical efficacy [122]. In pancreatic cancer, the barrier effect of ECM makes it difficult for T cells to reach tumor cells, limiting the efficacy of ICIs [123]. The high hardness of ECM also affects the migration and activation of T cells, making it difficult for them to exert anti-tumor effects. Moreover, dynamic changes in ECM components influence macrophage polarization and induce secretion of immunosuppressive factors, weakening the efficacy of immunotherapy, which we would discuss and analyze in detail in the latter part of this review. Currently, anti-tumor therapies based on immune cells, such as natural killer (NK) and T cells, face significant challenges and have low overall clinical responsiveness. Much of this is attributed to the tight ECM structure outside the tumor as well as the inhibitory TME, which makes it difficult for immune cells to infiltrate inside the tumor, thus limiting their ability to exert anti-tumor viability. Increasingly, studies have shown that by normalizing the tumor vasculature, nanoparticle carriers and biocarriers can effectively increase the oxygen concentration in the TME, improving drug delivery and immunotherapy efficacy [124].

ECM dynamics modulates tumor immunity

ECM organization and mechanics regulate immune cell function

Biomechanical signaling in immune cell dysfunction

CAF-mediated ECM deposition and remodeling alter the TME and influences tumor immunity by affecting the biomechanical properties and signaling pathways of the ECM [71] (Fig. 3). In addition, the migration and activation of immune cells can be affected by the components and arrangement of ECM [125]. For example, the spatial distribution and directional alignment of COL fibers influence the migration pathways of T cells within the TME, which is mentioned in the part of function of COL. A rigid and interlinked ECM results in an imbalance of tissue hydraulics, ultimately hindering chemotherapy drugs diffusion and immune cells infiltration, and inducing the inflammatory activation of dendritic cells (DCs) and macrophages [3, 126]. The signal pathways promoting the process include TAZ/YAP, mTOR, and calcium signaling pathways. Among them, the positive feedback loops of YAP function and ECM stiffness can enhance tumor invasion and metastasis, but the current relevant studies are mainly focused on breast cancer models, further validation in other cancers needed in the future [127]. T-cell activation has been confirmed to be correlated with biomechanics [128, 129], mainly through the regulation of the lifespan of the TCR-pMHC bond varying with the types of biomechanics [130]. Therefore, ECM biomechanics have an impact on tumor-responsive $CD8^+$T cells, though how it induces the dysfunction of $CD8^+$T cells is still unclear. One recent study revealed Osr2 as a biomechanical checkpoint in response to mechanical stress in the tumor hardness microenvironment through single-cell sequencing and in situ staining analysis, leading to the dysfunction and depletion of

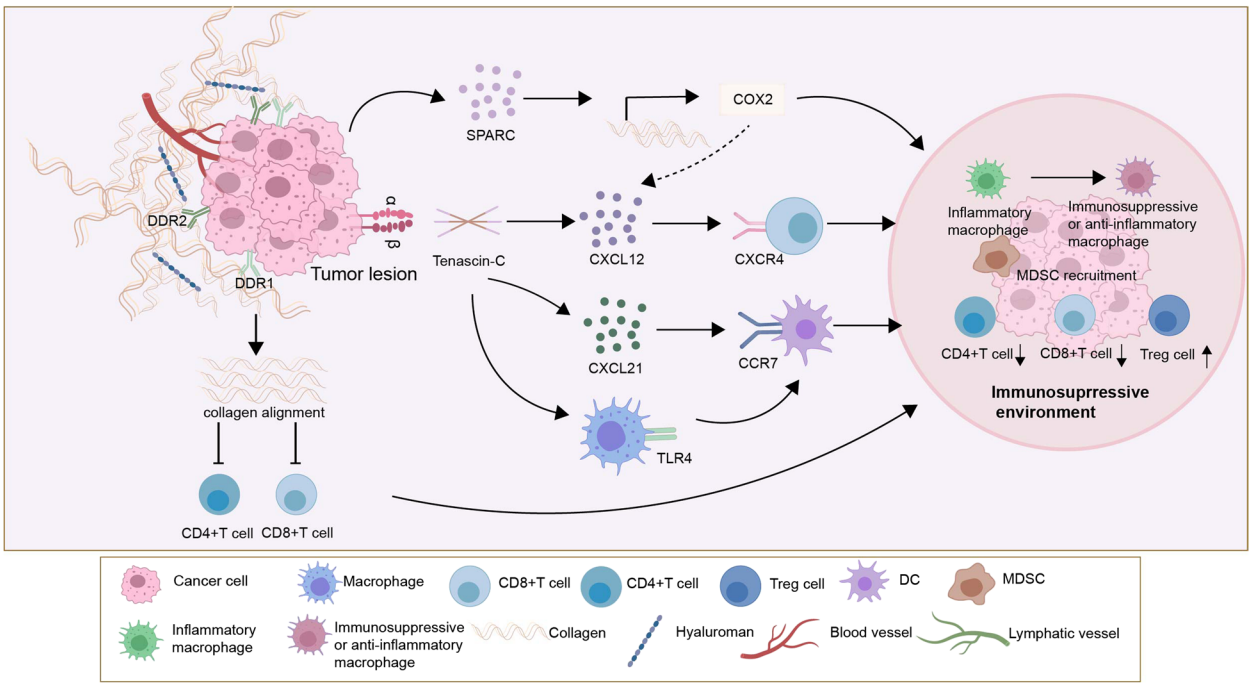

Fig. 3 ECM remodeling facilitates the formation of immunosuppressive TME. Tenascin-C (TNC) and SPARC are both intricate proteins in the matrix associated with dysregulated tumor immunity and tumor metastasis. In breast cancer, TNC, inducing CXCL12 through TLR4, not only promoted the activation of M2-polarised macrophages, but also inhibited the infiltration of CD8 +T cells into tumor cell islet. Higher SPARC mRNA levels correlated with the expression of macrophage-related pro-tumor genes in colorectal cancer (CRC), indicating the central role of M2-like macrophages in SPARC-driven matrix remodeling. Additionally, expressed SPARC in breast cancer cells were found to induce EMT and formation of MDSCs hindering the proliferation of $CD4^+$T cells and $CD8^+$T cells. Additionally, collagen in the ECM, primarily produced by CAFs, can influence cancer cell proliferation by activating the DDR signaling pathway

$CD8^+$T cells by recruiting HDAC3, the process of which is mediated by the surface mechanoreceptor Piezo1 [131]. In renal cell carcinoma, through the Ca^{2+}/calpain/YAP signaling pathway, Piezo1 promotes renal tumor cells migration driven by substate stiffness [132]. Tumor cell stiffness is crucial for T cell cytotoxicity, as demonstrated in previous studies, but how it regulates T cell exhaustion is controversial. In addition, methods for isolating T cells from the fibrotic TME require further optimization. Though dysregulated ECM remodeling in tumors often promotes immune evasion and therapy resistance, the ECM can also exert tumor-suppressive effects by maintaining tissue structural integrity and restricting cancer cell invasion through biomechanical signaling pathways [133]. Additionally, ECM degradation can enhance drug delivery within tumor tissues, thereby improving the efficacy of both chemotherapy and immunotherapy [134].

TGF-β signaling and immune suppression

The role of CAFs in ECM remodeling through TGF-β signaling inhibits the efficacy of immunotherapy in multiple cancers, including colorectal cancer, urothelial carcinoma, and pancreatic cancer [135–137]. The precise mechanisms underlying the dual roles of TGF-β in cancer, both tumor-suppressive and tumor-promoting, remain incompletely elucidated. Under physiological conditions, TGF-β, acting as a tumor suppressor, upregulates the activity of CDK inhibitors, activates Smad4 to inhibit 4E-BP1 activity, and downregulates the expression of the oncogene Myc [138–140]. TGF-β induces the polarization of immune cells into immunosuppressive phenotypes, such as immunosuppressive or anti-inflammatory-polarised macrophages, N2-polarised neutrophils, and Treg cells. These immune cells, in turn, secrete immunosuppressive cytokines and protease, promoting ECM degradation and remodeling [141]. The positive feedback loop exists between TGF-β, primarily derived from CAFs and stromal myofibroblasts and ECM remodeling [142, 143]. While the activation pathways of TGF-β secreted by CAFs are being studied, it remains unclear whether TGF-β1 is the predominant isoform secreted by CAFs. Furthermore, the TGF-β signaling pathway can modulate the activation of immune cells in the TME, including NK cells and T cells [141].

ECM remodeling modulates cancer progression through oncoimmunity regulation

Macrophage heterogeneity and ECM crosstalk

The central immune cells involved in ECM remodeling mediated by CAFs are macrophages, which exhibit different phenotypes with distinct roles in tumor progression and immune regulation [144]. The positive feedback loop between ECM and macrophages promotes COL deposition and enhances the ECM stiffness. In pancreatic cancer, both angiogenesis and immune suppression are closely linked to the TAMs within the TME. Studies have shown that TGFBI, a key molecule secreted and expressed by TAMs, serves as a critical link between macrophages and pancreatic cancer cells, promoting immunosuppressive or anti-inflammatory.

polarization of macrophages and facilitating the proliferation of pancreatic cancer cells [145].

Tissue-resident macrophages (TRMs) maintain tissue homeostasis and ECM remodeling through self-proliferation [146]. In the breast, a higher proportion of $TIM4^+$ PVMs, capable of regulating ECM remodeling, correlates with improved survival and enhanced activation of effector $CD8^+$T cells [147]. TRM-driven fibrosis exerts a protective effect in pancreatitis, but the production and remodeling of ECM molecules may contribute to the pathogenesis of pancreatic cancer [148]. Macrophage subpopulations are diverse, and their molecular characteristics differ between humans and mice. For instance, $GATA6^+$ macrophages are abundant in the mouse omentum but scarce in humans. Conversely, $CCR2^+$ or $GLUL^+$ macrophages, commonly observed in humans, have not been identified in corresponding subpopulations in mice. These discrepancies pose challenges for translational research between mouse models and human studies, highlighting the need for more precise characterization of macrophage subpopulations across species [149]. TRMs serve as key regulators of fibrosis, with FAP^+ fibroblasts and $SPP1^+$ macrophages in the TME, mediated by the interaction with TGF-β and IL-1, remodeling the ECM and correlating with poor prognosis in colorectal cancer (CRC) [150]. In addition, the pro-tumorigenic mechanisms of TRM varies in different tumor types, such as in lung adenocarcinoma (LUAD), TRM attenuating anti-tumor adaptive immune responses through prominent Treg cell induction [151]. However, in ovarian cancer, $CD163^+$ $TIM4^+$ TRMs are associated with metastatic spread of cancer cells by providing a protective ecological niche for tumor stem cells [152].

ECM remodeling influences cancer progression through immune cells, which is mainly caused by matrix-degrading proteases. For example, MMP1 and MMP13 derived from B cells can induce cancer invasion. Additionally, MMP9, predominantly expressed by neutrophils and macrophages, plays a crucial role in early pancreatic islet carcinogenesis by activating angiogenesis [153]. Dysadherin, the membrane glycoprotein correlated with cancer, promotes CRC metastasis by upregulating the expression of MMP9 through the Focal Adhesion Kinase (FAK)/c-JUN axis [154]. In conclusion, MMP9 contributes to the immunosuppressive TME by remodeling the ECM. During this process, MMP9 induces MDSC recruitment, activates CAFs, and hinders T cell infiltration.

Integrin-mediated immune microenvironment reshaping

Integrins mediate interactions with the ECM, participating in the regulation of cell signaling and controlling cell adhesion and migration. Tumor cells modify the composition and stiffness of the ECM through integrin-mediated signaling, thereby promoting tumor progression [155]. Integrins perform distinct functions across different tumor types. The αVβ3 integrin enhances tumor cell proliferation and migration through multiple signaling pathways, including the FAK/Src and PI3K/AKT/mTOR pathways. Additionally, it enhances ECM remodeling by upregulating TGF-β signaling, creating a type of TME conducive to tumor growth and invasion [156, 157]. Studies have shown that MYC can inhibit αVβ3-induced cell invasion in breast cancer [158]. Both α2β1 and α1β1 integrins are COL receptors, whose binding to COL inhibits tumor proliferation. For example, in brain metastatic tumors, COL deposition in the TME mediated by HSP47 promotes microglial polarization toward the immunosuppressive or anti-inflammatory macrophages via the α2β1 integrin/NF-κB pathway, suppressing the anti-tumor responses of $CD8^+$T cells [159]. Although theoretically integrin inhibitors can block tumor cell proliferation and migration, there are currently no effective drugs with relevant targets in clinical trials. In view of the dynamics and complexity of ECM in the TME, integrin-targeted therapies may be most useful in combination with other drugs. Additionally, the integration of molecular profiling and advanced imaging modalities enables real-time patient stratification, facilitating precision dosing strategies for integrin-targeted therapies in clinical oncology.

ECM components modulate tumor immunity

The ECM is primarily composed of the basement membrane and the stromal connective tissue matrix spatially [160]. The basement membrane is a sheet-like structure that separates epithelial cells, ECs, or other parenchymal cells from the surrounding stroma. Its main components include laminin, COL IV, and heparan sulfate, which not only serve as a barrier but also facilitate signal transduction within the TME. The stroma, on the other hand, is

a loose fibrous matrix that fills the space between cells and blood vessels. Its key components include COL I, COL III, HA, fibrin, and CAFs. It provides the physical framework for tumor tissues and regulates immune functions [49]. The dynamic nature of the ECM in the TME exerts immunomodulatory effects both through physical barriers and biological signal transmission. While promoting tumor progression, the ECM can also inhibit tumor growth by restricting metastasis and influencing nutrient metabolism [161]. Key components of the ECM, including COL, HA, and proteoglycans, promote tumor immune evasion by modulating IFP and immune cell activity [162]. In addition, the glycocalyx, a glycan layer on the extracellular surface of the cell membrane, mediates cell adhesion to the ECM and facilitates signal transduction, thereby regulating the TME [163, 164]. Therefore, it is crucial to understand the dynamic roles of individual ECM components in tumor immunomodulation (Table 2).

Collagen

Collagen, which differs from most protein structures by consisting of a right-handed triple helix formed by three polypeptide chains, is the most abundant protein in the ECM and mammalian tissues. The repeating Gly-X–Y sequence in its structure typically features proline and hydroxyproline as the X and Y amino acids [52, 198]. Tumor cells, TAMs, and CAFs are all sources of COL in the TME [199]. A total of 28 types of COL have been identified, including fibrillar COL, reticular COL, beaded filament COL, and transmembrane COL [200]. For example, COL I, II, III, V, and XI are fibrillar collagens; COL IX, XII, and XIV are fibril-associated collagens with interrupted triple helices; and COL IV, VIII, and X form network collagens. Among them, COL I, COL III, and COL V are primarily synthesized by fibroblasts, whereas COL IV is mainly produced by epithelial and endothelial cells. Therefore, the influence of collagen on tumor development depends on its type. Overall, in desmoplastic environments, fibrillar collagen promotes stromal stiffening, tumor invasion, and immune evasion by activating mechanosensitive pathways and restricting cytotoxic immune cell infiltration. Non-fibrillar collagen compartmentalizes tumor-stroma interactions, while abnormal collagen alignment enhances therapy resistance by limiting drug penetration and immune access [165].

Direct impacts

Not only can COL promote tumor growth through integrin signaling and ECM remodeling, but also form a physical barrier that restricts immune cell infiltration and excludes T cells. Meanwhile, COL exhibits tumor-suppressive effect, as its degradation fragments can enhance immune responses (Fig. 4). Additionally, the mechanical barrier limits tumor cell dissemination. And activated discoidin domain receptors (DDR) play dual roles in both tumor promotion and suppression [201]. However, how COL kinetics regulates tumor progression and its oncogenic effects in multiple carcinomas other than pancreatic cancer remain to be explored. This complexity underscores the need for targeted therapies that can manipulate COL dynamics to either enhance anti-tumor immunity or inhibit tumor progression, depending on the context.

Receptor and immune cell dynamics

DDR, a transmembrane tyrosine kinase receptor that can bind to COL [202], is involved in ECM remodeling. COL in the ECM, primarily produced by CAFs, can influence cancer cell proliferation by activating the DDR signaling pathway [82, 203], which is a key component in COL fiber alignment. In the mouse models of triple negative breast carcinoma (TNBC), DDR1-extracellular domain (ECD) remodels COL alignment and creates a physical barrier that hinders T-cell infiltration [204]. In contrast, in human models of TNBC and head and neck cancers, DDR1 not only maintains tumor cell dormancy through COL III and STAT1, but also remodels the ECM and restricts cancer cell proliferation [205]. However, DDR1 induces tumor cell transformation to a basal-like phenotype in basal-like breast cancer, enhancing mesenchymal fibrosis and tumor invasiveness [206]. Therefore, the role of DDR1 in tumor immune modulation may be cancer-type specific and species-specific. Nevertheless, how DDR1, as a relatively low-activity tyrosine kinase receptor, induces strong downstream effects and contributes to tumor immune regulation remains an unresolved question. Furthermore, the cell surface fibrillar COL receptor DDR2 in CAFs enhances the stiffness of the TME by regulating the activity and mechanotransduction functions of COL-binding β1 integrin [207]. COL not only spatially restricts T-cell migration but also inhibits T-cell proliferation at high densities. The upregulation of Treg cells by COL weakens anti-tumor immune responses [208].

COL I is the most abundant COL type, composed of a heterotrimer consisting of two α1 chains and one α2 chain [209]. Tumor progression is promoted by COL I binding to various cell surface receptors such as DDR1, DDR2, and leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1) [165]. However, its deficiency can upregulate CXCL5 through SOX9, leading to the recruitment of MDSCs and the suppression of anti-tumor immune responses [4]. The interaction between COL I and DDR1 activates the DDR1/PKCθ/SYK/NF-κB signaling pathway in the PDAC, promoting CXCL5 synthesis and the recruitment of tumor-associated neutrophils

Table 2 Overview of the impact of extracellular matrix component on tumor

ECM component	Nature	Main types	Receptor	Impact on tumor	Refs
Collagen	Structural proteins providing mechanical support	COL I	DDR1, DDR2, LAIR-1, OSCAR, Integrin α1β1, Integrin α2β1, Integrin α5β1	Increases tumor stiffness, and enhances tumor invasion and metastasis	[165–167]
		COL III	DDR1, OSCAR, GPR56, Integrin α1β1, Integrin α2β1	Remodels the ECM, maintains tumor cell dormancy, and restricts cancer cell proliferation	[168]
		COL IV	DDR1, Integrin α1β1, Integrin α10β1, Integrin α3β1, Integrin α2β1, Mannose receptor family	Loss or degradation promotes invasion by disrupting basement membrane integrity	[169]
		COL VI	Integrin α1β1, Integrin α10β1, Integrin α3β1, Integrin α2β1	Modulates tumor cell motility and survival, linked to poor prognosis	[170–172]
Tenascin-C (TNC)	Glycoprotein		TLR4, Integrins, TGF-β	Promotes tumor cell migration, invasion, and metastasis	[173–175]
Secreted protein acidic and rich in cysteine (SPARC)	Glycoprotein		TGF-β, VEGF	Alters tumor cell adhesion and motility, affecting tumor invasion and metastasis	[176, 177]
Thrombospondin 1 (TSP1)	A calcium ion-binding glycoprotein		Integrin α4β1, CD47、CD36, Integrin α6β1	Regulates T cell and tumor immunity, mainly maintaining tumor dormancy	[178–180]
Laminins (LMs)	Glycoprotein, non-collagenous components of the basement membranes		Integrins	Disrupts ECM signaling and contributes to tumor progression	[6]
Fibronectin (FN)	Glycoprotein		Integrins	Regulates tumor immunity and promotes tumor growth	[181]
Hyaluronic acid (HA)	A non-sulfated GAG composed of repeating disaccharide units	HMW HA	CD44, RHAMM, CD168, TLRs	Maintains ECM homeostasis and inhibits tumor metastasis	[182–184]
		LMW HA	CD44, RHAMM, TLRs, NLRs	Remodels the ECM and assists tumor cells in immune evasion	[185, 186]
Chondroitin sulfate (CS)	A highly sulfated glycosaminoglycan consisting of repeating disaccharide units		CD44, LRP1, TLRs	Influences growth factor signaling and angiogenesis, promoting tumor growth and immune escape	[187, 188]
Heparan sulfate (HS)	A sulfated glycosaminoglycan composed of repeating disaccharides		CD44, RHAMN, PSGL-1	Impacts tumor cell migration and ECM remodeling, facilitating tumor cell invasion and metastasis	[187]
Keratan sulfate (KS)	Glycosaminoglycan		CD44	Attracts immunosuppressive cells, creating a microenvironment that supports tumor growth	[189, 190]
Biglycan	A small leucine-rich proteoglycan		TLR2, TLR4, TGF-β	The potential of biglycan to be carcinogenic or tumor-suppressive is still uncertain	[191]
Decorin	A small leucine-rich proteoglycan		TGF-β, EGFR	The potential of decorin to be carcinogenic or tumor-suppressive is still uncertain	[192]
Lumican	A small leucine-rich proteoglycan		TLR2, Integrins	Mainly reduces responsiveness to chemotherapy	[193]

Table 2 (continued)

ECM component	Nature	Main types	Receptor	Impact on tumor	Refs
Matrix Metalloproteinases (MMPs)	Enzymes degrading ECM components	MMP2	LRP1, Integrins, CD44	Aid in ECM remodeling	[194]
		MMP9	LRP1, Integrins, CD44	Aid in ECM remodeling	[195]
Hyaluronan and Proteoglycan Link Protein 1 (HAPLN1)	A matricellular factor that binds to HA and various proteoglycans		CD44, Integrins, RHAMMM, TLRs	Promotes tumor growth, invasion and angiogenesis	[196, 197]

* *Abbreviations: Refs* References, *COL* Collagen, *ECM* Extracellular Matrix, *MMPs* Matrix Metalloproteinases, *HA* Hyaluronic Acid, *HMW HA* High Molecular Weight HA, *LMW HA* Low Molecular Weight HA, *DDR* Discoidin Domain Receptors, *TLR* Toll-like Receptor, *VEGF* Vascular Endothelial Growth Factor, *LAIR* Leukocyte-associated Immunoglobulin-like Receptor, *CD* Cluster of Differentiation Antigen, *LRP* Low-Density Lipoprotein Receptor-Related Protein, *HAPLN1* Hyaluronan and Proteoglycan Link Protein 1

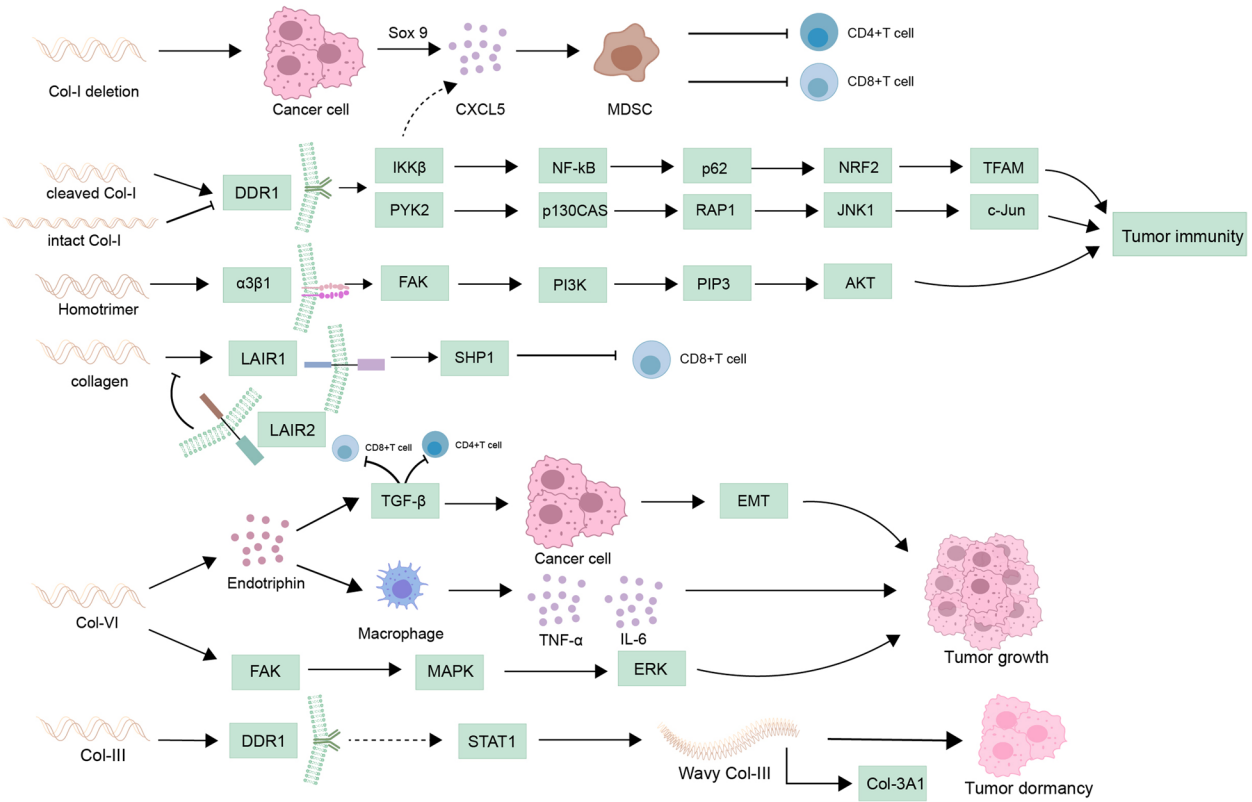

Fig. 4 Signaling pathways of diverse types of collagen affecting tumor progression by regulating tumor immunity. This figure illustrates mechanisms of diverse types of collagen (COL) regulating tumor immunity. The deficiency of COL I can upregulate CXCL5 through SOX9, leading to the recruitment of myeloid-derived suppressor cells (MDSCs) and the suppression of anti-tumor immune response. The interaction between cleaved COL I and DDR1 activates the DDR1/PKCθ/SYK/NF-κB signaling pathway in the PDAC, promoting CXCL5 synthesis. Additionally, DDR1/PYK2/JNK1/c-Jun is another signaling pathway through which cleaved COL I regulating tumor immunity. At the same time, intact COL I exerts the reverse effect. Moreover, an immunosuppressive microenvironment is formed by the activation of the downstream Integrin α3β1/FAK/AKT/ERK signaling pathway. The interaction of COL with LAIR-1, an inhibitory receptor expressed on the surface of immune cells, activates downstream SHP-1, inducing $CD8^+$ T cell exhaustion. LAIR2 inhibits this process. The endotrophin peptide (ETP), a c5 fragment of COL6A3 cleavage, enhances tumor metastasis by inducing TGF-β-dependent epithelial mesenchymal transition. In addition, COL VI ETP increases macrophage recruitment and upregulates inflammatory factors such as IL-6 and TNF-α to promote tumor inflammation. In human models of triple negative breast carcinoma (TNBC) and head and neck cancers, DDR1 maintains tumor cell dormancy through COL III and STAT1. These diverse mechanisms highlight how collagens can exert both pro-tumorigenic and anti-tumorigenic functions

(TANs) to form neutrophil extracellular traps (NETs), thereby enhancing tumor invasion and metastasis [166]. Furthermore, COL I deposition promotes neutrophil accumulation in breast cancer, suggesting that tumor progression and metastasis prefers a COL-dense TME [167]. COL I produced by pancreatic tumor cells is a homotrimer composed of three α1 chains due to the lack of the α2 chain encoded by Col Ia2, which regulates the recruitment and function of immune cells by binding to integrins. Moreover, an immunosuppressive microenvironment is formed through the activation of the downstream integrin α3β1/FAK/AKT/ERK signaling pathway [210]. Resistance to MMP cleavage by COL I homotrimers secreted by cancer cells affects their activation of DDR1 [211]. However, one study found that COL I homotrimer activated DDR, FAK, and AKT signaling, highlighting its clear pro-tumorigenic function [212]. Therefore, the absence of homotrimeric COL I promotes T-cell infiltration and improves the immune response to ICIs. As mentioned earlier, the intact and cleaved forms of COL I produced by CAFs exhibit distinct roles in PDAC [81, 82]. Among them, cCol I stimulates mitochondrial biogenesis and PDAC energy biology by regulating MMP activity and protein expression. Consequently, the cleavage status of COL I serves as an important prognostic marker in PDAC. Therapeutic strategies targeting the associated signaling pathways and mitochondrial biogenesis warrant further investigation.

The interaction between COL and LAIR-1, an inhibitory receptor expressed on the surface of immune cells,

activates downstream SHP-1, suppressing activating signal transduction and modulating immune cell numbers and phenotype. This pathway inhibits NK cell activation and facilitates bone metastasis of tumor cells in estrogen receptor-positive (ER-positive) breast cancer patients [213]. In human and murine lung tumors, the interaction between COL and LAIR-1 induces $CD8^+$T cell exhaustion, contributing to lung cancer resistance to ICIs. This finding highlights the potential application of LAIR-1 inhibitors in the treatment of patients with advanced lung cancer [214].

Though LAIR-1 expression has been found to be upregulated in various cancers, including brain, renal, and ovarian cancers [215], the effect of COL I-LAIR1 interactions on tumor immunity differs from the cancer types. In addition, the regulation of tumor immunity is influenced by the structural forms of COL. For example, COL III has been shown to maintain tumor dormancy. COL III inhibits breast cancer metastasis by enhancing stromal organization through regulating fibrillar collagen density and alignment, thereby suppressing tumor cell invasion via integrin-β1/FAK signaling. Additionally, COL III reduces cancer cell proliferation and promotes apoptosis, while its deficiency disrupts ECM homeostasis, facilitating NETs-mediated awakening of dormant cells [168]. Moreover, COL VI upregulates HIF-1α to participate in tumor angiogenesis [170], contributing to the metastasis of lung cancer, human glioblastoma, and breast cancer [171, 172]. Furthermore, the interaction between COL I and COL V hinders the function of COL I, leading to impaired autophagic flow in $CD8^+$ T cells, thereby exhibiting pro-tumor characteristics [38]. COL VI secreted by macrophage protects its phenotype of the matrix, regulates immune responses and remodels ECM. The anti-inflammatory and matrix-protective macrophage phenotype of the matrix is protected by COL VI secreted by macrophage because of its promotion of cell–cell adhesion and immune cell communication, regulating immune responses and remodeling ECM. Therefore, T6C production is associated with the activation status of macrophages. T6C may play a critical role in tissue repair and stabilization, while regulating immune responses and ECM remodeling [216]. It has been shown that COL VI, through its major mediator COL VI endotrophin peptide (ETP), recruits macrophages and upregulate inflammatory factors such as IL-6 and TNF-α to promote tumor-associated inflammation. The crucial role of COL VI ETP in promoting tumor growth within the TME of breast cancer is highlighted by the process [171]. It is interesting that a recent study confirms that obesity promotes an increase in COL VI in TNBC, which is related to the progress of tumor [217]. This may be due to the fact that COL VI is primarily produced by cells of the stromal vascular fraction and adipose stem and progenitor cells. Chronic obesity continuously stimulates its increased abundance, which leads to further reshaping of the TME. Therefore, targeting COL VI may be more effective in the early stage of obesity. In addition, COL VI participates in tumor metabolic reprogramming through various signaling pathways. Targeting COL VI to interfere with the anabolic metabolism of tumor cells warrants further exploration though the related research is limited. Normally, the infiltration of myeloid-lineage immune cells, such as neutrophils and macrophages plays a crucial role in shaping the TME and influencing disease progression in solid tumors. TAMs actively mediate the structural reorganization of COL I, VI, and XIV through fiber deposition, enzymatic crosslinking, and spatial alignment, which collectively reinforce ECM remodeling at invasive tumor margins [218]. Notably, in breast cancer, elevated stromal COL10A1 expression inversely correlates with reduced TILs, suggesting a collagen-mediated immunosuppressive microenvironment that dampens inflammatory cell recruitment despite myeloid cell dominance [219]. Other collagen types also serve important roles in various biological processes. For instance, the expression of COL IV has been linked to the levels of fibronectin and laminin in the context of central nervous system metastasis. Additionally, COL XV, in contrast to COL I, III, IV, and V, interacts with fibronectin, laminin, and vitronectin to impede the adhesion and migration of fibrosarcoma cells [220]. These findings underscore collagen isoform-specific regulation of metastatic niches through matrix receptor binding specificity and biomechanical signaling modulation.

Physical stress

COL deposition and degeneration stimulate macrophage activity. And the deposition and crosslinking of COL I, VI, and XIV can be regulated by TAMs [218, 221]. Immunosuppressive or anti-inflammatory macrophages promote immunosuppression and COL deposition, whereas inflammatory macrophages enhance the production of MMPs, facilitating COL degradation and activating NK cells to induce apoptosis of hepatic stellate cells [222]. Additionally, NF1-recruited mast cells promote COL deposition through the stem cell factor/c-kit signaling pathway [223]. COL-dense tumors can stimulate the production of granulocyte–macrophage colony-stimulating factor (GM-CSF) [167].

The highly crosslinked structure of COL, which is distributed around tumor nests in various cancers, increases ECM stiffness, thereby restricting T-cell infiltration and mobility [3, 224]. In addition, the migration pathways of T cells within the TME can be influenced by the spatial distribution and directional alignment of COL fibers

[225]. Immune cell nuclei migrate via amoeboid movement within loose and well-aligned COL matrices [226]. Studies have shown that COL alignment can regulate fibroblast morphology and behavior, influencing their activation and proliferation [227]. However, further investigation is needed to elucidate the mechanisms regulating COL fiber alignment and how COL fibers influence T-cell infiltration. Understanding these mechanisms could pave the way for innovative strategies to remodel the TME, potentially enhancing the efficacy of immunotherapies.

One research, classifying tumors into three subtypes based on COL activity and immune infiltration, found that the subtype characterized by low COL activity and high immune infiltration exhibited better responses to ICIs across various cancers [228]. The pro-tumorigenic or anti-tumorigenic roles of different COL subtypes vary across distinct cancer types, making more detailed understanding and classification of COL subtypes urgently needed. It is necessary to further investigate their roles in tumor immunoregulation. This classification could serve as a foundation for developing more effective immunotherapies tailored to the specific ECM characteristics of individual tumors, ultimately improving patient outcomes.

Glycoprotein

Tenascin-C (TNC) is intricate matrix protein associated with dysregulated tumor immunity and tumor metastasis [229, 230]. TNC was found to diminish cancer cell adhesion, a crucial characteristic of cancer invasion, which supports the interaction between TNC and cancer metastasis, commonly discovered in malignant tumors especially breast cancer and oral squamous cell carcinoma [231]. In breast cancer, TNC, inducing CXCL12 through TLR4, not only promoted the activation of immunosuppressive or anti-inflammatory-polarised macrophages, but also inhibited the infiltration of $CD8^+$T cells into tumor cell islets [232]. Furthermore, CXCL12 promoted the adhesion of $CD8^+$T cells to TNC fibers in vitro, emphasizing the role of matrix components in modulating tumor immunity.

Secreted protein acidic and rich in cysteine (SPARC), also known as glycoprotein osteonectin, is a secretory glycoprotein located in the ECM. Higher SPARC mRNA levels were correlated with the expression of macrophage-related pro-tumor genes in CRC, indicating the central role of immunosuppressive or anti-inflammatory macrophages in SPARC-driven matrix remodeling [233]. Additionally, SPARC expression in breast cancer cells has been shown to induce EMT and formation of MDSCs, which hinder the proliferation of $CD4^+$T cells and $CD8^+$T cells [234] (Fig. 3).

Thrombospondin 1 (TSP1) is a calcium ion-binding glycoprotein that regulates T cell and tumor immunity, which mainly maintains tumor cell dormancy [178]. TSP1 enhances macrophage recruitment and inflammatory macrophages polarization in tumors, promoting antitumor immunity through PAI-1-mediated macrophage activation and superoxide production [179]. Therefore, the combination of anti-angiogenic treatment with TSP1 and radiotherapy was conducted in the antitumor therapy [180].

Laminins (LMs), non-collagenous components of the basement membranes, assist in cell attachment to the basement membrane through integrin and non-integrin receptors. LMs are divided into several subtypes based on their chain composition. LMs may inhibit tumor progression in the early stages of tumorigenesis. For example, defective laminin anchoring, often due to reduced LARGE expression, disrupts ECM signaling and contributes to tumor progression, particularly in aggressive cancer subtypes like breast and brain cancers [235]. Meanwhile, in most human cancers, changes in the expression or distribution of various LMs and specific LM chains are linked to the poor prognosis [236]. For example, LAMC2 regulates critical pathways such as TGF-β signaling pathway to drive tumor metastasis [237]. Though several studies have proved that specific LM isoforms promote the tumor invasion, little investigated how the cancer stromal cell biology was impacted by them.

Fibronectin (FN), a kind of ECM Glycoprotein, regulates tumor immunity through activating TILs [181]. FN takes part in tumor cell adhesion and migration processes. The main pathway which FN induces macrophage migration is SFK-FAK/CSF-1R signaling pathway [238]. Additionally, in dormant breast cancer cells, FN was produced and assembled consistently through $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrin adhesion, and TGFβ2 stimulation [239]. Meanwhile, dormant tumor cells can be reactivated in certain conditions. For example, TGF-β-mediated FN deposition increases ECM stiffness, activates CAF and increases tumor invasiveness. P38 activity was suppressed by FN fibrils while ERK activity was activated, which interrupted the tumor dormancy [240]. In addition, FN promotes immune cell infiltration within the tumor, whereas it is able to promote tumor progression around the tumor [241].

Glycosaminoglycans

GAGs, composed of repeating disaccharide units, including aminohexoses and glyoxylates, is one of the important components of the ECM. Based on its disaccharide units and sulfation patterns, GAGs include HA, chondroitin sulfate, dermatan sulfate, heparan sulfate, heparin, and

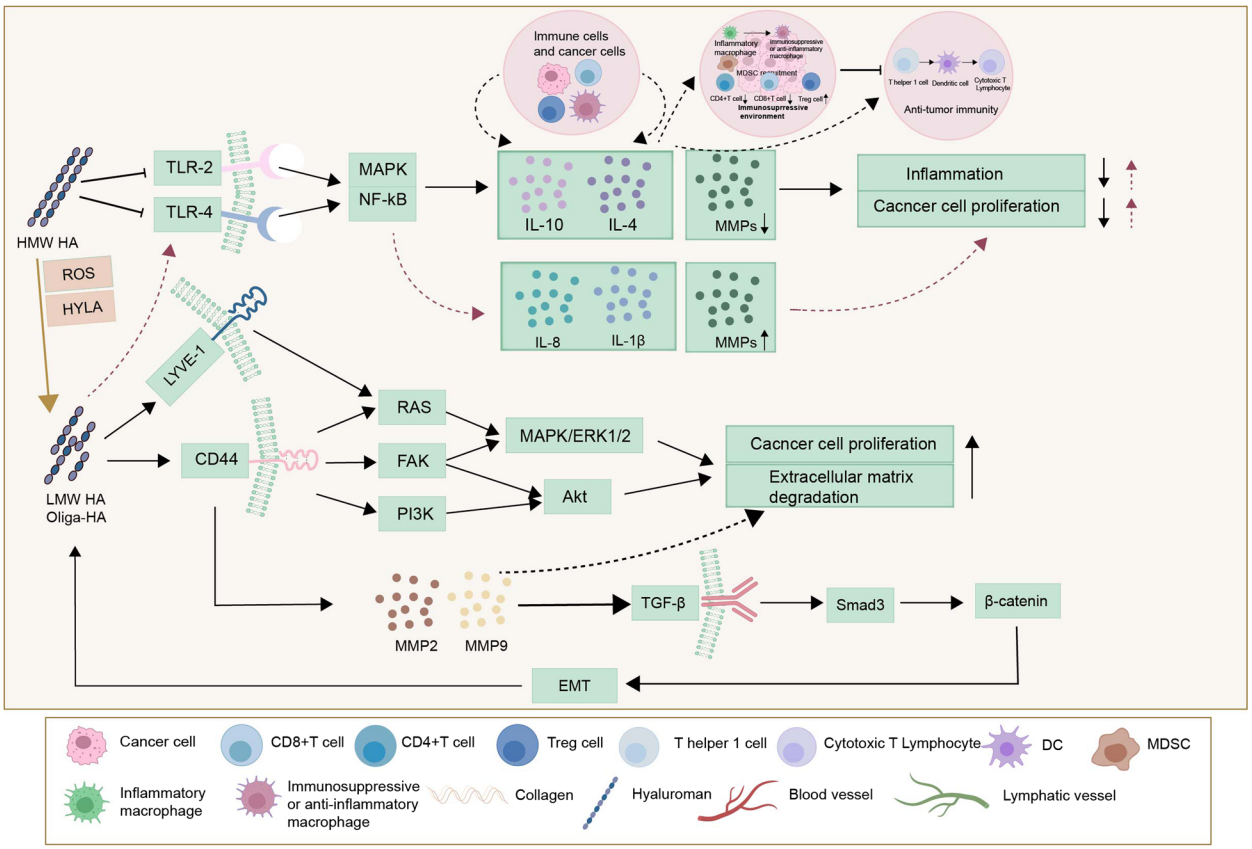

Fig. 5 Signal ways of diverse types of HA affecting tumor progression by regulating tumor immunity. High molecular weight HA (HMW HA) maintains ECM homeostasis and inhibits tumor metastasis. However, low molecular weight HA (LMW HA) not only remodels the ECM, induces immune response activation and signaling dysregulation, but also assists tumor cells in immune evasion. HMW HA inhibits the MAPK and NFκB signaling pathways and exhibits anti-inflammatory effects by producing IL-4 and IL-10. Moreover, MMP activation can be diminished by this pathway. The most common mechanism of HA remodeling the TME involves binding to CD44, which promotes the conversion of fibroblasts and macrophages to CAFs and TAMs, inhibiting the anti-tumor immune functions of NK and T cells. When LMW HA and Oliga HA bind to LYVE-1 and CD44, the MAPK/ERK and Akt pathways can be triggered. Therefore, ECM degradation and cancer cell proliferation are further promoted

keratan sulfate [189, 190]. This heterogeneity is essential for maintaining the dynamic nature of the ECM, as it influences tissue mechanics and cellular interactions. TME stiffness can be altered by dysregulation of GAG synthesis and degradation. Moreover, the combination of GAGs and cytokines modulates immune cell functions and influences the efficacy of anti-cancer therapies [242].

Hyaluronic acid

HA is a non-sulfated GAG composed of repeating disaccharide units, which are linked by β−1,3-glycosidic bonds between D-glucuronic acid and N-acetyl-D-glucosamine. In the TME, ECM remodeling is closely associated with structural and functional abnormalities of HA, whose role varies depending on its molecular weight [182]. High molecular weight HA (HMW HA) maintains ECM homeostasis and inhibits tumor metastasis. In contrast, low molecular weight HA (LMW HA) not only remodels the ECM, induces immune response activation and signaling dysregulation, but also assists tumor cells in immune evasion [184]. However, this issue remains controversial. HMW HA exerts anti-inflammatory effects by upregulating PPARγ and inhibiting the MAPK and NFκB signaling pathways [243]. Accumulation of HMW HA in the mouse model has been found to be accompanied by COL deposition and increased hypoxia, thereby promoting tumor drug resistance [244] (Fig. 5).

The most common mechanism of HA remodeling the TME involves binding to CD44, which promotes the conversion of fibroblasts and macrophages to CAFs and TAMs, while inhibiting the anti-tumor immune functions of NK and T cells. The phenotype of macrophages in the TME tends to polarize toward immunosuppressive or anti-inflammatory macrophages, which has an anti-inflammatory and pro-tumorigenic effect, but the polarization tendency depends on tumor stages. In a mouse model of breast cancer, the HA/CD44/ERK1/2/STAT3 pathway plays a crucial role in the process of HA

stimulating the formation of immunosuppressive or anti-inflammatory macrophages-like TAMs [245], consistent with the findings of Kim et al. [185]. How HA induces macrophage polarization needs to be further investigated. Additionally, the upregulation of hyaluronan synthase 2 (HAS2) may be associated with immunosuppressive macrophage synthesis [246]. Furthermore, HA recruits Treg cells to further impair the immune response [247].

CD44, as an adhesion receptor involved in immune cell activation and phenotypic remodeling, is associated with cancer cell progression and metastasis [248]. CD44 isoforms have distinct functions respectively, with CD44v6 promoting HA production by enhancing the expression of HA synthase genes [249]. Furthermore, CD44 activates breast cancer CSC characterization through the PDGFRβ/Stat3 pathway [250]. However, the roles and mechanisms of its various isoforms in tumor progression remain unclear, particularly with regard to the different roles of CD44s and CD44v [251]. The Sebastian team has been exploring the mechanisms by which HA-CD44 regulates macrophages. Following their discovery that CD44-HA mediates the endocytosis of iron ions to regulate the epigenetic plasticity during EMT [252], they further identified that copper ions in the mitochondria of macrophages can regulate cellular plasticity, thereby affecting cellular metabolism and epigenetic reprogramming [253].

Extracellular vesicles (EVs), as crucial mediators of intercellular communication, can remodel the ECM and influence the activation of immune cells within the TME [254]. CAF-derived EVs promote tumor proliferation and invasion by activating tumor signaling pathways. HA also promotes immunosuppressive or anti-inflammatory macrophage polarization, which is consistent with the immunosuppressive or anti-inflammatory macrophage polarization observed when macrophages are exposed to EVs in colorectal cancer [255]. Therefore, the activation of immune cells may be associated with HA carried by EVs. The PH20 hyaluronidase carried by EVs degrades HA in the TME, and the resulting oligo-HA during which promotes dendritic cell (DC) maturation and $CD8^+$ T cell activation [247]. However, only a few small-scale studies have been conducted in carcinomas such as colorectal cancer, and further exploration of the mechanisms involved is needed.

In addition to CD44, HA also binds to various other cell surface receptors, which have been summarized in several reviews [256]. For example, Pro-inflammatory cytokines such as IL-2 and IFN-γ can be generated during the activation of the NF-κB pathway by the interaction between LMW HA and TLR2. Additionally, the interactions between HA and other components of the ECM also play a role in immune regulation within tumors. For example, the proteoglycan secreted by tumor cells binds to HA, and through the activation of the TLR2/TLR6 complex and CD14, it induces the production of TNF-α, promoting an inflammatory microenvironment and enhancing the tumor's metastatic potential [257]. A proteoglycan of the ECM, Versican, and the ECM-associated protein TSG-6, by binding to HA, enhance the interaction between HA and CD44, thereby regulating the migration of inflammatory cells [258, 259].

The interactions between HA and various cell surface receptors, as well as ECM components, play a crucial role in tumor immune regulation. The molecular weight of HA influences its regulation of macrophage immune responses. However, the interactions between HA and some less common proteoglycans, fibrous proteins, and atypical ECM components remain unclear. Research on HA's impact on DCs is limited, but it is known that HA can promote the immune phenotypic maturation of DCs and stimulate the production of IL-1β, TNF-α, and IL-12.

Chondroitin sulfate, heparan sulfate and keratan sulfate

Chondroitin sulfate and Heparan sulfate, significant components of the ECM, take part in several physiological and pathological process such as angiogenesis and growth factor signaling especially when covalently attached to core proteins. Versican which is a large chondroitin sulfate proteoglycan has the ability to L-selectin, P-selectin, and CD44 [187]. It is has been proved that high expression of versican can inhibit $CD8^+$T cell infiltration [188].Additionally, the increase of TAM infiltration is associated with chondroitin sulfate derived from mast cell, the mechanism of which may explain the different functional changes [260]. Linker glycan, specific enzyme, and cofactor or substrate are all necessary factors for GAGs binding to core protein. Among them, B3 GALT6-mediated GAGs synthesis is associated with poorer survival outcomes for patients. One recent study revealed that heparin-6-O-sulfation enhances FGF1 signaling to promote RTC survival in both models of microenvironment-induced dormancy and treatment-related dormancy [261]. Moreover, the important for RTC survival of B3GALT6/HS6ST1/FGF1/FGFR2 pathways were proposed. Though most proteoglycans promote cancer progression, some chondroitin sulfate proteoglycans (CSPGs) such as Bikunin exert anti- inflammatory and anti-tumor effects by inhibiting the release of inflammatory factors such as TNF and IL-6.

Keratan sulfate (KS) mainly plays roles in electrosensation and neural guidance. KS is categorized into three types (KS-I, KS-II, and KS-III), each with distinct attachment sites to core proteins of keratan sulfate proteoglycans (KSPGs). Notably, compared to primary tumors, the

expression of CHST6, an enzyme involved in KS sulfation, is upregulated in pancreatic metastatic tissues, indicating a correlation between increased KS sulfation and tumorigenesis [262]. Highly sulfated KS chains can attract immunosuppressive cells, creating a microenvironment that supports tumor growth. Therefore, investigating the mechanisms by which keratan sulfate influences the TME could provide valuable insights for developing new strategies for anti-tumor immunotherapy.

Leucine-rich proteoglycans

The small leucine-rich proteoglycans (SLRP) are classified into five categories, which are further categorized into canonical and non-canonical classes. Biglycan and decorin are both SLRPs, which are mainly expressed among mammalian tissues, regulating inflammation and autophagy. The autophagy process of decorin helps maintain tumor cells metabolic integrity, supports the functionality of mitochondria, and reduces DNA damage. When autophagy is compromised, the homeostasis of lymphatic endothelial cells (LECs) can be disrupted. One recent research found that decorin inhibited the growth of breast cancer and induced tumor lymphangiostasis by interacting with the VEGFR3 signaling pathway [192]. Therefore, targeting decorin may be a promising therapeutic strategy due to its pro-inflammatory effects and its ability to inhibit tumor growth [263]. However, the potential of biglycan and decorin to be carcinogenic or tumor-suppressive is still uncertain. For example, biglycan may suppress tumorigenesis by selectively binding to a specific TLR and modulating downstream signaling through TLR adaptor molecules. Though most research has shown that biglycan plays a negative role in tumor immunity by being secreted by CAFs, which correlates with reduced patient survival and therapy response, likely due to its immunomodulatory effects. Besides biglycan and decorin, which belong to Class I of SLRPs, the expression of lumican, classified as Class II, is associated with tumor prognosis by modulating tumor development. The secretion of lumican mainly reduced responsiveness to chemotherapy while overexpression of lumican can enhance apoptosis in melanoma cells. Consequently, studying the correlation between small SLRPs and tumors in specific tissues is particularly crucial, as it can provide valuable insights into their roles in tumor biology and potential therapeutic implications.

ECM degradation

The disruption of protein cross-linking within the ECM, which contributes to its stiffness, can lead to ECM degradation. The functions of degrading enzymes have been extensively reviewed in the literature. In summary, MMPs, particularly MMP2 and MMP9, are the predominant hydrolases involved. Additionally, serine proteases, ADAM and ADAMTS family proteases, along with lysosomal enzymes, also play significant roles [194, 195]. Matrix proteins are primarily secreted by CAFs, which exhibit diverse phenotypes. Although the classification of CAF subtypes remains inconclusive, myCAF, iCAF, and apCAF are widely recognized as the three major subtypes. A study that established a CAF biobank from non-small cell lung cancer (NSCLC) patients identified three functional CAF subtypes. It revealed that the functional heterogeneity of CAFs is regulated by intrinsic TGF-β signaling, which suppresses the expression of HGF and FGF7. These findings provide valuable insights for personalized treatment strategies in NSCLC [264]. Single-cell sequencing in TNBC has confirmed the heterogeneity and plasticity of CAFs, revealing that $SPP1^{+}$ TAMs may facilitate tumor angiogenesis through interactions with adjacent CAFs undergoing EMT [265].

Small bioactive peptides produced during ECM degradation, referred to as matricellular factors, play critical roles in cell signaling and can exert either pro-tumor or anti-tumor effects [266]. CAF-derived Hyaluronan and Proteoglycan Link Protein 1 (HAPLN1) is a matricellular factor that binds to HA and various proteoglycans. It enhances the levels of HA and decreases the expression of ICAM1 in ECs, thereby maintaining the integrity of melanoma-associated vasculature and promoting tumor cell dissemination [196]. GF-β1 derived from gastric cancer cell activates the TGF-β1/Smad signaling pathway, upregulating the expression of HAPLN1 in gastric fibroblasts, thereby further contributing to ECM remodeling [197]. Furthermore, HAPLN1 contributes to the mechanism of bortezomib resistance in multiple myeloma (MM) by activating the NF-κB pathway [267]. HAPLN1 affects the arrangement, quantity, density, and length of COL fibers in the ECM, but the relationship between these factors and tumor invasiveness remains unclear [197, 268].

Biomarkers and therapeutic targets

Given that the reshapement of ECM can affect the efficacy of immunotherapy for cancers, major ECM components have significant potential value as biomarkers and therapeutic targets. In addition, altering ECM deposition by targeting ECM-remodeling enzymes and related receptors and molecules can also represent a potentially effective treatment strategy (Table 3).

Biomarkers

The various components of the ECM can regulate tumor immunity. We explore the value and potential of ECM components as biomarkers for immunotherapy within the dynamic and complex system of the TME.

Table 3 Overview of the therapeutic targets of extracellular matrix for cancer treatment

Therapy Name	Mechanism of Action	Disease	Clinical Trial Phase	Status	Trial Results	Trial Number
PEGPH20	Degrades hyaluronic acid, improving drug distribution and tumor microenvironment	Pancreatic Cancer	Phase II	Completed	Median OS: 11.5 vs. 8.5 months (HR 0.96; 95% CI 0.57–1.61; $P = 0.97$)	NCT01839487
		Metastatic Pancreatic Cancer	Phase III	Terminated	Median OS: 11.2 vs. 11.5 months; Median PFS:7.1 vs. 7.1 months	NCT02715804
Simtuzumab	Inhibits LOXL2, reducing collagen cross-linking	Pancreatic Cancer, Colorectal Cancer	Phase II	Completed	Median PFS: 3.7 (HR 1.09; 95% CI 0.74–1.61; $P = 0.73$) vs. 3.5 months (HR 1.13; 95% CI 0.76–1.66; $P = 0.61$) vs. 3.7 months	NCT01472198
		Myelofi-brosis	Phase II	Completed	SIM treatment alone or in combination with rux is safe but does not reliably reduce bone marrow fibrosis in pts with myelofibrosis	NCT01369498
Prinomastat	Synthetic inhibitor of MMPs 2, 9, 13, and 14	Prostate cancer	Phase III	Completed	Did not show significant improvement	NCT00003343
		NSCLC	Phase III	Completed	Median OS: 11.5 vs. 10.8 months ($P = 0.82$); Median PFS: 6.1 vs. 5.5 months ($P = 0.11$)	NCT00004199
BT1718	Bicyclic peptide–toxin coupled drug, targeting MT1-MMP, releasing toxin DM1	Multiple solid tumors	Phase I/II	Completed	Median OS: 7.0 vs. 5.7 vs 6.2 months; Median PFS: 2.4 vs. 3.8 vs. 1.9 months	NCT03486730
Copper depletion	Reduction of LOX activity, which is copper dependent	Colorectal Carcinoma	Phase II	Completed	NA	NCT00176774
Galunisertib	Inhibits TGF-β signaling pathway, reducing ECM deposition	Rectal Cancer	Phase II	Active, not recruiting	The addition of galunisertib to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer improved the complete response rate to 32%	NCT02688712
Losartan	Inhibits angiotensin II receptor, reducing ECM deposition	Pancreatic Cancer	Phase II	Active, not recruiting	No effects on the R0 resection rate, PFS, OS, and pCR rate	NCT03563248
Pamrevlumab	Inhibits CTGF/CCN2, reducing ECM deposition	Pancreatic Cancer	Phase I/II	Completed	Median PFS: 6.0 vs. 2.4 months (HR 0.59; 95% CI 0.36–0.96; $P = 0.032$)	NCT02210559
PXS-5505	Inhibits LOX family, reducing ECM cross-linking	Unresectable Hepatocellular Carcinoma	Phase I/IIa	Withdrawn	No accrual of eligible participants	NCT05109052
Volociximab	Inhibits integrin α5β1, reducing ECM stiffness	Pancreatic Cancer	Phase II	Completed	Best overall response was 1/16 and stable disease in 8/16 pts. Median time to progression was 112 + days	NCT00401570
Defactinib	Inhibits FAK, reducing ECM stiffness	Pancreatic Cancer	Phase II	Active, not recruiting	Phase II ongoing; preliminary data show 30% partial response	NCT03727880
		Pleural mesothelioma	Phase I	Withdrawn	Funding complications coupled with competing scientific objectives	NCT04201145

Table 3 (continued)

Therapy Name	Mechanism of Action	Disease	Clinical Trial Phase	Status	Trial Results	Trial Number
BAPN	Inhibits LOX enzyme, reducing collagen fiber cross-linking	Hepatocellular Carcinoma	Phase I	Withdrawn	No accrual of eligible participants	NCT05109052
Dasatinib	Targets DDR2	Advanced non-small cell lung cancer	Phase I	Terminated	The standard of care for the patient population changed, resulting in the inability to accrue patients	NCT02750514
Talazoparib	Inhibits FAP	Advanced and recurrent solid cancer	Phase II	Terminated	There is no PR/CR observed in the first stage, so study stopped without proceeding to the stage 2 of efficacy stage	NCT04171219
VCAN fragment versikine	Enhances T cell activation immunotherapy	Multiple Myeloma	Phase I	Recruiting	NA	NA
ESM-1 peptide	Increases leukocyte infiltration and enhances innate immune response	Not specified	Phase I	Recruiting	Phase I safety trial; no efficacy endpoints reported	NA
PlGF-2 HBD conjugate	Increases retention in tumor tissue, reducing systemic toxicity	Melanoma	Phase I	Recruiting	Phase I pharmacokinetics data pending	NA

* *Abbreviations: ECM* Extracellular Matrix, *NSCLC* Non-small Cell Lung Cancer, *PDAC* Pancreatic Ductal Adenocarcinoma, *LOXL* Lysyl Oxidase-Like, *MMP* Metalloproteinases, *FAK* Focal Adhesion Kinase, *FAP* Fibroblast Activation Protein, *EGFR* Epidermal Growth Factor Receptor, *VCAN* Versican, *ESM-1* Endothelial Cell-Specific Molecule 1, *BAPN* β-Aminopropionitrile, *PlGF-2 HBD* Placental Gwroth Factor 2 Heparin-Binding Domain, *PR* Partial Response, *CR* Complete Response, *PFS* Progression-Free Survival, *OS* Overall Survival, *HR*: Hazard Ratio

Collagen

Multiple studies have revealed the prognostic value of various subtypes of COL in cancers [199]. Not only can COL content prognose the clinical outcomes of cancer, but also the alignment and distribution of COL affect cancer prognosis [269]. Biomarkers reflecting alterations in COL metabolism, including secretion, post-translational modifications, and structural interactions, hold potential for early tumor detection and monitoring in cancers like hepatocellular carcinoma (HCC) [270]. Elevated collagen drives immunotherapy resistance via LAIR1-induced T cell exhaustion, while collagen depletion or LAIR1 inhibition restores anti-programmed cell death-1 (PD-1) response, with collagen-LAIR1 levels correlating with poor clinical outcomes in immunotherapy-treated patients [214].

Previously tumor-associated COL signatures (TACS) were presented by multiphoton microscopy (MPM), indicating different characteristics of COL which maybe associated with the survival of cancers, especially breast cancer [271, 272]. However, the prognostic value of the complete COL signature remains unclear. Well-organized COL fibers (TACS1, 4, 7) were generally recognized as favorable prognostic factors, while disorganized or perpendicular fibers (TACS5, 6, 8) promote invasion and predict poorer prognosis [272, 273]. One study recently incorporated the complete COL signature which includes TACS, TCMF1, and TCMF2 into the TNM staging system and discovered their independent prognostic value in breast cancer [274]. While TACS focuses on the tumor stage, it lacks specificity in terms of how ECM components might directly inform therapeutic outcomes, particularly in the context of immunotherapy. Emerging studies suggest that TACS act as physical barriers to T cell infiltration via DDR1-dependent collagen alignment, while computational models reveal their spatiotemporal constraints on tumor-immune interactions [275]. Additionally, TACS can accurately predict peritoneal recurrence of gastric cancer (GC) by the application of a multitask machine learning model [276]. COL-related biomarkers require further validation in clinical settings to establish their specificity, sensitivity, and utility in combination with existing diagnostic methods, offering potential to enhance early cancer detection and improve patient outcomes.

Glycoprotein

Recent advancements in liquid biopsy, along with chemical and AI technologies, promoting intensive study of glycoproteins, which may predict anti-tumor efficacy including immunotherapy [277]. The prognostic value of TNC has been proved in multiple cancers. For example, in breast cancer, it served as an early indication of invasion [278]. Increased TNC staining is more likely to be found in invasive carcinoma [174]. Additionally, the high expression of TNC is associated with several adverse clinicopathological features in breast cancer [173]. Promotion of the spread of lung adenocarcinoma cells of TNC, mainly originated from CAFs, was investigated by quantitative mass spectrometric profiling of the ECM composition [175].

TSP-1, effective endogenous angiogenesis inhibitory factor, reduced expression of which has been found in a variety of tumors, indicating poorer prognostic outcomes for patients. Laminin, a key component of the basement membrane barrier, is highly expressed in tumor tissues and significantly correlates with poor patient prognosis. Laminin maintains tumor dormancy by preserving integrity. However, during inflammation-induced neutrophil extracellular trap (NET) formation, proteolytic cleavage of laminin by neutrophil elastase (NE) and MMP-9 generates remodeled fragments that activate integrin α3β1 signaling, thereby awakening dormant cancer cells [279]. Tumors are more susceptible to infection and destruction if laminin expresses higher, which means better response to lysosomal virus therapy [6]. Therefore, laminin may serve as a biomarker to classify cancer patients and predict their response to H-1PV-based therapies.

Recently, one study carried in gastric cancer found that high SPARC expression indicated poor prognosis and high grade of GC, supporting the LCN2/24p3R/JNK/c-Jun/SPARC axis as novel biomarker for cancer [176]. Furthermore, the relationship between SPARC expression of pancreatic cancer, hepatocellular carcinoma and other cancers has been proved [177, 280]. Both versican and its bioactive protein hydrolyzed fragments are involved in cancer, inflammation and anti-tumor immune response. At the same time, versican exerts anti-apoptotic effects by enhancing cellular matrix interactions and protecting cells from oxidative stress-induced cell death, which supports versican as a prognostic marker and potential therapeutic target for cancer. Brevican expresses in the TME of glioma and performs complex functions due to its variable structure, which includes multiple splice variants, cleavage products, and glycoforms [281]. Therefore, proteoglycans in the ECM including versican, brevican, and several microproteoglycans are all potential biomarkers valuable of further investigation and application in clinical therapy.

HA

HA levels are higher in malignant carcinoma tissues than in benign or normal tissues, as shown by histological studies [282]. Multiple studies have shown that the HA level is a prognostic indicator for malignant carcinoma, such as NSCLC and prostate cancer [283–286]. Current

research suggests that HA is primarily concentrated in the stromal tissue surrounding tumors rather than in the tumor parenchyma, and its levels in the plasma of cancer patients could serve as a valuable predictive biomarker [287, 288]. With the increased synthesis of HA in tumors, the activity of hyaluronidase (HYAL) is also abnormally heightened, and HYAL1 in tumor tissue has been identified as a potential tumor marker [289, 290]. HYAL1 is the only HYAL isoform that can be secreted into the peripheral blood and detected, few studies have been conducted to confirm the prognostic value of it [289]. CD44, as the specific receptor for HA, is an important biomarker and target in cancer therapy in view of its upregulation in cancers [291, 292]. For example, The combination of CD44 and E-selectin can predict clinical outcomes of T-cell acute lymphoblastic leukemia (T-ALL) patients who are chemoresistant [293].

ECM degradation

The process of ECM degradation typically involves various MMPs and their inhibitors, which play important roles in tumor progression. Several studies have shown that high expression of specific MMPs, especially MMP2 and MMP9, is closely associated with enhanced invasiveness and metastatic potential of tumors. MMPs have been proved to be associated with reduced survival rates in most cancers, including colorectal cancer, lung cancer, breast cancer, ovarian cancer, and gastric cancer. Despite the numerous subtypes of MMPs, the potential of most subtypes as tumor biomarkers remains unclear.

As a molecule that has received significant attention in the field of tumor research in recent years, HAPLN1 has a complex and close relationship with tumor prognosis. For instance, in a mouse model for peritoneal carcinomatosis, HAPLN1 promotes TNF-mediated upregulation of HA by upregulating TNFR2, supporting tumor growth and metastasis. It serves as a potential prognostic marker for PDAC [294]. Higher levels of HAPLN1 are associated with poor prognosis in gastric cancer patients. Detecting HAPLN1 levels can help more accurately assess the severity and progression of the gastric cancer. Future research should focus on elucidating the specific mechanisms of HAPLN1 in different tumor types, as well as its potential for combined application with other biomarkers, in order to better utilize HAPLN1 as a tool for prognosis assessment and therapeutic intervention.

Therapeutic targets

Due to the dual roles of the ECM within the TME in promoting and suppressing tumor progression, a single-targeted ECM therapy is unlikely to achieve optimal clinical outcomes. Currently, targeting various ECM components, remodeling enzymes, inhibiting signal transduction pathways, modulating ECM stiffness, and modulating the function of CAFs are all potentially effective therapeutic strategies. Herein, we discuss the current progress in the clinical applications of targeting ECM.

Collagen

Immunotherapy has significantly improved survival in cancer patients, but some still derive limited benefit, and there is a lack of effective biomarkers to guide the use of ICIs. COL accumulation reduces T cell infiltration and induces T cell exhaustion, impacting the efficacy of immunotherapy, which makes COL a potential target for enhancing the effectiveness of ICIs [214]. The biological processes of COL, including production, modification, interaction, and degradation, all could emerge as promising therapeutic targets for cancers [295]. For example, post-translational modifications (PTM) COL undergo can lead to the creation of a nearly limitless variety of matrices, the process of which may enhance immune cell migration into the tumor if targeted. Therefore, targeting LOX, MMP, and PAD which take part in COL deposition and secretion can help inhibit tumor metastasis [296–298]. However, the treatment value of simply targeting extracellular LOXL2 such as Simtuzumab is limited, which indicates that it may be more effective to block both intracellular and extracellular LOXL2 [299]. Copper is a critical cofactor for LOXL's enzymatic function, the inhibition of which leads to anti-angiogenic and anti-fibrotic effects [300]. The precise mechanism of how the inhibition of copper regulates LOXL, contributing to T-cell infiltration remains unclear [301]. Above all, elucidating and addressing the biological mechanisms related to COL provide valuable insights for developing innovative therapeutic strategies.

COL-targeted agents mainly directly deplete COL or change COL alignment, the effects of which are still unclear. Traditional drugs have focused on regulating COL by targeting tumor cells [302]. The combination of COL-targeted drugs with other standard anti-tumor strategies maybe promising [303, 304]. In view of complicated functions of COL, which could play the opposite role in various cancer stages or continue to promote the metastasis of cancer though degraded, it is difficult to develop effective COL-targeted drugs. Currently, nano-mediated relevant therapeutic options exhibit the expected gratifying properties. For example, a bioadhesive immune niche domain (BIND) enhances cancer immunotherapy by delivering COL-targeted nanovaccines, dynamically modulating the TME, and promoting durable, non-exhausted T-cell responses [305]. RhCOLIII, a type of recombinant humanized COL, was reported to inhibit the invasion of OCCs and promote the infiltration of $CD8^+$T cells [306]. A dormant

collagenase-producing Clostridium, coated with a metal-anesthetic network, degrades tumor COL, causing the destruction of tumor matrix which causes tumor metastasis [307]. In summary, targeting COL involves not only its composition but also balancing its content and distribution to enable more precise treatments, while considering the genetic heterogeneity of tumors.

Glycoprotein

Changes in the expression and structure of glycoproteins in the ECM can promote the growth and metastasis of tumor cells. For example, increased TSP-1 normalizes blood vessels, metronomic chemotherapy which increases TSP-1 levels can help more cancer cells killed [308]. TSP-1 inhibits tumor angiogenesis by inducing endothelial cell apoptosis and other mechanisms, thereby preventing tumor growth. Therefore, promoting gene expression of the angiogenesis inhibitor TSP-1 is a potentially effective anti-tumor strategy. In addition, the prognostic model based on TNC expression along with clinicopathological characteristics is promising, which simultaneously investigated the clinical application value of inhibiting TNC [309]. Specific inhibitors targeting glycoproteins such as FN, versican, brevican, and several microproteoglycans also have the potential of inhibiting tumor growth. For example, one research showed that disrupting ECM-cell adhesions, especially by targeting laminin-associated integrins, can be a novel therapeutic strategy. Meanwhile, the importance of three-dimensiona lmodels for validation was emphasized since tumor biology failed to be preserved by 2D culture [310].

HA

As previously discussed, HA significantly promotes tumor progression and invasion. Therefore, oncological treatment aimed at diminishing HA activity may be efficient such as blocking the binding of HA and receptors, inhibiting HA synthesis, and accelerating HA breakdown [183]. UDP-GlcA is an essential substrate for HA synthesis and can be consumed by 4-MUG, which is converted from 4-MU [311]. 4-MU has been reported to decrease tumor proliferation by affecting downstream signaling pathways of HA and enhance the efficacy of chemotherapy and other anticancer drugs [312, 313]. 4-MU exerts its anti-prostate cancer effects by disrupting androgen receptor (AR) activity and its downstream signaling pathways [314]. Recently, it is reported that OVV-Hyal 1 enhanced antitumor efficacy by degrading HA in solid tumors, reshaping the TME to facilitate viral spread, drug delivery, immune cell infiltration, and immune activation [315].

It seems promising to treat with HA molecules as receptor and downstream signaling activation affected by HA size. Oligo-HA disrupts the HA-CD44 interaction, inhibiting the ErbB2/PI3K/AKT/β-catenin/COX-2 signaling pathway, thereby suppressing tumor cell survival and proliferation in colorectal cancer [316]. Additionally, oligo-HA may help enhance chemotherapy sensitivity in various cancers [317, 318]. HA can be degraded by the targeted delivery of hyaluronidase, with the limitation of unstable activity [319, 320]. Numerous articles have summarized PH-20, a member of the human hyaluronidase family, as an effective therapeutic agent for degrading HA and controlling tumor progression [321]. Exo-PH20-mediated hyaluronan degradation enhances DC activation and $CD8^{+}$T cell-mediated anti-tumor immunity [247]. A recent study showed that the coformulation of atezolizumab with PH20 for subcutaneous administration demonstrated noninferior drug exposure, comparable efficacy, safety, and immunogenicity to intravenous administration, providing a convenient alternative for advanced NSCLC treatment [322]. PEGPH20, a polyethylene glycol (PEG) recombinant human hyaluronidase, specifically degrades HA in the tumor stroma while enabling long-lasting in vivo recycling of hyaluronidase. Its therapeutic effect has been explored in pancreatic tumors, gastric cancer, and ovarian cancer [323, 324]. Increased H2O2 may help degrade HA and remodel the ECM, which has the potential of enhancing immune recognition [325]. HA-modified zinc peroxide-iron nanocomposites (FZOH) enhance breast cancer immunotherapy by remodeling the stromal microenvironment, inducing ferroptosis and pyroptosis, and boosting αPD-1 antitumor responses [326].

In addition, HA has emerged as an ideal nanocarrier for drug delivery in cancer therapy owing to its excellent biocompatibility and ease of modification. One study demonstrated that iron-platinum nanoparticles (FePt NPs) overcome TKI resistance in mesenchymal-state cancer cells by promoting HA-CD44-mediated endocytosis, inducing ferroptosis, and providing a promising new strategy for cancer treatment [327]. Coating nanocarriers with HA not only boosts therapeutic efficacy but also reduces side effects [186]. Controlled-release hydrogel based on HA can improve antitumor therapy in the TME by promoting the infiltration of immune cells and upregulating the production of key antitumor cytokines [328]. It has been widely used to target cancer cells by applying the interaction of HA and CD44 with nanoparticles. Soluble CD44 (solCD44) inhibits melanoma cell proliferation by interfering with HA-CD44 interactions, with mutations in the HA binding site preventing this effect [329]. Although HA-based nanomaterials are widely applied in targeting tumor cells, a key challenge remains in effectively controlling the degree of substitution on the HA backbone to maximize therapeutic efficacy.

ECM degradation

Given the important role of stromal factors in tumor cell migration and growth, they contribute to a more diverse approach to targeting and treating tumors. The regulation of ECM degradation is of great significance in tumor treatment, and a Zn2 + organometallic framework vaccine promotes antigen presentation and enhances the immune response by activating the cGAS-Sting signaling pathway, and enhances the activity of MMP2 to promote the degradation of ECM and exert anti-tumor effects, which provides an effective idea for the development of a new type of tumor vaccine [330]. ECM impairs endocytosis of nanoparticles, and therefore, degradation of COL, its key component, is beneficial for enhancing the radiosensitizing efficacy of nanoparticles in pancreatic cancer [331].

FAK inhibitors induce ECM invasion by preventing maturation of adhesion patches and reducing the activation of MMP, overcoming the fibrosis and enhancing response to immunotherapy [332]. However, FAK inhibitors have a limited effectiveness in cancer treatment. For example, FAK inhibitors, including GSK2256098, defactinib (VS-6063) and conteltinib (CT-707), showed limited clinical success in treating the tumor [333–335]. Ongoing clinical studies are combining FAK inhibitors with other antitumor agents to improve the effectiveness and are developing multitargeted types of FAK with ALK, EGFR, and S6K1 [336]. The results of such studies have not yet been reported. Additionally, Diosmin, an anti-FAK drug, inhibited LUAD metastasis by reversing the process of EMT.

Given the crucial role of CAFs in ECM deposition and remodeling, CAF depletion is theoretically an effective avenue for antitumor therapy. The most common targeted therapy in CAF-targeting strategies is the targeting of fibroblast activation protein (FAP), a classical marker of CAFs. However, multiple FAP blocking antibodies showed limited efficacy in controlling the progress of tumor in phase 1/2 trials [337]. A recent review summarized the research progress of CAF-targeted therapies in terms of directly or indirectly depleting CAF, targeting CAF-related signaling pathways, limiting ECM remodeling, and targeting TAMs [338]. Single-cell sequencing can help identify fibroblast subsets and understand their heterogeneity, which is closely related to tumor immunity. Additionally, beyond CAF depletion, reprogramming CAFs deserves further attention as a promising approach for CAF-targeted therapies [302, 339].

Promising targets and clinical applications

The renin-angiotensin system (RAS) inhibitors which are typically used to treat hypertension can attenuate matrix remodeling by inhibiting ECM deposition, LOX expression and COL production [340]. These changes induced by anti-RAS drugs probably promote T-cell migration to improve tumor immunity, which is currently being explored for efficacy in tumor immunotherapy applications [341]. It was recently reported that activation of the ACE2 axis mitigates the immunosuppressive microenvironment in hepatocellular carcinoma (HCC), which help enhance the effectiveness of immunotherapy [342]. Since anti-VEGF drugs can increase the expression of ECM components, such as HA and GAGs [341], the combined application of anti-RAS and anti-angiogenesis drugs can enhance sensitivity to anti-PD-L1 therapy [343, 344]. Additionally, ARBs inhibited COL I expression and improved therapeutic efficacy when combined with ICIs [345]. Recently, RAS inhibitors have been shown to improve survival in colorectal cancer, glioblastoma, and melanoma [346–348]. Whether its association with other antitumor agents plays a role in immunomodulation remains to be clearly demonstrated.

The formation of tunneling nanotubes (TNTs) requires the support of F-actin in the cytoskeleton. Local nanotubes facilitate the transmission of various substances and signaling molecules between cells [349, 350]. Nanotubes transmit substances such as mitochondria between tumor cells and stromal cells, enhancing the survival of tumor cells. Therefore, studies have explored the combination of ICIs with pharmacological agents that interfere with nanotube-mediated mitochondrial transport to assess their anti-tumor efficacy in breast cancer [351]. A recent study revealed that in the TME, mitochondria can be transferred from bone marrow-derived mesenchymal stromal cells to $CD8^+$T cells via nanotubes. This process enhances the metabolic activity of $CD8^+$T cells and improves the resistance to exhaustion, as well as boosting tumor suppression by both lymphocytes and engineered T cells. These findings pave the way for next-generation cell-based therapies [352]. With the widespread use of ICIs, nanotube-mediated intercellular interactions have the potential to not only enhance therapeutic efficacy but also lay the foundation for optimizing cell-based therapies.

We have reviewed in detail the role of DDR1 in tumor immunomodulation, supporting it as a novel target for tumor immunotherapy. Additionally, Remodeling of TME by DDR1 antibodies may have synergistic anti-tumor effects when combined with existing immunotherapies. Soft matrix induces DRP1 recruitment and mitochondrial fission and autophagy in breast cancer by promoting endoplasmic reticulum-mitochondrial calcium transport, indicating that ECM stiffness is a potential target for antitumor therapy [353]. Moreover, TMEM126A, a mitochondrial transmembrane protein, inhibits breast cancer metastasis by inhibiting mitochondrial dysfunction and

ROS production, preventing ECM remodeling and EMT, which is associated with breast cancer prognosis [354].

Researchers have found that by clustering mitochondria at the center of cancer cells, excessive ROS production leads to mitochondrial damage, causing cancer cells to die due to the inability to metastasize. This suggests a potential strategy for mitochondrial-targeted cancer therapy. However, the survival of some cancer cells, which switch to glycolysis to survive, remains an unresolved challenge [355]. Additionally, PAX mutation, the interaction between kindlin-2 and PYCR1, and the blockade of α5β1 integrin all affect mitochondrial function and structure [356–358].

Unlocking ECM's Potential in tumor Immunity

Development of effective biomarkers in ECM

Dynamic ECM alterations serve as critical biomarkers for predicting immunotherapy responses. For instance, abnormal COL deposition and HA accumulation create physical barriers that impede cytotoxic T-cell infiltration into tumor cores while recruiting immunosuppressive cells. Recent studies demonstrate that quantifying ECM stiffness or immunosuppressive ECM proteins can predict patient sensitivity to ICIs. Single-cell sequencing further enables the identification of ECM-immune cell interaction networks, providing precision biomarkers for optimizing combination therapies.

The predictive role of a single biomarker in tumor immunotherapy is limited, while the combined predictive potential of multiple ECM biomarkers is significant. However, the immune regulation of ECM within the TME is often overlooked, which may lead to the missing identification of promising predictive and prognostic biomarkers.

Dilemma of current biomarkers in ECM

Given the significant role of ECM in the TME, the development of biomarkers within the ECM holds great potential. With the development of single-cell sequencing and high-throughput omics techniques, the complex composition of the ECM can be analyzed more comprehensively. However, the temporal and spatial heterogeneity of the ECM determines its dynamic nature, which in turn leads to the lack of universality in biomarkers. This phenomenon leads to existing biomarkers lacking sufficient specificity and sensitivity, resulting in unsatisfactory outcomes in clinical applications. Due to the pivotal role of the ECM components in tumor immunity, the development of effective biomarkers within the ECM is crucial for predicting responses to immunotherapy. To date, there are no strong biomarkers within the ECM that signal responses to immunotherapy, nor are there any predictive biomarkers available for routine clinical use.

Perspective of effective biomarkers in ECM

In view of the dynamics of ECM, real-time monitoring of its changes can be enhanced to promptly capture variations in biomarkers. For instance, spatiotemporal single-cell sequencing can provide valuable insights into the dynamic interactions between ECM components and immune cells, facilitating the identification of ECM biomarkers that predict responses to immunotherapy. In addition, Analyzing the composition and function of the ECM by integrating multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics will aid in identifying potential biomarkers. In this era of advanced technologies, a novel biomarker discovery framework leveraging machine learning and multi-omics data should be established to systematically analyze the dynamic composition of the ECM, its interactions with immune cells, and its role in tumor progression. This approach will facilitate the identification of ECM-based biomarkers that can predict immunotherapy responses and improve the efficacy of targeted therapies.

Development of ECM-targeted therapy

ECM-targeted therapies aim to dismantle immunosuppressive barriers and amplify immunotherapy efficacy. For example, inhibiting COL-crosslinking enzymes or DDR enhances T-cell infiltration and suppresses tumor growth by disrupting ECM-mediated immune evasion. Nanoparticles engineered to degrade HA or deliver ECM-modulating drugs improve Chimeric Antigen Receptor T-Cell penetration and cytotoxicity. Additionally, targeting ECM-associated immune checkpoints reverses T-cell exhaustion, synergizing with ICIs. Emerging strategies, such as CAF reprogramming and mechanotherapy, further normalize ECM stiffness to restore immune surveillance.

Drugs targeting the ECM have been continuously developed, but their efficacy has not been entirely satisfactory. The inherent heterogeneity and dynamic nature of ECM components present both opportunities for therapeutic strategies and challenges that must be addressed and overcome.

Dilemma of ECM-targeted therapy

In most clinical trials, the efficacy of ECM-targeted therapy is limited. For one hand, the complexity and dynamic nature of the ECM result in numerous potential targets, but selecting precise and effective ones remains challenging. For another hand, precise regulation of multi-target synergistic effects still faces technical challenges, including insufficient specificity of the delivery system and the difficulty of dynamically adapting to the heterogeneous TME. Additionally, the off-target effects that ECM-targeted therapy may trigger and the potential adverse

impacts on the ECM of normal tissues are difficult to accurately assess. Concerns over safety have restricted its widespread clinical application. Moreover, existing animal models struggle to replicate the complexity of human ECM, leading to inconsistencies between preclinical data and clinical trial results. Future research needs to focus on the interactions between ECM, cancer cells, and stromal cells, in order to develop new therapeutic targets and strategies.

Perspective of ECM-targeted therapy

Though immunotherapy can improve the prognosis of tumor patients, only a limited number can significantly benefit from it and even exhibit innate resistance. ECM, as indispensable components of TME, which is one of mechanisms of resistance, if targeted, may offer a novel approach to enhance the efficacy of immunotherapy. ECM regulates tumor immunity dynamically in the TME, making it potential to enhance the efficacy of immunotherapy and overcome resistance. The rapid development of technologies such as gene sequencing and proteomics makes it possible for understanding the differences in ECM among individuals, enabling the customization of personalized treatment plans for patients. Precisely selecting the corresponding targeted drugs can not only improve the treatment effect but also reduce unnecessary drug side effects. Additionally, it is expected that smart drug delivery carriers will be developed, capable of responding to specific signals in the ECM to achieve precise drug delivery. Lastly, gene editing technologies may offer more effective means to regulate the expression of ECM-related genes. Moreover, Though various drugs inhibiting MMP, DDR, LOX, CD44 and other effective targets has made breakthroughs, the multi-targeted therapy based on the patient's ECM-specific characteristics is a more reasonable choice. Meanwhile, the combination of ECM-targeted drugs with other anti-tumor drugs is also promising. For example, the inhibition of LAMC2, which regulates a transcriptional network linked to tumor progression and survival, when combined with MEK1/2 inhibitors exhibits synergistic antiproliferative effects [359].

Conclusion

ECM-TME crosstalk affects tumor immune regulation, inhibiting or promoting tumor progression. Given its complex regulatory role, single-targeted therapy for ECM is insufficient. The clinical translation of ECM-based strategies, including the identification of biomarkers and development of novel therapeutic approaches, presents significant opportunities to enhance cancer treatment. However, we have mentioned the differences between animal models and human patients, which hinder clinical translation of results from animal models to clinical settings. Furthermore, the disruptions of mitochondrial function induced by ECM composition or stiffness can alter the metabolic reprogramming of immune cells, such as macrophages and T cells, thereby modulating their antitumor activities. This highlights a critical intersection between ECM remodeling, cellular metabolism, and immune response-an area that is rapidly gaining attention in the context of tumor immunology. Further elucidation of the mechanisms underlying ECM dynamics in tumor immunoregulation will optimize anti-tumor strategies and advance precision therapies. In conclusion, as our understanding of ECM-mediated tumor immunoregulation deepens, there is increasing potential to leverage ECM-targeted strategies in cancer therapy.

Abbreviations

ADAM	A Disintegrin and Metalloproteinase
ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin Motifs
AR	Androgen Receptor
ARBs	Angiotensin Receptor Blockers
BIND	Bioadhesive Immune Niche Domain
CAFs	Cancer-Associated Fibroblasts
ccRCC	Clear Cell Renal Cell Carcinoma
CD	Cluster of Differentiation Antigen
COL	Collagen
CR	Complete Response
CRC	Colorectal Cancer
CSPGs	Chondroitin Sulfate Proteoglycans
CTLA-4	Cytotoxic T Lymphocyte-Associated Antigen-4
DCs	Dendritic Cells
DDR	Discoidin Domain Receptors
DRP1	Dynamin-Related Protein 1
ECM	Extracellular Matrix
ECs	Endothelial cells
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-Mesenchymal Transition
ETP	Endotrophin Peptide
EVs	Extracellular vesicles
FAK	Focal Adhesion Kinase
FAP	Fibroblast Activation Protein
FN	Fibronectin
GAGs	Glycosaminoglycans
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HA	Hyaluronic Acid
HAPLN1	Hyaluronan and Proteoglycan Link Protein 1
HAS2	Hyaluronan synthase 2
HCC	Hepatocellular Carcinoma
HIF-1α	Hypoxia-inducible factor-1α
HMW HA	High Molecular Weight Hyaluronic Acid
HR	Hazard Ratio
HYAL	Hyaluronidase
ICIs	Immune Checkpoint Inhibitors
IFP	Interstitial Fluid Pressure
IGF	Insulin-like growth factor
KS	Keratan sulfate
KSPGs	Keratan sulfate proteoglycans
LAIR-1	Leukocyte-Associated Immunoglobulin-like Receptor 1
LECs	Lymphatic endothelial cells
LMs	Laminins
LMW HA	Low Molecular Weight Hyaluronic Acid
LOX	Lysyl Oxidase
LUAD	Lung Adenocarcinoma
MDSCs	Myeloid-Derived Suppressor Cells
MM	Multiple myeloma
MMPs	Matrix Metalloproteinases

NETs	Neutrophil Extracellular Traps
NK	Natural Killer
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
OSR2	Odd-Skipped Related 2
OXPHOS	Oxidative Phosphorylation
PD-1	Programmed Cell Death-1
PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed Cell Death Ligand 1
PEG	Polyethylene glycol
PFS	Progression-Free Survival
PH20	Hyaluronidase PH20
PLOD2	Procollagen-Lysine, 2-Oxoglutarate 5-Dioxygenase 2
PR	Partial Response
PTM	Post-translational modifications
RAS	Renin-angiotensin system
ROS	Reactive Oxygen Species
sE-cad	Soluble fragment of E-cadherin
SLRP	Small Leucine-Rich Proteoglycans
SPARC	Secreted Protein Acidic and Rich in Cysteine
TACS	Tumor-Associated Collagen Signatures
T-ALL	T-cell acute lymphoblastic leukemia
TAMs	Tumor-Associated Macrophages
TANs	Tumor-Associated Neutrophils
TGase	Transglutaminase
TGF-β	Transforming Growth Factor-β
TILs	Tumor-Infiltrating Lymphocytes
TME	Tumor Microenvironment
TNBC	Triple Negative Breast Carcinoma
TNC	Tenascin-C
TNTS	Tunneling Nanotubes
Treg	Regulatory T Cells
TRMs	Tissue-resident macrophages
TSP1	Thrombospondin 1
VEGF	Vascular Endothelial Growth Factor
YAP/TAZ	Yes-Associated Protein/Transcriptional Coactivator with PDZ-Binding Motif
α-SMA	Alpha-Smooth Muscle Actin

Authors' contributions
Q.H., Y.Z., Y. L. and G. Z. were involved in design of the work and the fgures. Q.H. and Y. L. performed the literature search and wrote the draft. Q.H. and J. M. prepared the figures and provided the critical revisions. Y. L. and G. Z. provided the critical revisions and contributed to editing the manuscript. Q.H., Y.Z. and Y. L. made significant revisions to the manuscript. All authors were involved in manuscript writing, read and approved the fnal manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
This manuscript has been read and approved by all the authors to publish and is not submitted or under consideration for publication elsewhere.

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