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Mechanical forces in the tumor microenvironment: roles, pathways, and therapeutic approaches

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Abstract

Tumors often exhibit greater stiffness compared to normal tissues, primarily due to increased deposition within the tumor stroma. Collagen, proteoglycans, laminin, and fibronectin are key components of the extracellular matrix (ECM), interacting to facilitate ECM assembly. Enhanced fiber density and cross-linking within the ECM result in elevated matrix stiffness and interstitial fluid pressure, subjecting tumors to significant physical stress during growth. This mechanical stress is transduced intracellularly via integrins, the Rho signaling pathway, and the Hippo signaling pathway, thereby promoting tumor invasion. Additionally, mechanical pressure fosters glycolysis in tumor cells, boosting energy production to support metastasis. Mechanical cues also regulate macrophage polarization, maintaining an inflammatory microenvironment conducive to tumor survival. In summary, mechanical signals within tumors play a crucial role in tumor growth and invasion. Understanding these signals and their involvement in tumor progression is essential for advancing our knowledge of tumor biology and enhancing therapeutic approaches.

Keywords Tumor, Extracellular matrix, Mechanical forces

Introduction

With advancements in early cancer detection and treatment technologies, cancer mortality rates have consistently declined from 1991 to 2021. However, the incidence rates of certain cancers, such as prostate, colorectal, and kidney cancer, have shown a continuous upward trend. The American Cancer Society's report indicates that in 2024, there will be an estimated 2 million new cancer cases and 610,000 cancer-related deaths in the United States [1]. Statistics suggest that only 5–10% of cancers are attributed to genetic defects, while more than 90% of cancer cases arise from environmental factors and lifestyle choices [2]. In recent years, the interaction between cancer cells and the tumor microenvironment (TME) has garnered considerable attention. The TME consists of non-tumor cells, extracellular matrix (ECM), and various bioactive molecules [3]. This environment can reprogram cancer cells, promoting tumor growth, invasion, metastasis, and response to therapies [4]. Mechanical signaling within the TME plays a crucial role in these processes, with mechanical signals primarily originating from solid stress due to excessive cellular proliferation within the confined tissue space [5], increased interstitial fluid pressure from the collapse of

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tumor-associated vasculature [6], and enhanced matrix stiffness due to cross-linking of fibrin, collagen, and hyaluronan [7]. Various methods have been established for detecting mechanical forces within the tumor microenvironment in in vivo, in vitro, and patient models. These techniques include 3D traction force microscopy, molecular force sensors, ultrasound elastography, magnetic resonance elastography, and optical coherence tomography elastography [8].

Mechanical cues in the TME significantly influence tumor growth, invasion, and therapeutic resistance. For instance, solid stress compresses blood and lymphatic vessels, reducing perfusion and causing hypoxia, which further promotes immune evasion and metastasis [9]. Furthermore, the compression of lymphatic and blood vessels elevates interstitial fluid pressure, impeding the delivery of therapeutic agents and thereby reducing the efficacy of chemotherapies [10]. Mechanical signals are also sensed by receptors on cell surfaces, translating these cues into intracellular biochemical signals that alter gene expression and regulate cellular morphology, motility, proliferation, and migration [11]. Given this, the physical characteristics of the TME may critically impact cancer treatment outcomes. Understanding the mechanical properties of the TME may enhance our insights into therapeutic strategies. In this review, we will focus on the major contributor to mechanical properties within the TME, the ECM, and discuss how mechanical signals within the ECM promote tumor proliferation and migration.

Composition and mechanical properties of the ECM

The TME is a complex assembly composed of tumor cells, non-tumor cells, ECM, and various non-cellular components. Within the TME, biochemical and mechanical signals coexist and interact, collectively promoting tumor proliferation and invasion [12]. For instance, biochemical factors such as TGF-β can activate cancer-associated fibroblasts (CAFs), enhancing their stiffness and promoting their elongation, cell spreading, lamellipodia formation, and spheroid invasion [13]. Conversely, mechanical signals can induce M1 polarization of macrophages, stimulating inflammatory responses that further support tumor progression [14]. Therefore, as the primary contributor to mechanical signaling within the TME, understanding the composition and key mechanical properties of the ECM is essential.

Composition and functional characteristics of the ECM

As a non-cellular component within the TME, the ECM provides both biochemical and structural support to tumor cells, playing a critical role in cell adhesion and proliferation. The ECM primarily comprises fibrin, proteoglycans, growth factors, minerals, and water [15]. Among these, collagen, proteoglycans, laminin, and fibronectin constitute the core components of the ECM (Fig. 1). These components and their main functions are summarized in Table 1.

Collagen: a key regulator of tumor matrix stiffness

Collagen is a protein characterized by a triple-helical structure with a repeating Gly-X-Y sequence, where X and Y are commonly proline or hydroxyproline [16]. Collagen precursors are translated and transported to the endoplasmic reticulum (ER), where they undergo hydroxylation of proline and lysine residues by hydroxylases [17]. Hydroxylysine serves as a potential glycosylation site, undergoing glycosylation in the ER through the action of glycosyltransferases and subsequently transferring to the Golgi apparatus in preparation for secretion into the ECM [18]. Collagen contains extension structures at both the N- and C- termini (N-propeptide and C-propeptide), which contribute to forming the triple-helical domain. Research indicates that this domain guides the assembly of collagen precursors in the ER and facilitates triple-helix formation [19]. Additionally, 4-hydroxyproline stabilizes the triple helix through intramolecular hydrogen bonding. Studies have shown that inhibitors of prolyl 4-hydroxylase can block C-propeptide formation, thus inhibiting α-chain associations necessary for collagen maturation [20]. Immature collagen remains highly soluble and unable to form fibrillar structures [21], leading to an ECM lacking adequate mechanical support. Mature collagen undergoes C-propeptide removal via C-proteinase, while N-propeptide is retained in type V and type XI collagen [22]. Post-cleavage, procollagen self-assembles in the ECM to form long, stable collagen fibers [23]. In the tumor microenvironment, collagen synthesis is often significantly increased [24]. Collagen content has been shown to correlate with the prognosis of patients with pancreatic ductal adenocarcinoma, with elevated levels of PRO-C22 being indicative of poorer overall survival [25]. Research by Levental et al. has demonstrated that induced collagen cross-linking promotes ECM stiffening and enhances the invasive potential of breast cancer cells. Conversely, inhibition of lysyl oxidase (LOX)-mediated collagen cross-linking can prevent tumor progression by inhibiting excessive collagen synthesis and cross-linking in the MMTV-Neu mouse model, thereby reducing tumor incidence [26].

Collagen interacts with cell surface receptors to enable cellular responses to changes within the TME. These receptors include collagen-binding integrins and non-integrin receptors (DDR1 and DDR2) [27, 28]. Collagen-binding integrins recognize and bind the GFOGER sequence within the collagen triple helix (where O represents 4-hydroxyproline) through their αI domains [29].

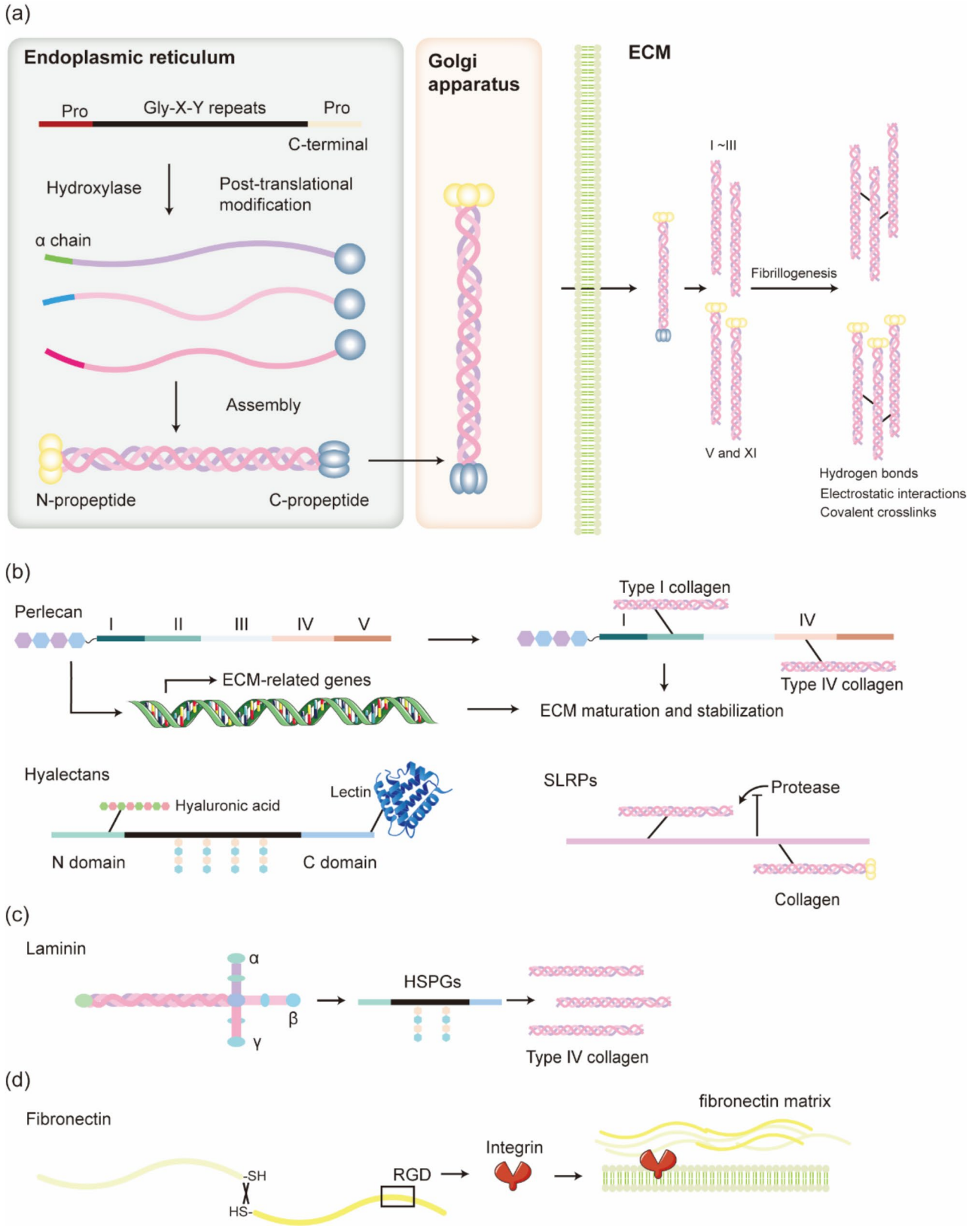

Fig. 1 (See legend on next page.)

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Fig. 1 Major components of the ECM: collagen, proteoglycans, laminin, and fibronectin. (**a**) Collagen is synthesized in the endoplasmic reticulum and undergoes preliminary assembly into a triple-helix structure before being transported to the ECM via the Golgi apparatus. The N-propeptides (retained in type V and XI collagen) and C-propeptides are cleaved by proteases in the ECM, allowing collagen to self-assemble into collagen fibrils. (**b**) Proteoglycans in the ECM primarily include perlecan, hyalectans, and SLRPs. Perlecan not only cross-links with collagen to promote ECM maturation but also regulates ECM-related gene expression. Hyalectans interact with integrins and hyaluronan within the ECM, facilitating ECM remodeling. SLRPs bind to collagen and protect it from proteolytic degradation, thereby maintaining ECM structural stability. (**c**) Laminin consists of α, β, and γ polypeptide chains forming a trimeric structure. This laminin trimer binds to type IV collagen via HSPGs in proteoglycans, thereby contributing to matrix formation. (**d**) Fibronectin forms dimers through C-terminal disulfide bonds, which further assemble into fibronectin fibrils. These fibrils interact with integrins via the RGD sequence to stabilize the ECM structure

Studies reveal that the availability of cell surface DDR1 pools is regulated by metalloproteinases, such as MMP-14, MMP-15, and MMP-16, which cleave the extracellular domain of DDR1, reducing receptor availability [30]. This cleavage potentially modulates ECM remodeling by adjusting collagen deposition rate, amount, and adhesion properties [31, 32]. Furthermore, collagen contains RGD sequences, which, when exposed due to hydrolysis or deformation, bind to the integrin receptor αvβ3. Under ECM damage, additional RGD sequences become exposed and engage with αvβ3 [33]. Elevated αvβ3 expression has been observed in vertical growth and metastatic melanoma compared to benign melanomas [34], suggesting that melanoma cells may promote invasion and metastasis by disrupting the ECM, exposing RGD sequences, and enhancing αvβ3 interactions.

Proteoglycans: core components of ECM hydration and lubrication

Proteoglycans are essential components and functional modulators of the ECM, consisting of a protein core covalently linked to glycosaminoglycans (GAGs), such as heparan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, or keratan sulfate [35]. The negatively charged GAGs attract water molecules and form hydration layers, providing the ECM with essential lubricating properties [36]. Based on their cellular localization, proteoglycans are categorized as intracellular, cell-surface, pericellular, and extracellular proteoglycans. Those primarily involved in ECM formation include pericellular and extracellular proteoglycans, where pericellular proteoglycans are primarily heparan sulfate proteoglycans (HSPGs) and extracellular proteoglycans are mainly hyalectans and small leucine-rich proteoglycans (SLRPs) [37].

Among pericellular proteoglycans, HSPGs prominently include Perlecan [36]. Perlecan is a highly conserved, large (> 400 kDa) ECM proteoglycan [38]. Perlecan binds to ECM proteins, contributing to cellular proliferation and enhancing the basement membrane [39]. For example, Domain I of Perlecan binds to collagen IV and fibronectin, promoting cell-ECM adhesion and stabilizing the matrix [40]. Domain IV binds to collagen IV, fibronectin, fibrillin-2, and nidogen, playing roles in cell adhesion and motility [41]. Domain V interacts with endothelin, ECM1, FGF7, fibrillin-2, integrins, and nidogen, regulating cell-ECM communication and cell migration [42, 43]. Additionally, Perlecan modulates ECM-related gene expression; studies by Johnson et al. demonstrate that suppression of the *HSPG2* gene (encoding Perlecan) in human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) reduces ECM-related gene expression, indicating that Perlecan promotes ECM maturation and stability by regulating ECM gene expression [44]. Furthermore, Perlecan has been shown to play a role in the development of various types of cancer. For instance, Perlecan mRNA expression is significantly elevated in salivary gland adenoid cystic carcinoma cells forming small pseudocysts, suggesting that Perlecan may be essential for the growth of these tumors [45]. In human ameloblastoma cell nests and around human intrahepatic cholangiocarcinoma, Perlecan mRNA expression is significantly increased, particularly at the invasive front of the cancer cells, indicating its potential involvement in tumor cell invasion [46, 47].

In terms of extracellular proteoglycans, hyalectans form a proteoglycan family with similar structural properties, including aggrecan, versican, neurocan, and brevican [48]. Hyalectans could interact with ECM components, including hyaluronic acid, tenascin R, fibulin-1, and fibulin-2, thereby facilitating ECM remodeling [49]. Additionally, versican is known to maintain a loose ECM structure, often associated with cancer cell proliferation and invasion [50, 51]. Studies have shown that hyalectans are upregulated in various cancers, including prostate cancer, breast cancer, ovarian cancer, gastric cancer, laryngeal cancer, and pancreatic cancer [51]. Furthermore, the accumulation of hyalectans has been linked to poor prognosis in breast cancer [52]. Research by Yang et al. has shown that glioblastoma cell lines expressing versican V2 can survive in serum-free environments. The expression of versican V2 upregulates fibronectin, enhancing the adhesion of tumor cells to endothelial cells, thus promoting tumor angiogenesis [53]. SLRPs are proteoglycans with relatively small core proteins (36–42 kDa) and are characterized by a central domain rich in leucine repeats [54]. SLRPs interact with collagen fibers (types I, II, III, V, VI, and XI) to regulate lateral collagen aggregation into proper fibrils. They also protect collagen fibers from proteolytic degradation by spatially

Table 1 ECM components and their roles in Cancer progression

Components	ECM-Related Properties	Implications in Cancer Progression	Reference
Collagen	Forms a triple helix structure, providing mechanical support to the ECM; regulates ECM stiffness and fluid pressure.	Increased collagen fiber quantity and cross-linking promote tumor invasion.	[21, 94]
Proteoglycan	Promotes ECM stability, regulates cell adhesion and motility, mediates cell-ECM communication, and aids ECM maturation and stability. Promotes ECM remodeling; protects collagen fibers from proteolytic degradation, maintaining ECM stability.	Promotes tumor proliferation and invasion. Promotes ECM to retain its loose characteristics, enhancing tumor proliferation and invasion. Enhances adhesion between tumor cells and endothelial cells, promoting tumor angiogenesis.	[40–44, 49, 53, 55]
Laminin	Maintains the mechanical strength and stability of the basement membrane.	Binds integrins and promotes tumor cell invasion.	[65, 70]
Fibronectin	Facilitates ECM assembly.	Remodels ECM to provide a pre-metastatic niche for tumors; inhibits tumor cell apoptosis.	[79–86]

restricting collagenases from accessing cleavage sites, thereby maintaining ECM stability [55].

Laminins: bridge between cell-matrix adhesion and basement membrane stability

Laminins are heterotrimeric cross-shaped proteins composed of α, β, and γ polypeptide chains, with a molecular weight ranging from 400 to 800 kDa [56]. The laminin G-like (LG) domain of laminin is capable of binding to cell surface receptors, such as integrins, thereby mediating the interaction between the cell and the ECM e. The N-termini of the α, β, and γ chains form shorter arms of varying lengths, each containing a laminin N-terminal (LN) domain. The LN domains are crucial for laminin oligomerization and for maintaining the structural integrity and function of the basement membrane [57]. The α, β, and γ polypeptide chains exist in multiple isoforms—α1 to α5, β1 to β4, and γ1 to γ3—resulting in a theoretical 60 possible trimeric combinations [57]. Laminins are indispensable for cell migration. Studies have shown that skin cell migration on substrates such as plastic, fibronectin, and collagen matrices requires the secretion of laminins by the cells themselves [58]. The adhesive properties of laminins are largely due to their LG domains on the C-terminal α chain, which bind integrins, dystroglycan, Lutheran glycoprotein, or sulfatides [59]. The LN domains on the short arms, such as those on α2 and α5 chains, have also been reported to bind integrins [60, 61]. In addition to the α chain, the short arm of the γ2 subunit has been shown to bind integrin α2β1, facilitating cell spreading on the ECM [62]. Integrin-binding domains are critical for laminin function. Through integrin interactions, laminins anchor keratinocytes to the ECM, promoting basement membrane formation and subsequent assembly of collagen type V and nidogen [63]. Collagen IV, the main scaffold of the basement membrane, assists in organizing laminins into ordered supramolecular structures. Studies have shown that mice with *Col4a1/2* gene (encoding the α chains of collagen IV) knockouts experience embryo mortality due to the basement membrane's inability to meet the mechanical demands of late embryonic development [64]. Laminins also tightly associate with collagen IV networks through proteoglycan interactions, maintaining the mechanical strength and stability of the basement membrane [65]. Given that heparin binds both the 7 S and NC1 domains of collagen IV, modulating its aggregation and network formation [66], and laminins also interact with heparin [67], it is plausible that laminins connect to collagen IV through HSPGs, forming a highly ordered structure within the basement membrane [67]. Laminin γ2 is notably expressed in colon adenocarcinoma, breast cancer, squamous cell carcinoma, and malignant melanoma, with increased levels of γ2 expression found at the invasive front of these

tumors, suggesting its involvement in cancer cell invasion [68]. As one of the integrins binding laminin, α6β4 integrin promotes breast cancer cell migration toward the basement membrane by enhancing the binding of breast cancer cells to laminin-1 [69]. Additionally, glioblastoma cells express laminin α3, β3, and γ2 chains, and laminin-5 promotes glioma cell adhesion, migration, and invasion through its interaction with integrin α3β1 [70]. These studies demonstrate that laminins, as key ECM components, participate in tumor invasion through their interactions with integrins.

Fibronectin: integrin-mediated cell adhesion and fiber formation

Fibronectin is a glycoprotein with a molecular weight of 230–270 kDa that forms a dimer through disulfide bonds at its C-terminus [71]. These covalent disulfide bonds are crucial for subsequent fibrillogenesis. Research by Schwarzbauer et al. has shown that recombinant fibronectin lacking cysteine residues fails to form dimers and does not undergo further fibril formation [72]. Each fibronectin monomer consists of repeating structural units, including 12 type I domains, 2 type II domains, and 15–17 type III domains [73].

Fibronectin matrix assembly is mediated by interactions with cell surface integrin receptors, particularly the RGD sequence in fibronectin's III10 domain and a synergy site in the III9 domain, which together bind to the α5β1 integrin [74]. While α5β1 integrin can bind fibronectin even in the absence of the synergy site [75], studies suggest that both the RGD and synergy sites are essential for fibril formation [76]. Blocking the interaction between fibronectin and integrins with anti-integrin or anti-fibronectin antibodies has been shown to inhibit fibronectin fibril assembly [77]. Upon binding to integrins on the cell surface, the actin cytoskeleton exerts tension on fibronectin molecules, causing conformational changes that expose binding sites for other ECM proteins, such as heparan sulfate [15]. Heparan sulfate has been reported to facilitate the integration of tenascin-C into the ECM [78]. Additionally, the incorporation of collagen, fibrillin, elastin, and latent TGF-β binding proteins into the ECM relies on fibronectin, which aids in ECM assembly and structural organization [79–83]. Fibronectin is considered a key factor in promoting tumor progression. Tumor cells secrete growth factors such as VEGF, which activate fibroblasts to upregulate fibronectin expression, thereby remodeling the ECM microenvironment. This provides favorable conditions for subsequent tumor cells to adhere and survive [84]. Fibronectin can attract tumor cells and inhibit their apoptosis by binding to integrin receptors [85]. Additionally, integrins can respond to changes in matrix stiffness through the JNK/c-JUN signaling pathway, which promotes fibronectin production, enhances MMP9 expression, and upregulates CXCL12. These processes, in turn, facilitate the recruitment of bone marrow-derived cells, contributing to the formation of a pre-metastatic niche [86].

Mechanical properties of the TME and their role in tumorigenesis

As discussed, the ECM comprises interconnected fibers and various macromolecules, which impart physical properties (stiffness, solid stress, fluid stress) that provide structural support for cells and play crucial roles in tumor progression (As shown in Fig. 2).

Matrix stiffness: driving the formation of invasive tumor phenotypes

The TME includes not only tumor cells but also non-tumor cells and ECM. During tumor formation, extensive ECM remodeling occurs, making it a primary contributor to tumor stiffness [13]. Collagen, an abundant ECM component, undergoes cross-linking during breast tumor progression, which leads to increased matrix stiffness. Inhibition of lysyl oxidase (LOX) activity reduces collagen cross-linking, consequently lowering ECM rigidity [26]. This suggests that LOX promotes tumor progression and breast epithelial cell invasion by enhancing fibrillar collagen and ECM stiffness, consistent with findings by Szauter et al., who observed LOX's role as a key enzyme in collagen cross-linking and tensile strength enhancement [87]. Similarly, Erler et al. reported LOX accumulation at pre-metastatic sites, promoting collagen IV cross-linking in the basement membrane and creating a favorable environment for breast cancer cell metastasis [88]. Additionally, ribose-induced nonspecific collagen cross-linking also increases ECM rigidity, implying that certain proteoglycans and nonspecific advanced glycation end-products (AGEs) in the ECM may also contribute to ECM stiffness regulation and tumor invasion [26]. LOX also regulates TGF-β levels. TGF-β1, the major isoform within the TGF-β family, has been shown to bind LOX and inhibit downstream TGF-β1 signaling; LOX inhibitors increase TGF-β1 levels, thus stimulating collagen synthesis [89]. Previous studies indicate that TGF-β1 can upregulate LOX levels [90], suggesting a dynamic interdependence between LOX and TGF-β1, whereby cells maintain matrix stiffness through a homeostatic balance between these two factors.

In addition to cross-linking, fiber density also impacts ECM stiffness. CAFs are major ECM protein contributors, and TGF-β participates in CAF activation. Activated CAFs produce increased collagen, tenascin-C, and fibronectin, leading to ECM remodeling in tumors [91]. Moreover, within the TME, CAFs display an increase in actin stress fibers and focal adhesions (FAs) [92], which enhances CAF contractility and further drives ECM

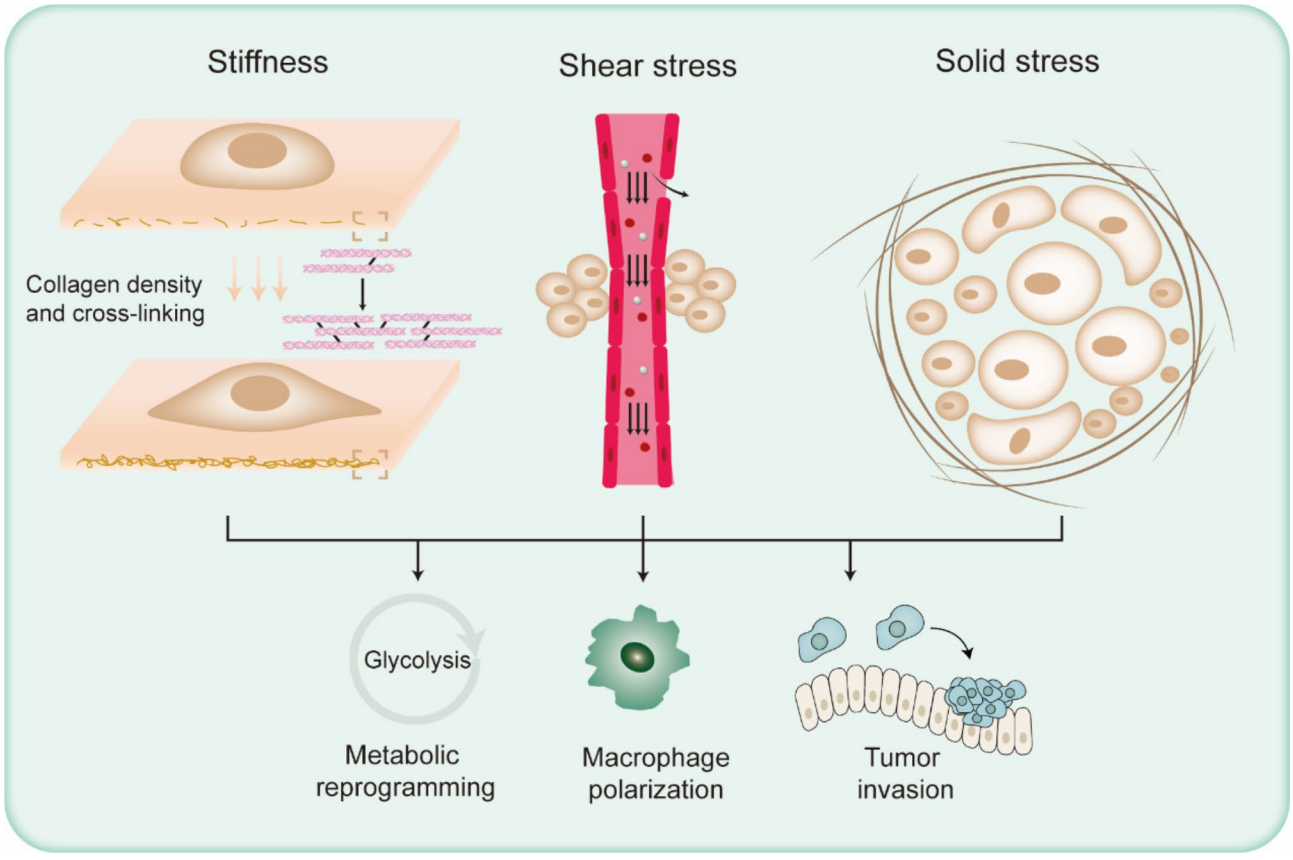

Fig. 2 Physical properties of the ECM. The ECM exhibits key physical characteristics, including stiffness, shear stress, and solid stress. Stiffness arises from an increase in fibrillar protein content and cross-linking in the ECM. Shear stress results from plasma leakage due to abnormal tumor vasculature and tumor-induced vascular compression. Solid stress originates from the excessive growth of tumor cells and surrounding tissues. These mechanical properties of the ECM contribute to metabolic reprogramming in tumor cells, influence macrophage polarization, and facilitate tumor invasion

deposition and stiffening [93]. Matrix stiffening activates Rho-associated protein kinase (ROCK), which is known to correlate with collagen deposition. In pancreatic tumors, ROCK1 expression is markedly upregulated, and the use of fasudil (a small-molecule ROCK1 inhibitor) significantly reduces collagen deposition and inhibits tumor invasion [94]. Besides collagen deposition, collagen alignment within the ECM appears to influence tumor invasion. Collagen fibers aligned longitudinally in parallel to the tumor are associated with enhanced invasive capacity of tumor cells [95].

Fluid pressure: a key factor in tumor perfusion and cellular adaptation

Tumor growth demands a substantial supply of nutrients and oxygen, prompting the overexpression of angiogenic factors such as VEGF and PDGF. Tumor blood vessels, however, often exhibit abnormal structure and function [96, 97]. This vascular abnormality creates significant fluid pressure within the TME, encompassing capillary pressure, interstitial fluid pressure, and shear stress [98, 99]. Tumor vessel walls typically have much larger gaps than normal vessels, leading to plasma leakage into the interstitial space and an increase in blood viscosity [100, 101]. Additionally, elevated solid stress within the TME compresses tumor vasculature, further increasing blood flow resistance [10]. Consequently, blood flow within tumor vessels is highly heterogeneous and generally 1–3 orders of magnitude slower than in normal tissues [102]. Shear stress, exerted by blood flow on the vascular endothelial surface, is influenced by blood viscosity and flow rate [103]. It plays a critical role in regulating tumor metastasis, as breast cancer cells under shear stress exhibit reduced adhesion, elongation, enhanced epithelial-mesenchymal transition (EMT), and decreased stiffness [104]. These adaptive responses allow tumor cells to become more flexible in fluid environments, aiding in their survival and transit through the bloodstream. Similarly, research by Sun et al. indicates that low shear stress (2 dyne/cm^2) can reduce liver cancer stem cell (LCSC) stiffness via the phosphorylation of FAK and ERK1/2 pathways, thereby enhancing LCSC migratory capacity [105]. Low shear stress also affects integrin β1 distribution, induces cytoskeletal remodeling, and activates the

ROCK/HDAC6 pathway to promote cell migration and FA turnover, further facilitating tumor migration [106]. Additionally, research by Yan et al. shows that shear stress upregulates autophagy markers like LC3B aggregation and autophagosome formation in hepatocellular carcinoma. This effect is inhibited by integrin and actin inhibitors, indicating that fluid shear stress (FSS) promotes HepG2 cell migration and invasion via integrin and cytoskeleton-induced autophagy [107].

Tumor tissues are often accompanied by ECM remodeling and alterations in fluid channels, which impact fluid mobility. Chary et al. found that the diffusion coefficient of albumin in normal tissues is slightly lower than in tumor tissues [108]. As discussed, the ECM in tumors is densely packed with proteins and molecules, reducing hydraulic conductivity [109], which significantly elevates interstitial pressure [110]. Additionally, the collagen fiber network within the tumor ECM correlates inversely with hydraulic conductivity in fibrous media [111]. As a result, tumors with high collagen content exhibit higher interstitial fluid pressures than those with lower collagen content. Collagenase treatment has been shown to enhance macromolecule diffusion rates within tumor stroma significantly [112]. The negatively charged GAGs in the ECM retain water, increasing fluid flow resistance. Studies demonstrate a significant negative correlation between GAG concentration in the interstitium and hydraulic conductivity [113]. Correspondingly, Mok et al. found that degrading sulfated GAGs in the ECM using MMP-1 and MMP-8 markedly increases hydraulic conductivity [114].

Solid stress: regulating cell proliferation and tumor morphology

Solid stress in tumors can be classified into growth-induced stress and externally applied solid stress from surrounding tissues [5, 115]. Growth-induced stress accumulates within the tumor as it expands, resulting in the stretching of the TME and storage of strain energy. This stress persists within the tumor tissue and does not dissipate even if the tumor mass becomes isolated [9]. Helmlinger et al. used an agarose matrix to simulate the solid stress exerted by surrounding tissues and found that solid stress inhibits tumor growth in vitro [116]. Notably, high solid stress areas show enhanced suppression of cell proliferation and induction of apoptosis [117]. Under solid stress, overexpression of crmA (an inhibitor of the death receptor apoptotic pathway) does not affect tumor spheroid death rates, while overexpression of Bcl-2 (an inhibitor of the mitochondrial apoptotic pathway) significantly reduces cell death under compression, indicating that the tumor-suppressive effect of solid stress is mediated through the induction of mitochondrial pathway apoptosis [117]. This apoptosis-inducing phenomenon of mechanical stress is generally reversible; once the applied solid stress is removed, tumor growth typically resumes [118]. Solid stress is not uniformly distributed across the tumor, leading to growth inhibition in high-stress regions, which compels the tumor to grow towards areas with lower stress [119]. Unlike non-tumor cells, invasive tumor cells exhibit higher sensitivity to mechanical stimuli. Consequently, stressed cell layers form "leader cells" at the forefront of invasive breast cancer cells, extending pseudopodia and exhibiting enhanced invasion capabilities [120]. Additionally, Stylianopoulos et al. reported that solid stress levels in tumor tissues can reach 1.3 to 13.0 kPa, a pressure sufficient to compress tumor vasculature, resulting in poor perfusion and hypoxia [9].

The role of matrix stiffness and nuclear morphology in tumor invasion

Malignant tumors often exhibit the ability to spread and metastasize to distant sites, a process during which cellular organelles undergo dynamic structural and morphological changes. The nucleus is the hardest organelle in the cell, and its structural integrity is crucial for maintaining genomic function [121]. In breast cancer cells, it has been reported that a decrease in ECM stiffness reduces the expression of PIP4K2B protein, leading to the downregulation of UHRF1, a protein involved in DNA methylation and chromatin remodeling. The loss of UHRF1 results in decreased chromatin condensation, reduced nuclear membrane tension, cytoplasmic retention of YAP, and a decrease in cell migration ability [122]. This suggests that increased matrix stiffness influences the nuclear localization of YAP via chromatin remodeling, thereby promoting tumor invasion. The nucleus not only serves as the storage site for genetic information but also plays a crucial role in the structural and functional aspects of the cell. Research has shown that the nucleus is the largest compartment in the cell, with a stiffness approximately ten times that of the cytoplasm [123]. Recent studies indicate that nuclear compliance is a key determinant of cancer cell metastasis ability. Higher nuclear compliance allows the nucleus to pass through pores, facilitating the migration of cancer cells [124]. Nuclear compliance is closely linked to the cytoskeleton, which is connected to the nuclear membrane through the SUN domain of the LINC complex and the KASH domain proteins on the nuclear membrane, allowing cytoskeletal forces to directly act on the nucleus [125, 126]. The strength of the connection between the cytoskeleton and the nucleus is regulated by ECM stiffness. For example, Li et al. demonstrated that cells cultured on polar matrices exhibit stronger actin-mediated nuclear coupling than those on isotropic matrices [127]. Similarly, fibroblasts on rigid matrices exhibit stronger actin-mediated nuclear coupling compared to those on soft

matrices [128]. Inside the nucleus, DNA molecules are wrapped around histones to form chromatin, which condenses through interactions between histone tails, counteracting the outward entropy pressure within the DNA molecule [129]. Mazumder et al. observed nuclear membrane and lamina rupture after enzymatic disruption of this interaction, indicating that chromatin structure plays a critical role in maintaining nuclear mechanical stability [129]. Condensed chromatin interacts with the nuclear lamina and inner nuclear membrane through adaptor proteins and responds to mechanical signals from the ECM via coupling between the nuclear membrane and cytoskeleton [130, 131]. Thus, actin and myosin contraction not only alters cell shape but also leads to nuclear deformation, thereby regulating gene expression. Consequently, cellular morphology and nuclear shape can respond to changes in matrix stiffness, influencing transcription levels and playing a pivotal role in tumor invasion [132, 133].

Tumor cell plasticity and ECM remodeling in tumor invasion and migration

The plasticity of tumor cells enables them to switch between different modes of migration, thereby allowing them to adapt to the complex mechanical environment [134]. Crosslinking of collagen in the ECM leads to an increase in ECM stiffness, which not only promotes tumorigenesis but also enhances the invasiveness of malignant epithelial cells [26]. Additionally, invasive tumor cells exhibit a softer characteristic compared to normal cells [135]. Cancer cells undergoing epithelial-to-mesenchymal transition (EMT) lose their epithelial adhesive properties and undergo rearrangement of the actin cytoskeleton, which alters the tension between the cells and the ECM [85]. Similarly, studies by Osborne et al. have shown that during EMT, cells exhibit a decrease in stiffness and become softer [136]. These changes in plasticity help cancer cells migrate and invade more effectively through the ECM network [136]. During EMT, cancer cells not only become softer but also increase the secretion of matrix metalloproteinases (MMPs), which facilitates the creation of migration pathways for tumor cells [137]. Invadopodia, actin-based protrusions of the cell membrane, possess enzymatic activity to degrade ECM [138]. In a more rigid ECM environment, tumor cells promote their penetration of the ECM by increasing the number of invadopodia, thus facilitating invasion and migration [139]. Therefore, in the process of tumor migration, on the one hand, tumor cells become softer due to plasticity changes, while on the other hand, the increased number of invadopodia promotes ECM degradation, enhancing their ability to invade and migrate. Moreover, research by Peng et al. revealed that in ZEB1-activated mesenchymal lung cancer cells, the expression of collagen crosslinking gene LOXL2 was significantly increased, further enhancing ECM stiffness and providing pathways for tumor cell migration [140]. High expression of LOXL2 has also been found to be associated with higher EMT scores in cervical cancer, and knockdown of LOXL2 expression was shown to reverse the EMT process in cervical cancer cells [141]. These studies indicate that LOXL2 not only promotes the invasion of cancer cells by increasing ECM stiffness but also further drives the EMT process through a positive feedback loop, thereby promoting tumor invasion. Additionally, tumor cells and CAFs connect to the ECM via integrin receptors and apply force to the ECM through actin cytoskeleton and myosin-mediated contraction, which leads to ECM deformation and strain stiffening, ultimately increasing ECM rigidity [142].

Impact of mechanical environment on tumor cell behavior and metabolism

Mechanotransduction mechanisms

As shown in Fig. 3, cells can sense mechanical signals in the ECM and convert them into biochemical signals, thereby regulating cellular energy metabolism, invasion, and migration capabilities [143]. This process is primarily mediated through the integrin signaling pathway, the Rho signaling pathway, and the Hippo signaling pathway. This section will discuss the main signal transduction routes of these three pathways and explain how they promote the proliferation and invasion of tumor cells [144].

Integrins: sensors of mechanical signals and activators of downstream pathways

Integrins are heterodimeric receptor proteins composed of α and β subunits, which associate non-covalently to form the integrin protein complex [145]. The α subunit contains a β-propeller domain, and the β subunit has a βA domain that together form the binding site for ligands [146]. When mechanical changes occur in the environment, the fibers in the ECM exert tension on integrins bound to them, pulling and activating the integrin receptors [147]. Upon activation, integrins recruit and activate downstream factors, including FA kinase (FAK) [148]. Activated FAK subsequently triggers RhoA and its downstream effector, ROCK, leading to actin cytoskeleton rearrangement, formation of cellular protrusions, and tumorigenesis [149]. As ECM stiffness increases, tumors tend to adopt a more invasive phenotype, a process marked by phosphorylation and activation of FAK at the Y397 site. Activated FAK recruits and clusters Src [150]. The activated FAK-Src complex facilitates the binding of p130CAS to Src, keeping Src in an active state [151]. Recent studies suggest that some integrins can directly activate Src independently of FAK; for instance, the cytoplasmic tail of integrin αvβ3 can bind directly to the SH3

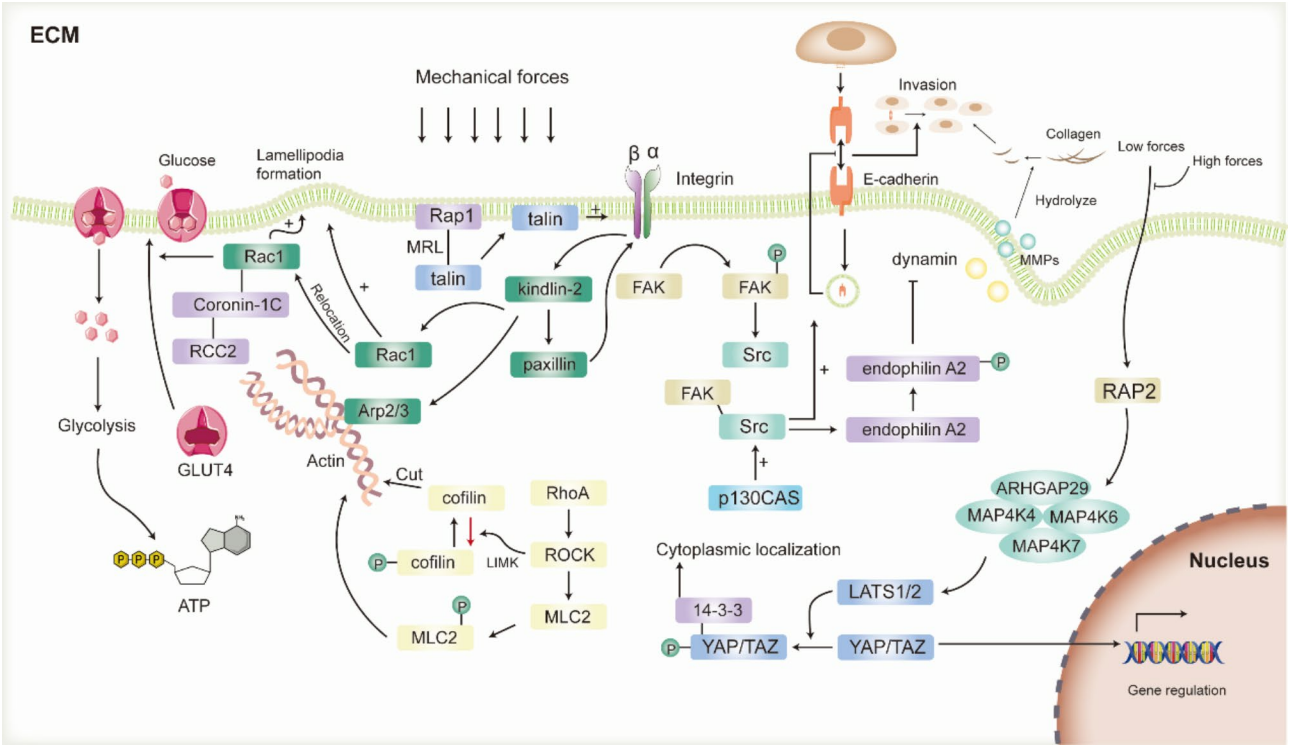

Fig. 3 Mechanotransduction in tumor cells: sensing and transducing mechanical signals from the ECM into intracellular biochemical signals. Mechanical signals are primarily transduced into the cell via integrins, the Rho signaling pathway, and the Hippo signaling pathway. Integrin activation promotes invasion and cytoskeletal remodeling through the FAK-Src pathway and actin signaling. In the Rho pathway, RhoA maintains actin structure, while Rac1 facilitates lamellipodia formation and regulates glucose uptake. The Hippo pathway, through phosphorylation and dephosphorylation of YAP/TAZ, translocates these factors to the nucleus, where they regulate actin-associated and invasion-related gene expression

domain of Src, activating it [152], and integrin α4β1 can activate Src independently of FAK through the involvement of the α4 cytoplasmic domain [153]. Although FAK-deficient tumor cells still migrate in response to integrin stimulation, they lose invasive capacity, underscoring FAK's critical role in promoting tumor invasiveness [154]. The activation of the FAK-Src complex promotes E-cadherin endocytosis, thereby enhancing tumor cell migration and EMT [155]. Furthermore, FAK-Src can inhibit endocytosis by phosphorylating endophilin A2 at the Tyr315 site via Src, thereby disrupting endophilin's interaction with dynamin. This inhibition increases the expression of MMPs on the cell surface, facilitating tumor invasion [156]. In addition to FAK-mediated outside-in signaling, integrins can also respond to intracellular signals. Intracellular activation of integrins requires binding with talin, whose localization and activation are mediated by MRL proteins. MRL proteins serve as scaffolds that link the membrane-targeting sequence of Rap1 to talin, precisely positioning talin on the plasma membrane to facilitate integrin activation [157]. Moreover, the β subunit of integrins can bind to kindlin-2, which further associates with paxillin and integrins to enhance cell adhesion. Kindlin-2 also binds directly to Rac1 and the Arp2/3 complex, supporting membrane protrusion and expansion [158].

Rho signaling pathway: core axis in regulating cell shape and migration

The Rho family of GTPases plays a significant role in various cancers and is considered a potential target for malignancies [159]. Rho signaling regulates cell shape, adhesion, migration, and invasion through the control of actin cytoskeletal contraction [160]. Rho family GTPases operate by cycling between GTP-bound (active) and GDP-bound (inactive) forms, making them essential regulators of actin dynamics and cytoskeletal reorganization [161]. There are around 20 known Rho GTPase family members, with RhoA, Cdc42, and Rac1 being the most studied [162]. The primary downstream target of RhoA is ROCK, a serine-threonine kinase that phosphorylates and activates myosin light chain 2 (MLC2) and LIM kinase (LIMK) [163]. Activated MLC2 enhances actomyosin contractility, facilitating cell movement and mechanical force generation [164]. LIMK, a direct regulator of cofilin, phosphorylates cofilin at Ser3, rendering it unable to sever and depolymerize actin filaments, thus stabilizing actin fibers [165]. Rac1 is involved in the formation of lamellipodia and membrane protrusions in cancer

cells, promoting cell migration [158]. During cell migration, coronin-1 C interacts with RCC2 (a Rac1 inhibitor) and Rac1, guiding Rac1 to the cell's leading edge, where it inhibits off-axis protrusions and enhances Rac activation at the leading edge. This activates the actin cytoskeleton, generating protrusive force for forward movement [166]. Additionally, Rac1 plays a role in metabolic regulation in response to mechanical stress; stretch stimulation activates Rac1, which promotes GLUT4 translocation to the membrane, increasing glucose uptake [167]. Cdc42 is involved in cytoskeletal reorganization, inducing filopodia formation in epithelial cells [168]. Studies indicate that DOCK10, a guanine nucleotide exchange factor (GEF) for Cdc42, can promote the switch from mesenchymal to amoeboid migration through Cdc42 activation. This suggests that the Cdc42 signaling pathway enables tumor cells to adapt their migration mode to different environments, enhancing their adaptability and migratory efficiency [169].

Hippo pathway: central link between mechanical signals and gene expression

The Hippo signaling pathway regulates various physiological processes, including tumor initiation and metastasis [170]. This pathway integrates numerous upstream signals, such as cell-cell junctions, cytoskeletal dynamics [171], and ECM mechanical properties, including matrix stiffness and shear stress [172]. Additional regulatory factors of the Hippo pathway include mechanical signals, ligands for G-protein-coupled receptors (GPCRs), cell polarity, energy status, and hormonal signals [173]. The kinase cascade within the Hippo pathway ultimately converges on nuclear effectors Yki/YAP/TAZ, which modulate gene expression programs [174]. YAP/TAZ act as mediators of mechanical signals from ECM stiffness and cell shape, transmitting these cues to the nucleus. This regulation depends on Rho activity and the actin-myosin cytoskeleton [175]. Further studies indicate that the Ras-related GTPase RAP2 plays a crucial role in this process [176]. Under low ECM stiffness, RAP2 becomes activated and interacts with MAP4K4, MAP4K6, MAP4K7, and ARHGAP29, leading to activation of LATS1/2 kinases. LATS1/2 then phosphorylate the transcriptional co-activators YAP/TAZ [176]. Phosphorylated YAP/TAZ bind to 14-3-3 proteins, which sequesters them in the cytoplasm, preventing nuclear translocation and transcriptional co-activation [177]. Conversely, in a highly rigid ECM, the H2 domain of the cytoskeletal protein vinexin α interacts with the D1b subdomain of FA protein vinculin, promoting the formation of a talin-vinculin-vinexin α ternary complex. This complex facilitates YAP/TAZ nuclear localization [178]. Once in the nucleus, unphosphorylated YAP/TAZ regulate gene expression by enhancing the promoter activity of genes associated with cell migration and invasion [179]. Furthermore, nuclear YAP increases the expression of myosin regulatory light chain 2 and promotes ATP production, enhancing contractile actin structures [180]. ARHGAP29 has also been identified as a transcriptional target of YAP, which, by upregulating ARHGAP29, inhibits the RhoA-LIMK-cofilin pathway. This inhibition destabilizes F-actin, leading to cytoskeletal reorganization and promoting tumor cell migration [181].

Mechanical environment alterations and tumor metabolic reprogramming

As discussed, the ECM in tumors exhibits abnormal mechanical properties and mechanical stress compared to normal tissues. In cancers such as breast cancer, ECM stiffness within tumor tissues is significantly higher than in normal tissues. To meet the energy demands of migration, cancer cells respond to mechanical cues from the matrix, actively adjusting their cellular energy metabolism to support cytoskeletal dynamics and force generation.

The mechanical features of the cellular microenvironment regulate cell growth, apoptosis, and migration by modulating cytoskeletal remodeling and actomyosin contractility, processes that require substantial energy [182]. This enables cells to sense mechanical signals from the matrix and adjust their energy homeostasis accordingly [183], with increased energy supply supporting cytoskeletal organization and matrix remodeling [184]. The serine/threonine kinase AKT, a downstream factor of phosphoinositide 3-kinase (PI3K), has been found to be persistently activated in malignant tumors, stimulating glucose uptake, enhancing glycolysis rates, but not affecting oxidative phosphorylation rates [185]. Besides the PI3K-AKT pathway, PI3K can also be activated by growth factors, directly activating Rac, which modifies actin structures and releases aldolase A, thereby promoting glycolysis [186]. PI3K and Rac accumulate at the leading edge of migrating cells; inhibiting PI3K or Rac induces apoptosis and morphological changes in leading cells, indicating the critical role of PI3K- and Rac-mediated glycolysis in tumor cell migration [187]. Rac activity is also regulated by integrin β1, although this regulation is slower than that mediated by PI3K, inhibiting integrin β1 can still suppress Rac signaling activation [187]. Given the role of integrins in mechanical sensing and mechanotransduction [188], this integrin β1-dependent glycolysis regulation allows cells to respond more rapidly to environmental mechanical cues and adjust their energy supply accordingly.

Increased matrix stiffness within the TME also influences tumor metabolism, as higher collagen density enhances ECM rigidity. With collagen accumulation, triple-negative breast cancer cells MDA-MB231 and

MDA-MB468 exhibit increased glycolysis, which can be inhibited by ROCK inhibitors [189], suggesting that matrix stiffness promotes the Warburg effect and modulates cell invasiveness. In softer matrices, stress fibers disassemble, releasing the E3 ubiquitin ligase TRIM21, which targets phosphofructokinase for degradation to reduce glycolytic activity. In non-small cell lung cancer, TRIM21 downregulation or sequestration in stress fibers insensitive to matrix stiffness maintains high PFK expression and a high glycolytic rate [182]. ECM rigidity modulates energy metabolism during tumor cell migration; in dense matrices, migration is hindered, leading to increased energy consumption and an elevated ATP/ADP ratio, while in aligned collagen matrices, this ratio decreases [190]. Tumor cell invasion often occurs in small groups, known as collective invasion. During collective invasion, the energy level (ATP/ADP ratio) of leader cells must exceed a specific threshold to enable successful invasion [191]. As energy depletes in leader cells, the ATP/ADP ratio drops, prompting a switch between leader and follower cells. This switching frequency increases with collagen matrix density, allowing energy reallocation to facilitate migration in dense matrices [191]. Changes in matrix rigidity alter cell migration modes; in confined spaces, cells tend to utilize water-driven mechanisms for migration, which require higher energy expenditure than actin-driven migration [192].

Stiffness testing has shown that metastatic cancer cells are more than 70% softer than benign cells in body cavities [193]. Softer cells deform more easily, and lower matrix stiffness results in cell rounding [194]. In contrast, a stiffer matrix reinforces cellular protrusions, enhancing localized adhesion formation, facilitating cell expansion, generating higher traction forces, and extending cell movement [195]. Under these conditions, cancer cells plastically "pry open" pathways by forming invasive pseudopods, and as matrix density increases, cancer cells further rely on proteases to degrade the matrix for path clearance [196]. As cells migrate, nuclear compression is limited, and passage through gaps created by pseudopods depends on the Rho-mediated actomyosin contractile force [196]. With increased matrix density, actin fiber density also increases by an order of magnitude, making the cytoskeleton tougher and more resistant to mechanical stress, though at the cost of greater energy consumption [197].

Mechanical environment and immune response: inflammation and macrophage polarization

Inflammation is recognized as a risk factor for various cancers; chronic inflammatory responses can lead to tissue damage, cellular mutations, and gene alterations, all of which promote tumor formation [198]. As illustrated in Fig. 4, tumor tissues often exhibit high levels of immune cell infiltration, with cancer progression closely linked to increased inflammation [199]. Studies suggest that increased ECM stiffness is linked to tumor invasiveness and macrophage infiltration, with highly invasive breast cancer cells exhibiting greater stiffness and more infiltrating macrophages at the leading edge of the matrix [200]. Elevated TGF-β expression has also been observed at the tumor invasion front. This TGF-β, produced by tumor-infiltrating immune cells, activates LOX and promotes collagen synthesis and cross-linking [201].

M1-polarized macrophages secrete pro-inflammatory factors and induce inflammation, while ECM stiffness can influence macrophage polarization through epigenetic regulation. For instance, matrix stiffness affects miRNA expression within macrophages [202]. Shear stress has been shown to increase miR-214 expression in fibrous layers; inhibiting miR-214 expression raises TGF-β1 levels and collagen production, suggesting that miR-214 may function as a mechanosensitive miRNA in cellular responses to mechanical signals [203]. In macrophages, miR-214 promotes M1 polarization and enhances the secretion of pro-inflammatory factors [204]. Additionally, DNA methyltransferase 1 (DNMT1), which regulates DNA methylation, is responsive to shear stress [205]. DNMT1 is a major maintenance DNA methyltransferase that modulates the methylation of promoters for PPAR-γ and KLF4, thereby suppressing their expression and promoting M1 polarization, resulting in the overproduction of inflammatory factors [206]. As the predominant myeloid cell type within the tumor microenvironment, tumor-associated macrophages (TAMs) undergo differentiation into the M2 phenotype, which is a critical contributor to tumor resistance [207]. Cai et al. demonstrated that macrophages can sense mechanical signals through Piezo1, mediating calcium ion influx and promoting macrophage polarization toward the M2 phenotype [208]. However, this result requires further validation within the context of the tumor microenvironment. Additionally, interstitial fluid flow has been reported to sense mechanical signals via the integrin/Src pathway, which leads to the phosphorylation of FAK and Akt, promoting macrophage polarization toward the M2 phenotype, as evidenced by increased expression of M2 macrophage markers such as ArgI, CD206, and TGFβ [209]. It is known that the phosphorylation of FAK and Akt can enhance macrophage motility and generate microtracks in the ECM, facilitating cancer cell invasion through these tracks [210, 211]. Macrophages treated with interstitial fluid flow exhibit migration rates similar to those of M2 macrophages [209]. This suggests that interstitial fluid pressure can promote macrophage M2 polarization and enhance their migration speed, thereby supporting tumor proliferation.

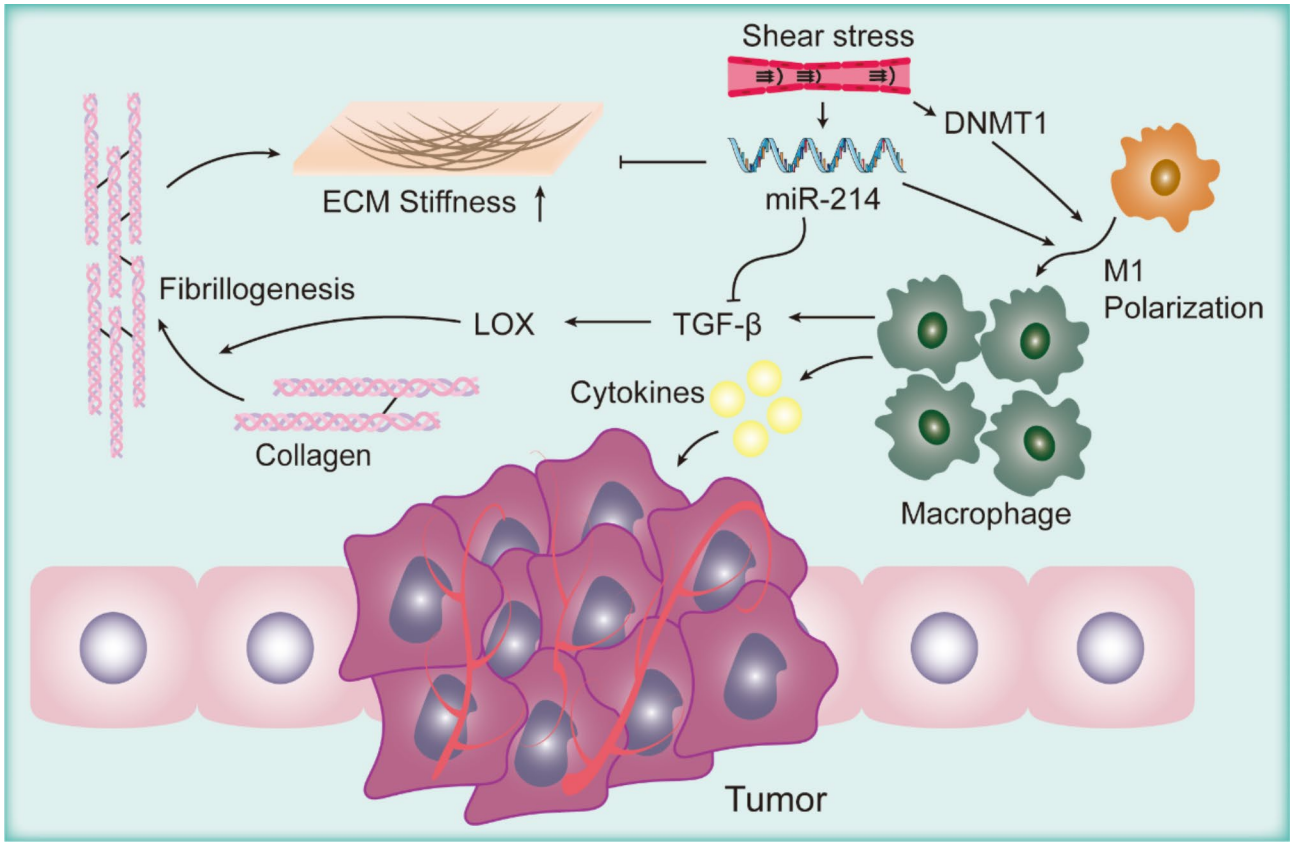

Fig. 4 Physical Properties and the Tumor Immune Microenvironment. Increased macrophage infiltration occurs near tumor tissues, where macrophage-secreted TGF-β promotes collagen production, thereby enhancing matrix stiffness. Within this microenvironment, miR-214, in response to shear stress, facilitates macrophage M1 polarization. Shear stress also activates DNMT1, which further promotes M1 polarization. M1-polarized macrophages then secrete pro-inflammatory cytokines, contributing to further tumor progression and deterioration

In addition to macrophages, lymphocytes also play a significant role in tumor suppression. Within the tumor microenvironment, regulatory T cells suppress anti-tumor immune responses by disrupting cell-cell contact, surface molecule expression, and cytokine secretion, facilitating tumor immune evasion and progression. Studies have shown that these mechanisms are regulated by the presence of hyaluronic acid in the ECM [212]. Research indicates that T cells are sensitive to mechanical signals generated in the TME, modulating their activation, adhesion, migration, and immune responses through these signals [213]. This sensitivity is attributed to the mechanical signal sensor YAP in T cells, which can sense mechanical signals in the microenvironment and inhibit effector T cell proliferation in an ECM stiffness-dependent manner by restricting the translocation of NAFT1 to the cell nucleus [214]. In addition to T cells, B cells can also recognize antigens via their B cell receptor (BCR), and studies have found that the cytoplasmic IgG tail of the BCR can sense mechanical forces, promoting the binding to phosphatidylinositol (4,5) bisphosphate phospholipids and thereby activating the BCR [215]. Natural killer (NK) cells target tumor cells directly by secreting extracellular vesicles (EVs) and exert anti-tumor activity [216]. Mechanical stimuli such as shear forces and turbulence have been reported to increase the number of EVs produced by NK cells, which effectively kill melanoma and liver cancer cells in vitro and suppress melanoma growth in vivo [217].

Therapeutic strategies targeting TME mechanical properties

As discussed, the primary mechanical forces within the TME include matrix stiffness, fluid pressure, and solid stress. Table 2 summarizes current therapeutic drugs and their effects on these three main mechanical forces.

The primary strategy to reduce ECM stiffness focuses on decreasing fiber cross-linking and reducing matrix rigidity. LOX has been shown to promote collagen accumulation and fibrosis, and β-aminopropionitrile (BAPN) acts as a LOX inhibitor to reverse collagen accumulation and fibrosis [218]. Studies indicate that BAPN and magnolol, either alone or in combination, effectively inhibit LOX activity, thus suppressing the migration and invasion of MDA-MB-231 cells [219]. However, due to the significant side effects of BAPN, it is no longer used clinically

Table 2 Therapeutic strategies targeting mechanical forces in the TME

Therapeutic Agent	Target	Experimental Model	Key Effects	Reference
β-APN	LOX	MDA-MB-231 cell	Inhibit LOX enzyme activity and protein expression, reduce the phosphorylation of paxillin at Tyr-31 and Tyr-118 mediated by the FAK/Src complex, and suppress collagen cross-linking.	[219]
magnolol	LOX	MDA-MB-231 cell		
PAT-1251	LOX2	MDA-MB-231 cell	Inhibit CAF activation and reduce new blood vessel formation.	[223]
Cilengitide	Integrin	NSCLC A549 cell	Inhibit TGF-β1-induced expression of cancer cell migration markers, activation of Smad2/3, and invasion capability of NSCLC A549 cells.	[227]
Saridegib	Smoothened	KPC mice	Deplete tumor stroma, increase vascular density, and enhance tumor perfusion	[235]
PEGPH20	Hyaluronan	KPC mice	Degradation of HA in PDA tumor endothelial cells induced the formation of fenestrations and intercellular gaps, increasing macromolecular permeability.	[236]
Losartan	Angiotensin-II-receptor-1	E0771 tumor model in wild-type C57BL/6 mice	Reduce the expression of profibrotic signals TGF-β1, CCN2, and ET-1, and decrease the production of stromal collagen and hyaluronan.	[237]
Bevacizumab	Vascular endothelial growth factor	Patients with advanced rectal cancer	Reduce the interstitial fluid pressure and blood flow in the tumor.	[191]
Bediranib	VEGF receptor tyrosine kinase	glioblastoma patients	Inhibit vascular growth factors to control abnormal tumor vascular proliferation and improve tumor blood flow and oxygenation.	[243]

[220]. This has led to the development of a series of LOX inhibitors based on BAPN derivatives, including PXS-5120 A [221], PXS-5153 A [222], and PAT-1251 [223]. While PXS-5120 A and PXS-5153 A are currently used primarily to reduce collagen deposition in pulmonary and hepatic fibrosis, their efficacy in cancer treatment is still under investigation [221, 222]. Selective LOXL2 inhibitors have shown efficacy in suppressing breast cancer growth, reducing angiogenesis, and decreasing liver and lung metastasis [223]. The anti-LOXL2 monoclonal antibody AB0023 effectively reduces collagen density within the pancreatic cancer microenvironment in murine models [224]. Although the humanized version of this antibody, Simtuzumab, extended survival in a mouse model of bone-metastatic MDA-MB-231 cells, it failed to demonstrate improvements in pancreatic cancer in clinical trials [225]. In addition to directly inhibiting LOX enzymes, it is also possible to inhibit the transmission of stiffness-induced mechanical signals, with integrins serving as primary receptors for mechanical cues. The integrin antagonist cilengitide has shown effective anti-glioma activity [226] and enhances the effect of gefitinib on TGF-β1-induced mesenchymal marker expression, Smad2/3 phosphorylation, and the invasion of NSCLC A549 cells [227]. Furthermore, statins such as simvastatin have been reported to activate matrix metalloproteinase 2 and membrane-type 1 matrix metalloproteinase, reduce collagen expression, promote ECM degradation, and significantly decrease uterine leiomyoma volume in xenograft mouse models [228]. Similar studies have also shown that simvastatin inhibits the expression of key ECM proteins, including collagen I, collagen III, and fibronectin, in smooth muscle tumor cells, thereby suppressing tumor proliferation [229]. Additionally, osteopontin (OPN) has been reported to upregulate the expression of integrin receptors in tumor cells, promoting the binding of tumor cells to the ECM and enhancing their migration and invasion. Simvastatin, on the other hand, inhibits OPN and integrin expression, thus reducing the ECM invasion ability of cancer cells [230]. These findings suggest that simvastatin can degrade ECM protein content and reduce the interaction between integrin receptors and the ECM, thereby exerting therapeutic effects on tumors. Tumor-associated fibroblasts secrete the inflammatory cytokine IL-6, which is transmitted in an endocrine manner to the liver. Upon binding to IL-6R on hepatocytes, IL-6 activates the STAT3 signaling pathway, leading to increased ECM deposition in hepatocytes and creating a pre-metastatic niche for pancreatic ductal adenocarcinoma (PDAC) liver metastasis [231]. In the orthotopic model of SCID/bg mice, the use of the anti-IL-6 receptor antibody tocilizumab to block the IL-6 pathway has been shown to reduce tumor weight and metastasis in PDAC [232]. Resistance to tyrosine kinase inhibitors (TKIs) and

anti-EGFR therapies presents a significant challenge in the treatment of triple-negative breast cancer. Research has demonstrated that overexpression of the scaffolding protein NHERF1 enhances tumor cell sensitivity to gefitinib (an EGFR-specific TKI) and inhibits ECM protein degradation mediated by EGFR-driven tumor cells through invadopodia [233]. These results suggest that TKIs may play a role in the suppression of ECM protein degradation, though the specific mechanisms still require further investigation.

Increased solid stress compresses surrounding tissues, exacerbating fluid pressure and impeding targeted drug delivery [234]. Strategies to alleviate solid stress aim to reopen compressed blood vessels, improving perfusion to enhance drug delivery and efficacy [10]. Saridegib, a Hedgehog pathway inhibitor, reduces solid stress by depleting tumor stroma, thereby increasing tumor perfusion [5]. Olive et al. demonstrated that saridegib increases vascular density, gemcitabine concentration, and improves disease status [235]. Similarly, PEGylated recombinant human hyaluronidase PH20 (PEGPH20) degrades hyaluronic acid in the ECM, and its combination with gemcitabine significantly enhances molecular permeability and prolongs survival [236]. Losartan, an angiotensin II receptor 1 antagonist, reduces the expression of pro-fibrotic TGF-β1, leading to decreased collagen and hyaluronic acid production. This alleviates solid stress and increases vascular perfusion, improving drug and oxygen delivery in tumors [237]. A clinical trial combining losartan with FOLFIRINOX showed effective downstaging in patients with locally advanced pancreatic ductal adenocarcinoma [238].

Tumor vasculature typically displays abnormal leakiness and distortion, leading to elevated interstitial fluid pressure and poor perfusion [239]. Vascular normalization strategies aim to promote angiogenesis to transform tumor vasculature toward a more normal phenotype, reducing interstitial fluid pressure and enhancing perfusion efficiency [240]. Clinical studies suggest that anti-angiogenic drugs can normalize tumor blood vessels [241]. A clinical trial of bevacizumab combined with chemoradiotherapy in patients with locally advanced rectal cancer demonstrated effectiveness, reducing interstitial fluid pressure and plasma VEGF levels [242]. Additionally, glioblastoma patients treated with cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, showed improved perfusion, which correlated with better overall survival in nGBM patients [243].

Conclusion and future perspectives

This review highlights the primary components of the ECM, focusing on the various mechanical stresses present within the ECM and the mechanisms by which cancer cells translate these mechanical signals into biochemical cues that drive cell proliferation and invasion. The ECM, composed of collagen, proteoglycans, laminins, fibronectin, biochemical factors, and water, possesses inherent mechanical properties that not only provide structural support but also influence tumor cell proliferation and invasion. Through pathways involving integrins, Rho signaling, and Hippo signaling, tumors sense mechanical cues within the ECM and harness these signals to promote their own growth, metastasis, and invasion. Additionally, mechanical signals can reprogram tumor metabolism, favoring glycolysis to rapidly obtain energy and support cellular migration. Increased matrix stiffness also promotes macrophage M1 polarization and macrophage infiltration, sustaining an inflammatory microenvironment within the tumor.

Targeting the mechanical properties of the TME has led to significant progress, with therapies aimed at reducing matrix stiffness, alleviating solid stress, and restoring vascular function. However, as the TME is a dynamic process, monitoring and adjusting therapeutic interventions in real time in response to the TME's changing mechanical signals may further improve treatment outcomes. Furthermore, due to the interactions between different mechanical signals, accurately measuring the distinct mechanical properties within the TME and determining the specific contributions of each to tumor progression will be key areas for future research.

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