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Developmental Cell 25 YEARS

Review

Tissue mechanopathology of cancer

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https://doi.org/10.1016/j.devcel.2026.06.006

SUMMARY

Cancers are complex cellular communities comprising tumor cells and their microenvironment. Recent advances in cancer biology have emerged from efforts to analyze tumors as tissues, in which emergent properties arise as tumor cells interact with one another, their microenvironment, and the host tissue. In this review, we consider interactions involving mechanical forces and mechanosignaling pathways that detect changes in physical inputs to regulate cellular behavior. This rapidly developing field provides perspectives for understanding cancer biology and tumor interactions with the host ecosystem.

INTRODUCTION

Our appreciation of the pathobiological diversity of cancer has expanded substantially over the past half-century. The molecular genetics revolution revealed how cancer cell behavior is altered by genetic mutations and epigenetic modifications. This viewpoint was enriched by a growing appreciation of the complex interplay between tumor cells and their microenvironment,[1] including stromal cells, the extracellular matrix (ECM), tumor vascular and lymphatic systems, and the immune system.[2,3] This interplay led to the concept that cancer can be interpreted as aberrant development and wound healing,[1] where physiological processes are hijacked and repurposed to fuel tumor growth and to sculpt a cancer-permissive tumor microenvironment (TME).[2,3] In this context, cancers are understood as tissues comprising many different cell and matrix components that each—individually and collectively—contribute to tumor development and outcome. In this review article, we explore another perspective, focusing on the influence of tissue mechanics on cancer.

Mechanical factors regulate many aspects of cell and tissue behavior in development.[4,5] Cells sense externally applied forces and the mechanical properties of their immediate environment to respond accordingly.[6] Isolated cancer cells display altered mechanical properties *in vitro* that have been linked to disease progression and are considered important physical hallmarks of cancer.[7,8] In this review, we ask how the processes that control tissue mechanics and mechanotransduction may similarly be hijacked in cancer. Co-option of mechanobiological processes is especially pertinent for carcinomas, which derive from epithelial tissues whose constituent cells interact through cell-cell adhesions and other junctions.[4] We begin by outlining recent advances in characterizing mechanisms that control epithelial mechanics and mediate mechanotransduction. We then consider how these processes are altered during tumor progression and invasion, modified by changes in the stroma or oncogenes, and potentially exploited therapeutically.

EPITHELIAL MECHANICS AND MECHANOTRANSDUCTION

A variety of physical changes have been described as hallmarks of cancer.[8] These hallmarks include (1) elevated compressive and tensile solid stresses; (2) altered material properties; (3) elevated interstitial fluid pressure; and (4) altered physical microarchitecture. These abnormalities reflect dysregulation of physical features that operate in epithelial tissues during development and post-embryonic homeostasis.[4] Accordingly, understanding how aberrant mechanical processes promote cancer will require insights into the regulators of the epithelial mechanical landscape and the ways in which cells interpret their mechanical environment.

The mechanical landscape of epithelia

The mechanical inputs experienced by epithelial cells during development and homeostasis can be broadly divided into (1) the forces (tension, compression, and shear) that are applied to the cells and (2) the material properties of their environment (e.g., stiffness and viscoelasticity).[4,6,9] In this section, we will discuss cell biological mechanisms that determine these parameters. Interestingly, these mechanisms often affect both mechanical force and material properties, and we therefore consider them together. We subdivide these in terms of epithelial cell-*intrinsic* processes and epithelial cell-*extrinsic* processes associated with the stroma. This distinction is necessarily artificial, as these processes also interact.

Cell-intrinsic determinants

Epithelial cell-intrinsic processes primarily relate to the cytoskeleton and cell adhesions (Figure 1A), especially the actomyosin and intermediate filament (IF) systems and their associated adhesions. These cytoskeletal and adhesion systems are best considered as integrated networks for three reasons. First, adhesions, especially cell-cell adherens junctions (AJs) and desmosomes, integrate the cytoskeletons of constituent epithelial cells into supracellular networks to influence tissue mechanics.[10–12] Second, actomyosin and IFs engage with specific adhesion

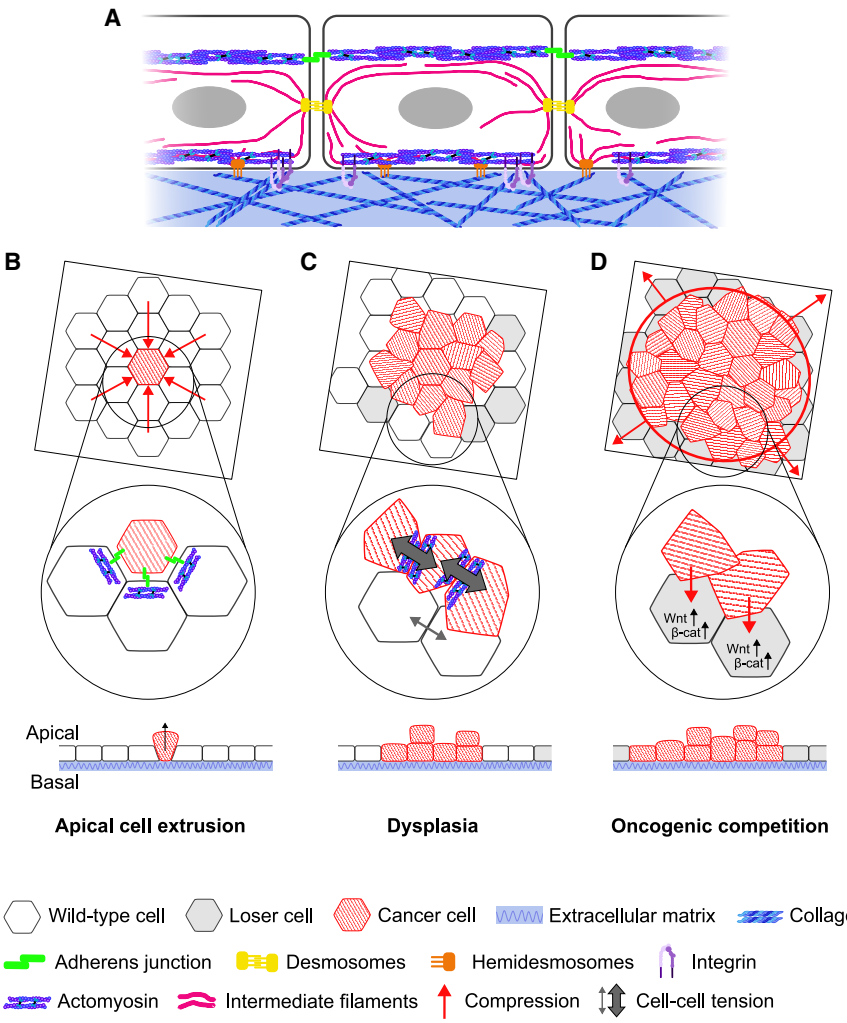

Figure 1. Determinants and evolution of tissue mechanics during cancer progression

(A) In healthy epithelia, tissue organization is maintained through coordinated cell-cell and cell-matrix interactions. Actomyosin networks couple neighboring cells via adherens junctions (AJs), while basal integrin-based adhesions anchor cells to the extracellular matrix (ECM), enabling force transmission. Intermediate filaments connect adjacent cells through desmosomes and link to the ECM via hemidesmosomes, allowing them to act as stress absorbers.

(B) When a single oncogene-expressing cell arises in the epithelium, it is eliminated by apical extrusion. The cell becomes hypercontractile, activating tension-sensitive pathways at AJs and inducing actomyosin responses in neighboring cells. This generates compressive forces from surrounding wild-type cells that drive the removal of the cell.

(C) As oncogene-expressing cells expand into multicellular clusters, cell-cell tension and actomyosin accumulation at AJs increase relative to surrounding wild-type cells. This accumulation reduces extrusion efficiency and enables tumor cells to outcompete neighboring cells, leading to local overcrowding and dysplasia.

(D) In later-stage tumors, expanding cancer cell populations exert compressive forces on surrounding cells. This force promotes Wnt/β-catenin signaling in non-tumorous cells, supporting tumor progression, and generates interfacial tension at the tumor boundary (red circle), triggering apoptosis in neighboring cells and facilitating tumor expansion.

systems. Actomyosin interacts with AJs and integrin-based cell-ECM adhesions, whereas IFs associate with desmosomes and hemidesmosomes through specialized desmosomal cadherins and integrins, respectively.[13–15] Third, thesecytoskeletal-adhesion systems confer distinct tissue mechanical properties by regulating both cytoskeletal organization and adhesion dynamics.[6,16]

Actin filaments of the actomyosin cytoskeleton physically associate with classical cadherin and nectin adhesion complexes at AJs and with integrin-based complexes at cell-ECM adhesions.[13,14] This association generates adhesion-based actin scaffolds that recruit actin regulators controlling actin assembly and disassembly,[17] as well as activated non-muscle Myosin II (NMII[13]). Consequently, the actomyosin cytoskeleton can generate force at adhesions while also modulating epithelial material properties. However, the precise mechanical outcome depends on the exact cytoskeletal state that is engaged. For example, actin assembly can apply protrusive force at adhesions,[18–20] whereas NMII contractility creates tensile forces.[21,22] For material properties, crosslinking and stabilization of actin networks increase their resistance to deformation, enhancing their stiffness and elasticity.[13,23,24] Conversely, actin filament severing and turnover can limit the level of contractile tension that is generated in tissues and promote viscoelasticity, thereby dissipating mechanical energy and protecting adhesions from mechanical stress.[25,26] These effects are further shaped by the dynamic properties of cell adhesions themselves. Clustering of cadherin or integrin receptors enhances adhesion strength, stabilizing them against disruptive mechanical forces.[27,28] Mechanical integration of cells with other cells or the ECM would likely be facilitated by this clustering. Since adhesion receptor clustering is promoted by cortical contractility,[28,29] this may establish a positive feedback system. Both actomyosin and cell adhesions can be dysregulated in cancer, but these observations suggest that the mechanical outcome may be difficult to predict from biochemical changes alone, given that both excessive and insufficient force generation or adhesion strength and turnover can give rise to similar phenotypes of impaired migration and mechanotransduction.

IF-adhesion systems are currently best understood as regulators of the material properties of epithelia. Their unique property is that IF networks stiffen both upon stretch and compression.[30] When physically connected to desmosomes or hemidesmosomes, IF networks function as stress absorbers within epithelia and protect against tensile and compressive stresses. Indeed, simple epithelia display strain-stiffening[31] and limit the accumulation of epithelial tension when they are stretched,[32] a process that prevents fracturing and requires IFs. However, it is possible

for IF-adhesion systems to contribute indirectly to active force generation.[33,34] Desmosomes can also recruit signaling pathways that regulate the actomyosin cytoskeleton, including protein tyrosine kinases and Rho-family GTPases,[35,36] and crosstalk with mechanotransduction pathways that activate cell contractility.[33]

Cell-extrinsic determinants

The stroma, consisting primarily of ECM and fibroblasts, constitutes the principal epithelial-extrinsic mechanical input for epithelial cells. Proteomic analyses have shown that the ECM (or matrisome[37]) consists of core matrix proteins (e.g., collagens and fibronectin) and matrisome-associated secretory factors and regulatory proteins.[38] Matrisome components are secreted by epithelial and stromal cells and become organized through self-organization and forces applied by fibroblasts and epithelial cells.[39]

The stroma contributes to the mechanical environment of untransformed epithelial and tumor cells through the material properties of the ECM and the forces it generates and transmits. Type I collagenis a key determinant of ECM material properties that can vary substantially, ranging from the soft environments of the mammary gland to more rigid tissues such as skeletal muscle.[40] Its specific mechanical impact is determined by factors such as crosslinking, bond turnover dynamics, local architecture,[41] and the forces applied.[42] Stromal alterations can also generate diverse stresses that are applied to epithelial or tumor cells.[43] For example, contractile fibroblasts apply tension to the ECM, which can be transmitted to epithelial cells. Cancer-associated fibroblasts (CAFs) can also directly interact with, and exert force on, epithelial tumor cells.[44] Similarly, hygroscopic components of the ECM, such as hyaluronan, can drive osmotic swelling in the stromal compartment, exerting hydrostatic forces and solid stresses that deform epithelia and alter the physical properties of the TME.[45] Consistently, the spatial pattern of solid stress in mouse tumors correlates with collagen and hyaluronan distribution,[46] as it does during inner ear development.[45]

Epithelial mechanotransduction

Mechanical diversity is complemented by a rich variety of mechanotransduction pathways that allow epithelial cells to sense and interpret these inputs. These pathways can be broadly divided into (1) mechanosensors that detect mechanical inputs and (2) the biochemical mechanotransduction or mechanosignaling pathways that elicit functional responses.[47]

Mechanosensors

Epithelial cells use a wide range of molecular mechanisms to detect (1) the forces applied to cells; and (2) the material properties of their local environment. Force sensors include cell-cell and cell-ECM adhesion systems,[6,21] which contain components with tension-sensitive catch-bond properties.[6] Sensor components can also recruit signaling apparatuses, including guanine nucleotide exchange factors (GEFs) for Rho-family GTPases, protein tyrosine kinases,[13] and components of the Hippo transcriptional regulator pathway.[48] These adhesion-based systems are complemented by membrane components, such as mechanosensitive ion channels[49] and caveolae,[50,51] myosins[52] and actin filaments,[53] and a variety of nuclear mechanotransduction pathways.[54–56]

Some of these mechanisms, such as integrins and ion channels, can operate in isolated cells, whereas cell-cell adhesion systems respond to, and potentially integrate, forces acting across supracellular scales. This integrative impact of cell-cell interactions is illustrated by the phenomenon of durotaxis, which is the process by which cells direct migration in response to gradients of ECM stiffness.[57,58] Isolated fibroblastic and tumor cells often display positive durotaxis, migrating toward stiffer substrates. However, cells can also undergo negative durotaxis.[58] In contrast, MDCK epithelial cells show little capacity to durotax when grown as single cells but acquire this capacity through cell-cell adhesion.[59] This effect is explained by the integration of local integrin dynamics into the tissue level by cell-cell adhesion.[59] Cell-cell adhesions therefore mediate emergent mechanosensitive properties at the multicellular level.

Mechanosignaling pathways and their functional outputs

The mechanosensing apparatuses outlined above can engage a broad range of downstream signaling pathways, including cytoplasmic signals, such as intracellular calcium, as well as transcriptional regulators associated with canonical signaling pathways such as Wnt and Hippo. Specific examples are discussed later in this review. Here, we highlight four broad functional features of mechanosignaling. First, many mechanotransduction pathways regulate core cellular functions, including the cytoskeleton and cell metabolism,[60] which in turn support cell mechanics and morphogenetic transitions.[13] Second, transcriptional programs can regulate cell state changes. For example, integrin-based sensing allows ECM stiffness to guide stem cell differentiation.[61] Similar principles apply to other physical inputs, such as osmotic pressure, which facilitates the exit of a stem cell from the pluripotency state in a manner that requires adhesion- and actin-dependent cell and nuclear shape changes.[56,62] Third, cytoplasmic signaling pathways typically support functional responses that operate over relatively short timescales, whereas responses to transcriptional regulation, such as state changes, can persist for longer periods. Finally, it should be noted that these pathways can interact. For example, ERK signaling regulates both cytoskeletal outputs and transcription. Together, these observations indicate that mechanosensing and mechanotransduction allow cells to integrate many mechanical inputs to generate a rich diversity of functional outcomes.

MECHANOBIOLOGY IN CANCER

Tissue mechanics during cancer progression

Epithelia are mechanically active tissues. One aspect of activity includes the variety of forces that their constituent cells can exert on one another, which can manifest over diverse length scales. The best characterized of these are tensile forces, which arise when the actomyosin cytoskeleton exerts contractile force at AJs to support tissue tension.[63] Regulated tissue tension participates in morphogenetic processes, for example, epithelial invagination[64] and homeostatic processes such as apical extrusion of injured cells.[65] Other forms of tissue mechanical force can also be found in epithelia. Expansion of proliferating cells can generate compressive forces on surrounding cells.[66] Shear forces are also generated when populations of cells move relative to one another, such as during embryonic elongation[67] or when cells move collectively in streams.[68] Thus, epithelia can

potentially display a rich variety of mechanical phenomena within their tissues.

Importantly, transformation and cancer progression can create local mechanical heterogeneity in the tissue, with functional consequences that depend on multiple factors. These include the forces generated by the tumor cells, the mechanical state of its surrounding tissue, and the mechanical interactions between tumor and surrounding tissue. Broadly, cancer development can be viewed as beginning with a "first" transformed cell arising within wild-type or genetically predisposed tissue, followed by expansion into early *in situ* tumors and ultimately local carcinoma masses. Even within this simplified framework, it is possible to identify different patterns of mechanics (Figure 1).

The first cancer cell and its host epithelium

The expression of oncogenes, such as mutant Ras or Src, in a small number of epithelial cells is often used to model early cancer.[69,70] When only a small number of cells express oncogenes, they can be eliminated from the epithelium by apical extrusion, a small-scale morphogenetic event used to eliminate injured or unfit cells (Figure 1B).[65,69,71] Apical extrusion is often a cell non-autonomous process that involves mechanical and metabolic changes intrinsic to the extruded cells[65,69,71] and active mechanical responses from their near neighbors.[72] These are coordinated through communication between the extruded cell and the cells immediately surrounding it. Mechanical forces appear to mediate communication in oncogenic extrusion, as in other forms of apical extrusion.[65] Oncogenes such as Ras or epithelial-mesenchymal transition (EMT)-inducing factors[73] can stimulate NMII, which is predicted to cause hypercontractility in the transformed cells[70] and a local tensile force imbalance in the epithelium (Figure 1B). Actomyosin is also enhanced in the surrounding epithelium,[69] suggesting that it may provide contractile force to eliminate transformed cells, as occurs during apoptotic extrusion.[65] The mechanotransduction process that mediates communication between transformed cells and their neighbors has yet to be identified.

However, sequencing studies have revealed that over 25% of cells in phenotypically normal epidermis carry cancer-causing mutations,[74] suggesting that apical extrusion has a limited capacity to eliminate transformed cells. As noted above, extrusion becomes ineffective when transformed cells proliferate to form clusters of even more than a handful of cells.[73] Additionally, extrusion is reduced when the pre-existing mechanical tension (pre-stress) of the host epithelium is increased.[75] *In vitro*, this leads to retention and proliferation of oncogene-expressing cells in monolayers.[75] How tensile pre-stress antagonizes extrusion remains to be elucidated. Interestingly, pre-stress is increased by several maneuvers that increase the risk of cancer, such as manipulating caveolae[75] and exposure to inflammatory cytokines.[76] It will be interesting to test if altered tissue mechanics can increase the risk of cancer development by compromising the elimination of early transformed cells by apical extrusion.

Mechanics of developing early cancers

Mechanical changes are also apparent in experimental models of early cancer, defined as multicellular groups of oncogene-expressing cells before hyperplasia or overgrowth are evident. These lesions often exhibit higher cell-cell tension than the surrounding tissues,[70] associated with increased actomyosin at AJs (Figure 1C).[77] This difference in tissue tension has been implicated in promoting the ability of oncogenic cells to compete for growth with surrounding cells, allowing nascent oncogenic populations to expand.[70,78] This mechanical heterogeneity can also drive progression of the early transformed clones themselves. Recent studies using *in vivo* tumor models in *Drosophila* showed that increased contractile tension at AJs cooperated with pathways such as Yorkie to induce early cancers to progress, overgrow, and become dysplastic.[77] These effects appeared to involve at least two tension-activated processes: disruption of apical-basal cell polarity, which has been extensively implicated in cancer, and mechanical induction of apoptosis in the growing tumor, which facilitates EMT and invasiveness by disrupting cell-cell junctions. Together, these observations highlight how increased mechanical tension in early tumors may represent a tumor-intrinsic factor that promotes progression.

The impact of later-stage tumors on their surroundings

As pre-invasive tumors grow, they are expected to exert compressive forces upon the surrounding host tissue, which can have a range of effects (Figure 1D). In mouse models, growing tumors were associated with increased levels of Ret and Wnt/β-catenin signaling in adjacent non-tumorous tissue.[79] These signals could be activated by applying compressive forces alone, suggesting that growing tumors might elicit classic oncogenic signals in their non-transformed neighbors by mechanical compression. More recent studies combining vertex modeling with biophysical measurements have revealed yet more complex mechanical changes at the interface between a growing tumor and its surrounding tissue. In particular, interfacial tension (or LaPlace pressure) can be generated at the tumor-tissue interface, especially in regions of high curvature.[66] Both these modes of mechanical heterogeneity promote the elimination of surrounding cells by apoptosis, providing a mechanism for growing tumors to "make space" by eliminating their neighbors. These findings emphasize that growing tumors can regulate their surroundings in different ways using multiple mechanical mechanisms. They also highlight a broader influence of tissue geometry on tumor development, including the direction of tumor growth.[80]

Stromal mechanics in tumor development

ECM stiffness

The concept that cancer cells might be influenced by the material properties of their environment was demonstrated in early landmark studies by Valerie Weaver and Mina Bissell.[81] They showed that inhibition of β1 integrin in invasive breast cancer cells grown in basement membrane-like Matrigel resulted in a striking morphological and functional reversion to a normal phenotype. Conversely, more recent studies using mechanically tunable 3D matrices showed that switching normal mammary epithelial acini from soft to stiff matrices induced a dramatic Piezo- and β1 integrin-dependent invasive phenotype.[82] These observations were complemented by the discovery that increased collagen crosslinking in a genetically engineered mouse model of breast cancer enhanced tumor progression through activation of integrin signaling.[83] Subsequent studies showed that increased tissue stiffness accompanies tumor progression across many cancer types and promotes malignancy through enhanced adhesion signaling, integrin clustering,

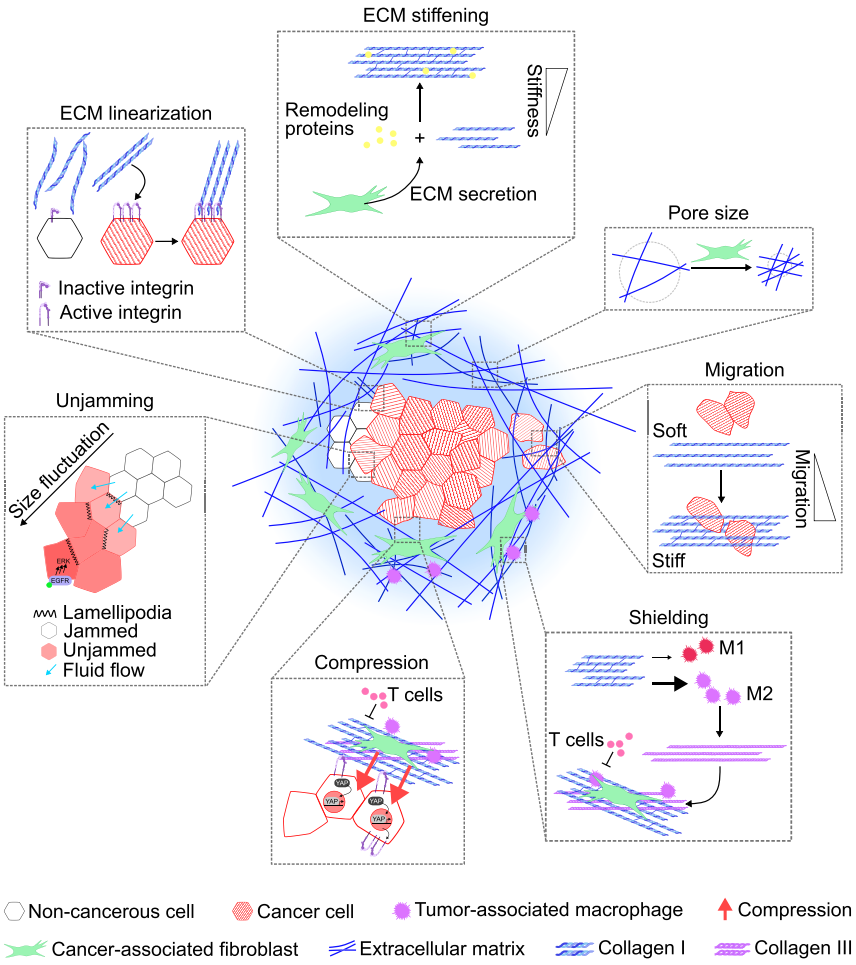

Figure 2. Cancer-associated remodeling of the ECM and tumor microenvironment

Cancer cells influence the surrounding microenvironment through interactions with cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs), promoting extracellular matrix (ECM) production, deposition, fiber alignment, and crosslinking. These changes linearize and stiffen the matrix, reduce pore size, and support integrin clustering and activation, thereby promoting tumor cell migration and force generation. ECM components derived from TAMs and CAFs, including collagen I and collagen III, contribute to matrix densification and the formation of a protective "shield" that limits immune cell infiltration. In parallel, increased ECM density and accumulation of CAFs and TAMs generate compressive forces that activate mechanosensitive signaling pathways, such as YAP, thereby enhancing cell rigidity, proliferation, and integrin production, reinforcing ECM stiffening. At the tissue level, the ECM organization and cell-cell interactions regulate jamming-unjamming transitions, where dynamic cell-cell remodeling permits rearrangements alongside increased lamellipodia activity and fluid exchange, enabling a shift from immotile (jammed) to motile (unjammed) states.

altered transcriptional programs, and increased migration and invasion[84] (Figure 2).

A key driver of tumor stiffness is aberrant synthesis and crosslinking of the ECM by cancer cells and their associated fibroblasts.[37] During cancer progression, normal stromal fibroblasts are activated to become CAFs through complex reciprocal interactions with cancer cells[85] (Figure 2). Although CAFs comprise multiple subtypes, many display an activated, contractile myofibroblast phenotype and increased production of ECM and ECM-remodeling proteins.[86] Together, this results in a stroma that is both stiffer[87] and subject to greater mechanical stress.[43] Similar to epithelial mechanics (Figure 1), CAF-driven matrix alterations in the TME can have distinct effects at different stages of tumor progression. In early stage *in situ* tumors, tumor cells are constrained by the basement membrane, which acts as a barrier to invasion in breast cancer.[88] Filopodia promote invasion and metastasis in later-stage invasive disease. Yet, in pre-invasive *in situ* lesions they instead function in an opposite manner by supporting basement membrane assembly and maintenance, thereby limiting invasion.[88] The impact of ECM stiffness also varies across cancer types. For example, soft microenvironments promote metastatic tropism of ovarian cancer.[89]

The impact of ECM stiffness is also influenced by the 3D organization of tissues, as exemplified by mechanosignaling through Yes-associated protein (YAP) and its paralog TAZ.[48] Early studies in 2D culture systems showed that YAP/TAZ signaling is activated on rigid matrices[90,91] and downregulated on soft matrices.[90,92] This effect involved assembly of contractile stress fibers on stiff substrates, which stretched the nuclear membrane and facilitated entry of YAP and other mechanosensitive transcription factors, including twist family bHLH transcription factor 1 (TWIST) and myocardin-related transcription factor (MRTF).[93] Increased YAP/TAZ signaling can alter tumor cell behavior by enhancing transcription of integrins, focal adhesion scaffold proteins,[94–96] and pro-oncogenic programs.[97]

More recent studies using 3D culture systems have revealed greater complexity. CAFs accumulate and produce excessive ECM in growing tumors, forming a capsule that surrounds cancer cells. Recent work combining advanced 3D models, computational modeling, and *in vivo* experiments demonstrated that encapsulating CAFs compress the tumors, thereby decreasing nuclear tension and promoting nuclear export of YAP.[98–101] The stiff 3D CAF-rich stroma *in vivo* triggers responses opposite to those observed on stiff 2D substrates.[102–104] Compression can also alter cytoskeletal organization and calcium signaling[105,106] and increase cancer motility, apoptosis resistance, and invasion.[107,108]

Stiffness, reflected by the elastic modulus, is not the only ECM property that influences cell behavior. Biological materials are commonly viscoelastic, behaving as solid-like elastic materials over short timescales but showing more viscous, liquid-like behavior over longer periods.[16] Stem cell differentiation is

influenced by time-dependent changes in ECM mechanics, such as stress-stiffening[109] and viscoelasticity.[110,111] These features are also evident in tumors. ECM viscoelasticity is altered together with changes in pore size and the linear organization of the collagen network.[111] Changes in ECM viscoelasticity independent of stiffness[112–114] influence breast cancer cell migration and invasion, modulate tissue symmetry and tumor growth, and promote β1 integrin-dependent cancer progression in precirrhotic liver.[115] These stromal ECM changes arise primarily through CAF-mediated remodeling, although the specific contributions of individual CAF subtypes remain incompletely understood. Future progress will likely require integration of TME omics studies that focus on identifying CAF subtypes with physical analyses of the ECM architecture and material properties. Further, conventional hydrogel models do not fully capture the complex architecture of native and tumor ECM. Architectural changes, such as variation in collagen fiber thickness and tortuosity, influence mammary epithelial development, cancer cell behavior, and stem cell differentiation.[116–119] Therefore, developing tunable collagen matrix architectures and 3D bioprinting methods may improve the physiological relevance of cell culture models.[120,121]

Tissue fluidity and cancer motility

Regulated cell motility is a fundamental feature of epithelial biology that becomes perturbed in cancer.[122,123] Diverse forms of epithelial motility are seen during development[124] and tissue homeostasis.[125] Conversely, aberrant motility that drives local invasion and metastasis is a critical feature as late-stage tumors progress to their most clinically significant and therapeutically refractory states.[123] Tumor motility has often been viewed as pathological activation of the intrinsic capacity of epithelial cells to migrate, even when these cells seem quiescent. Classically, tumor motility has been interpreted through the framework of EMT.[126,127] However, epithelia can also migrate independently of EMT via mechanisms influenced by tissue organization and cellular interactions,[122,128,129] as exemplified by the emerging role of cellular jamming in cell locomotility (Figure 2).

Tissue density has long been recognized as an important regulator of epithelial motility. Epithelial cells move and exchange neighbors, creating apparently random swirls of motion both in migrating monolayers and in stationary tissues.[130] However, this intraepithelial motion diminishes as epithelial density increases. Although many mechanisms have been proposed to explain this density-dependent behavior, recent interest has focused on its resemblance to the phenomenon of jamming, which is observed in soft materials such as colloids. As particle density increases, colloid motility is reduced as they become confined by their neighbors; hence, the notion of "jamming" arises.[131,132] Physical modeling studies of soft matter have identified criteria that distinguish jammed from unjammed states.[133,134] These criteria include transitions from fluid-like to solid-like behavior, accompanied by increased spatial correlation of cell velocities as density rises.[132,133] Similar dynamic features are apparent as epithelial monolayers become increasingly dense.[131,135–137] These observations suggest that local confinement by cell-cell interactions suppress motility through jamming. Conversely, release of confinement can restore motility through "unjamming." In cancer (Figure 2), the transition to a jammed state could suppress cell motility, thereby acting as a tumor-suppressive mechanism.[138] Conversely, unjamming, which could be considered "kinetic awakening" of tumor cells, may enable a collective fluid-like movementas *in situ* tumors progress to invasive carcinomas, thereby facilitating tumor dissemination.[134,139] Jamming is also influenced by tissue boundary conditions: confinement of cell collectives can promote jamming,[68] whereas the release of confinement may promote unjamming.

Jamming and unjamming transitions in inert materials, such as colloids, have been analyzed in terms of particle density, kinetics, and energetics. However, unlike inert particles, cells utilize multiple active mechanisms that govern cell-cell interactions. Indeed, strengthening of cell-cell and cell-substrate adhesions may contribute more strongly to jamming behavior than cell density alone.[136] Cell-cell adhesion systems, such as cadherins, promote physical interactions between cells and mediate friction, while also engaging mechanotransduction processes that suppress lamellipodia and support cell locomotion.[29,140] As an example, overexpression or activation of the endosomal protein Rab5A increases E-cadherin turnover and promotes transition from a jammed, immotile tumor *in situ* to an unjammed, migratory invasive tumor.[141–143] This transition was accompanied by the formation of cryptic lamellipodia beneath cell-cell junctions together with increased integrin expression and focal adhesion dynamics.[141–144]

Fluctuations in cell volume may also contribute to unjamming by helping cells overcome the energy barriers required for the transition. Mammary epithelial spheroids embedded in hydrogels display increased cell volumes at their periphery and in invading cells, and this swelling is mediated by gap junctions.[145,146] Epidermal growth factor (EGF)-induced unjamming involves the upregulation of connexin gap junction proteins together with increased intercellular fluid exchange and variation in cell volume.[147] Aggressive vocal fold cancer cells that exhibit EGF-independent, continuous fluid-like behavior[148] also display constitutively high connexin expression,[147] suggesting that connexin overexpression may contribute to invasive behavior across multiple cancer types. Together, these findings indicate that cells actively regulate jamming and unjamming transitions through mechanisms that may be co-opted in cancer.

Hijacking mechanosignaling in cancer: The case of ERK

Many signaling pathways co-opted in cancer also participate in mechanosignaling. This is exemplified by the ERK/mitogen-activated protein kinase (MAPK) pathway, which is constitutively activated and stimulates cell proliferation in many cancers.[149] ERK/MAPK signaling has recently been implicated in mechanotransduction as it is activated when epithelia are stretched[150] or when tension is applied to E-cadherin adhesions[151] or focal adhesions.[152] A stiff ECM can also enhance mechanotransduction through integrin signaling,[153] which engages the ERK/MAPK pathway among others. Imaging of ERK signaling dynamics using biosensors in living cells[154,155] showed that it is activated in contexts where cells are exposed to mechanical stress. These include epithelial migration, where it is enriched in leader cells[156,157] and at protruding edges,[158] as propagating ERK waves across epithelial sheets,[159,160] and during collective rearrangements within 3D aggregates.[161]

Mechanical activation of ERK often involves molecular cooperation between cell adhesion receptors and co-receptors, such as the EGF receptor (EGFR).[151,156] For example, EGFR can associate with E-cadherin complexes. This lateral association allows EGFR to be activated by cadherin tension independently of EGF itself.[151,162] EGFR has an intrinsic kinase activity that may be enhanced by conformational changes induced by E-cadherin binding. In a second model, EGFR activation occurs in a ligand-dependent fashion. Here, A Disintegrin and Metalloproteinase 17 (ADAM17) localizes near E-cadherin at cell-cell junctions. Mechanical tension applied to the cadherin activates ADAM17, which catalyzes shedding of surface-bound EGF ligands and subsequent EGFR-ERK signaling.[150]

How can mechanically activated ERK signaling participate in morphogenetic and homeostatic events? One major mechanism involves adhesion and cytoskeletal processes that support morphogenesis.[163] ERK regulates the actin cytoskeleton through phosphorylation of cytoskeletal regulators[164] and stimulates NMII by directly phosphorylating the regulatory light chain and activating GEFs for Rho-family GTPases.[165] Together, these effects strengthen adhesions, increase cytoskeletal tension, and regulate migration and mechanosensitive gene expression. ERK also mediates mechanotransduction by controlling focal adhesion dynamics and gene expression, enabling cells to sense, transmit, and adapt to forces in their environment.[163,166,167] Collectively, these findings emphasize the central role of ERK in the generation and sensing of mechanical forces within epithelia.

From this perspective, pathological ERK activation in many cancers may co-opt mechanosignaling pathways that support aberrant morphogenetic behavior. ERK-driven contractility promotes switching between different cell migration modes, potentially enabling cancer cells to navigate diverse mechanical landscapes within the TME.[167] These mechanisms may operate at several different stages of tumor development. In breast cancer cells, activated SRC signaling induces ERK activity, leading to actin stress fiber formation and cell stiffening during premalignant transformation.[168] Recent single-cell analyses further implicate altered ERK signaling in CAF-mediated remodeling of the TME. In head and neck squamous cell carcinoma, secreted amphiregulin signaling between EMT-like tumor cells and an ECM-rich stroma increases EGFR signaling to promote invasion.[91] In pancreatic cancer, which is characterized by extensive desmoplasia, epithelial ERK signaling promotes secretion of TGF-β, activates EGFR signaling in both cancer cells and fibroblasts, and increases ECM-integrin signaling in fibroblasts, thereby promoting a myofibroblastic CAF subtype.[169]

Mechanotherapeutics

The central role of tissue mechanics and mechanosignaling in cancer inspired the development of cancer therapeutics that target mechanotransduction pathways (e.g., inhibition of the Rho kinase pathway, ERK, or YAP-TEAD activity) or modulate the mechanical environment (e.g., altering stromal stiffness), notably through CAFs (Figure 3). Conversely, aspects of tumor mechanobiology can also promote therapeutic resistance. These effects reflect the behavior of cancers as mechanically aberrant tissues and highlight the interplay between tumor cells, stromal cells, the ECM, and mechanosignaling pathways.

Targeting mechanosignaling for cancer therapeutics

The identification of mechanosignaling pathways in cancer provides a framework for the development of new therapeutics (Figure 3). Several mechanotherapeutic approaches are already under investigation. Some promising approaches have yet to be approved for the treatment of solid tumors. These include Rho-family kinase (ROCK; [170]) and YAP/TAZ pathway inhibitors.[171–173] Toxicity may limit clinical efficacy, such as nephrotoxicity of YAP/TAZ inhibitors.[174] The complexity of ECM signaling pathways and the multifunctional nature of the ECM may mean that tissue mechanics and mechanosignaling exert distinct effects at different stages of tumor development.[175] If so, patient stratification and stage-specific therapeutic targeting may become increasingly important.

The pleiotropic relationship between signaling and tumor mechanics is further illustrated by efforts to target the ERK/MAPK pathway. Despite its central role in cancer biology, ERK pathway-targeted therapies commonly become ineffective due to resistance. The mechanisms for resistance often involve mechanoregulatory processes associated with matrix stiffening or altered ECM composition.[176] For example, melanoma resistance to BRAF inhibition arises from a drug-induced activation of stromal fibroblasts, which generate a rigid, collagen-rich (desmoplastic) microenvironment that activates β1 integrin/FAK signaling and ultimately the ERK/MAPK pathway.[177] FAK-inhibitor "priming" prior to chemotherapy attenuates ECM remodeling and improves chemosensitivity *in vivo*,[178] suggesting that short-term, appropriately timed FAK inhibition may provide clinical benefits. Based on these pre-clinical findings, two phase 1 clinical trials are ongoing to determine whether FAK-inhibitor priming or combination therapy improves responses in pancreatic cancer.[179,180] FAK targeting can also be beneficial in other contexts. Given that MEK inhibition can result in compensatory activation of FAK,[178] a combination of MEK and FAK inhibition (with avutometinib and defactinib) was recently approved by the FDA to treat recurrent low-grade serous ovarian cancer with known KRAS mutations.[181]

Targeting CAFs

The stage-dependent effects of mechanotherapeutics are illustrated by the many roles played by the TME. As described above, numerous studies have highlighted the pro-oncogenic effects of CAF-driven ECM stiffening during cancer progression. Consequently, CAFs have emerged as attractive therapeutic targets (Figure 3). For example, targeting CAFs with the fibroblast activation protein (FAP)-directed immunotoxin αFAP-PE38 effectively suppresses tumor growth and TME remodeling and shows synergistic antitumor effects when combined with paclitaxel in a murine model of breast cancer.[182] In contrast, attempts to eliminate CAFs from the TME in pancreatic cancer unexpectedly accelerate tumor progression.[183–185] This result emphasizes that CAFs have context-dependent roles in both the suppression and promotion of tumor progression and highlights the need to selectively target tumor-promoting CAF functions while preserving their tumor-suppressive roles.

CAFs synthesize excessive collagen and secrete soluble factors that further stimulate CAFs and tumor cells, forming a positive pro-oncogenic feedback loop. Targeting these signaling pathways may provide mechanotherapeutic approaches that directly modulate CAF function or collagen remodeling. For

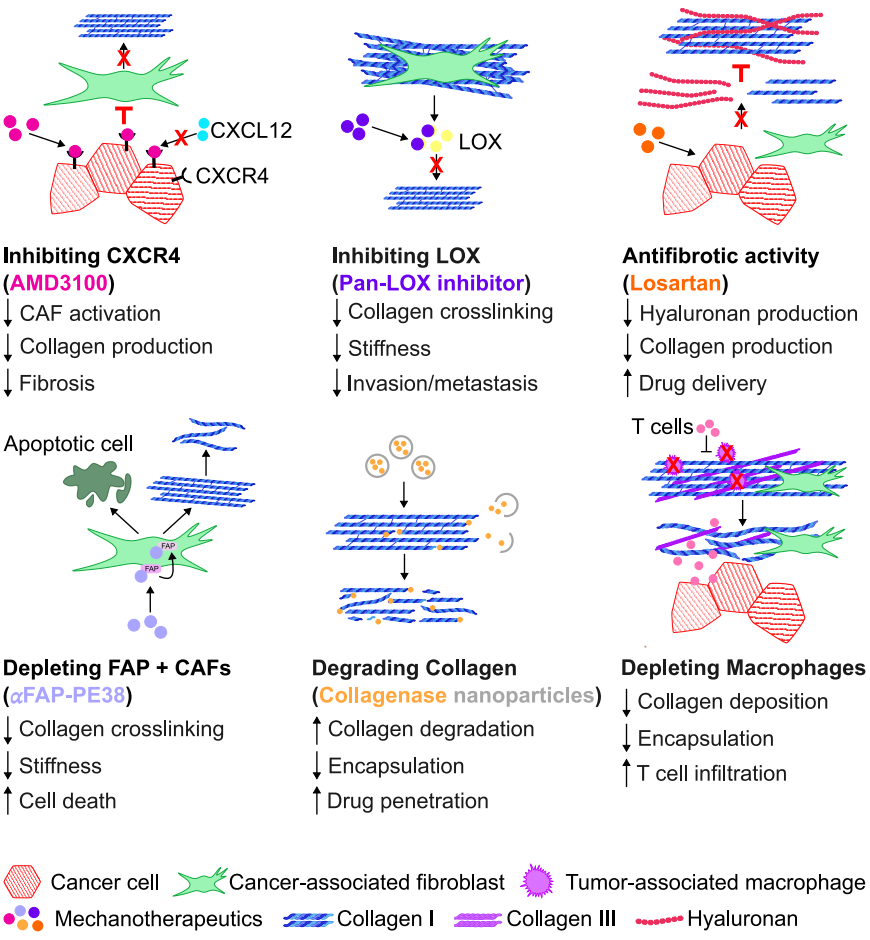

Figure 3. Mechanotherapeutic strategies targeting the tumor microenvironment

This schematic illustrates therapeutic approaches that target cancer-associated fibroblasts (CAFs), the extracellular matrix (ECM), and tumor-associated macrophages (TAMs) to modulate tumor mechanics and progression. Disruption of CAF signaling (e.g., CXCR4 inhibition via AMD3100) or direct CAF targeting (FAP$^+$ cell depletion via αFAP-PE38) attenuates fibroblast activation and collagen production, reducing fibrosis and matrix stiffness. Targeting ECM remodeling through inhibition of lysyl oxidase (LOX; via pan-LOX inhibitor) decreases collagen crosslinking and stiffness, while enzymatic degradation of collagen (via collagenase-loaded nanoparticles) enhances matrix turnover, reduces stromal encapsulation, and improves drug penetration. The angiotensin II receptor antagonist losartan reduces stromal collagen and hyaluronan production, lowering solid stress and desmoplasia and enhancing chemotherapeutic drug delivery. Modulation of TAMs alters ECM deposition and organization, reducing physical barriers to immune infiltration and promoting T cell access to tumor cells.

example, stromal cell-derived factor-1 (SDF-1/CXCL12) is secreted by CAFs and stimulates collagen production via its receptor CXCR4. CXCR4 inhibition with AMD3100 limits profibrotic signaling in the liver,[186] suggesting that this pathway may represent a viable therapeutic target.

Targeting the ECM

Another strategy focuses on directly modifying the ECM within the TME (Figure 3), which contributes to chemotherapy-associated fibrosis[187] and drug resistance.[188,189] Specifically, lysyl oxidases (LOXs), which stabilize collagen fibers and promote collagen crosslinking in tissues,[190] have become attractive targets for reversing chemotherapy-induced desmoplasia. In one study using a genetically engineered mouse model, pan-LOX inhibition reduced chemotherapy-induced pancreatic desmoplasia, decreased cancer cell invasion and metastasis, and improved tumor perfusion *in vivo*. The treatment also demonstrated antifibrotic effects in human patient-derived xenografts of pancreatic cancer.[191] Alternative approaches include the delivery of collagenase enzymes to the TME using nanoparticle carriers to degrade the collagen-rich ECM barrier in solid tumors.[192] Losartan, an angiotensin II receptor antagonist approved for treatment of hypertension, also has antifibrotic activity. It inhibits collagen and hyaluronan production, reducing solid stress and desmoplasia while improving delivery of oxygen, chemotherapeutic drugs, and oncolytic viruses.[193,194]

Other Mechano-targets

Although CAFs are an important contributor to ECM stiffening, macrophages are also abundant in the TME and can generate a stiff, collagen III-rich ECM network that encapsulates colon tumors (Figure 3). Importantly, macrophage depletion is sufficient to promote T cell infiltration into the tumor.[195] ECM mechanics may also influence macrophage behavior. Tumor-associated macrophages (TAMs) are broadly categorized into pro-inflammatory M1 and anti-inflammatory M2 phenotypes.[196] Immunosuppressive M2 macrophages are clinically associated with poor prognosis.[197] ECM stiffness and collagen promote polarization of TAMs toward the pro-tumorigenic M2 phenotype[198] and induce cytokines that further support M2 polarization.[198,199] In addition, confinement of macrophages within elongated thin tracks in the ECM is sufficient to induce M2 marker expression and reduce secretion of M1-associated inflammatory cytokines.[200] Repolarization of TAMs from the M2 to the M1 state has been proposed as a potential therapeutic strategy.[201,202] In principle, alterations of the mechanical properties of the TME could also reprogram TAMs, although this possibility remains largely unexplored.

CLOSING REMARKS

In this review, we have highlighted the potential for tissue mechanobiology to provide insights into the pathobiology of cancer. A key challenge for the future is to characterize the mechanical complexity of tumors, which may be influenced by their tissue of origin and change through intratumoral heterogeneity as cancers progress. Host epithelia vary in their mechanical properties, ranging from comparatively quiescent epithelia, such as the mammary gland, to actively stretching and moving tissues, such as the lung, colon, or vocal folds. Consequently,

mechanical cues that represent physical hallmarks of cancer[8] in one carcinoma type, such as breast cancer, may represent homeostatic or differently regulated mechanical conditions in another tissue. However, the variety in outcomes remains poorly understood, and much of our current understanding of cancer mechanopathology derives from relatively static tissues, such as the breast. Intratumoral heterogeneity also creates cellular neighborhoods composed of different cell types and ECM. These are increasingly recognized as important functional units that influence outgrowth of cancer lesions.[91] The genetic and epigenetic heterogeneity within these regions is being resolved through careful 3D assessments of multiple tissue sections.[203,204] Cancers are also likely to display mechanical heterogeneity, but how this heterogeneity may affect the natural history or clinical outcome of tumors remains to be determined. To answer these questions, it will be necessary to develop new approaches to mechanotyping. Examples could include biophysical tools that measure forces in tumor samples; assays for clinically applicable proxies of mechanical changes[205]; and quantitative or machine-learning approaches capable of integrating large, complex data sets. Such integrated strategies would deepen our understanding of tumor mechanics and provide opportunities to translate these findings for clinical oncology.

ACKNOWLEDGMENTS

J.I. was funded by Research Council of Finland Centre of Excellence program (grant nos. 346131 and 364182) and Academy professorship (369992). This project was supported by an ERC grant (BorderControl; grant agreement number 101142305 to J.I.) funded by the European Union. The views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

S.S. and A.S.Y. were funded by the National Health and Medical Research Council of Australia (grants 2010704 and 2036946) and the Australian Research Council (DP220103951 and DP260103470). A.S.Y. is an Australian Laureate Fellow of the ARC (FL230100100).

AUTHOR CONTRIBUTIONS

Conceptualization, J.I. and A.S.Y.; writing and editing, J.I., A.S.Y., and S.S.; figure preparation, S.S.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

Generative AI and AI-assisted technologies were not used in the writing process.

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