



Mechanobiology of Tumor Invasion: Combining Biomechanical Knowledge into Cancer Treatments

Elnaz Abedini*

Faculty of Engineering, Department of Biomedical Engineering, Karabuk University, Karabuk, Turkey

*Corresponding author: Elnaz Abedini, abedinielnaz@gmail.com

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Abstract

Genetic alterations and biochemical signaling are central to malignant transformation; however, biomechanical cues within the tumor microenvironment (TME) also shape tumor behavior and treatment response. This narrative review critically evaluates how extracellular matrix (ECM) stiffness, solid stress, interstitial fluid pressure, and fluid shear stress influence invasion, metastasis, and therapeutic resistance. These cues engage integrin-focal adhesion kinase (FAK) signaling, RhoA-ROCK-dependent cytoskeletal tension, and the mechanosensitive transcriptional co-activators Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). We discuss how these routes interact with Wnt/ β -catenin and transforming growth factor- β (TGF- β)/SMAD signaling, and how their effects depend on tumor type, matrix architecture, and disease stage. Rather than treating stiffness, solid stress, and fluid pressure as interchangeable, we compare their biological consequences and measurement approaches. We also assess the strengths and limitations of microfluidic and organ-on-chip platforms, elastography, and *ex vivo* nanomechanical assays. ECM-directed remodeling, mechanical decompression, and pathway inhibition offer complementary treatment strategies, but variable clinical efficacy, off-target effects, and biomarker standardization remain significant barriers. Integrating spatially resolved biomechanical measurements with molecular profiling may improve patient stratification and guide rational combination therapies.

1. Introduction

Metastatic dissemination is a major contributor to cancer-related mortality. Although genetic and biochemical drivers of tumor progression are well established, the physical microenvironment is increasingly recognized as an important, context-dependent regulator of malignant behavior [1,2]. Solid tumors interact with extracellular matrix (ECM), cancer-associated fibroblasts (CAFs), vascular networks, and immune infiltrates, forming a mechanically heterogeneous tumor microenvironment (TME) [3,4]. Key physical factors include ECM stiffness, solid stress, interstitial fluid pressure, and fluid shear stress; these are distinct mechanical quantities with different measurement approaches and biological consequences [5,6]. Mechanical cues can modulate cytoskeletal remodeling, cell migration, invasion, and treatment response through signaling networks rather than acting as independent causes of cancer progression [7,8]. Mechanotransduction thus provides a framework for linking mechanical context with molecular pathways and therapeutic vulnerabilities [9,10].

This narrative review synthesizes mechanistic and translational evidence in cancer mechanobiology. The primary literature search covered January 2021 to June 2026 in PubMed, Web of Science, and Scopus, using terms related to tumor mechanobiology, ECM stiffness,

YAP/TAZ, solid stress, immune mechanoregulation, and mechano-targeted treatment. Peer-reviewed mechanistic and translational studies were prioritized; foundational pre-2021 studies are included where necessary to explain established signaling cross-talk. The review integrates the Hippo-YAP/TAZ, integrin-FAK, and RhoA-ROCK axes and critically examines the additional influence of Wnt/ β -catenin and TGF- β /SMAD signaling on mechanosensitive cell states [11,12]. It assesses the mechanical regulation of local invasion, intravasation, circulating tumor cell survival, extravasation, and immune surveillance. Engineered tumor models, microfluidic platforms, and *in vivo* and *ex vivo* measurements are compared in terms of biological relevance, measurement scale, and limitations for clinical translation [13,14]. The scope is restricted to the mechanobiology of solid tumors and clinically relevant strategies for mechanical normalization, biomarkers, and combination therapy [15].

2. Biophysical Characteristics of the Tumor Microenvironment

2.1 Matrix Rigidity and Development of Malignancies

A major physical feature of solid tumors, clinically obvious, is the significant increase in tissue stiffness that can be felt during routine physical examination.

Activation of cancer-associated fibroblasts (CAFs) and dysregulation of lysyl oxidase (LOX) activity lead to excessive deposition and abnormal cross-linking of extracellular matrix (ECM) components, e.g. collagen types I and III, fibronectin and hyaluronan, which result in pathological rigidity [16,17]. There is increasing evidence that not only is the stiffened matrix a passive structural effect of tumorigenesis, but it is also a strong factor in the malignant transformation. Increased stiffness of the substrate supports epithelial-mesenchymal transition (EMT), increases proliferation promoting pathways and can provide resistance to apoptosis and enhance the progression of tumors in many cancer types [10,18].

Importantly, there is a positive feedback mechanism between matrix stiffness and tumor cells and/or CAFs: Mechanical tension is detected by the cells through integrin-mediated adhesion and induces further production and remodeling of ECM proteins, further increasing the rigidity of the matrix [16]. Cancer stem cells (CSCs), a subpopulation responsible for tumor initiation, therapy resistance and disease recurrence, may benefit from this mechanically permissive niche that supports their maintenance and expansion [19]. The physical stiffness of the TME cooperates with CSC self-renewal abilities by mechanosensitive transcription programs in a way that links the mechanical state of the tissue to the hierarchical organization and aggressive capability of the tumor.

2.2 Compressive Forces and Solid Stress

In addition to ECM rigidity, expanding tumors generate mechanical forces collectively termed solid stress. These stresses may contain compressive, tensile, and shear components and arise from cellular proliferation, tissue

confinement, and matrix remodeling [5,20]. Solid stress is transmitted through the load-bearing solid constituents of the tumor (cells and ECM), whereas interstitial fluid pressure describes hydrostatic pressure within interstitial fluid and fluid shear stress arises from fluid flow. These quantities should not be conflated. Elevated solid stress can compress blood and lymphatic vessels, increase hypoxia, and impair therapeutic transport, although the magnitude and distribution depend on tissue architecture and tumor type [21]. Stress-release or cut-and-relax approaches combined with mechanical reconstruction can estimate residual solid stresses; finite-element models depend on boundary conditions and constitutive assumptions. Magnetic resonance elastography primarily characterizes effective tissue mechanical properties and does not directly measure solid stress [20,22].

2.3 Mechanical Heterogeneity Among Cancer Types

The biomechanical properties of the TME are extremely diverse, both at the tumor level and between different cancer types. Glioblastoma is a particular example of a mechanically paradoxical tumor as it grows in soft neural parenchyma and creates a very tight environment in the rigid cranial vault, which has important mechanical cues associated with the adaptation of mechanotransduction pathways that can be regulated via YAP/TAZ [23]. The stroma in breast carcinoma is usually very fibrotic and very stiff, with many densely packed bundles of collagen, and physical signals from the ECM have a major impact on both the trajectory of disease and how it responds to therapy [4]. Table 1 presents illustrative stiffness ranges; these estimates depend strongly on measurement method, tissue preparation, loading rate, and tumor region, and should not be interpreted as universal diagnostic thresholds.

Table 1. Mechanical properties of tumor tissues.

Tissue Type	Stiffness (Young's Modulus)	Solid Stress Level	Key Mechanical Feature
Breast Carcinoma	High (10-100 kPa)	Elevated	Dense collagen cross-linking and linearization
Glioblastoma	Low to Moderate (0.5-10 kPa)	Variable	High physical confinement within the cranium
Colorectal Cancer	High (5-45 kPa)	Elevated	Significant stromal stiffening and CAF activation
Normal Tissue	Low (0.1-2 kPa)	Negligible	Compliant, organized, and homeostatic ECM

Table 2. Biomechanical parameters: Units, measurement modalities, biological effects, and translational considerations.

Biomechanical parameter	Units	Measurement technique	Representative cellular/tissue responses	Therapeutic/translational implications
ECM/tissue stiffness (Young's or indentation modulus)	Pa or kPa	AFM/microindentation <i>ex vivo</i> ; elastography/MRE <i>in vivo</i> (method-dependent modulus)	Focal-adhesion remodeling; YAP/TAZ localization; migration/differentiation	ECM-targeted therapy; imaging biomarker (cross-method harmonization required)
Solid stress (tissue-borne; compressive, tensile, shear)	Pa or kPa	Cut-and-relax/stress-release assays plus model reconstruction; finite-element inference	Vessel compression, altered perfusion and hypoxia; force-sensitive signaling	Stress-alleviation and vascular decompression (not directly measured by MRE)
Interstitial fluid pressure (IFP)	mmHg or kPa	Wick-in-needle/microcatheter/pressure probes; imaging provides model-dependent surrogates	Reduced convective transport; altered interstitial flow and drug penetration	Pressure-modifying ECM strategies; drug-delivery optimization
Fluid shear stress (vascular or interstitial flow)	Pa or dyn/cm ²	Flow chamber/microfluidics; inferred from viscosity and velocity gradient	Endothelial responses; CTC deformation, adhesion and survival	Vascular/CTC models; flow-sensitive treatment design
Matrix viscoelasticity/stress relaxation	Relaxation time: s; modulus: Pa or kPa	Oscillatory rheometry, stress-relaxation tests, AFM dynamic indentation	Spreading, cytoskeletal remodeling, traction and cell-state changes	Time-dependent hydrogel/scaffold engineering
Mechanical strain/cyclic deformation	% or dimensionless	Imposed stretching with imaging or digital image correlation; deformable chips	Mechanosensitive transcription; cell shape and motility	Strain-controlled experimental models; loading-aware therapy studies

Measurement scales, loading conditions, geometry, and constitutive assumptions affect reported values. For example, elastography-derived modulus is not a direct solid-stress measurement, and imaging-based estimates of interstitial fluid pressure require validation against direct pressure measurements [20,24,25]. The listed units are not universal diagnostic cutoffs.

3. Mechanotransduction Routes in Cancer Spread

3.1 Integrin-FAK Mechanosensing

Specialized protein complexes at the cell-ECM interface mediate mechanosensing of the cell's microenvironment by cancer cells. Integrins are the main mechanoreceptors, clustering when they bind to ligands in the ECM and nucleating macromolecular structures that attach the extracellular matrix to the intracellular actin cytoskeleton and are paired with adapter proteins such as FAK, vinculin, talin and paxillin to facilitate the molecular

signal processing [7,11] (Figure 1). The dynamic assembly and maturation of focal adhesions are key mechanisms linking ECM mechanosensing to cancer-cell migration.

The surrounding matrix becomes stiffer, causing the integrin-ECM bond to stretch and lead to autophosphorylation and activation of FAK. This sets off a phosphorylation-dependent cascade that activates downstream pathways such as Src kinases, PI3K-Akt and MAPK/ERK which stimulate cytoskeletal reorganization, formation of invadopodia and directional migration [11]. This mechanosensitive apparatus enables the cancer cell to "probe" the mechanical environment and move through the dense stromal tissues during invasion. Importantly, there is spatial polarization of FAK activity in individual focal adhesions, which determines the directionality of cell motion, revealing exquisite mechanochemical coupling at the adhesion interface [11,26].

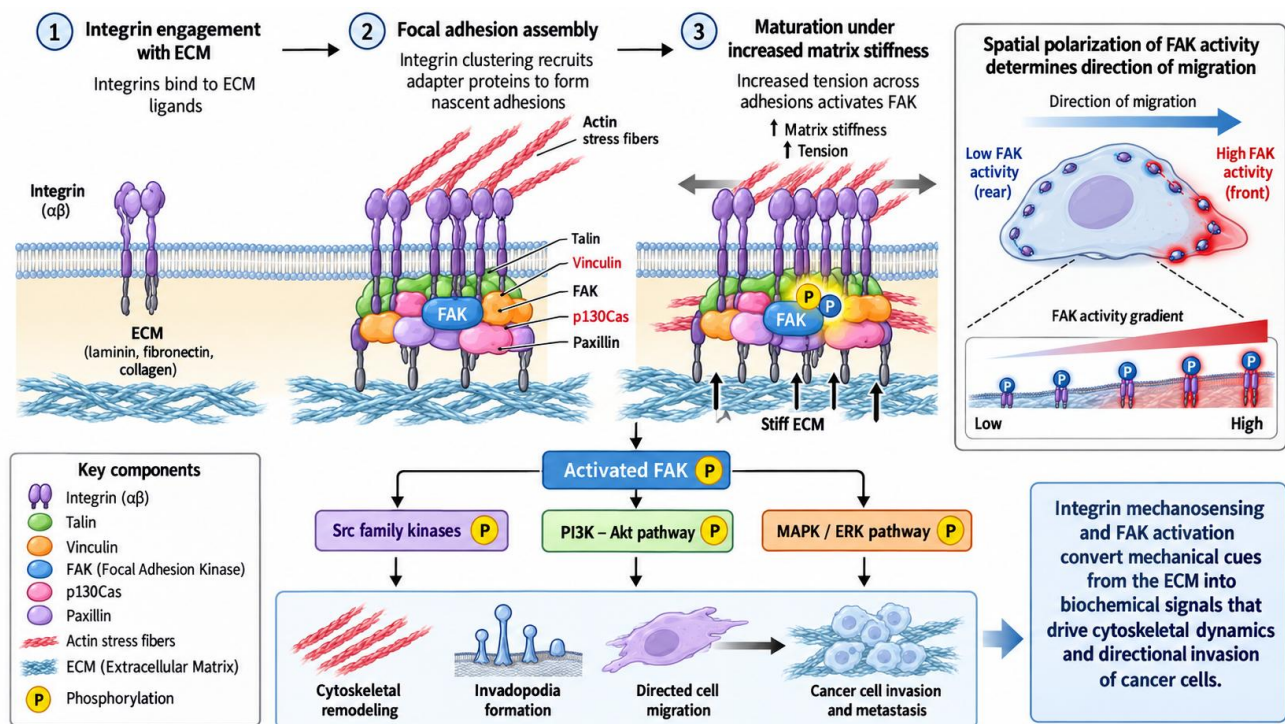


Figure 1. Integrin-mediated mechanosensing in focal adhesions. Upon engagement with the ECM, integrins cluster and recruit adapter proteins such as FAK, talin, vinculin, and p130Cas to form mature focal adhesions. As matrix stiffness increases, tension on these complexes rises, resulting in FAK activation and downstream signaling to promote cytoskeletal remodeling and directed migration of cancer cells. The direction of invasive movement is dictated by the spatial polarization of FAK activity within individual adhesions. (Figure created by the author specifically for this review using Canva).

3.2 Central Mechano-Regulators: YAP/TAZ

YAP and TAZ are mechanosensitive transcriptional co-activators that integrate biophysical and biochemical signaling. Increased ECM stiffness and cell spreading can promote YAP/TAZ nuclear accumulation through integrin-FAK signaling and RhoA-ROCK-mediated actomyosin tension; the contribution of the Hippo MST1/2-LATS1/2 cascade varies with cellular context. In the nucleus, YAP/TAZ associate with TEAD factors and regulate proliferation, motility, and matrix remodeling [10,26]. In colon cancer models, matrix stiffness has been linked to YAP1-associated invasive phenotypes [26], while experiments on focal adhesions identify FAK, vinculin, and talin as regulators of mechanosensitive YAP localization [11]. Nevertheless, nuclear YAP/TAZ localization is a pathway readout rather than sufficient proof that YAP/TAZ activity drives invasion or predicts responsiveness to a given inhibitor [10].

Mechanistic cross-talk with Wnt/ β -catenin and TGF- β /SMAD signaling provides an additional layer of context. Increased matrix stiffness can modulate integrin-dependent β -catenin signaling, while YAP/TAZ may associate with components of the β -catenin destruction complex or cooperate with nuclear β -catenin, depending on Wnt pathway activity. In parallel, cell-generated traction can activate ECM-sequestered latent TGF- β , and activated SMAD2/3 can cooperate with nuclear YAP/TAZ-TEAD complexes to regulate matrix production and epithelial-mesenchymal plasticity

[10,16,27]. However, these interactions are not uniformly tumor-promoting: TGF- β may act differently across disease stages, and YAP/TAZ can either restrain or facilitate Wnt responses depending on pathway state and cell type. Consequently, therapeutic strategies targeting a single mechanotransduction node should be evaluated against compensatory Wnt/TGF- β signaling, stromal feedback, and functional rather than solely molecular readouts [16,27].

3.3 Dynamics of Cytoskeletal RhoA Signaling

The biological switches converting mechanical signals to cellular motion are the Rho family of small GTPases [12]. When integrin binds to stiffened matrix, RhoA is stimulated by guanine nucleotide exchange factors (GEFs) and promotes activation of the RhoA protein effector Rho-associated kinase (ROCK) which in turn promotes phosphorylation of the myosin light chain (MLC), leading to the action of actomyosin to contract, to stress fiber assembly and to increase the cell's force generating power [12]. The cytoskeletal tension is closely related to epithelial-mesenchymal plasticity (EMP). The mechanisms of EMP are crucial for cancer cells to adapt from epithelial to mesenchymal in the face of local invasion and migration [18]. The mechanical environment is a rheostat of cellular plasticity. The stiffened tumor stroma creates a highly tensile environment that favors mesenchymal cell states.

Critical integration: ECM stiffness rarely operates in isolation. Fiber alignment, geometric confinement,

matrix stress relaxation, cytokine signaling, and cell lineage can redirect the FAK-Rho-YAP/TAZ response. Comparisons across 2D substrates, 3D matrices, and patient specimens are further confounded by differences in mechanical length scale, loading rate, and readout. Thus, correlative changes in nuclear YAP/TAZ or epithelial-mesenchymal markers should be complemented by pathway perturbation, rescue experiments, and invasion or treatment-response endpoints before assigning causal or therapeutic significance [7,12,18].

3.4 Epigenetic Control and Mechanical Memory

The most interesting finding was that cancer cells have a kind of memory of the mechanical environment they have been exposed to in the past, which is called mechanical memory [28]. These epigenetic changes, such as DNA methylation, histone acetylation and chromatin accessibility, change the transcriptional landscape and are encoded in that memory. The epigenetic profile may be affected by biomechanical forces and potentially sustain altered gene-expression states beyond the initial mechanical exposure. What does this mean for metastasis? Experimental models suggest that prior mechanical exposure can influence subsequent cellular responses even after the cue is removed, but the duration and relevance to human metastasis remain incompletely established. This means that mechanical 'education' by the primary TME can have sustained effects on the metastatic competence, and that the mechanical history should be considered when interpreting experimental models and designing future interventions [29].

4. Mechanical Regulation of Metastatic Development

The metastatic cascade is the most lethal part of the malignant process and new evidence suggests that mechanical forces play an active role in each step of the primary tumor to distant metastasis journey. Local invasion is the first stage, during which cancer cells cross the basement membrane and enter neighboring stromal tissue. The mechanical structure of the tumor microenvironment is a powerful influence on this first step. The aligned collagen fibers that are deposited by activated cancer-associated fibroblasts act as structural "highways" that help to direct cancer cells toward

adjacent blood and lymphatic vessels, effectively acting as a direction cue for invasive migration [7]. At the same time, as a tumor grows, it generates solid stress that may compress local vessels and alter perfusion. The resulting effect on intravasation depends on endothelial integrity, local matrix organization, and tumor-endothelial signaling (Figure 2) [5,20]. Matrix-guided migration and compressive force-driven barrier disruption create a mechanical basis for successful dissemination.

Once tumor cells enter the circulation, they encounter a markedly different mechanical environment characterized by high fluid shear stress, continuous hemodynamic forces, and frequent collisions with blood cells and platelets. The ability of circulating tumor cells (CTCs) to survive these harsh biomechanical conditions is a critical requirement for their survival and a key determinant of their ability to change their physical properties. Microfluidic technology has played a key role in modeling these vascular environments *in vitro*, allowing researchers to understand how CTCs change their deformability and surface adhesion to survive shear-induced damage while traveling [30]. More recently, mathematical and computational modeling approaches have led to further insights through prediction of how cell mechanical properties affect the likelihood of arrest in distant capillary beds, which is a prerequisite for subsequent extravasation and secondary tumor formation. Interestingly, CTCs that pass the circulatory 'gauntlet' are frequently found to have changed their cytoskeletal stiffness and increased their mechanoresilience, which are mechanically selected during their time in the stiffer primary tumor and which make them more likely to colonize other sites [3,30].

Mechanically regulated immune surveillance introduces a second, partly independent axis of metastatic control. Dense ECM and poorly perfused tumor regions can impede immune-cell trafficking, while force-sensitive stromal and immune signaling may change immune-cell localization and function [31]. However, immune exclusion should not be attributed to stiffness alone: Vascular dysfunction, chemokine gradients, antigenicity, and prior therapy can also shape immunotherapy response [31,32]. A critical translational priority is to combine spatially resolved mechanics with immune phenotyping and perturbation-based studies to determine in which tumor settings stromal normalization improves immune-cell entry and antitumor activity [31,32].

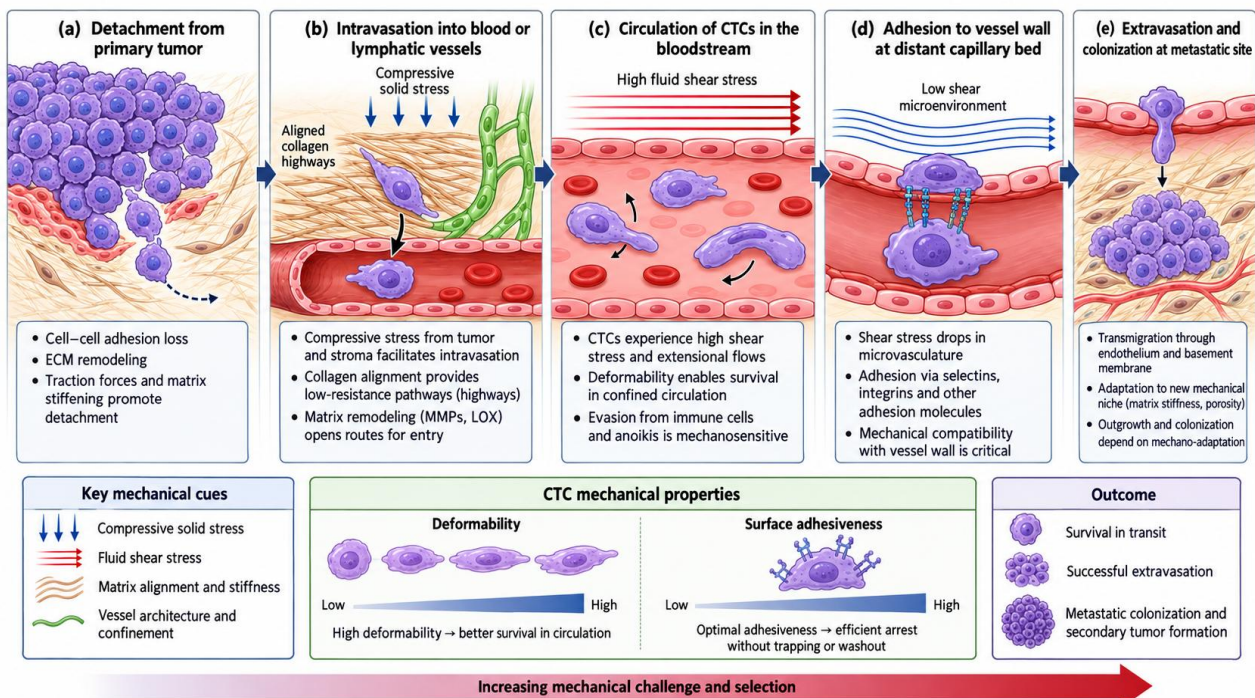


Figure 2. Mechanical landscape of the metastatic cascade. The figure shows the main biomechanical processes leading to cancer dissemination, (a) detachment of the cell from the primary tumor, (b) intravasation into blood or lymphatic vessels, associated with local solid stress and aligned collagen architectures, (c) circulation of highly deformed CTCs in the bloodstream under high fluid shear stress, (d) adhesion on the vessel wall at the distal capillary beds, and (e) extravasation and colonization at the site of metastasis. The mechanical properties of CTCs, including deformability and surface adhesiveness, are essential for survival during transit and for subsequent development of secondary tumors. (Figure created by the author specifically for this review using Canva).

5. Engineered Designs for Mechanobiological Research

5.1 Organ-on-Chip and Microfluidic Systems

Microfluidic and organ-on-chip platforms allow precise, biomimetic recapitulation of dynamic mechanical microenvironments, including fluid flow, interstitial pressure gradients, and shear stress profiles [30]. Advanced "Mechano-Organ-on-Chip" models integrate cyclic mechanical strain, dynamic perfusion, and tunable ECM stiffness into 3D multi-compartment architectures [13], enabling high-resolution, real-time investigation of metastatic intravasation, vascular arrest, and drug penetration under physiologically relevant conditions.

5.2 Tissue-Engineered Tumor Models

Conventional 2D culture fails to capture the 3D architectural and mechanical complexity of solid tumors. 3D tissue-engineered models, built from natural hydrogels (collagen, Matrigel, decellularized ECM) or tunable synthetic polymers, faithfully recreate physiological pore sizes, fiber orientations, and stiffness gradients [3,14]. Incorporating CAFs, endothelial cells, and immune components into 3D bioprinted constructs provides predictive platforms for evaluating mechanotherapeutic responses and overcoming translational hurdles in drug discovery.

5.3 Mechanical Measurement Approaches

Mechanical characterization requires complementary *in vivo* and *ex vivo* approaches. *In vivo* magnetic resonance elastography (MRE) and ultrasound-based elastography

probe effective tissue stiffness at organ or lesion scale, whereas *ex vivo* atomic force microscopy (AFM), indentation testing, and rheometry resolve local or bulk properties of collected tissue. These methods differ in spatial resolution, loading regime, sample preparation, and assumptions, so measurements cannot be directly equated [24]. In particular, MRE-derived stiffness is not a direct measurement of solid stress, and clinically meaningful stiffness thresholds require standardization across instruments and tumor types.

At cell and tissue-microregion scales, *ex vivo* AFM can estimate indentation modulus and local viscoelastic responses, while microfluidic assays can quantify deformation under controlled flow. Such measurements are promising candidate biomarkers, but associations with survival or metastatic potential depend on cancer type, sampling conditions, and prospective validation [8,24]. Solid stress can instead be estimated using stress-release assays and validated mechanical models, whose outputs depend on specimen geometry and boundary conditions [20,22]. Combining repeated *in vivo* imaging with *ex vivo* tissue mechanics and histopathology may improve interpretability, although cross-platform harmonization remains a major barrier.

6. Therapeutic Translation of Mechanobiology

6.1 Targeting Mechanotransduction Pathways

FAK, Rho/ROCK, and YAP/TAZ-TEAD are plausible therapeutic nodes because they couple external mechanical conditions to survival and migration programs. Experimental FAK inhibition can attenuate focal-adhesion signaling, whereas ROCK and

YAP/TEAD pathway modulation may alter contractility and transcriptional responses [33]. However, results from cell lines and animal models must not be interpreted as established clinical benefit; for example, pharmacological tools such as verteporfin have mechanisms and limitations beyond selective inhibition of YAP/TAZ-TEAD signaling [9,15]. Pathway redundancy, adaptive feedback through Wnt/TGF- β signaling, and the physiological roles of these pathways in healthy tissues complicate both efficacy and tolerability. Rational combinations should therefore be based on demonstrated tumor-specific pathway engagement and validated mechanical or functional endpoints [21].

6.2 ECM-Directed Therapeutic Approaches

ECM-directed strategies seek to alter mechanical and transport barriers rather than directly inhibit tumor-cell signaling. Inhibition of lysyl oxidase (LOX)-family activity may reduce aberrant collagen cross-linking in selected models, while hyaluronan depletion may lower interstitial fluid pressure in hyaluronan-rich lesions [6,33]. Depending on tumor composition and stage, matrix remodeling may improve vascular patency and drug distribution, but these effects cannot be assumed to occur uniformly across tumor types. Furthermore, lowering interstitial fluid pressure and relieving solid stress represent distinct therapeutic aims: One should not be used as a surrogate readout for the other.

Matrix normalization might also facilitate immune-cell trafficking or alter hypoxia-driven immunosuppression, but the response is contingent on vascular function,

stromal cell states, and immunological context [31,32]. It is therefore premature to assume that all ECM-depleting treatments convert an immunologically 'cold' tumor into a 'hot' one. Such combinations require tumor-specific biomarkers, dose optimization, and prospective evidence that improved penetration translates into meaningful patient outcomes.

6.3 Mechanical Biomarkers and Diagnostics

Nanomechanical profiling and elastography function as "biophysical biopsies," offering dynamic prognostic biomarkers that complement conventional histopathology [8,24]. In addition to morphological assessment of tumor structure, these methods measure the mechanical response of tumors *in vivo* and *ex vivo* and provide complementary *in vivo* and *ex vivo* readouts of disease aggressiveness, metastatic potential and response to therapeutic interventions. For example, in breast cancer the mechanical signature of the tumor microenvironment can be used to predict metastatic risk and stratify patients based on their risk [4]. The incorporation of these mechanical biomarkers into the clinic may contribute to improved prognostic stratification and earlier detection of therapeutic resistance and personalized treatments based on the biophysical state of the tumor of each patient. As the field advances, tumor mechanobiology may contribute to precision oncology if measurement reproducibility and clinical utility are demonstrated. Table 3 presents illustrative mechano-based therapeutic strategies; clinical development stages require indication-specific confirmation.

Table 3. Illustrative mechano-based therapeutic targets and translational strategies (clinical stage is indication-specific and must be independently verified).

Target Level	Molecular Target	Therapeutic Agent/Strategy	Translational/Clinical Stage	Intended Biological Effect
Extracellular	LOX/LOXL2	Simtuzumab/Small-molecule LOX inhibitors	Phase II clinical trials	Inhibit collagen cross-linking; soften matrix
Extracellular	Hyaluronan	PEGPH20 (PEGylated recombinant hyaluronidase)	Phase II/III clinical trials	Deplete ECM hyaluronan; decrease interstitial pressure
Membrane/Adhesion	FAK/Integrins	Defactinib (VS-6063)/Cilengitide	Phase I/II clinical trials	Inhibit mechanosensing; attenuate focal adhesion signaling
Cytoskeletal	Rho/ROCK	Fasudil/Ripasudil	Phase II clinical trials (repurposing)	Reduce actomyosin contractility and cell stiffness
Nuclear	YAP/TAZ-TEAD	Verteporfin/Small-molecule TEAD inhibitors	Preclinical & Phase I trials	Block nuclear YAP-TEAD complex; suppress metastatic programs
Tissue/Systemic	Solid Stress & Perfusion	Losartan/Anti-fibrotic & anti-angiogenics	Phase II clinical trials	Decompress tumor vessels; improve perfusion and drug delivery

7. Challenges and Future Directions

Although we have made great progress in understanding tumors, there are still many questions to be answered that require a new understanding of tumor mechanobiology to realize its translational potential. The remarkably complex and heterogeneous mechanical tumor microenvironment is one of these factors, where the value of mechanical variables can differ between patients with the same type of cancer as well as between different regions within the same tumor mass [1]. This intra-tumoral mechanical variety could imply that therapy is effective in one region of a tumor but not in another region and so needs spatially resolved mechanical characterization and tailored therapy. Moreover, mechanical forces are dynamic and continuously change as the tumor grows, reacts to treatment, and interacts with the host tissue, presenting an enormous clinical challenge, one that only a few imaging and diagnostic tools are starting to tackle via longitudinal examination of the mechanical state.

An additional challenge is the ability to develop drugs that are able to target mechanically abnormal tumor tissue and not affect healthy, normally stiff organs, like bone, cartilage, and contracting muscle. The therapeutic window of mechano-targeted drugs is intrinsically narrow, because many of the signaling pathways that regulate mechanotransduction, including integrin-FAK and YAP/TAZ, also play fundamental roles in healthy tissue maintenance, wound healing and stem cell maintenance. Mechanically responsive drug release mechanisms or prodrugs that release active drug at a mechanical stimulus, such as stiffness, or delivery systems that target the proper tissues within the body, in cases where tumors make up the targets, would constitute a significant achievement in mechano-medicine [9,15]. In the future, further integration of biomechanical data with genomic, transcriptomic, and proteomic profiles will be critical to the development of truly multimodal patient models that form the foundation of mechanobiology in oncology. These integrative efforts would lead to the ability to not only predict the response of a tumor to a particular therapy as a function of its genetic mutations, but also predict how its mechanical environment will promote drug delivery, immune infiltration, and development of resistance. This vision could be advanced by developing artificial intelligence-based platforms that integrate mechanical imaging with molecular profiling.

Mechanobiology is now well on its way to becoming a key pillar of modern precision oncology alongside the genomic revolution, which has revolutionized cancer care.

8. Conclusions

Cancer progression emerges from reciprocal interactions among genetic alterations, biochemical signals, and the mechanical tumor microenvironment. ECM stiffness, solid stress, interstitial fluid pressure, and fluid shear stress are distinct, spatially variable cues whose effects on invasion, metastatic dissemination, drug transport,

and immune surveillance depend on tumor context. The integrin-FAK, RhoA-ROCK, and Hippo-YAP/TAZ axes integrate these cues, but their activity is modified by Wnt/ β -catenin, TGF- β /SMAD, stromal remodeling, and mechanical memory. A mechanobiology-guided approach may complement existing therapies through selective targeting of signaling pathways, ECM normalization, or vascular decompression. Nevertheless, correlations between tissue mechanics and malignant behavior do not by themselves establish causal targets, and many proposed interventions remain at preclinical or indication-specific translational stages. Future progress requires harmonized *in vivo* and *ex vivo* measurements, spatially resolved biomarkers, functional validation, and controlled studies of rational combination therapies. Integrating biomechanical information with molecular and clinical data may ultimately refine patient stratification without replacing established oncological principles.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author, Elnaz Abedini, upon request.

Ethics Statement

Not applicable.

Conflicts of Interest

There are no conflicts of interest to declare.

Extra Notes

This article was prepared in accordance with the journal's guidelines for review articles.

The designated author is solely responsible for the completeness of the work and the correctness of all the

information displayed.

The Applications of Artificial Intelligence

The author used ChatGPT (OpenAI) solely for English-language editing and grammar correction to improve the readability and clarity of the manuscript. No generative artificial intelligence tools were used to draft the scientific content, perform data analysis, or formulate scientific conclusions. The literature assessment, scientific interpretations, and conclusions were independently developed by the author. The author has carefully reviewed and approved the final manuscript and assumes full responsibility for its accuracy, originality, and content.

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