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Review Article

The mechanics of anoikis resistance in cancer

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ABSTRACT

Metastatic cancer cells display a remarkable ability to resist the mechanical and biochemical challenges associated with detaching from the extracellular matrix and metastasize. A key adaptive mechanism in this process is resistance to anoikis. In this review, we explore the molecular and biophysical mechanisms that enable cancer cells to resist anoikis, with a focus on mechanotransduction. We discuss the roles of integrin signaling, the YAP/TAZ pathway, the mechanosensitive ion channels, and actomyosin contractility in sustaining survival under mechanical stress conditions. Furthermore, we highlight the emerging contribution of soluble mediators, particularly the myokine irisin, which acts as mechanical mimetics by activating survival pathways typically triggered by matrix engagement. We also examined how mechanical heterogeneity across tumor types and metastatic routes shapes context-specific adaptation strategies. By bridging physical forces and cell survival signaling, this review underscores mechanostransduction as fundamental driver of metastatic competence and a promising target for therapeutic intervention.

1. Introduction

Metastasis remains the leading cause of cancer-associated mortality [1]. Despite significant research, the detailed molecular and biophysical processes that allow tumor cells to escape their original microenvironment, survive the turbulence of the circulatory system, and eventually colonize distant organs remain only partially understood [2,3]. Among these mechanisms, the capacity of cancer cells to resist anoikis, a specialized form of apoptosis activated by the loss of adhesion to the extracellular matrix (ECM), has emerged as a pivotal factor in the determination of metastatic capability [4]. Typically, anoikis serves as a protective mechanism that eliminates cells that have lost their appropriate anchorage, thereby preventing proliferation in non-native tissue environments. The evasion of anoikis is an active, finely regulated adaptation that enables malignant cells to survive and disseminate. Although multiple signaling pathways have been individually associated with both mechanical sensing and cellular survival (for instance, integrin-mediated PI3K/AKT, Hippo-YAP/TAZ, and ion channels such as Piezo1), a cohesive understanding of how these pathways interact, compensate, or diverge across various cancer types is still lacking.

Furthermore, although preclinical investigations increasingly utilize mechanical models, ranging from variable-stiffness hydrogels to microfluidic devices, many continue to depend on overly simplified systems that do not accurately replicate the complexity of the metastatic cascade.

In this context, soluble mediators such as myokine and adipokines have emerged as potential modulators of mechanical and metabolic adaptation, with particular attention to Irisin, and its role in anchorage-independent survival.

This review synthesizes the current knowledge regarding the influence of mechanotransduction on anoikis resistance in solid tumors, seeking to bridge biochemical signaling and physical forces. We examine how tumor cells adapt to mechanical constraints to evade cell death, travel heterogeneous environments, and ultimately achieve metastasis. Additionally, we also discuss the limitations of experimental models, highlight emerging therapeutic targets, and emphasize the necessity for integrated approaches that combine biomechanics, metabolism, and immunomodulation.

2. Mechanical stress and cancer survival

Mechanotransduction enables cells to translate mechanical cues from the microenvironment, such as ECM stiffness, cell-cell interaction, tension, and shear stress, into biochemical input that regulate survival, differentiation, metabolism, and migration. These signals are particularly relevant in cancer development and dissemination. Mechanical

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stimuli support oncogenic transformation and contribute to tumor progression regulating invasion, therapy response, and metastatic process. To survive and disseminate cancer cells must continuously adapt to a mechanical altered environment characterized by space confinement, ECM remodeling and loss of adhesion. In particular metastatic cells migrate through confined environments and colonize distant niches by dynamically responding to heterogeneous mechanical cues and resist anoikis (Fig. 1).

The Hippo-YAP/TAZ pathway is a central mediator of is mechano adaptation, translating physical cues into gene expression programs that govern processes essential for tissue homeostasis and tumor progression [5]. Under mechanical stress or contact inhibition, the canonical Hippo pathway is activated: Mammalian STE20-like 1/2 (MST1/2) and large tumor suppressor 1/2 (LATS1/2) kinases phosphorylate YAP and TAZ, leading to cytoplasm retention and degradation [6]. However, in mechanically stressed environments Hippo signaling is suppressed, allowing nuclear translocation of YAP/ TAZ where interacting with the transcriptional enhancer associated domain (TEAD) molecules and drive the expression of genes involved in cytoskeletal remodeling, ECM synthesis, and anti-apoptotic pathways [7]. This mechanical induced nuclear localization of YAP/TAZ is particularly relevant in the context of anoikis resistance. Detached cancer cells which would normally undergo apoptosis in the absence of anchorage, reprogram their transcriptional landscape to mimic anchorage dependent survival. In breast cancer models, cell growth on stiff substrates ≥30 kPa, activates YAP and cooperates with β-catenin/TCF4 to induce the expression of connective tissue growth factor (CTGF) and cysteine-rich angiogenic inducer 61 (CYR61), promoting cell survival and migration [8]. This highlights a synergic interface between mechanotransduction and oncogenic signals.

Moreover, the YAP/TAZ axis is modulated by upstream inputs including integrin, Rho GTPases, PI3K/AKT, and FAK signaling which converge to fine-tune its nuclear accumulation and transcriptional output. Moreover, metabolic stress further shapes YAP function. Indeed, YAP promotes antioxidant responses and glycolytic reprogramming, facilitating redox homeostasis during cell detachment [9,10]. Recent studies indicate that metastasis in solid tumors may depend more on

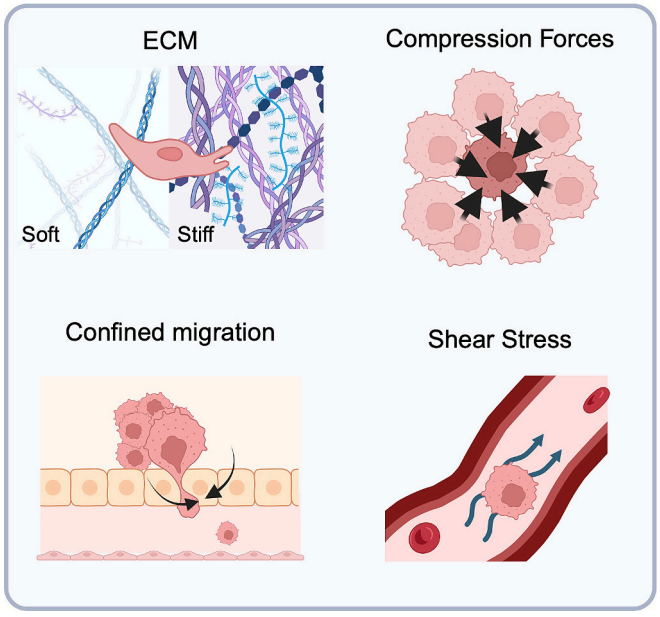

Fig. 1. Mechanical forces experienced by cancer cells during metastasization. Tensile forces are generated by the interaction between cancer cells and the remodeled ECM. Compressive forces arise from the uncontrolled proliferation of cancer cells within the confined and dense tumor core. Cells detaching from the tumor mass are then exposed to forces exerted by the endothelial monolayer during extravasation, and fluid shear stress in the vessel.

epigenetic activation of the Adherent-to-Suspension Transition factors, that reprograms adherent cells by suppressing integrin and ECM gene expression through YAP–TEAD inhibition and inducing hemoglobin genes that confer anoikis resistance, thereby promoting cell-state transitions without lineage differentiation [11]. Therapeutically targeting YAP/TAZ is challenging. Pharmacological inhibition of the YAP-TEAD interaction using verteporfin or genetic silencing of TEADs reduces survival and resensitizes cells to anoikis. However, feedback loops and redundancy pathways limit the long-term efficacy of direct inhibition. Compensatory inhibition of β-catenin or myocardin-related transcription factors (MRTFs) can restore the mechanosensitive transcriptional programs upon YAP inhibition [11–13]. To overcome these barriers, indirect YAP strategies targeting the upstream regulators including FAK, Src, or chromatin modifiers, like bromodomain containing protein 4 (BRD4), are under investigation. These approaches aim to disrupt the transcription plasticity that underlies cancer cell adaptation to mechanical detachment. Their function encompasses mechanosensing, transcriptional reprogramming, metabolic resilience, and immune modulation, positioning them as intricate targets in cancer therapy.

The cellular mechanical response requires the coordination of several interconnected signaling pathways, including integrin-mediated adhesion, mechanosensitive ion channels, cytoskeletal contractility, and organelle-level mechanosensing.

2.1. *Integrin signaling and anoikis resistance*

Integrins are heterodimeric transmembrane receptors composed of one α and one β subunits that physically link the ECM to the actin cytoskeleton [14]. Integrins function as bidirectional signaling hubs that translate mechanical and biochemical information across the plasma membrane. To this, integrins promote the assembly of focal adhesion (FA) and cytoskeletal reorganization in response to ECM stiffness, tension, cell adhesion or detachment [15]. Proteomic analysis identified more than 200 experimentally validated proteins in the "*integrin-adhesome*" and more than 2400 proteins in the a "*meta-adhesome*". These proteins include structural scaffolds, kinases, phosphatases, adaptors, and cytoskeletal regulators whose dynamic recruitment determine the maturation and signaling activity of FAs [16,17]. The spatial and temporary regulation of these complexes responds to the alteration of mechanical environmental stimuli. The assembly, maturation and disassembly of FAs modulate the activation of downstream signaling cascades, including the FAK–Src–PI3K/AKT axis.

FAK autophosphorylation at Tyr397 enables the recruitment of Src-family kinases and PI3K, leading to AKT activation, which in turn inhibits pro-apoptotic signals, such as Bcl-2 associated death promoter (BAD) [3,18]. In addition, FAK signaling supports anoikis resistance promoting the transcription of survival genes via the FOXO and mTOR pathways [19]. This signaling also modulates the cellular mechanical cues by cytoskeletal tension, creating a feedback loop in which integrin signaling sustains actomyosin contractility and reinforces FA stability and mechanical resilience. A more recently characterized GSK3β–FTO–mTORC1 axis links FA-integrin signaling to metabolic adaptation in mechanically stiffness microenvironment [20], where β1 integrin engagement leads to the inhibition of GSK3β with consequent stabilization of the m6A demethylase FTO. In turn FTO enhances the mTORC1 pathway by demethylating key mRNAs, thereby promoting autophagy and metabolic flexibility in anchorage-independent condition [20]. These pathways enable cancer cells to maintain ATP production and redox homeostasis during detachment, particularly under nutrient deprivation or hypoxic conditions. Among the key effectors of integrin-mediated signaling the scaffold pseudokinase Integrin-linked kinase (ILK) directly interacts with β1 and β3 integrins anchoring them to the cytoskeleton via the ILK-PINCH-Parvin (IPP) complex, which connects to F-actin and coordinates downstream signaling including AKT, GSK3β, and NF-κB [21–23]. ILK also regulates cytoskeletal reorganization via Snail and Twist expression, establishing a

mechanistic link between mechanotransduction to transcriptional plasticity [24,25].

Accordingly, elevated ILK expression, reported in several tumors including breast, colorectal, and pancreatic cancers, correlates with increased resistance to anoikis, enhanced cell migration, and greater metastatic potential [21]. This suggests that integrin-ILK signaling not only sustains the anchorage-independent survival but also reprogram cells for invasion and colonization at distant sites. Pharmacological inhibition of integrin signaling has shown promising preclinical results [26]. Agents targeting β1 or αvβ3 integrins, FAK inhibitors, and ILK antagonists disrupt FA turnover, impair survival signaling, and sensitize tumor cells to anoikis in both 2D and 3D models [27–29]. However, the therapeutic efficacy in vivo is often limited by compensatory pathways and redundancy among integrin subtypes, underscoring the need for combination strategies or context-specific targeting. In summary, integrins and their associated complexes operate at the frontline of mechanical sensing, orchestrating survival, metabolism, and plasticity in response to detachment. Their role in anoikis resistance is not limited to adhesion but extends deep into intracellular signaling networks that sustain metastatic competence under mechanical stress.

2.2. Mechanosensitive ion channels

Mechanotransduction is not only mediated by adhesion complexes. Mechanosensitive ion channels (MSCs) constitute a critical component of cellular machinery that enable the perception and the transduction of mechanical stimuli. Among MCSs members, the best characterized in cancer are Piezo, P2X, and Transient Receptor Potential (TRP) families [30]. These channels are particularly relevant in the context of metastasis, where they transduce mechanical signals from tumor microenvironment (TME) into biochemical pathways that modulate adhesion, migration, survival, and anoikis resistance. Among them Piezo1, a large trimeric ion channel, modulates the cytoskeleton remodeling via Ca^{2+}-dependent pathways, contributing to anoikis resistance and enhancing metastasis [30,31]. For instance, in breast cancer its activation enhances invasiveness through E-cadherin downregulation and cytoskeletal remodeling. Similarly, in gastric, colon, prostate cancers, and melanoma Piezo1 overexpression correlates with metastatic potential and activation of PI3K-AKT-mTOR pathway, a key mediator of anchorage-independent survival [32].

Piezo1 also regulates intracellular calcium flux, directly influencing mitochondrial function and cell migration. Notably, Ca^{2+} influx through Piezo1 activates calpain, a calcium-dependent protease that cleave FAK and other FA components, promoting their turnover and cell motility [33,34]. Calpain activation also contributes to anoikis resistance through the cleavage of Bcl2 family members and the modulation of mitochondrial outer membrane permeability [35].

In addition to Piezo channels, TRPV4, TRPM7, and P2X7 have been shown to regulate mechanotransduction and cancer cell dissemination. TRPV4 promotes actomyosin contractility and transendothelial migration [36,37], while P2X7 facilitates matrix degradation and intravasation [38,39].

2.3. Contractile forces and actomyosin cytoskeletal remodeling

Contractile forces, sustained by the actomyosin cytoskeleton are essential mediators of both physiological and pathological processes. The actomyosin network, composed of F-actin and the type II myosin, functions as sensor and an effector of mechanical stress [40]. Contractile tension, regulated by RhoA/ROCK and myosin II, modulates cell stiffness and shapes cellular responses to environmental mechanical cues Cytoskeletal reorganization increases membrane tension through ERM (Ezrin, Radixin, Moesin) -mediated linkages, enabling cells to dynamically adapt their morphology, migrate, and respond to environmental mechanical signals. Membrane tension, generated by changes in surface area, adhesion, or intracellular pressure, can in turn reorganize cortical F-actin and modulate the dynamics of protrusion, adhesion, and spreading [41]. This bidirectional coupling defines the so-called cortex tension, a key determinant of mechanotransduction and survival under detachment. Durotactic migration depends on actomyosin contractility and focal adhesion reinforcement, enabling metastatic cells to sense and respond to local variation in ECM rigidity. Durotactic migration depends on actomyosin contractility and focal adhesion reinforcement, allowing metastatic cells to sense and respond to local variations in ECM rigidity, thereby promoting migration toward and colonization of stiffer microenvironments, a phenomenon referred to as *mechanical tropism* [42]. This biomechanical matching enhances survival at secondary sites and promotes escape from anoikis. During metastasis, confined spaces such as dense ECM regions, basement membrane pores, and endothelial junctions expose cells to extreme mechanical deformation. To transit through constricted openings as small as 1–5 μm, cells must compress and remodel their internal architecture, leading to elevated membrane and intracellular tension, nuclear envelope distortion, and transient DNA damage. Mechanical confinement has been shown to upregulate inhibitors of apoptosis proteins (IAPs), such as XIAP, cIAP1 and 2, which block caspase activation and apoptotic signaling, promoting anoikis resistance [43,44]. Mechanistically, increased actomyosin contractility enhances RhoA/ROCK signaling and promotes NF-kB activation, a transcriptional regulator of IAPs expression. This occurs through the transmission of cytoskeletal tension to focal adhesion, leading to FAK/Src-dependent activation of the IkB kinase (IKK) complex and subsequent IkB degradation, which allows NF-kB nuclear translocation and transcriptional activation of pro-survival genes [45,46]. Recently, pharmacological inhibition of the FAK-Src axis using the small-molecule inhibitor JP153 has been shown to suppress cytoskeletal tension and sensitize cells to apoptosis, supporting the therapeutic potential of targeting this mechanotransductive pathway [47]. The therapeutic relevance of this axis has been further supported using Second Mitochondria-derived Activator of Caspases (SMAC) mimetic molecules (SMAC/DIABLO). SMAC mimetics bind and neutralize IAPs restoring apoptotic competence in mechanically stressed tumor cells [48].

2.4. Organelle-level mechanotransduction in anoikis resistance and metastasization

Recent evidence has expanded the concept of mechanotransduction beyond membrane receptors and cytoskeletal signaling, identifying intracellular organelles, particularly the nucleus and mitochondria, as active mechanosensors and effectors during metastasis [49]. The nucleus is mechanically connected to the cytoskeleton through the linker of the nucleoskeleton and cytoskeleton (LINC) complex, enabling external mechanical forces to be transmitted directly to the nuclear lamina and chromatin. Beyond this structural coupling, mechanical stresses at the nuclear envelope can be activated lipid-based signaling through cytosolic phospholipase A2 (cPLA2). Upon nuclear stretch or swelling, cPLA2 translocate to the inner nuclear membrane and hydrolyzes phospholipids to release arachidonic acid in Ca^{2+}-dependent manner, linking nuclear mechanics to lipid signaling and proinflammatory eicosanoid production [50]. Mechanical deformation of the nucleus, which commonly occurs during confined migration or ECM-induced stress, results in chromatin condensation, nuclear envelope rupture, DNA damage, and altered transcriptional profiles [49,51–53]. In the context of anoikis resistance, these mechanical perturbations activate DNA damage response (DDR) pathways and stress-responsive transcription factors, such as ATF3, cJun, and NRF2, which together orchestrate cytoprotective programs [54].

Similar to nuclei, mitochondria are sensitive to mechanical cues. Under matrix detachment or deprivation, mitochondrial homeostasis is compromised by disrupted energy signaling, increased production of reactive oxygen species (ROS), and the loss of cytoskeletal anchoring. In response, detached cells demonstrate remarkable adaptability:

mitochondrial network elongates, membrane potential becomes hyperpolarized, and oxidative phosphorylation is enhanced sustaining ATP production and buffering ROS [55]. This metabolic reprogramming is partially mediated by YAP/TAZ axis which drive the expression of antioxidant enzymes such as SOD2, and GCLC, as well as metabolic regulators like PGC-1α, linking mechanical cues to enhanced metabolic resilience during detachment [56]. Autophagy, particularly mitophagy, plays a role in this adaptive process. When matrix stiffness increases or adhesion is lost, mechanically regulated autophagy facilitates mitochondrial quality control, protein homeostasis, and energy balance. This process often operates downstream of mTORC1 signaling, itself regulated by integrin-mediated mechanosensing and substrate stiffness [56].

Furthermore, endoplasmic reticulum (ER) stress responses are also engaged in these adaptive processes under mechanical or detachment-induced stress. Activation of unfolded protein response (UPR), including ATF6 and PERK pathways, promotes cell survival through chaperone induction and redox regulation integrating with mitochondrial and cytoskeletal signaling [57].

In summary, both the nucleus and mitochondria are not passive targets but actively interpret mechanical stress, shaping the balance between anoikis and survival (Fig. 2). This organelle-level mechanotransduction represents an emerging frontier in metastasis research, providing novel mechanisms of tumor cell adaptation and pointing to potential therapeutic vulnerabilities, in metastatic process.

3. The mechanical microenvironment

In a wide range of solid tumors, the ECM becomes progressively stiffer driven by collagen crosslinking, fibrosis, and the aberrant activity of cancer-associated fibroblasts (CAFs). This mechanical remodeling is not merely structural change. It profoundly influences cancer cell survival enhancing integrin clustering and FA downstream signaling. For instance, in breast cancer models, a stiffened matrix activates the integrin-GSK3b-FTO-mTOR pathway promoting autophagy and metabolic adaptation during detachment [20]. Matrix stiffness also regulates the nuclear translocation and the transcriptional activity of YAP/TAZ. By contrast, a softer matrix prevents nuclear localization of YAP and restores sensitivity to anoikis, highlighting the stiffness-dependent manner of the cell [58]. ECM stiffness is heterogeneous across tumors and metastatic sites. This mechanical heterogeneity may act as a selective pressure, favoring mechanically adaptable clones. Highly contractile cancer cells, for example, exhibit preferential colonization of stiffer tissues such as the lungs or liver, whereas less adaptable cells are often confined to softer tissue [56]. Cells acquire a mechanical form of memory from their microenvironment, enabling them to maintain a mechanoactivated phenotype even after leaving stiff matrices. This phenomenon, first observed in stem and epithelial cells, involves a YAP/TAZ- and RUNX2-dependent transcriptional program and epigenetic remodeling that modulate gene expression even after the mechanical stimulus is removed [59,60]. Mechanically "stiff-primed" cancer cells generate higher contractile forces, remodel collagen fibers more

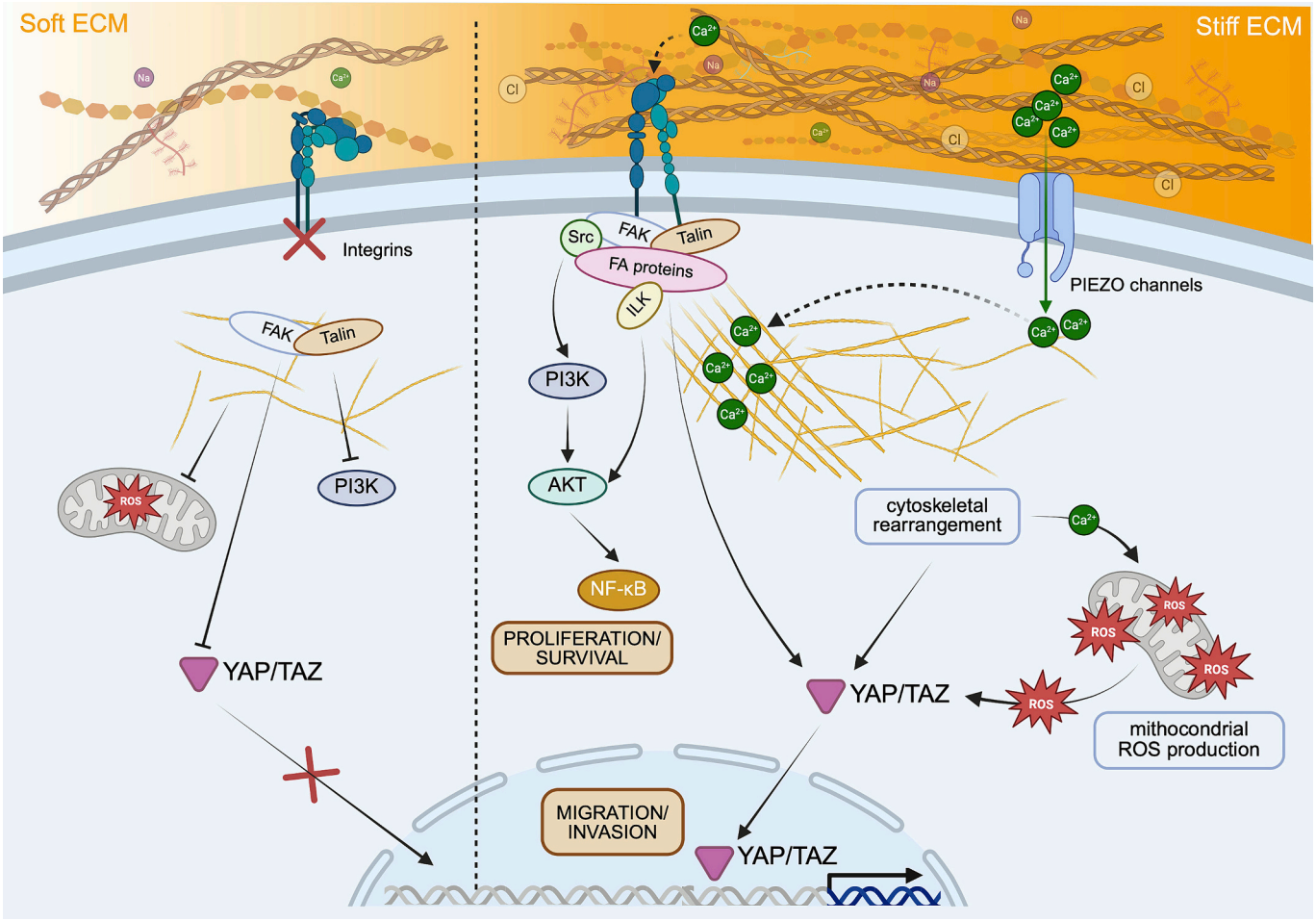

Fig. 2. Mechanotransduction pathways involved in cellular response to mechanical cues. Mechanical stresses derived from the environment are translated in biochemical signals through integrins and mechanosensitive ion channels. These mechanical signals lead to cytoskeletal rearrangement on one side and metabolic rewiring on the other side, eventually leading to Hippo-pathway activation and nuclear translocation of YAP/TAZ.

efficiently, and invade softer matrices through sustained actomyosin activation and collagen alignment. Such priming enhances cell survival and migration under low adhesion conditions, effectively preconditioning cells to resist anoikis during detachment and circulation [59,60]. In addition to matrix stiffness, cancer cells must contend with various non-adhesive mechanical forces during dissemination, including shear stress, compression, and physical confinement. Within the bloodstream or lymphatic system, cancer cells are exposed to fluid shear stress, which induces membrane deformation, cytoskeletal tension, and increases oxidative stress. Mechanosensitive ion channels, such as Piezo1, convert these mechanical inputs into calcium fluxes, activating survival pathways and modulating cytoskeletal dynamics [30]. This mechanotransduction is particularly relevant for circulating tumor cells (CTCs), which must evade both anoikis and immune surveillance [61]. In solid tissue, cancer cells often migrate through dense matrices or narrow interstitial spaces encountering compression and spatial confinement. These forces induce cytoskeletal mechanical stress, nuclear deformation and trigger the expression of inhibitors of apoptotic proteins (IAPs) enhancing immune evasion and resistance to natural killer (NK) cell-mediated cytotoxicity. Ultimately, the interplay among these mechanical forces creates a dynamic selection process in which only cells capable of resisting both mechanical insult and anoikis can complete the metastatic cascade.

4. Conserved mechanisms and cancer-specific adaptation

While the core components of mechanotransduction and resistance to anoikis are generally conserved across various cells, growing evidence indicates that tumors of different tissue origin deploy these pathways in distinct context-dependent ways. These differences reflect the tumor tissue origin, the mechanical and biochemical properties of its primary and metastatic microenvironment. Understanding the balance between these different pathways and their specific context dependence is essential for designing effective therapies and for accurately interpreting findings across different experimental models.

4.1. Common mechanotransductive strategies

Several pathways involved in mechanotransduction and anoikis resistance appear to be broadly conserved among solid tumors (Table 1).

The integrin-FAK-PI3K/AKT axis activated by ECM stiffening or cell detachment, supports both cellular survival and metabolic rewiring [62]. It is consistently observed in breast, pancreatic, and colorectal cancers [63,64]. Similarly, the YAP/TAZ axis drives transcriptional programs that reinforce cytoskeletal structure, promote ECM production, and mitigate oxidative stress. Such mechanisms are especially evident in breast, liver, and pancreatic tumors [65–67].

RhoA/ROCK-mediated contractility, is another conserved feature which increases invasive capacity and mechanical resilience during detachment or migration through confined spaces [68]. In melanoma, breast, lung, and colorectal cancer models, the mechanosensitive ion channels sense mechanical forces like shear stress or compression and activate calcium-dependent survival pathways [39]. Collectively, these mechanisms comprise a conserved mechanoadaptive toolkit that cancer cells exploit to overcome mechanical challenges encountered during metastasis.

These pathways exemplify convergent solutions to the problem of surviving detachment and mechanical stress during metastatic progression. While the relative contribution of each pathway may vary based on tissue origin and microenvironment context, their recurrent activation across tumor types suggest that mechanical adaptation is a hallmark of malignancy and not merely a secondary byproduct of genetic transformation.

Table 1
Mechanotransduction pathways involved in anoikis resistance across solid tumors.

Pathway	Function in Mechanotransduction	Relevance to Tumor Types	Reference
Integrin-FAK-PI3K/AKT	Transduces ECM stiffness and detachment into survival signaling and metabolic rewiring.	Breast cancer PDAC Melanoma Colorectal cancer	[61–63]
YAP/TAZ activation	Drives transcription of cytoskeletal, ECM, and antioxidant genes in response to mechanical cues.	Breast cancer Hepatocellular cancer PDAC	[64–66]
Cytoskeletal contractility	Enhances cytoskeletal tension, migration and resistance to mechanical deformation	Pancreatic cancer Breast cancer Ovarian cancer	[39,67]
Piezo1 and mechanosensitive channels	Convert shear and compression stress into calcium-dependent pro-survival signals	Breast cancer Lung cancer Colorectal cancer Melanoma	[29,37]

4.2. Tissue- and route-specific adaptations

The mechanical adaptations are determined by intrinsic cellular features, anatomical and physical properties of the surrounding stroma, vasculature, and metastatic niches. For instance, melanoma, derived from neural crest melanocytes, demonstrates notable plasticity in cytoskeletal and integrin organization in response to mechanical constraints supporting both mesenchymal and ameboid migration modes [69,70]. Suspended melanoma cells may sustain independent of direct ECM engagement integrin signaling and mechanotransduction through YAP and ILK, conferring resistance to anoikis and maintaining readiness for reattachment and invasion once encountering a new matrix [71].

Breast cancer, particularly triple-negative subtypes, exemplifies another context in which mechanical adaptation is critical. These tumors typically evolve within a stiff, fibrotic stroma that directly activates YAP and β-catenin pathways, thereby enhancing anoikis resistance and promoting metastatic behavior. Interestingly, unlike melanoma, breast cancer cells can also adopt quiescent or dormant states under intermediate levels of matrix stiffness, indicating that mechanical inputs may drive divergent outcomes depending on the balance of signaling and environmental factors [72,73].

Pancreatic ductal adenocarcinoma (PDAC), characterized by dense desmoplasia, pronounced stiffness, and low perfusion, resist to detachment by integrin and ILK-dependent metabolic stress adaptation, especially via autophagy and redox homeostasis. [74–76]. While during hematogenous dissemination of colorectal cancer fluid shear stress is the predominant mechanical force, and mechanosensitive channels such as Piezo1 mediate adaptation to flow by a calcium-dependent signaling and cytoskeletal remodeling [77].

Lung adenocarcinoma exemplifies a unique case in which cancer cells experience cyclic stretch and variable oxygenation. In this context mechanotransduction is linked to hypoxic signaling and FA remodeling promoting survival following detachment. Mitochondrial plasticity and cytoskeletal flexibility, are essential for these cells to remain viable during dissemination through compressive or low-adhesion environments [78,79].

Collectively these examples demonstrate that, despite relying on core survival pathways, tumors deploy distinct mechanoadaptive strategies tailored to their specific mechanical microenvironment (Table 2). These differences reflect not only the intrinsic biology of each tumor type, but also the mechanical constraints imposed by their metastatic route, whether via blood, lymphatics, or serosal surfaces. Understanding the interplay between shared and context-specific adaptation is essential for

Table 2
Mechanoadaptive features in tumors.

Tumor Type	Mechanical Context	Key mechanoadaptive features	Main survival signaling pathways	Metastatic routes	Reference
Melanoma	Variable stiffness, low adhesion during dissemination	High cytoskeletal plasticity; ability to switch between mesenchymal and amoeboid motility; integrin-independent mechanotransduction via YAP/ILK	YAP, ILK, integrin signaling; anoikis resistance	Hematogenous	[68–70]
Breast Cancer (TNBC)	Fibrotic and stiff ECM; high interstitial preassure	Activation of YAP/β-catenin by stiffness; capacity for dormancy under intermediate stiffness	YAP, β-catenin, FAK	Hematogenous and lymphatic	[71,72]
Pancreatic ductal adenocarcinoma	Dense desmoplasia, high stiffness and low perfusion	Integrin- and ILK-dependent metabolic adaptation; autophagy and redox homeostasis	ILK, AMPK, autophagy, ROS signaling	Local invasion; peritoneal dissemination	[73–75]
Colorectal cancer	Fluid shear stress during hematogenous spread	Mechanosensitive ion channels mediate Ca^{2+} influx and cytoskeletal remodeling	Piezo1, Ca^{2+} signaling, cytoskeletal dynamics	Hematogenous	[76]
Lung adenocarcinoma	Cyclic stretch, variable oxygenation, compressive stress	Coupling of mechanotransduction with hypoxia signaling; focal adhesion remodeling; mitochondrial and cytoskeletal plasticity	HIF, YAP/TAZ, FA remodeling	Airway and hematogenous	[77,78]

appreciating the mechanical basis of metastatic competence.

5. Myokines and adipokines as soluble modulators of mechanotransduction

While most mechano-adaptive mechanisms in cancer are initiated by physical cues, emerging evidence highlights the role of soluble factors, such as myokines, adipokines, and cytokines, in modulating or mimicking mechanotransduction. These circulating molecules, released by skeletal muscle, adipose tissue, or stromal compartments, can activate pathways typically involved in mechanical adaptation, including integrin-FAK-AKT, YAP/TAZ, and mTOR signaling. In this context, they act as "mechanical surrogates", providing cancer cells with anchorage-independent survival inputs even in the absence of classical adhesion-based stimuli.

5.1. Myokines as mechanical surrogates

Among other, Irisin has emerged as a particularly relevant myokine at the intersection of mechanical stress, metabolic regulation, and anoikis resistance. Irisin is a cleavage product of fibronectin type III domain-containing protein 5 (FNDC5). It was originally characterized for its role in exercise-induced browning of white adipose tissue [80]. Since then, it has been implicated in a wide range of processes, including inflammation, oxidative stress, and mitochondrial protection, many of which overlap with mechano-adaptive mechanisms in cancer cells. Structurally, Irisin interacts with αV-class integrins, especially αVβ1 and αVβ5, which function as mediators of mechanotransduction and anchorage-independent growth. Through this interaction, Irisin can influence integrin clustering and focal adhesion turnover, thus restoring or substituting survival signaling in cells deprived of matrix contact [81]. This mechanism may be particularly relevant during detachment or transit in the bloodstream, where integrin-ECM interactions are disrupted. Thus, as a soluble ligand, Irisin offers a way to maintain outside-in signaling in the absence of physical anchorage. Experimental studies in non-cancerous tissues support this role. In hypoxic cardiomyoblasts, Irisin activates the AKT pathway, promoting resistance to apoptosis and reducing reactive oxygen species (ROS) accumulation [82,83]. Similarly, in models of lipotoxicity and acute pancreatitis, Irisin upregulates anti-apoptotic markers such as Bcl-2, downregulates pro-apoptotic Bax, and reduces caspase-3 activity [84]. Notably, genetic ablation of FNDC5 in ischemia-reperfusion models exacerbates tissue injury, underscoring a potential protective role against detachment- or hypoxia-induced cell death [85]. In cancer contexts, Irisin has been reported to promote anchorage-independent survival, especially in melanoma, breast, and liver cancer models [86]. These effects correlate with ERK and AKT activation, both of which support survival and migration under detachment [86]. Irisin has been also implicated in mitochondrial remodeling in oxidative metabolism, suggesting a role not only by mimicking adhesion signals but also mitigating metabolic stress during detachment. FNDC5 expression has been reported to correlate with increased metastatic potential in some tumor types, including melanoma, although these associations are context-dependent and require further validation in large patient cohorts. Recent findings suggest that Irisin may intersect with YAP/TAZ activity, potentially regulating transcriptional programs linked to mechanical sensing and metabolic rewiring [87]. This points to a broader role for Irisin in modulating mechanoresponsive transcription factors, although the precise molecular events remain incompletely defined. In addition to its action on tumor cells, Irisin may also influence the tumor stroma, for example by promoting ECM remodeling through MMP induction, thereby indirectly altering the mechanical properties of the metastatic niche and its permissiveness to colonization. In addition to Irisin, other myokines and adipokines have been increasingly implicated in modulating mechanical signaling and survival under detachment, providing cancer cells with adaptive advantages during the metastatic cascade. These factors do not directly impose mechanical force, but act as soluble mechanical mimetics, activating many of the same intracellular cascades triggered by ECM contact or cytoskeletal tension. Interleukin-6 (IL6), released by muscle and immune cells [88], promotes the expression of anti-apoptotic proteins, enhances cytoskeletal tension, and YAP/TAZ activation through the JAK/STAT3 axis. Under conditions of mechanical stress, IL6 potentiates anoikis resistance by reinforcing inflammatory and metabolic signaling networks [89]. Myostatin, also known as growth differentiation factor 8, is a negative regulator of muscle mass, that exerts pro-tumorigenic effects by activating SMAD2/3 and repressing differentiation programs. Notably, myostatin suppresses anoikis in prostate cancer promoting mitochondrial stability and inhibiting caspase activity [90–92].

Finally, FGF21, an exercise-induced myokine, is involved in systemic metabolic regulation and cellular stress responses. In preclinical models, FGF21 activates the ERK1/2-AMPK axis, reduces oxidative stress, and modulates glucose utilization [93,94]. Although direct evidence for its role in anoikis resistance is limited, its capacity to promote mitochondrial resilience and redox balance suggests it could contribute to survival under detachment or confinement [95].

5.2. Mechanical effects of Adipokines

Among the adipokines, leptin often upregulated in obesity-related cancers, promotes PI3K/AKT and FAK activation, enhances integrin expression, and promotes FA assembly, thereby supporting anchorage-independent survival in breast and endometrial cancers [96,97]. Leptin also induces YAP nuclear localization, linking it directly to

mechanotransduction transcriptional programs [98]. Furthermore, leptin stimulates MMPs expression and ECM remodeling, indirectly altering the mechanical properties of the TME. In contrast, Adiponectin, typically reduced in obesity, exerts more complex and context-dependent roles. It increases ATP and modulates mitochondrial function, oxidative stress response, and influences cytoskeleton remodeling. While adiponectin has tumor suppressive effects in particular context it can also enhance survival by reducing ROS and stabilizing mitochondria, mechanisms relevant to anoikis resistance [99]. Other adipokines such as resistin and visfatin, also promote tumor progression via activation of AKT and NF-kB axis which are central to both mechanotransduction and anoikis evasion [100].

Taken together, these observations position myokines and adipokines as an emerging class of systemic modulators of mechano-adaptive behavior in cancers (Table 3). While their functions are pleiotropic and often context-dependent, their convergence in integrin-linked, cytoskeletal, and redox-sensitive survival pathways makes them highly relevant to anchorage independence and metastatic competence.

6. Experimental models

Understanding the interplay between mechanotransduction and anoikis resistance requires experimental systems that accurately recapitulate the physical and biochemical complexity of TME. Most current models fail in representing this complexity. Indeed, many studies still rely on 2D plastic substrates or static 3D matrices, and not capture the dynamic, heterogenous, and multi-scale mechanical cues encountered during metastatic dissemination. These simplified models often fail to reproduce key features such as ECM stiffness gradients, confinement, or fluid shear stress. As a result, our understanding of how cells integrate mechanical information to evade anoikis remains incomplete and often oversimplified.

6.1. 2D and simplified 3D models

Traditional 2D cultures offer limited control over mechanical parameters such as stiffness, or tension. Also, they induce unnatural cell spreading, hyper-adhesion, and loss of tissue polarity thereby masking key mechano-dependent responses. Although 2D detachment assays (e.g., poly-HEMA-coated dishes or forced suspension culture) are widely used to study anoikis, they rarely include mechanical variables such as fluid shear or matrix tension [101]. By contrast, 3D matrix models based on collagen, matrigel, or synthetic hydrogels better approximate the tissue architecture and allow more realistic assessment of cell-ECM interactions. However, these models often lack precise control in stiffness tunability, porosity, or ligand density. To address this, advanced models have employed tunable-stiffness hydrogels or photo-crosslinkable matrices that allow real time modulation of ECM rigidity [102,103]. These platforms have revealed, for example, that increasing substrate stiffness enhances integrin clustering, YAP activation, and anoikis resistance [20]. Despite these advances, most current systems lack dynamic features such as matrix remodeling, active forces, or directional shear, which are integral to in vivo metastasis.

6.2. Microfluidics and dynamic platforms

Static and 2D culture systems fail to recapitulate the dynamic mechanical forces and spatial constraints experienced by disseminating cancer cells. Microfluidic chips, and dynamic bioreactors have emerged as powerful tools to model shear stress, compression, confinement, and cyclic strain. These systems enable controlled manipulation of flow rates, matrix stiffness, and channel geometry, allowing quantitative assessment of cell deformability, adhesion kinetics, and survival during detachment [104]. Confinement assays with narrow microchannels (3–10 μm) have demonstrated that nuclear deformation and transient DNA damage trigger adaptive signaling pathways, including RhoA/ROCK and NF-kB, that sustain anoikis resistance [106]. Similarly microfluidic models that mimic the hematogenous dissemination, reveal that metastatic cells withstand high shear-stress by activating mechanosensitive Piezo1 and reinforcing cytoskeletal structures [105]. Moreover, combined microfluidics and single-cell RNA sequencing, the mechanotransductive responses has been time- and spatial-resolved under physiologically relevant mechanical input, providing new insights into intermediate states between anchorage and detachment [107]. These dynamic platforms therefore bridge the gap between traditional in vitro models and the complex mechanical microenvironment encountered in vivo, offering new opportunities for drug testing and mechanopharmacology. However, widespread adoption of these systems remains limited by technical complexity, lack of standardization, and challenges in the combination with high-throughput analysis or co-culture [108].

6.3. The stromal components

One of the most critical limitations of current models is the absence of physiological integration. Most in vitro systems are devoid of stromal (e.g., fibroblasts, endothelial cells) or immune components, as well as tissue-level architecture [109], which are essential for

Table 3
Mechanosensitive Adipokines and Myokines.

Molecule	Type	Main molecular target	Key signaling pathway	Mechanoadaptive/survival effect	Cancer Contexts	Reference
Irisin (FNDC5 cleavage product)	Myokine	αV-class integrins	Integrin–FAK–AKT, ERK, YAP/TAZ, mTOR	Mimics outside-in signaling; promotes anoikis resistance; supports metabolic adaptation	Melanoma, Breast, and liver cancers	[79–86]
IL6	Myokine/ cytokine	IL6R-gp130	JAK-STAT3, YAP/TAZ, AKT	Increases cytoskeletal tension, induces anti-apoptotic proteins, potentiates anoikis resistance	Multiple tumor types	[87,88]
Myostatin	Myokine	Activin receptor IIB	SMAD2/3, mitochondrial signaling	Suppresses anoikis by stabilizing mitochondria and inhibiting caspases; promotes metabolic adaptation	Prostate, colorectal cancers	[89–91]
FGF21	Myokine	FGFR1 – β-Klotho complex	ERK1/2, AMPK	Enhances mitochondrial resilience, reduces oxidative stress; potential support for survival under detachment	Hepatic, metabolic, and stress related cancers	[92–94]
Leptin	Adipokine	Leptin receptor (LEPR), integrins	PI3K-AKT, FAK, YAP/TAZ, NF-kB	Enhances integrin expression and FA assembly; promotes ECM remodeling; induces YAP nuclear localization	Breast, liver, and obersity related cancers	[95–97]
Adiponectin	Adipokine	AdipoR1/R2	AMPK, PPARa, ROS	Modulates oxidative stress and cytoskeleton; context-dependent pro- or anti-survival effects; stabilizes mitochondria	Breast, liver, and metabolic cancers	[98]
Resistin/Visfatin	Adipokine	TLR4, NAMPT	AKT, NF-kB	Promote survival and inflammation; enhance anoikis resistance via AKT activation	Breast, colorectal, prostate cancers	[99]

mechanotransduction and anoikis resistance. Cancer-associated fibroblasts (CAFs) actively remodel the ECM, enhancing the stiffness and guiding mechanical signaling [110]. Macrophages and neutrophils release matrix modified enzymes responsible for the processing of the ECM remodeling, including MMPs, tissue inhibitors of MMPs (TIMPs), disintegrin (ADAMs, and ADAMTs), that affect integrin signaling and survival [111,112].

In vivo models such as zebrafish xenograft, chick embryo CAM assays, or mouse orthotopic implants, capturing stroma and immune interactions, provide a more physiological context. However, these generally lack the molecular resolution and mechanical specificity required to dissect how individual forces contribute to cell survival. Moreover, genetic tools to visualize mechanotransduction in vivo remain underdeveloped, often lacking spatial or temporal control.

To overcome these challenges, the field is moving toward integrative models that combine mechanical control with stromal complexity, metabolic gradients, and immune crosstalk. Co-culture systems, organ-on-chip platforms, and mechanically tunable organoids represent promising steps in this direction. These tools may eventually allow researchers to dissect not only how cells resist anoikis mechanically, but also when, where, and under what physiological constraints they do so during metastasis.

7. Concluding remarks

Mechanotransduction and anoikis resistance are not only side effects of tumor progression but essential, highly adaptive processes that allow cancer cells to survive and navigate the mechanical challenges of metastasis. Integrins, the Hippo-YAP/TAZ pathway, mechanosensitive ion channels, and cytoskeletal dynamics play interconnected roles in translating mechanical signals into pro-survival cues. Notably, emerging factors like Irisin may link metabolic and mechanical adaptation, adding another layer of complexity. Understanding the interplay of these pathways across tumor types provide mechanistic insights and points toward new therapeutic directions. Beyond their mechanistic implication, several components of the mechanotransduction machinery represent promising therapeutic targets. Inhibitors of FAK, Src, and integrins have already entered clinical trials, while modulators of YAP/TAZ-TEAD interaction and mechanosensitive ion channels are emerging as innovative strategies to counteract metastatic dissemination. In parallel, mechanical signaling is increasingly recognized as a determinant of tumor immune evasion. Elevated matrix stiffness and cytoskeletal tension foster an immunosuppressive milieu by limiting cytotoxic T cell infiltration, promoting macrophage polarization toward M2 phenotypes, and enhancing the release of inflammatory cytokines such as IL6 that further reinforce survival and mechanoadaptive programs. Thus, integrating biomechanical targeting with metabolic and immunomodulatory interventions could help reprogram both tumor cells and their microenvironment toward a state less permissive to metastatic outgrowth.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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