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Review

Piezo1-Mediated Mechanotransduction in Cancer: A Comprehensive Up-to-Date Review of Emerging Mechanistic and Therapeutic Insights

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Abstract

Mechanical forces have emerged as key determinants of cancer progression, influencing cellular behavior, tumor architecture, and therapeutic response. Among mechanosensitive molecules, the ion channel Piezo1 functions as a central transducer that converts physical cues - such as extracellular matrix (ECM) stiffness, compression, and shear stress - into biochemical signals that reshape tumor cell fate. Accumulating evidence indicates that Piezo1 exerts dualistic, context-dependent roles in cancer, promoting either tumor progression or cell death depending on the mechanical landscape, tissue context, and metabolic state. Rather than focusing solely on its molecular interactions, this review provides an integrative overview of Piezo1's context-dependent roles across diverse malignancies, including breast, ovarian, cervical, hepatocellular, gastric, colorectal, pancreatic, and brain cancers. In each setting, Piezo1 governs distinct aspects of tumor biology - ranging from epithelial - mesenchymal transition (EMT), angiogenesis, and metabolic adaptation to immune evasion and therapy resistance-through Ca^{2+} - dependent mechanotransduction. Experimental and clinical studies consistently identify PIEZO1 overexpression as a marker of poor prognosis and metastatic potential, while genetic silencing or pharmacologic modulation alters invasion, apoptosis, or ferroptosis in a tumor-type-specific manner. By consolidating evidence from structural, cellular, and translational studies, this review delineates how Piezo1 acts as a mechanobiological hub that interprets the physical landscape of the tumor microenvironment. These findings position Piezo1 as both a mechanobiological biomarker and a therapeutically actionable target whose functional impact is dictated by tissue mechanics, malignant lineage, and the surrounding microenvironmental context.

1. Introduction

Cancer progression is governed by mechanical cues in the tumor microenvironment - such as ECM stiffness, solid stress, shear stress, and geometric confinement - that reprogram malignant and stromal cell states via force-dependent signaling. Mechanotransduction converts these physical inputs into biochemical outputs that drive oncogenic transcription, invasive remodeling, angiogenesis, and treatment resistance across solid tumors. Among cellular mechanosensors, the cation-permeable ion channel Piezo1 is a principal conduit that links membrane tension to calcium influx with broad effects on tumor and stromal behavior [1-4].

Piezo1 activation elevates cytosolic Ca^{2+} and triggers Hippo/YAP-TAZ, MAPK/ERK, and Wnt/β-catenin signaling, which collectively regulate EMT, invasion–metastasis, angiogenesis, metabolic adaptation, and survival under mechanical stress. This shared Ca^{2+}-dependent signaling architecture underlies the dualistic nature of Piezo1 in cancer, enabling similar pathways to promote either pro-tumorigenic programs or regulated cell death depending on biomechanical and metabolic context. Solid compression enhances invasive phenotypes and matrix proteolysis in breast cancer through Piezo1-dependent Ca^{2+} signaling, illustrating direct conversion of physical stress into metastatic competence. In high-grade serous ovarian cancer (HGSOC), Piezo1 activity promotes ECM remodeling and collective detachment, linking mechanosensitivity to dissemination dynamics. Endothelial Piezo1 integrates hemodynamic forces to shape abnormal tumor angiogenesis and perfusion, with implications for hypoxia and drug delivery barriers [5-8].

Across malignancies, dysregulated PIEZO1 expression and activity correlate with aggressive clinicopathologic features and poorer outcomes, positioning Piezo1 as both a biomarker and a mechanistic driver of progression. At the signaling interface, Piezo1 crosstalks with integrin-mediated focal adhesions and RhoA-driven actin remodeling to establish stiffness-dependent positive feedback loops that stabilize invasive states. Beyond tumor-intrinsic programs, Piezo1 modulates antitumor immunity by shaping T cell cytotoxicity, macrophage polarization, and immunosuppressive niche formation, influencing responsiveness to immune checkpoint blockade. Piezo1 also links mechanical inputs to forms of regulated cell death, such as apoptosis and ferroptosis,

a relationship that explains its context-dependent pro- and anti-tumor effects [9-12].

This review provides a comprehensive synthesis of current evidence on the diverse roles of Piezo1 in cancer. Rather than focusing exclusively on its structural or biophysical gating mechanisms, it systematically examines how Piezo1 contributes to tumor progression across major malignancies - including breast, ovarian, cervical, hepatocellular, gastric, colorectal, pancreatic, lung, prostate, renal, and brain cancers. The discussion integrates findings from molecular, cellular, and translational studies to elucidate how Piezo1-mediated mechanotransduction governs EMT, angiogenesis, metabolic adaptation, immune modulation, and therapy resistance in a context-dependent manner. Furthermore, the review highlights the dualistic nature of Piezo1 signaling - its capacity to promote or suppress tumor growth depending on the mechanical landscape - and evaluates preclinical advances in chemical, genetic, and mechanical modulation of this channel. By consolidating tumor-specific insights and emerging therapeutic strategies, this work aims to define Piezo1 as a unifying mechanobiological hub and a potential target for precision mechanomedicine in oncology.

2. Molecular Structure and Mechanogating of Piezo1

Piezo1 is a large and evolutionarily conserved mechanosensitive ion channel that converts mechanical stimuli directly into electrical and biochemical signals, serving as a crucial mediator of mechanotransduction in animal cells [13-15]. Its discovery has substantially advanced our understanding of how cells sense and respond to physical cues during morphogenesis and tissue homeostasis.

Recent cryo-electron microscopy (cryo-EM) and electrophysiological studies have directly demonstrated that mechanical force applied to the plasma membrane can rapidly and reversibly open Piezo1 channels, supporting its direct role as a mechanotransducer without the need for intermediate second messengers [16].

2.1 Protein Architecture of Piezo1

Structurally, Piezo1 is an extraordinary homotrimer, with each subunit comprising ~2,500-2,547 amino acids and containing 38 transmembrane helices (TM1-TM38) [14,17]. The three subunits assemble to form a distinctive three-bladed, propeller-like structure embedded in the lipid bilayer, generating a highly curved, bowl-shaped indentation in the plasma membrane [14,15].

Most structural studies, including those by Zhao et al. and Guo & MacKinnon, agree on the 38 transmembrane helices per subunit, some recent modeling suggests possible variations in certain species or under different physiological conditions, and the precise boundaries of some domains remain under discussion [13,16]. Each peripheral blade consists of nine repetitive four-transmembrane helical units (THUs), forming the extended arms of the propeller and imparting exceptional sensitivity to changes in membrane tension. These blades interface with a long intracellular beam (residues 1300-1362) that runs parallel to the membrane and acts as a mechanical lever, transmitting force toward the central pore module [15]. The anchor domain (residues 1363-1448) further stabilizes this connection and helps coordinate conformational changes during activation.

At the core of the channel, the C-terminal domains from each subunit (residues 2186-2547) create the ion-conducting pore, which includes the outer helix, cap domain, inner helix, and C-terminal domain [14]. Three critical constriction points-LV (L2475/V2476), MF (M2493/F2494), and PE (P2536/E2537)-serve as hydrophobic and electrostatic gates, tightly regulating ion selectivity, gating, and rapid inactivation. Piezo1 is a non-selective cation channel with a marked permeability to Ca^{2+}, and its opening initiates intracellular signaling cascades essential for morphogenesis. High-resolution cryo-EM structures visualize conformational changes in the propeller blades and central pore during activation, showing that membrane deformation is a critical step in gating [13,16]. Beyond the central ion pore, cryo-EM maps also reveal lateral fenestrations/portals within the Piezo1 architecture that can influence permeation properties (Figure 1) [13,17].

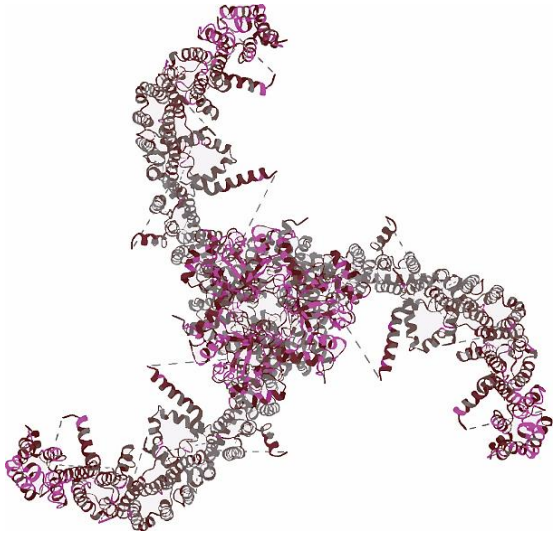

Figure 1. Protein architecture of Piezo1, adapted from EMDB entry EMD-39219 (Electron Microscopy Data Bank) [18].

Despite significant structural advances, aspects of Piezo1's mechanosensitive modules and their precise coupling to membrane tension remain incompletely understood. For example, the relative contributions of specific lipid-protein interactions and membrane microdomain composition (such as cholesterol content) to Piezo1 gating have been highlighted in recent studies [19,20], but mechanistic details are still emerging. The roles of specific lipid interactions and the effects of cellular environment on channel gating are active areas of research, highlighting the need for further high-resolution and functional studies. Additionally, some studies suggest that post-translational modifications or auxiliary partners-such as stomatin-like protein 3 (STOML3)-may modulate Piezo1 properties *in vivo*, although the extent of their influence remains uncertain [21].

2.2 Mechanisms of Activation by Mechanical Force

Piezo1 is directly gated by a range of mechanical stimuli, including membrane stretch, shear stress, compression, and changes in ECM stiffness [22-24]. The predominant model, termed "force-from-lipids," posits that increases in membrane tension or curvature cause the propeller blades to flatten and relay force via the intracellular beam to the central gate, thereby opening the channel. Cryo-EM studies of Piezo1 in different states provide structural evidence for dramatic conformational changes during gating, supporting this lever-like mechanogating model [25]. Concomitantly, the trimeric cap undergoes a downward/rotational displacement, while a spring-like linker to the inner helix acts as a mechanical coupler that facilitates gate opening [13,17]. In particular, coordinated flattening of the peripheral blades occurs as membrane tension rises, in register with lever-like motion of the intracellular beam [13,16].

Guo & MacKinnon directly observed that application of lateral membrane tension resulted in flattening of the propeller blades and opening of the central pore. Additional models such as "force-from-filament" suggest that Piezo1 may also be regulated by tethers to the cytoskeleton or ECM, though the physiological importance of these mechanisms is still debated [16]. Experimental evidence supports both cytoskeletal coupling (force-from-filament) and the 'force-from-lipids' model for Piezo1 gating. However, recent comprehensive reviews indicate that force-from-lipids is the dominant mechanism in most physiological contexts, while the contribution of cytoskeletal or extracellular tethers may vary depending on cell type and environment (Figure 2) [26].

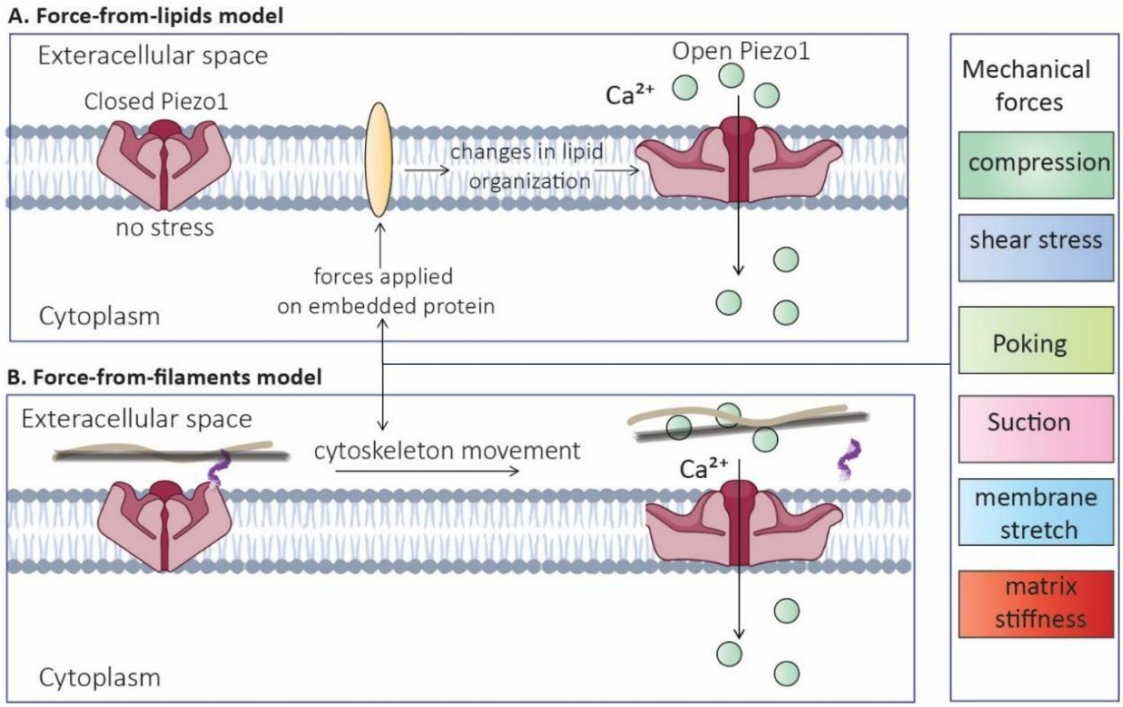

Figure 2. Mechanisms of Piezo1 activation by mechanical forces. Mechanical cues such as compression, shear stress, suction, membrane stretch, and ECM stiffness can activate Piezo1 channels, allowing calcium influx that triggers downstream signaling involved in cellular adaptation, proliferation, and differentiation. Two principal models have been proposed for Piezo1 gating: (A) *Force-from-lipids model* - mechanical tension alters lipid organization within the membrane, leading to conformational changes that open the channel; (B) *Force-from-filaments model* - forces are transmitted through cytoskeletal or extracellular tethers, coupling structural movement to channel opening.

At the molecular level, certain transmembrane domains (notably TM21-TM30) have been implicated as key mechanotransduction modules, facilitating the transfer of force from the membrane periphery to the central pore. Upon activation, Piezo1 channels rapidly and transiently open, permitting a robust influx of calcium ions and

triggering downstream signaling events vital for development. The rapid, reversible gating of Piezo1 provides cells with dynamic responsiveness to fluctuating physical environments [27]. Consistently, Piezo1 activates rapidly and inactivates rapidly, producing transient Ca^{2+} signals in relevant physiological contexts [15].

However, the extent to which auxiliary proteins, cytoskeletal components, or post-translational modifications modulate Piezo1 gating *in vivo* remains uncertain. Ongoing work with advanced biophysical and genetic approaches seeks to clarify these regulatory influences. For instance, it is proposed that the cytoskeletal protein spectrin and the scaffolding protein STOML3 might influence Piezo1 sensitivity, but their roles in native tissues require further validation [21,28]. The lipid milieu-including phosphoinositides such as Phosphatidylinositol 4,5-bisphosphate (PIP_2)-can tune Piezo1 sensitivity and inactivation behavior [26]. Overall, cellular context and cytoskeletal components can shift gating thresholds and kinetics; evidence involving STOML3 and bilayer-tension unmasking underscores this context dependence [20,21].

Distinct from other mechanosensitive ion channels such as bacterial MscL/MscS and mammalian TRP channels, Piezo1 possesses a unique trimeric, three-bladed architecture that directly couples membrane tension to channel opening [29-31]. This "force-from-lipids" gating enables rapid Ca^{2+} influx without secondary messengers, endowing Piezo1 with exceptional mechanosensitivity within physiological ranges. Such structural specialization underlies its selective activation in stiff or compressed tumor microenvironments, distinguishing Piezo1 as the principal mechanical transducer in cancer-associated tissues [29,32-34].

3. Piezo1 Expression and Oncogenic Function Across Malignancies

Piezo1 is increasingly recognized as a central mechanotransducer whose dysregulation contributes to tumor initiation, progression, and therapy resistance across multiple malignancies. By converting extracellular mechanical cues into Ca^{2+}-dependent biochemical signals, Piezo1 regulates proliferation, migration, angiogenesis, immune evasion, and metabolic adaptation. In normal tissues, it maintains vascular homeostasis, epithelial integrity, and red blood cell volume through finely tuned mechanosensation [35]. In cancer, however, matrix stiffening, elevated solid stress, and heightened cytoskeletal tension aberrantly activate Piezo1, amplifying oncogenic signaling [36]. Transcriptomic and proteomic analyses consistently show PIEZO1 upregulation in breast, hepatocellular, gastric, ovarian, cervical, glioblastoma, and renal cancers, with high expression correlating with advanced stage, metastasis, and poor survival [2].

Across tumor types, Piezo1-induced Ca^{2+} influx activates conserved pathways-including YAP/TAZ, MAPK/ERK, PI3K-AKT, and Wnt/β-catenin-that link membrane tension to transcriptional remodeling and invasive behavior [37,38]. Increased tissue stiffness and geometric confinement further create feed-forward loops that enhance Piezo1 activity and reinforce cytoskeletal contractility and ECM remodeling [39]. Beyond tumor cells, Piezo1 also modulates stromal and immune elements of the microenvironment, with endothelial Piezo1 regulating angiogenic responses to shear stress [35] and Piezo1 activity in macrophages and T cells shaping polarization and antitumor immunity [40].

Although Piezo1 signaling is predominantly pro-tumorigenic, context-dependent activation can also induce apoptosis or ferroptosis under specific mechanical or metabolic stresses [5]. Thus, Piezo1 functions as a dual-acting mechanosensor whose biological output depends on tissue mechanics, cellular state, and microenvironmental cues. Subsequent subsections focus on cancer-specific patterns, emphasizing unique mechanobiological features that distinguish Piezo1 function across malignancies.

3.1 Piezo1 in Breast Cancer

Breast cancer provides a highly informative model for mechano-oncogenic signaling because mammary epithelia undergo dynamic changes in stiffness and tension. Across independent datasets, PIEZO1 functions as an adverse prognostic marker-particularly in hormone-receptor-negative and triple-negative breast cancer (TNBC) subtypes-where high expression correlates with reduced $CD8^+/CD4^+$ infiltration and enrichment of EMT, hypoxia, and therapy-resistance programs [9]. Broader analyses similarly associate elevated PIEZO1 with poor outcomes across multiple clinicopathologic categories, supporting its value as a pan-cancer biomarker and potential therapeutic target [41].

Mechanistically, Piezo1 links ECM stiffness and physical confinement to sustained Ca^{2+} influx, actin remodeling, and invasive behavior. Patch-clamp studies confirm functional Piezo1 currents in malignant breast cells, with GsMTx-4 reducing motility, while benign cells lack such mechanosensitivity [42]. In collagen-patterned matrices, metastatic MDA-MB-231 cells show enhanced fiber alignment and directional migration that is abolished by PIEZO1 or integrin β1 (ITGB1) silencing [43]. Additional work demonstrates that Piezo1 regulates cell stiffness, contractility, invadopodia formation, and force-sensitive invasion phenotypes [44]. Atomic force microscopy (AFM) confirms Piezo1 activation in response to localized mechanical force [45].

Piezo1 also links cell geometry to EMT plasticity, as shape perturbations alter Ca^{2+} dynamics through Piezo1, and Yoda1-mediated activation promotes EMT-like transitions [46]. Beyond mesenchymal migration, Piezo1 modulates bleb-based motility; Yoda1 or gentle compression suppress thrombin-induced blebbing via reduced ezrin-radixin-moesin (ERM) phosphorylation, whereas Piezo1 loss abolishes this effect [47].

Therapeutically, Piezo1 modulation has translational potential. Ultrasound-activated piezoelectric nanoparticles targeted to human epidermal growth factor receptor 2-positive ($HER2^+$) cells inhibit proliferation by

altering Ca^{2+} homeostasis and spindle organization [48]. Yoda1 enhances photothermal therapy by amplifying reactive oxygen species (ROS) production, while modulation of a Piezo1-Notch1-glutathione peroxidase 4 (GPX4) axis suppresses bone metastasis and improves survival in combination with zoledronic acid [49].

The homolog PIEZO2 exhibits subtype-specific functions, with PIEZO2 overexpression in TNBC enhancing metastasis through Akt-dependent SNAIL stabilization and promotion of EMT [50]. In contrast, reduced PIEZO2 correlates with Hedgehog pathway activation and poor prognosis in ER^+ tumors, suggesting context-dependent protective functions [51]. Clinicopathologic analysis links PIEZO2 positivity to higher Ki-67 and perineural invasion, while mechanistically PIEZO2 controls RhoA activation, actin organization, and YAP translocation-defining a regulatory axis essential for matrix remodeling and metastatic adaptability [52].

Overall, Piezo1 predominantly drives EMT, matrix remodeling, and immune exclusion in breast cancer, whereas Piezo2 exerts dualistic, subtype-specific effects. These insights underscore the therapeutic relevance of targeting Piezo-dependent mechanotransduction in aggressive breast cancer.

3.2 Piezo1 in Ovarian Cancer

Across epithelial ovarian cancer (EOC), Piezo1 integrates key mechanical features of the peritoneal environment-matrix stiffening, ascites-driven shear stress, and geometric confinement-to promote detachment, dissemination, and therapy resistance. PIEZO1 is overexpressed in clinical samples and preclinical models, where its knockdown reduces tumor growth, metastasis, and EMT markers, while pharmacologic activation with Yoda1 engages the Hippo/YAP pathway and enhances invasive transcriptional programs [53].

Collective detachment, a hallmark of HGSOC, is critically Piezo1-dependent. In spheroid detachment assays, increased substrate stiffness augmented spheroid release through Piezo1-mediated upregulation of MMP-1/MMP-10 and reduction of collagen I/fibronectin. *In vivo*, PIEZO1-deficient OV90 cells generated less ascites, fewer free-floating spheroids, and reduced mesenteric tumor burden. Notably, PIEZO1 expression is prominent in omental metastases from stage III/IV patients, underscoring clinical relevance [3].

Beyond invasion, Piezo1 modulates regulated cell death. TRIM25 drives K63-linked ubiquitination and degradation of PIEZO1, thereby suppressing ferroptosis and supporting proliferation and metastasis-implicating a TRIM25/PIEZO1/ferroptosis axis as a potential therapeutic target [54]. Mechanical cues also reshape metabolic programs. Under physiological shear stress, SKOV3/OVCAR3 cells undergo cytoskeletal remodeling and nuclear Yes-associated protein 1 (YAP1)/sterol regulatory element-binding protein 2 (SREBP2) translocation, increase cholesterol acquisition, and become less sensitive to BOLD-100, linking mechanotransduction to lipid metabolism and chemoresistance. Given the sensitivity of Piezo1 to membrane lipid composition, these findings suggest mechanistic convergence between shear stress, cholesterol content, and Piezo1 gating [55].

Systems-level analyses further position PIEZO1 as a prognostic mechanosensitive ion channel. Mechanogenomic clustering identifies PIEZO1-together with CACNA1C and transient receptor potential vanilloid 4 (TRPV4)-as a key determinant of high-risk EOC subsets enriched for focal adhesion, ECM-receptor interaction, Wnt, and Hippo signaling pathways [56].

Collectively, these findings establish Piezo1 as a central driver of EOC dissemination and adaptive behavior by promoting spheroid detachment, enabling peritoneal colonization, integrating mechanical cues into YAP-dependent programs, regulating ferroptosis, and contributing to mechano-metabolic rewiring underlying therapy resistance. Therapeutically, these insights support Piezo1-targeted modulation, TRIM25-axis intervention, and mechanics-aware combinations (e.g., YAP/SREBP2 or lipid-handling inhibitors) to disrupt peritoneal spread and treatment failure.

3.3 Piezo1 in Cervical Cancer (CC)

CC is characterized by pronounced mechanical remodeling, including ECM stiffening, solid stress, and cellular crowding, which collectively shape invasion and therapeutic resistance. Across multiple studies, Piezo1 emerges as a key mechanotransducer linking these biomechanical cues to Ca^{2+}-dependent signaling, ferroptosis regulation, and cytoskeletal dynamics.

Matrine suppresses CC growth by activating Piezo1 and triggering ferroptosis. In SiHa xenografts, it reduced tumor burden and induced characteristic ferroptotic changes-including increased Fe^{2+} and lipid peroxidation together with reduced GPX4-effects that were lost upon Piezo1 knockdown [57]. Complementary work demonstrated that Piezo1 is upregulated in CC tissues-particularly in patients with lymph node metastasis-and promotes ATP-driven migration and invasion. Silencing Piezo1 impaired wound closure and transwell migration, whereas Yoda1 enhanced pseudopodia formation and tumor growth *in vivo*, with extracellular ATP blockade eliminating the pro-migratory effects [58].

Mechanical stiffening serves as an upstream driver of Piezo1 activation. Lysyl oxidase-like 2 (LOXL2)-induced matrix rigidity increases Piezo1 expression and enhances invasion via cytoskeletal remodeling. Inhibition of LOXL2 reduces ECM stiffness, downregulates Piezo1, and suppresses tumor growth *in vivo*, establishing a LOXL2-ECM stiffness-Piezo1 axis in CC progression [59]. Additionally, live-cell extrusion-a crowding-induced mechanism of collective dissemination-generates migratory, anoikis-resistant cells with elevated transforming growth factor-beta (TGF-β) signaling, a pathway linked to Piezo1 mechanotransduction, suggesting an extrusion-based escape route complementing conventional invasion [60].

Together, these findings identify Piezo1 as a context-dependent regulator in CC, capable of inducing anti-

tumor ferroptosis in some settings while promoting ATP-mediated invasion and stiffness-driven metastasis in others. This duality highlights Piezo1 as both a therapeutic target (e.g., matrine analogs, LOXL2 inhibition) and a mechanobiological biomarker integrating mechanical stress, metabolic vulnerability, and survival programs.

3.4 Piezo1 in Hepatocellular Carcinoma (HCC)

The liver's mechanically dynamic environment-characterized by ECM stiffening, fibrosis, and hemodynamic forces-strongly influences tumor evolution. Within this context, Piezo1 has emerged as a key mechanotransducer linking physical deformation to angiogenic, metabolic, inflammatory, and invasive signaling in HCC.

Matrix stiffening is a major upstream trigger of Piezo1 activation. Li et al. demonstrated that increased matrix stiffness upregulates Piezo1 in HCC cells and drives pro-angiogenic signaling through a Piezo1/Ca^{2+}/HIF-1α axis, stabilizing HIF-1α and promoting vascular endothelial growth factor (VEGF), C-X-C motif chemokine ligand 16 (CXCL16), and insulin-like growth factor-binding protein 2 (IGFBP2) secretion (Figure 3) [61]. In orthotopic "stiff-liver" models, PIEZO1 knockdown reduced tumor vascularization, growth, and lung metastasis, confirming its role as a stiffness-gated angiogenic driver. Piezo1 also promotes EMT and invasion, as high PIEZO1 expression correlates with advanced stage and metastasis and mechanistically enhances TGF-β activation through Rab5c. Similarly, matrix stiffness increases invadopodia formation and migration through ITGB1/FAK/Src/Arg/cortactin and Piezo1/Ca^{2+}/MLCK/MLC2 signaling, with Src acting as a central regulatory hub [62].

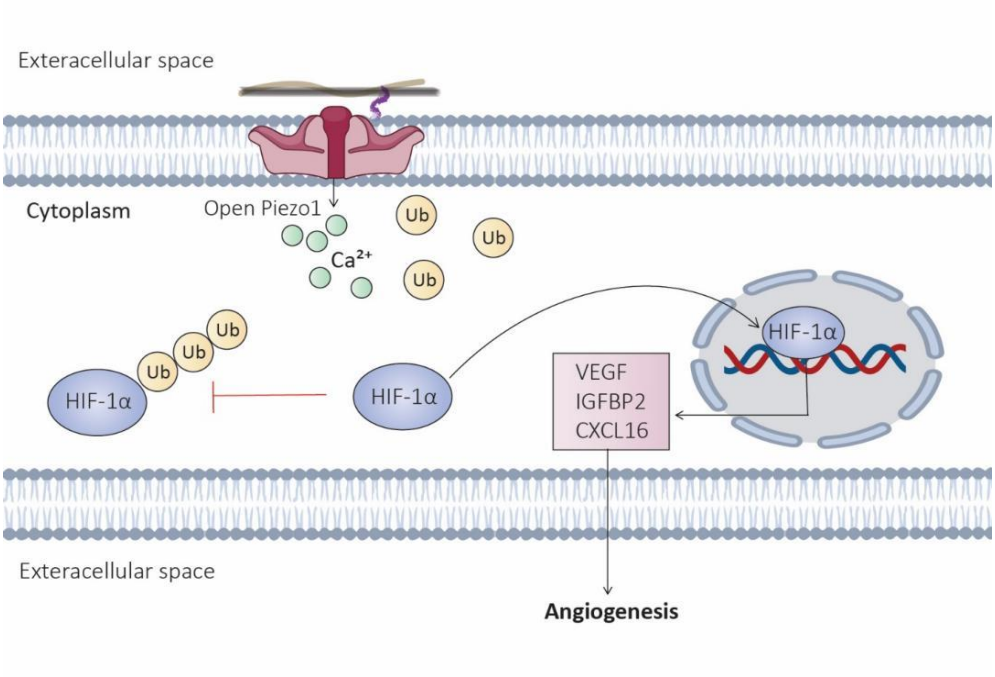

Figure 3. Matrix stiffening or cytoskeletal tension activates the Piezo1 ion channel, leading to calcium influx that stabilizes HIF-1α by inhibiting its ubiquitination and degradation. Stabilized HIF-1α translocates to the nucleus and induces the transcription of pro-angiogenic genes, including VEGF, IGFBP2, and CXCL16, thereby promoting aberrant neovascularization within the tumor microenvironment.

Piezo1 further couples mechanical stress to major oncogenic pathways. In HepG2 cells, Piezo1-dependent Ca^{2+} influx activates JNK, p38, and ERK signaling, culminating in YAP nuclear translocation; Piezo1 silencing disrupts this MAPK-YAP axis and impairs tumor growth in Piezo1-haploinsufficient mice [63]. Mo et al. extended these findings by showing that Piezo1 activation induces ERK1/2- and AKT-dependent upregulation of CXCL8 and MTHFD2, linking mechanotransduction to inflammatory cytokine release and mitochondrial one-carbon metabolism. Piezo1 antagonists (GsMTx4 and arachidonic acid) synergized with oxaliplatin to inhibit tumor growth, suggesting mechanosensory blockade as an approach to enhance chemosensitivity [64].

The systemic consequences of PIEZO1 dysregulation underscore its broader physiological relevance. Gain-of-function PIEZO1 mutations suppress hepatic hepcidin through ERK1/2 activation and BMP/SMAD inhibition, promoting iron-loading phenotypes [65]. Reduced arterial flow in transplant settings activates PIEZO1/SRC-mediated NET formation, contributing to bile duct injury [66]. Special contexts further highlight its oncogenic versatility, as Piezo1 functions upstream of a HIF-1α-VEGF axis that promotes migration and invasion in hepatoblastoma [67], and the Jianpi Huayu (JPHY) decoction enhances doxorubicin sensitivity by downregulating Piezo1 and inhibiting PI3K/AKT/mTOR, thereby reducing xenograft tumor burden [68]. Additionally, matrix stiffening in non-tumorous hepatocytes activates Piezo1-ERK1/2 signaling, suppressing HNF4α, elevating IL-6, and inducing DNA

damage-effects reversible by Piezo1 silencing or ERK inhibition-linking fibrotic mechanics to premalignant transformation [69].

Together, these findings position Piezo1 as an integrative mechanotransductive hub in HCC, linking ECM stiffness and Ca^{2+} signaling to downstream pathways including HIF-1α, TGF-β, YAP, and PI3K/AKT. Through these convergent mechanisms, Piezo1 orchestrates angiogenesis, EMT, metabolic plasticity, and inflammation-core hallmarks of HCC progression. Therapeutically, targeting Piezo1 or its associated signaling modules represents a promising mechanopharmacologic approach to counter stiffness-driven tumorigenesis and enhance existing chemotherapeutic and anti-fibrotic strategies.

3.5 Piezo1 in Gastric Cancer (GC)

Piezo1 has emerged as a critical mechanosensitive ion channel in GC, integrating mechanical tension, hypoxia, and inflammatory cues to promote tumor progression and peritoneal dissemination. Early work by Zhang et al. showed that Piezo1 is markedly upregulated in primary GC tissues and cell lines, with high expression correlating with poorer disease-specific survival. Functionally, Piezo1 enhances proliferation, invasion, and xenograft growth by modulating Rho GTPase activity-elevating Rac1 while suppressing RhoA-to preserve a motile cytoskeletal phenotype. Its silencing inhibits GC progression and increases sensitivity to cisplatin and 5-fluorouracil, underscoring its therapeutic relevance [70].

Building on these findings, Wang et al. demonstrated that Piezo1 overexpression drives omental and lymphatic metastasis through Ca^{2+}-dependent activation of the HIF-1α/Calpain1/2 axis. This pathway promotes migration, angiogenesis, and EMT, while PIEZO1 knockdown reverses these effects and markedly reduces peritoneal implantation *in vivo*, positioning Piezo1 as a mediator of hypoxia-driven metastatic adaptation [71].

More recently, Chen et al. identified a *Helicobacter pylori*-NF-κB-Piezo1-YAP1-CTGF signaling cascade linking chronic inflammation to mechanotransductive remodeling. NF-κB-dependent transcriptional upregulation of PIEZO1 enhances YAP1 signaling and increases CTGF-mediated CAF recruitment and collagen deposition, establishing a stiffening feed-forward loop that further augments Piezo1 activation. Inhibition of CTGF or Piezo1 knockdown sensitized tumors to 5-FU and suppressed peritoneal dissemination, highlighting this axis as a tractable therapeutic target [72].

These studies reveal that Piezo1 integrates diverse microenvironmental signals-including mechanical stress, hypoxia, and inflammation-to shape the malignant behavior of GC, making it an increasingly relevant target for therapeutic intervention.

3.6 Piezo1 in Colorectal Cancer

Piezo1 functions as a key mechanotransducer in colorectal cancer (CRC), linking extracellular mechanical forces to oncogenic signaling circuits that promote tumor progression, metastasis, and therapy resistance. PIEZO1 is consistently overexpressed in CRC and associates with poor prognosis and enhanced migratory behavior. Mechanistically, Piezo1 forms a functional axis with the mitochondrial calcium uniporter (MCU) and HIF-1α, coupling Ca^{2+} influx and mitochondrial depolarization to hypoxia-driven VEGF expression; Piezo1 overexpression or MCU suppression increases invasion through this Piezo1-MCU-HIF-1α-VEGF pathway [73].

Circulating CRC cells encounter fluctuating fluid shear stress (FSS), and metastatic derivatives such as SW620 exhibit greater shear resilience mediated partly by Piezo1-dependent Ca^{2+} influx. Yoda1 further amplifies this mechano-activation, and resveratrol enhances Piezo1 sensitivity via lipid-raft co-localization, showing that biochemical modulators can tune mechanosensory thresholds relevant to metastatic survival [74].

Cancer stem-like cells also depend on Piezo1. Elevated PIEZO1 expression sustains colorectal cancer stem cell (CCSC) self-renewal through a Ca^{2+}-nuclear factor of activated T cells 1 (NFAT1) axis, while Piezo1 knockdown destabilizes NFAT1 and suppresses stemness properties, identifying Piezo1 as a hierarchical regulator of tumor-initiating potential [75].

Mechanical cross-talk among collagen I, integrins, and mechanosensitive calcium channels reprograms CRC cells toward a fetal-like YAP-driven transcriptional state that favors invasion, highlighting the broader microenvironmental context through which Piezo1 is likely to operate, even when not directly interrogated [76].

An immune dimension further refines Piezo1's role, with tumor-intrinsic Piezo1 promoting immune evasion, while Piezo1 inhibition in cytotoxic T cells strengthens traction forces and enhances tumor killing. This positions Piezo1 as an immunomechanical checkpoint linking mechanotransduction to antitumor immunity [77].

Other Piezo family members participate in CRC progression. PIEZO2 upregulation enhances proliferation and angiogenesis via the SLIT2/ROBO1/VEGFC pathway [78], and emerging evidence connects PIEZO2 channelopathies with microbiota-associated and early-onset CRC, expanding the mechanobiological spectrum of Piezo dysfunction [79].

Altogether, Piezo1 integrates biomechanical stress, metabolic adaptation, and immune modulation in CRC, and targeting its Ca^{2+}-dependent signaling circuitry-alone or in combination with immunotherapy or anti-angiogenic strategies-represents a promising direction for precision mechanomedicine.

3.7 Piezo1 in Pancreatic Ductal Adenocarcinoma (PDAC)

PDAC develops within one of the most rigid and fibrotic microenvironments of any solid tumor, where elevated ductal pressure, desmoplasia, and hypoxia continuously engage mechanosensitive pathways. Within this biomechanical landscape, Piezo1 functions as a key

transducer coupling mechanical stress to oncogenic signaling and therapeutic resistance.

Initial evidence for Piezo1's mechanosensitivity came from pancreatic acinar cells, where mechanical pressure or Yoda1 induced Ca^{2+} influx and zymogen activation, causing acute pancreatitis; genetic deletion of Piezo1 conferred protection, identifying Piezo1 as a gatekeeper of pancreatic injury [80]. In PDAC cells, Piezo1 is highly expressed and drives malignant behavior, as activation by stiffness or Yoda1 stimulates Ca^{2+} influx, ERK and YAP signaling, EMT, proliferation, and migration, whereas inhibition suppresses these processes and reduces tumor growth *in vitro* and *in vivo* [81].

Piezo1 also operates within the stromal compartment. Pancreatic stellate cells (PSCs)-the major source of fibrosis-express abundant Piezo1 and convert mechanical compression into Ca^{2+}-dependent myofibroblastic activation, promoting TGF-β1, fibronectin, and collagen I secretion. Genetic or pharmacologic inhibition of Piezo1 attenuates fibrosis, indicating a stiffness-Piezo1 feedback loop that reinforces desmoplasia [82]. PSCs additionally sense stiffness gradients through cooperative activity of Piezo1, TRPV4, and transient receptor potential canonical 1 (TRPC1), regulating durotaxis and stromal remodeling [83].

Within tumor cells, high mechanical load induces metabolic reprogramming through a stiffness-Piezo1-Ca^{2+}-glycolysis axis. Three-dimensional PDAC cultures showed that Piezo1 activation increases glucose uptake and lactate production by upregulating *GLUT2*, *HK2*, and *LDHA*, conferring gemcitabine resistance; inhibition of Piezo1 or glycolysis reverses this phenotype [84].

Piezo1's mechanosensitivity has also motivated therapeutic strategies. Ultrasound combined with microbubbles (US+MB) produces robust Piezo1-mediated Ca^{2+} influx and apoptosis in PDAC cells, an effect abolished by PIEZO1 knockdown [85]. Ultrasound-targeted microbubble destruction (UTMD) induces both autophagy and apoptosis, and autophagy inhibition enhances UTMD cytotoxicity, suggesting context-dependent crosstalk between survival and death pathways [86].

Additional studies reveal broader microenvironmental integration. Acidic extracellular pH diminishes Piezo1-dependent Ca^{2+} influx in PSCs yet paradoxically increases cytoskeletal tension and motility, indicating that acidosis modulates mechanosensing thresholds [87]. Piezo1 also influences immune remodeling by engaging a Piezo1-integrin-PYK2 pathway that regulates monocyte-to-macrophage differentiation and polarization, thereby contributing to the immunosuppressive stromal milieu characteristic of PDAC [88] (Figure 4).

Together, these findings portray Piezo1 as an active orchestrator of PDAC progression, synchronizing epithelial transformation, stromal fibrosis, metabolic adaptation, and immune modulation. Its dual therapeutic potential is noteworthy, as inhibition may reduce fibrosis and chemoresistance, while controlled activation-such as through ultrasound-can trigger apoptosis and disrupt biomechanical homeostasis, positioning Piezo1 as a promising target for precision mechanomedicine in pancreatic cancer.

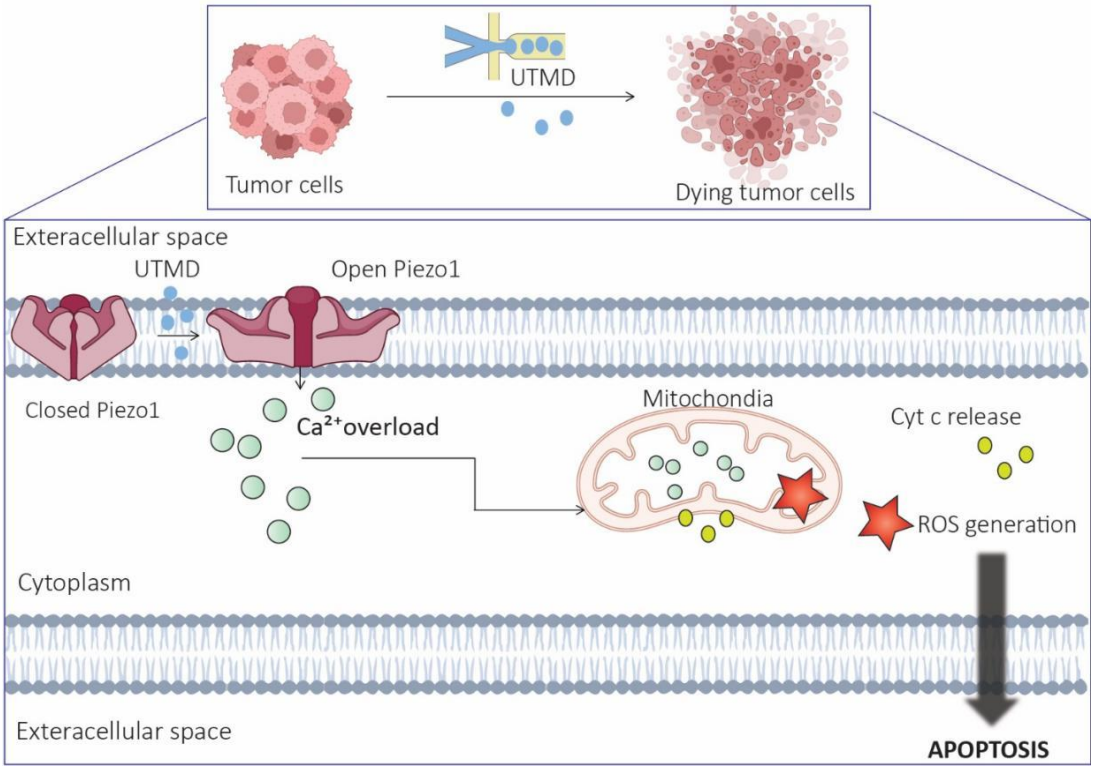

Figure 4. At the macroscopic level (top panel), UTMD enhances the penetration of therapeutic macromolecules into the tumor mass, resulting in widespread tumor cell injury. At the cellular level (bottom panel), ultrasound-induced mechanical stress opens Piezo1 channels, triggering excessive Ca^{2+} influx. The resulting mitochondrial Ca^{2+} overload leads to ROS generation and cytochrome c (Cyt c) release, activating intrinsic apoptotic pathways and promoting tumor cell death.

3.8 Piezo1 in Lung Cancer

Mechanical changes in the lung tumor microenvironment-particularly reduced cyclic stretch and increased ECM stiffness-impair responses to immunotherapy in non-small-cell lung cancer (NSCLC). Mechanical or pharmacologic activation of Piezo1 reverses this effect by promoting YAP nuclear translocation, increasing PD-L1 expression, and inducing CXCL10 secretion, thereby supporting a T cell-infiltrated, immunotherapy-responsive microenvironment. Computational modeling shows that cyclic stretch converts the stiffness-dependent bimodal PD-L1/CXCL10 pattern into a unified response, indicating that mechanical cues can reset the immune setpoint. Consistent with this, combining a Piezo1 agonist with anti-PD-1 enhances tumor control and $CD8^+$ T-cell recruitment in NSCLC liver metastasis models [89].

Genomic analyses add further nuance, showing that PIEZO1 and PIEZO2 are frequently downregulated in NSCLC relative to adjacent tissue, with PIEZO1 exhibiting recurrent deletions and PIEZO2 carrying mutations. Higher PIEZO expression correlates with improved survival-especially in LUAD-while Piezo1/2 knockdown accelerates migration and tumor growth, suggesting a tumor-suppressive role in specific epithelial contexts [90].

Mechanobiological studies help reconcile these observations. Unlike most solid tumors, stiff matrices suppress Piezo1 signaling and Ca^{2+} influx in lung cancer cells, enhancing migration via cofilin phosphorylation and filopodia formation. Pharmacologic activation of Piezo1 (Yoda1) or elevating Ca^{2+} reverses this phenotype, whereas Piezo1 inhibition mimics the effects of stiffness. This defines a stiffness-dependent regulatory mode in which Piezo1 restrains migration under physiological tension but becomes ineffective under pathological rigidity [91].

Stromal states further shape Piezo1 function. Single-cell and spatial transcriptomics identify a population of $PIEZO1^+$ cancer-associated fibroblasts (CAFs) enriched for ECM-remodeling programs and associated with reduced $CD8^+$ infiltration, elevated Treg density, and poor response to checkpoint blockade. Clinically, PIEZO1-high CAF signatures predict shorter progression-free and overall survival, implicating stromal Piezo1 in immunotherapy resistance [92].

At the regulatory level, PIEZO1 is suppressed by miR-942-5p, which activates MAPK signaling via filamin A (FLNA), RRAS, and MAP3K6. Restoring PIEZO1 expression reduces migration and improves survival, whereas miR-942-5p-mediated downregulation promotes aggressiveness [93]. Piezo channels also participate in physiologic pulmonary mechanosensation-including airway stretch responses, vascular tone, and alveolar integrity-highlighting the need for Piezo1-directed therapies to preserve essential respiratory function [94].

Taken together, these findings show that Piezo1 exerts context-dependent roles in lung cancer, enhancing immune responsiveness in metastatic niches while restraining migration in primary epithelial settings. The suppression of Piezo1 signaling by matrix stiffening distinguishes NSCLC from other solid tumors and provides a mechanistic basis for its dual behavior. These insights position Piezo1 as a mechanically tunable regulator whose modulation could recalibrate immune sensitivity, limit metastatic dissemination, and reconfigure stromal interactions while maintaining core respiratory mechanics.

3.9 Piezo1 in Prostate Cancer (PCa)

PCa is highly sensitive to mechanical cues arising from luminal fluid shear, stromal remodeling, and matrix stiffening. Across molecular and functional datasets, Piezo1 emerges as a principal mechanotransducer coupling these biomechanical inputs to proliferative and metastatic signaling. PIEZO1 is markedly upregulated in human PCa, and its depletion reduces viability, migration, and tumorigenicity. Mechanistically, Piezo1-mediated Ca^{2+} influx activates Akt/mTOR signaling and promotes G_0/G_1-S progression through induction of CDK4 and cyclin D1, establishing a canonical Piezo1-Ca^{2+}-Akt/mTOR axis that sustains proliferation [11].

Mechanical forces also regulate metastatic behavior. Physiological interstitial shear activates Piezo1 and engages Src-YAP signaling to reorganize the cytoskeleton, retain YAP/TAZ in the nucleus, and enhance motility. Yoda1 further amplifies shear-induced migration, whereas PIEZO1 knockdown suppresses this response and limits metastatic outgrowth in orthotopic models [95]. Increased matrix stiffness elicits similar Piezo1-dependent transitions, producing elevated intracellular Ca^{2+}, increased vimentin expression, and cell elongation, together with reduced E-cadherin. These EMT-like changes are reversed by GsMTx-4, demonstrating that stiffness and shear converge on a shared Piezo1-Ca^{2+}-YAP program driving epithelial-mesenchymal plasticity [96].

The mechanosensitivity of PCa has translational implications. Focused ultrasound (FUS), particularly when combined with physiologic shear, co-activates Piezo1 and markedly enhances TRAIL-mediated apoptosis; this synergy is abolished by Ca^{2+} chelation, mechanosensitive-channel blockers, or PIEZO knockdown. Multi-dose FUS plus TRAIL reduces tumor burden *in vivo*, supporting a non-thermal mechanotherapeutic strategy for sensitizing PCa to apoptosis [97].

Piezo1's influence extends to metastatic bone colonization. Osteocytes, which are highly mechanosensitive, respond to oscillatory fluid flow by suppressing PC-3 adhesion and trans-endothelial migration via VCAM-1-dependent signaling, reducing metastatic seeding despite the pro-migratory effects of tumor-intrinsic Piezo1 [98]. This highlights a microenvironment-specific dichotomy in mechanotransduction.

Overall, these findings define a dualistic paradigm in which Piezo1 promotes proliferation and EMT in primary and soft-tissue metastatic niches through Ca^{2+}-

Akt/mTOR and Src-YAP signaling, whereas mechanotransduction within the osseous microenvironment can oppose early metastatic colonization. Therapeutically, modulating Piezo1-either by inhibition to restrain oncogenic signaling or by controlled activation to enhance apoptosis-offers a promising mechanomedicine strategy for PCa.

3.10 Piezo1 in Renal Cell Carcinoma (RCC)

Clear cell renal cell carcinoma (ccRCC) arises within a collagen-rich and progressively stiffening microenvironment, where mechanical cues strongly influence tumor behavior. Across transcriptomic and proteomic datasets (TCGA, CPTAC), PIEZO1 expression correlates with tumor grade, stage, and poor overall survival, establishing it as an independent prognostic marker in ccRCC. Immunohistochemistry further shows elevated cytoplasmic PIEZO1 in high-grade tumors relative to adjacent tissue, consistent with enhanced mechanical adaptation during disease progression [99].

Stiffness serves as a principal upstream regulator of Piezo1 activation. Using collagen-based hydrogel systems that reproduce physiologic rigidity, Zhu et al. showed that increasing stiffness promotes proliferation, migration, EMT, stemness, and metabolic reprogramming in kidney renal clear cell carcinoma (KIRC) cells. These effects require Piezo1-dependent Ca^{2+} influx, which activates the calpain-YAP axis; calpain promotes cytoskeletal remodeling and YAP nuclear translocation, driving transcriptional programs that support survival and motility. Genetic or pharmacologic inhibition of PIEZO1 abrogates these responses, demonstrating that the Ca^{2+}/calpain/YAP pathway constitutes the core mechanotransductive circuit through which matrix rigidity fosters malignant progression in RCC [100]. These findings point to Piezo1 as a central mediator of stiffness-driven signaling in RCC, linking ECM mechanics to Ca^{2+} influx, cytoskeletal remodeling, and YAP activation, and defining a therapeutic vulnerability within the RCC mechanotransductive network.

3.11 Piezo1 in Bladder (Urothelial) Carcinoma

Bladder carcinoma (BLCA) develops within a highly dynamic mechanical environment shaped by repetitive filling and voiding cycles that alter urothelial tension and remodel ECM stiffness. Within this fluctuating setting, Piezo1 has emerged as a key mechanotransducer that converts physical deformation into downstream oncogenic signaling.

Clinical and experimental studies show marked upregulation of PIEZO1 and PIEZO2 in human and murine BLCA, with expression levels correlating with tumor size, stage, and grade, and associating with increased proliferative and angiogenic activity [101]. These findings suggest that Piezo channels participate directly in carcinogenic signaling rather than serving solely as passive mechanosensors.

Mechanistic work by Ma et al. further defines a stiffness-driven feedback loop centered on cooperative Piezo1-ITGB1 signaling. ECM stiffening activates the Piezo1/ITGB1 complex, inducing Ca^{2+} influx and YAP nuclear translocation. YAP then upregulates CTGF, α-SMA, and COL1A1, enhancing collagen deposition and reinforcing matrix rigidity. Blocking either Piezo1 or ITGB1 disrupts Ca^{2+} signaling and prevents stiffness-induced proliferation, demonstrating their synergistic role in amplifying mechanochemical signaling [102].

Together, these studies position Piezo1 as a mechanobiological amplifier in BLCA-linking integrin-mediated adhesion with Ca^{2+}-YAP transcriptional programs to drive ECM stiffening and malignant progression. This mechanistic framework highlights Piezo1-integrin signaling as a potential therapeutic entry point for disrupting stiffness-dependent tumor evolution in urothelial carcinoma.

3.12 Piezo1 in Glioma and Glioblastoma

Gliomas arise within a mechanically abnormal brain milieu shaped by solid stress, perivascular stiffness, and edema. Across transcriptomic datasets and functional models, PIEZO1 consistently appears as a central mechanosensor that converts these aberrant forces into oncogenic signaling. PIEZO1 localizes to focal adhesions, where force-evoked activation engages integrin-FAK pathways to remodel the ECM; the resulting stiffening further elevates PIEZO1 expression, forming a reciprocal circuit that links tissue mechanics to tumor aggression [103]. Clinical analyses identify PIEZO1 as a strong adverse prognostic marker [104], and radiogenomic studies show that higher PIEZO1 expression correlates with more severe peritumoral edema, connecting channel activity to mass-effect physiology [105].

Mechanical compression-ubiquitous in intracranial tumors-further induces PIEZO1 and a growth differentiation factor 15 (GDF15)-driven migratory phenotype while elevating CTLA-4, suggesting a PIEZO1-GDF15-CTLA4 axis coupling solid stress to invasion and immune evasion [106]. Angiogenic control intersects with this circuitry, as VEGF-Myc signaling increases myosin-Ib (Myo1b) in glioblastoma endothelium, enhancing PIEZO1-mediated Ca^{2+} influx and promoting neovascular proliferation [107].

Additional regulatory inputs converge on PIEZO1. Glioma stem-like cells elevate PIEZO1 via circZNF800-mediated miR-139-5p suppression, activating Akt to support growth and migration [108]. Neuronal shedding of neuroligin-3 similarly activates PIEZO1 to maintain progenitor-like states, while PIEZO1 overexpression in astrocytes shortens survival in transgenic models, indicating that glial mechanosensitivity contributes to a pro-tumor niche [109,110].

Mechanistically, PIEZO1-mediated Ca^{2+} entry also supports volume regulation through large-conductance calcium-activated potassium channel (BKCa)/ intermediate-conductance calcium-activated potassium channel (IKCa) channels, facilitating migration through

the narrow extracellular spaces of brain parenchyma [111]. Therapeutically, activating PIEZO1 with Yoda1 or fluid shear enhances TRAIL-induced apoptosis, including in temozolomide-resistant cells, suggesting opportunities for mechanically primed cytotoxic strategies [112]. By coupling mechanical stress, ECM dynamics, vascular responses, and stem-associated signaling, PIEZO1 shapes several core processes in glioma progression and identifies tractable nodes for therapeutic targeting.

3.13 Piezo1 in Melanoma

Transcriptomic datasets and functional studies identify PIEZO1 as a consistently upregulated mechanosensor in melanoma, where elevated expression correlates with poor survival and aggressive histopathology. Loss of PIEZO1 reduces Ca^{2+} influx, viability, and transendothelial invasion, while melanoma metastasis models show impaired colonization upon genetic silencing, positioning PIEZO1 as an important driver of metastatic competence. Mechanistically, Piezo1 activity sustains proliferation and survival through Ca^{2+}-dependent activation of the AKT/mTOR pathway [113].

Mechanical constraints encountered during circulation further amplify this program. Passage through microcapillary constrictions triggers rapid Piezo1-mediated Ca^{2+} influx, inducing chromatin remodeling and a stem-like transcriptional state that enhances extravasation and seeding capacity. Genetic or pharmacologic inhibition of PIEZO1 prevents this mechanical reprogramming, whereas Yoda1 activation reproduces it in the absence of compression, revealing a feed-forward link between confinement and tumor-initiating potential [114].

Plasma membrane composition also modulates Piezo1 gating. Cholesterol depletion blunts bleb-based amoeboid migration in confined environments by impairing Piezo1 tension sensing and lowering intracellular Ca^{2+} levels; cholesterol restoration or Piezo1 activation rescues motility. Clinically, high cholesterol biosynthetic signatures associate with poor survival, suggesting that metabolic regulation of membrane mechanics shapes Piezo1-driven metastasis [115].

Conversely, under soft anchorage-independent 3D conditions, Piezo1 activation with Yoda1 disrupts spheroid integrity in melanoma cells, indicating that channel activation can produce anti-aggregative or cytotoxic effects when mechanical context differs from stiffness or confinement cues [116]. The melanoma phenotype shaped by Piezo1 is therefore not fixed but mechanically determined, with compression, confinement, and membrane composition dictating whether signaling promotes invasion or disrupts cellular cohesion. Therapies engaging Piezo1 must account for these contextual switches.

3.14 Other PIEZO1-Associated Malignancies

Across several less-characterized malignancies, PIEZO1 functions as a mechanically tuned regulator whose downstream consequences vary by lineage and microenvironmental context. In cholangiocarcinoma, cyclic tissue stretch activates PIEZO1 to induce YAP nuclear translocation, EMT, and metastatic dissemination; genetic loss of PIEZO1 diminishes these behaviors, defining a stretch-responsive PIEZO1-YAP axis as a core driver of biliary cancer progression [117]. Under certain loading conditions, however, the same stretch input can provoke catastrophic Ca^{2+} influx and apoptosis in mesenchymal-like cells, indicating that PIEZO1 gating thresholds may be therapeutically exploitable when aligned with tumor biomechanics [118].

In epithelial tumors dependent on nutrient scavenging, PIEZO1 activation can have anti-metabolic effects. In A431 epidermoid carcinoma, Yoda1-induced PIEZO1 opening suppresses EGF-driven macropinocytosis through Ca^{2+}-intermediate-conductance calcium-activated potassium channel 3.1 (KCa3.1) signaling, impairing amino-acid uptake and limiting proliferation in Ras-transformed cells [119]. Distinctly, in esophageal squamous cell carcinoma, PIEZO1 functions as a druggable surface protein, where antibody binding triggers receptor internalization and enables targeted delivery of monomethyl auristatin E (MMAE), resulting in tumor regression with limited toxicity [120].

Sarcomas generally show a survival dependency on PIEZO1. Synovial sarcoma and osteosarcoma cells exhibit high PIEZO1 activity, and its knockdown reduces viability, invasion, and tumor growth, nominating PIEZO1 as a potential therapeutic target in mesenchymal malignancies [91,92]. In hematologic settings, PIEZO1 supports leukemic blast fitness in acute myeloid leukemia (AML) by maintaining cell-cycle progression and DNA damage responses, whereas T-cell PIEZO1 inhibition enhances cytotoxic traction forces and antitumor activity-emphasizing the need for compartment-selective targeting strategies [77,121,122].

Additional contexts illustrate diagnostic and microenvironmental implications. PIEZO1 upregulation in salivary glands after radiation exposure suggests utility as a biomarker of tissue injury [123], while in oral squamous carcinoma, increased stiffness elevates PIEZO1/CD44 expression in tumor spheroids and extracellular vesicles, hinting at mechanosignal export mechanisms relevant to metastasis and liquid biopsy approaches [124]. A structured overview of Piezo1 expression patterns, functional roles, clinical associations, and mechanistic pathways across cancer types is summarized in Table 1.

Table 1. Expression, functional roles, and mechanisms of Piezo1 across cancer types.

Cancer type	Expression pattern	Functional roles	Clinical correlations	Mechanistic insights	References
Breast cancer	Upregulated	Promotes proliferation, migration, ECM remodeling, ferroptosis resistance	Lymph node metastasis; poor overall survival	Ca^{2+}-YAP/TAZ and ERK/MAPK activation; Notch1 and cytoskeletal remodeling	[9,41-52]
Ovarian cancer	Upregulated	Enhances spheroid detachment, invasion, peritoneal implantation	Advanced FIGO stage; ascites formation	Piezo1-YAP-MMPs axis; TRIM25-Piezo1 regulates ferroptosis	[3,53-56]
Cervical cancer (CC)	Upregulated	Drives migration and EMT; can trigger ferroptosis context-dependently	Lymph node metastasis; poor PFS	Ca^{2+}-ATP-YAP signaling; LOXL2-ECM-Piezo1 feedback loop	[57-60]
Hepatocellular carcinoma (HCC)	Upregulated	Induces angiogenesis, proliferation, metastasis, chemoresistance	Vascular invasion; poor OS	β1-Integrin-Piezo1-Ca^{2+}-HIF-1α/VEGF; ERK/AKT/YAP cascades	[61-69]
Gastric cancer (GC)	Upregulated	Promotes proliferation, invasion, angiogenesis	Poor EFS and OS	HIF-1α/Calpain and NF-κB-YAP-CTGF axis	[70-72]
Colorectal cancer	Upregulated	Stimulates proliferation, migration, invasion	Deeper invasion; poor prognosis	Piezo1-MCU-HIF-1α-VEGF signaling; enhances glycolysis	[73-79]
PDAC	Context-dependent	Induces apoptosis under acute mechanical load; promotes EMT under matrix stiffness	Fibrotic TME; therapy resistance	ERK/YAP mechanosignaling; metabolic rewiring	[80-88]
Non-small-cell lung cancer (NSCLC)	Variable	Modulates migration, cytoskeletal tension, immune evasion	Advanced stage; metastasis	Ca^{2+}/cofilin-YAP modulation; $Piezo1^{+}$ CAFs suppress immunity	[89-94]
Prostate cancer (PCa)	Upregulated	Promotes tumorigenesis, proliferation, invasion	Advanced WHO grade; poor OS	AKT/mTOR and Src-YAP pathways	[11,95-98]
Renal cell carcinoma (RCC)	Upregulated	Induces EMT, migration	Poor OS	Ca^{2+}-Calpain-YAP axis	[99,100]
Bladder cancer	Upregulated	Enhances proliferation, migration, invasion	Distant metastasis; shorter OS	Piezo1-Integrinβ1-YAP feedback promoting stiffness-dependent growth	[101,102]
Glioblastoma	Upregulated	Promotes angiogenesis, migration, stemness; sensitizes to mechanical apoptosis	Higher grade; poor OS	Integrin-FAK-Piezo1-YAP loop; potentiates TRAIL response	[103-112]
Melanoma	Context-dependent	Promotes invasion in stiff ECM; triggers apoptosis in soft matrices	Variable metastatic potential	Ca^{2+}-AKT/mTOR and YAP/TAZ mechanotransduction	[113-116]
Cholangiocarcinoma	Upregulated	Promotes YAP nuclear translocation, EMT, metastasis	Enhanced invasiveness *in vitro* and *in vivo*	Stretch-Piezo1-YAP axis; Ca^{2+}-dependent mechanotransduction	[117,118]
Esophageal squamous cell carcinoma	Upregulated	Facilitates proliferation and invasion; serves as ADC surface antigen	Poor OS; strong Piezo1 internalization response	Anti-Piezo1-MMAE ADC triggers apoptosis and cell-cycle arrest	[120]
Epidermoid carcinoma	Upregulated	Anti-metabolic role-blocks nutrient scavenging and macropinocytosis	Reduced tumor growth *in vitro*	Yoda1-Piezo1 activation inhibits EGF-driven macropinocytosis via KCa3.1	[119]
Acute myeloid leukemia (AML)	Upregulated	Maintains leukemic blast survival; modulates apoptosis	Poor response to therapy; essential for viability	Basal mechanosensing via Piezo1-Ca^{2+}-DNA repair; knockdown arrests G0/G1	[77,121,122]
Oral squamous cell carcinoma	Upregulated	Increases migration and EV-mediated stiffness signaling	Poor OS; elevated Piezo1/CD44 in stiff matrices	3D stiffness elevates Piezo1 and EV export; mechanosignal priming	[123,124]

4. Piezo1 in the Tumor Microenvironment

Piezo1 extends its mechanosensory functions beyond malignant cells and critically shapes stromal and immune compartments of the tumor microenvironment (Figure 5). In this broader context, Piezo1 operates as a system-level mechanotransducer that converts physical properties of the tumor niche into coordinated biochemical responses across multiple cellular compartments, thereby influencing tumor architecture, vascular organization, and immune surveillance. By integrating cues such as ECM stiffness, compression, and shear stress, Piezo1 enables dynamic communication between tumor cells and their surrounding microenvironment.

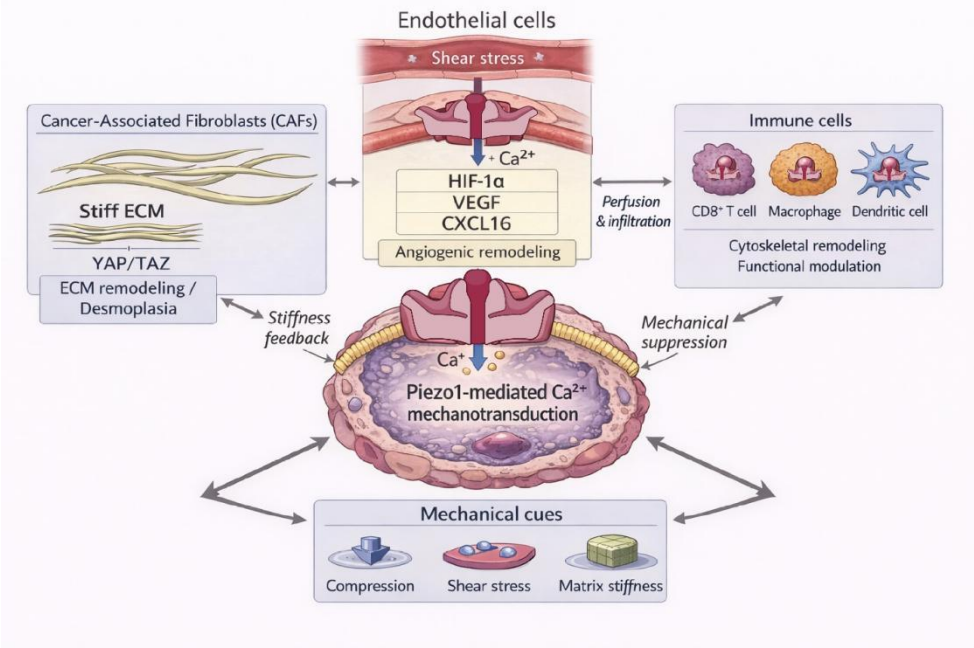

Figure 5. Piezo1 as a cross-compartmental mechanoregulator within the tumor microenvironment. Mechanical cues such as matrix stiffness, compression, and shear stress activate Piezo1 channels across malignant, stromal, endothelial, and immune compartments. Piezo1-mediated Ca^{2+} influx integrates these physical signals to coordinate ECM remodeling, angiogenic adaptation, and immune regulation, positioning Piezo1 as a central mechanobiological hub governing ecosystem-wide tumor behavior.

In CAFs, Piezo1 integrates matrix stiffness cues into fibroblast activation, promoting YAP/TAZ-dependent transcription of ECM-remodeling genes and reinforcing desmoplastic stiffening [125]. This fibroblast-centered mechanotransduction amplifies matrix deposition and alignment, which in turn alters force distribution within the tumor mass and feeds back onto mechanosensitive pathways in neighboring malignant and endothelial cells. Mechanical compression activates a β1 integrin-FAK-Piezo1 signaling axis in 3D breast epithelium, enhancing collagen deposition and invasive architecture [126,127]. Together, these mechanisms highlight how Piezo1-dependent stromal remodeling establishes a mechanically permissive landscape that supports collective invasion and tissue-level reorganization.

In endothelial cells, Piezo1 serves as a critical shear-stress sensor guiding angiogenic remodeling. Through its ability to sense both luminal flow and matrix-derived mechanical resistance, endothelial Piezo1 aligns vascular behavior with the evolving mechanical demands of growing tumors. In HCC, stiffened matrices activate endothelial Piezo1, leading to HIF-1α stabilization and upregulation of VEGF and CXCL16, which promote aberrant neovascularization [61]. In glioblastoma, Piezo1 signaling-mediated through Myo1b-dependent mechanotransduction-enhances endothelial sprouting and migration under compressive load [106]. These vascular adaptations contribute not only to tumor expansion but also to spatial heterogeneity in oxygenation, nutrient delivery, and therapeutic accessibility.

Mechanical regulation of immune cells represents a further dimension of Piezo1 function within the tumor microenvironment. As immune cells infiltrate mechanically heterogeneous tissues, Piezo1-mediated calcium signaling provides a means to translate physical stress into functional immune outcomes. In cytotoxic T lymphocytes, PIEZO1 suppresses effector function under mechanical stress by triggering a GRHL3-RNF114-dependent actin-remodelling program, thereby reducing cytotoxicity against tumor cells [77]. This mechanosensitive attenuation of T-cell activity suggests that local tissue mechanics can directly influence antitumor immunity. Piezo1 in macrophages senses substrate stiffness or mechanical stress and can influence macrophage polarization and inflammatory responses under controlled conditions (e.g. *in vitro*) [128]. Similarly, Piezo1 in dendritic cells participates in mechanosensation that can modulate antigen presentation and cell maturation in response to mechanical cues (e.g. substrate stiffness) [129]. Collectively, these effects imply that Piezo1 acts as a mechanical checkpoint regulating immune activation, tolerance, and functional plasticity within solid tumors.

Importantly, the simultaneous engagement of Piezo1 across stromal, vascular, and immune compartments suggests that mechanotransduction in tumors is not compartmentalized but highly coordinated. Mechanical remodeling driven by fibroblasts influences endothelial shear patterns, while vascular architecture and immune cell infiltration further reshape local force distributions. Piezo1 sits at the center of this reciprocal network, enabling mechanical information to propagate across cell types and scales.

Taken together, these cross-compartmental functions position Piezo1 not only as a tumor-intrinsic mechanosensor but as a mechano-immune orchestrator of the tumor ecosystem-coordinating matrix remodeling, angiogenesis, and immune regulation-thus offering a systemic therapeutic target that transcends malignant cells. By acting at the interface of physical forces and cellular decision-making, Piezo1 provides a unifying framework for understanding how biomechanical

heterogeneity is translated into ecosystem-wide tumor behavior.

5. Mechanistic Basis for Piezo1's Divergent Roles

A coherent mechanobiological framework emerges from accumulating evidence across diverse solid tumors, indicating that the divergent outcomes of Piezo1 activation-ranging from pro-invasive signaling to apoptosis or ferroptosis-are governed by the integration of mechanical stimulus patterns, metabolic state, and molecular co-regulators [5].

In stiffness-enriched tumors such as HCC, GC, colorectal cancer, breast cancer, and ovarian cancer, chronic or low-amplitude mechanical loading consistently activates Ca^{2+}-dependent YAP/TAZ, PI3K-AKT, SRC-FAK, and HIF-1α pathways, thereby driving EMT, angiogenic remodeling, and metastatic adaptation [1,6,130]. In contrast, acute or high-intensity forces-such as ultrasound-induced mechanical bursts in PDAC and glioblastoma, or abrupt capillary constriction in melanoma-trigger rapid Piezo1 gating and mitochondrial Ca^{2+} overload, shifting signaling toward apoptosis or ferroptosis [5,85,114]. These outcomes are further shaped by tumor-specific metabolic and redox states: cervical carcinoma cells with impaired GPX4 activity are markedly more sensitive to Piezo1-driven ferroptosis [84], whereas metabolically adaptable tumors such as PDAC and HCC redirect Ca^{2+} influx toward glycolytic reprogramming or inflammatory cascades [64].

Molecular partners further modulate the outcome of PIEZO1 activation in tumors. For instance, in breast cancer, a β1-Integrin-FAK-PIEZO1 signaling axis has been implicated in extracellular-matrix stiffening, basement-membrane disruption and enhanced invasive behavior of 3D breast epithelium under mechanical compression [131]. Similarly, in ovarian cancer high expression of TRIM25 appears to promote K63-linked ubiquitination of PIEZO1, which correlates with suppression of ferroptosis and increased tumor cell survival and/or proliferation [54]. Moreover, in glioblastoma, mechanical compression was shown to activate PIEZO1 and upregulate GDF15 expression, contributing to tumor progression via a PIEZO1-GDF15 axis [106].

Plasma-membrane lipid composition and cytoskeletal prestress, known regulators of Piezo1 gating thresholds, add an additional layer of context-specific control [20,26]. Together, these findings support a unified model in which Piezo1 acts as a mechanotransductive decision hub, with its downstream biological fate emerging from the combined mechanical, metabolic, and molecular constraints unique to each tumor ecosystem. This unified framework refines the conceptual basis for understanding how distinct mechanical and biochemical contexts bias Piezo1 signaling toward either tumor-promoting or cytotoxic outcomes (Table 2).

Table 2. Context-dependent determinants of Piezo1 signaling outcomes in cancer.

Context / condition	Piezo1 activation pattern	Dominant downstream bias	Predominant biological outcome	References
Chronic matrix stiffening / fibrosis / desmoplasia	Sustained or recurrent mechanogating; persistent Ca^{2+} signaling	YAP/TAZ, ERK/MAPK, PI3K–AKT, HIF-1α; integrin–FAK feedback loops	Pro-tumor (EMT, invasion, angiogenesis, growth, chemoresistance)	[61-64,81,100,102]
Solid stress and long-lasting compression (3D confinement)	Sustained mechanical loading	Ca^{2+}-dependent cytoskeletal remodeling; invadopodia and matrix proteolysis	Pro-tumor (invasive architecture, matrix remodeling)	[5-8, 42-45]
Shear stress (ascites flow, hemodynamics, circulation)	Repeated transient gating tuned by flow	Endothelial mechanotransduction; mechano-metabolic adaptation	Context-dependent, often pro-adaptive	[35,55,74]
Acute high-intensity mechanical bursts (e.g. ultrasound, UTMD)	Abrupt high-amplitude channel opening; large Ca^{2+} influx	Mitochondrial Ca^{2+} overload; ROS/Cyt c signaling	Pro-death (apoptosis ± autophagy)	[85,86,112]
Abrupt geometric constriction or extreme confinement	Rapid transient Ca^{2+} spikes	Nuclear/chromatin remodeling or lethal overload	Context-dependent (metastatic priming or cytotoxicity)	[114]
Ferroptosis-permissive metabolic/redox state	Ca^{2+} influx coupled to oxidative stress	Lipid peroxidation and iron-dependent death pathways	Pro-death (ferroptosis)	[54,57]
Metabolic plasticity under mechanical load	Sustained mechanogating integrated with lipid/cholesterol or glycolytic rewiring	Glycolysis, inflammatory and one-carbon metabolism programs	Pro-tumor (survival advantage, chemoresistance)	[55,64,84]
Stromal and immune compartment engagement (CAFs, endothelium, immune cells)	Compartment-specific Piezo1 activation	ECM remodeling, angiogenesis, immune suppression	Ecosystem-level tumor support	[61,77,125,128,129]

6. *In Vivo* Research Progress Toward Clinical Translation

Extensive *in vitro* work has established Piezo1 as a key driver of tumor-stroma mechanotransduction, but *in vivo* studies provide the most persuasive evidence for translation and, critically, expose its context dependence.

In HCC, matrix stiffening upregulates Piezo1 and engages a β1-integrin/Piezo1/Ca^{2+}/HIF-1α axis that amplifies angiogenic outputs; Piezo1 silencing in orthotopic "stiff-liver" models reduces tumor vascularization, growth, and lung metastasis, indicating direct *in vivo* control of stiffness-driven malignancy [73]. Mechanistically aligned inhibition with Piezo1

antagonists (GsMTx4, arachidonic acid) synergizes with oxaliplatin to suppress tumor growth via ERK1/2 and AKT attenuation [61].

In PDAC, ultrasound-based mechanotherapy leverages Piezo1 hypersensitivity: low-intensity ultrasound with microbubbles (US+MB) triggers massive Ca^{2+} influx through Piezo1 to induce apoptosis [85]; Silencing Piezo1 abrogates this response, and UTMD elicits concurrent autophagy/apoptosis that can be pharmacologically tuned [86].

Glioblastoma models similarly reveal a pro-apoptotic window under controlled Piezo1 activation: chemical agonism with Yoda1 augments TRAIL-mediated apoptosis, including in temozolomide-resistant lines, nominating a "mechanically primed apoptosis" strategy [112].

Other systems underscore the bidirectionality of Piezo1 modulation. In cervical carcinoma, Yoda1 promotes extracellular ATP release and accelerates invasion via YAP/TAZ signaling, with *in vivo* growth enhancement upon agonist treatment [58]. In pancreatic cancer, Piezo1 activation under high mechanical load reinforces EMT and glycolytic rewiring that correlates with chemoresistance [84]. In ovarian cancer, genetic PIEZO1 knockout diminishes ascites burden, spheroid seeding, and mesenteric implants *in vivo*, supporting a pro-dissemination role for the channel in peritoneal spread [3]. In melanoma, Yoda1 disrupts tumorsphere formation in soft 3D conditions, suggesting context-specific anti-aggregative effects [116].

Finally, beyond epithelial compartments, *in vivo* and *ex vivo* findings indicate that tailored Piezo1 modulation can interact with immunity and the metastatic niche (e.g., breast cancer bone metastasis models with combined interventions), but these remain heterogeneous and model-dependent [114]. Complementary anti-metabolic effects of Piezo1 activation-such as Yoda1-mediated suppression of EGF-driven macropinocytosis in Ras-transformed epidermoid carcinoma-have been demonstrated [128].

Taken together, *in vivo* studies position Piezo1 as a double-edged mechanosensor: controlled activation (ultrasound/Yoda1) can be cytotoxic in selected mechanical contexts (PDAC, GBM) [85,86,112], whereas inhibition or genetic loss constrains angiogenesis, dissemination, and drug tolerance where stiffness-biased signaling dominates (HCC, OC) [3,61,64]. Effective translation will require calibrating stimulus mode, dose, and duration against each tumor's mechanical state and pathway bias.

Although diverse *in vivo* studies highlight the therapeutic promise of Piezo1 modulation, several barriers still constrain clinical translation. Piezo1 is broadly expressed in essential non-malignant tissues, raising concerns about on-target, off-tumor toxicity with systemic agonists, antagonists, or mechanical activation approaches. Moreover, Piezo1 responses are highly context-dependent and often divergent across tumor, stromal, and immune compartments, complicating prediction of net therapeutic effects. Finally, truly tumor-selective delivery strategies-whether chemical, genetic, or mechanically guided-remain underdeveloped. These limitations underscore that successful translation will require spatially confined delivery, biomarker-guided patient selection, and refined modulation strategies tailored to each tumor's mechanical state.

7. Development of Piezo1 Modulators and Gene-Intervention Strategies

Building on evidence from Section 4 that Piezo1 activity can yield either cytotoxic or tumor-promoting effects depending on the biomechanical milieu, current research has turned toward controlled chemical and genetic modulation of this mechanosensor. Therapeutically, Piezo1 represents both an opportunity and a challenge: it translates physical cues into Ca^{2+}-dependent biochemical signaling with remarkable sensitivity, yet its biological output varies across tissues and tumor types-ranging from apoptosis induction in high-stress conditions to pro-survival activation in stiff, hypoxic matrices [85,86,112].

The best-characterized pharmacologic modulators-Yoda1 (agonist) and GsMTx4 (inhibitory peptide)-embody this paradox. Yoda1, a small-molecule surrogate of mechanical stress, promotes Ca^{2+} influx and downstream YAP/TAZ and MAPK activation [85,86,112]. In glioblastoma and PDAC, controlled Piezo1 stimulation with Yoda1 enhances apoptosis and sensitizes tumors to TRAIL or ultrasound-mediated therapy; in contrast, in cervical and pancreatic models, the same compound drives extracellular ATP release, YAP nuclear translocation, and invasive remodeling [58,81].

Conversely, GsMTx4 suppresses Piezo1-mediated Ca^{2+} influx and downstream mechanotransduction. In HCC, its use-alongside arachidonic acid-dampens ERK1/2 and AKT signaling and restores chemosensitivity to oxaliplatin [64], underscoring potential in stiffness-dominated tumors. However, both Yoda1 and GsMTx4 lack selectivity and stability, restricting their translational value; for now, they remain experimental mechanopharmacology tools rather than clinical therapeutics.

Efforts to refine these agents leverage high-resolution cryo-EM structures that define the anchor, beam, and cap domains as allosteric control sites [13-15]. Early Yoda1 analogs bearing benzoic-acid or fluorinated moieties have achieved improved potency *in vitro*, though their pharmacokinetic and safety profiles remain undefined. Until more selective compounds emerge with tunable gating kinetics, Piezo1 modulation will likely remain a research probe paradigm.

Genetic interventions aim for durable channel reprogramming. siRNA knockdown of Piezo1 reduces invasion in cervical carcinoma [58] and, when paired with the JPHY formulation in hepatocellular models, enhances autophagy and doxorubicin sensitivity [68]. CRISPR/Cas9-mediated deletion of Piezo1 in hepatocytes alleviates stiffness-induced DNA damage by suppressing ERK1/2 activation [69], showing that mechanical stress phenotypes can be reversed through permanent channel silencing.

Emerging nanomechanical delivery systems unite physical and genetic control. Elasticity-tunable silica nanoparticles (81-837 MPa) can mechanically engage Piezo1 via gentle membrane indentation, re-polarizing macrophages toward an M1 phenotype and curbing hypoxic tumor expansion [130]. Likewise, the biomimetic alloy Ti2448 activates Piezo1-dependent YAP phosphorylation in macrophages, enhancing vascular and bone regeneration at tumor interfaces [132].

Together, these findings position Piezo1 not as a binary on/off switch but as a programmable interface linking tissue mechanics to tumor fate. Future therapies will depend less on simply activating or blocking the channel, and more on tuning its rhythm and amplitude-aligning mechanical communication with therapeutic intent.

8. Future Perspectives

Piezo1 has emerged as a pivotal molecular interpreter of mechanical cues within the tumor microenvironment, yet its clinical translation remains at a conceptual stage. The collective data from multiple tumor systems in this study suggest that Piezo1 does not operate as a simple on–off switch, but as a dynamic mechanotransductive rheostat whose biological consequences depend on mechanical magnitude, temporal persistence, and cellular context. This realization reframes future research around three interrelated questions: *how*, *when*, and *where* Piezo1 should be modulated to favor anti-tumor outcomes.

The first direction involves defining mechanical thresholds and temporal codes of Piezo1 activation. Evidence across hepatocellular, pancreatic, and glioblastoma models indicates that transient, acoustically induced activation can trigger apoptosis and autophagy, while sustained or matrix-driven activation supports angiogenesis, invasion, and metabolic adaptation. Quantitative mapping of Ca^{2+} flux amplitude, frequency, and recovery kinetics in response to different force modalities-shear, compression, ultrasound-could delineate precise “pro-apoptotic” versus “pro-invasive” signaling windows. Such temporal profiling would also clarify how Piezo1 cross-talks with YAP/TAZ, ERK, and PI3K/AKT in a time-dependent manner.

A second frontier lies in integrating mechanosensation with tumor immunology. As shown in this work, Piezo1-mediated calcium signaling shapes macrophage polarization, dendritic-cell maturation, and T-cell function, implying that the channel may serve as a biophysical checkpoint of immune competence. Future studies should investigate how Piezo1 controls metabolic-immune coupling-particularly the balance between glycolytic and oxidative programs that dictate immune exhaustion versus activation. Combining Piezo1 modulation with immune-checkpoint inhibitors or macrophage-reprogramming agents may provide a rational route to transform fibrotic, “mechanically cold” tumors into responsive, immune-permissive environments.

The third and most translational challenge is developing controllable and tissue-specific modulators. Chemical agents such as Yoda1 or GsMTx4 provide critical mechanistic insight but lack therapeutic precision. Next-generation strategies should merge *biophysical activation* (ultrasound, mechanical loading, or magnetic modulation) with *spatiotemporally confined delivery* systems, such as nanocarriers or biomaterials that respond to local stiffness or pressure. Integrating these with CRISPR-based editing or siRNA approaches could enable transient or permanent regulation of Piezo1 within selected cell populations, minimizing systemic toxicity while preserving mechanical signaling in normal tissue.

Finally, systems-level modeling and organoid platforms represent essential tools for future translation. Multiscale models that couple ECM stiffness, Piezo1 kinetics, and downstream signaling fluxes could predict therapeutic outcomes before *in vivo* experimentation. Organoid and organ-on-chip systems incorporating tunable elasticity and fluid dynamics would allow real-time monitoring of Piezo1 activity, bridging the gap between reductionist assays and physiological complexity.

Although ultrasound-based mechanotherapy has shown the ability to trigger pro-apoptotic Piezo1 activation in preclinical models, the specific mechanical dose parameters that reliably separate cytotoxic from potentially pro-invasive signaling remain undefined and are highly context dependent. Clinically, delivering controlled mechanical forces to deep or structurally fragile tumors also requires careful management of focal precision, off-target exposure, and thermal or cavitation-related risks. While these technical considerations lie beyond the scope of this biologically oriented review, they highlight the need for dedicated translational studies to establish safe and selective frameworks for Piezo1-targeted mechanotherapy.

In summary, the next phase of Piezo1 research demands a transition from descriptive to quantitative and integrative mechanobiology. By decoding the “force-time-context” logic that governs Piezo1 signaling, and by engineering technologies capable of precise mechanical communication with tumor cells, it will be possible to convert this channel from a hallmark of malignancy into a mechanotherapeutic axis-one that aligns mechanical homeostasis with immune restoration and therapeutic responsiveness.

9. Conclusion

Across diverse tumor contexts, Piezo1 emerges as the molecular nexus linking physical forces to cancer cell fate, angiogenesis, and immune regulation. Its activation transforms mechanical stress into biochemical language-translating stiffness, tension, and compression into Ca^{2+} signaling cascades that orchestrate proliferation, migration, and metabolic adaptation. In HCC, PDAC, and glioblastoma models, Piezo1 acts as both a driver of malignancy and, under defined conditions, a conduit for cell death. This duality defines the essence of its biological significance: Piezo1 is not inherently oncogenic or suppressive, but contextually interprets the mechanical environment it inhabits.

Within the tumor microenvironment, Piezo1 extends its influence beyond cancer cells, modulating fibroblast

activation, ECM remodeling, and the polarization of immune cells. By linking mechanotransduction to immune signaling, the channel integrates two of the most powerful forces governing tumor evolution - physical stress and immunologic tone-into a unified regulatory axis. Yet, this very integration also complicates therapeutic targeting, as interventions that relieve one form of mechanical pressure may inadvertently activate another compensatory pathway.

Collectively, the evidence situates Piezo1 at the crossroads of mechanical biology, metabolic control, and immunomodulation. The future of its clinical application depends on transforming this conceptual convergence into therapeutic precision: defining when to activate, when to inhibit, and how to spatially confine either response. As emerging technologies in ultrasound modulation, nanomechanics, and gene editing begin to converge, Piezo1 is poised to evolve from a mechanistic hallmark into a therapeutic interface- capable of restoring biomechanical balance, reawakening immune function, and overcoming resistance in the complex ecosystem of solid tumors.

Abbreviations

AFM: Atomic force microscopy

AML: acute myeloid leukemia

BLCA: Bladder carcinoma

CAFs: cancer-associated fibroblasts

CC: Cervical cancer

ccRCC: Clear cell renal cell carcinoma

CCSC: colorectal cancer stem cell

CRC: colorectal cancer

cryo-EM: cryo-electron microscopy

CXCL16: X-C motif chemokine ligand 16

ECM: Extracellular matrix

EMT: epithelial - mesenchymal transition

EOC: epithelial ovarian cancer

ERM: ezrin-radixin-moesin

FLNA: filamin A

FSS: fluid shear stress

FUS: Focused ultrasound

GBM: Glioblastoma

GC: Gastric cancer

GDF15: growth differentiation factor 15

GPX4: glutathione peroxidase 4

HCC: Hepatocellular Carcinoma

$HER2^+$: human epidermal growth factor receptor 2-positive

HGSOC: high-grade serous ovarian cancer

IGFBP2: insulin-like growth factor-binding protein 2

ITGB1: integrin β1

JPHY: Jianpi Huayu

KIRC: kidney renal clear cell carcinoma

LOXL2: Lysyl oxidase-like 2

MCU: mitochondrial calcium uniporter

MMAE: monomethyl auristatin E

Myo1b: myosin-Ib

NFAT1: nuclear factor of activated T cells 1

NSCLC: non-small-cell lung cancer

PCa: Prostate Cancer

PDAC: Pancreatic Ductal Adenocarcinoma

PSCs: Pancreatic stellate cells

RCC: renal cell carcinoma

ROS: reactive oxygen species

SREBP2: sterol regulatory element-binding protein 2

STOML3: stomatin-like protein 3

TGF-β: transforming growth factor-beta

THUs: transmembrane helical units

TNBC: triple-negative breast cancer

TRPC1: transient receptor potential canonical 1

TRPV4: transient receptor potential vanilloid 4

UTMD: Ultrasound-targeted microbubble destruction

VEGF: vascular endothelial growth factor

YAP1: Yes-associated protein 1

Competing Interests

There is no conflict of interest.

Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

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