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Review

PIEZO Channels in Breast Cancer: Emerging Roles and Therapeutic Potential

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Abstract

The mechanosensitive PIEZO family channels, PIEZO1 and PIEZO2, are essential for mechanotransduction and play roles in many cellular processes, including cell volume regulation, tissue development, touch sensation, and proprioception. Emerging evidence suggests roles for PIEZO channels in cancer biology; however, direct mechanistic evidence in breast cancer remains limited. They have been shown to promote proliferation, epithelial-to-mesenchymal transition (EMT), and migration; however, these roles are varied and context-dependent. In breast cancer specifically, the two PIEZO channels may play opposing and complex roles in tumor progression, the tumor microenvironment (TME), and the tumor immune microenvironment (TIME), potentially impacting therapeutic response and prognosis. Where breast cancer-specific mechanistic data are lacking, we integrate findings from other tumor types to generate testable hypotheses relevant to breast cancer. In this review, we will explore the importance of PIEZO channels in breast cancer development, progression, and therapeutic response, and explore therapeutics and potential strategies to improve patient outcomes.

Keywords: PIEZO channels; mechanotransduction; breast cancer; tumor microenvironment; calcium signaling

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1. Introduction

The PIEZO channels, PIEZO1 and PIEZO2, are non-selective mechanosensitive cation channels embedded in the cell membrane that open in response to mechanical stimuli, such as compression, stretch, shear stress, etc., allowing cation influx, particularly calcium (Ca^{2+}), for intracellular signaling [1,2]. The channels are closely related; however, they only share about 42% sequence homology [1]. Despite this, the two have remarkably similar structures. Cryo-electron microscopy studies of mouse PIEZO1 and PIEZO2 revealed that both proteins form propeller-shaped homotrimers that sit within the cell membrane [3]. Each channel consists of three blades, a central extracellular "cap," and a transmembrane ion-conducting pore [3,4]. Each blade, formed from nine transmembrane helical units (THUs) [4,5], sits within the membrane and curves upward, forcing the surrounding membrane into a dome shape [4,6]. These blades, connected to the center by intracellular "beam" structures, are proposed to function as force sensors when mechanical force is

applied to the membrane [3,5,7]. The transmembrane ion-conducting pore sits directly below the cap [3] and is formed by two of the membrane-spanning helices of the THUs of each blade [4,5]. It is currently proposed that when mechanical force is applied to the membrane, the blades will stretch and flatten, forcing the beam structures to pivot around the center, which opens the pore and allows ion influx for intracellular signaling [5,7] (Figure 1).

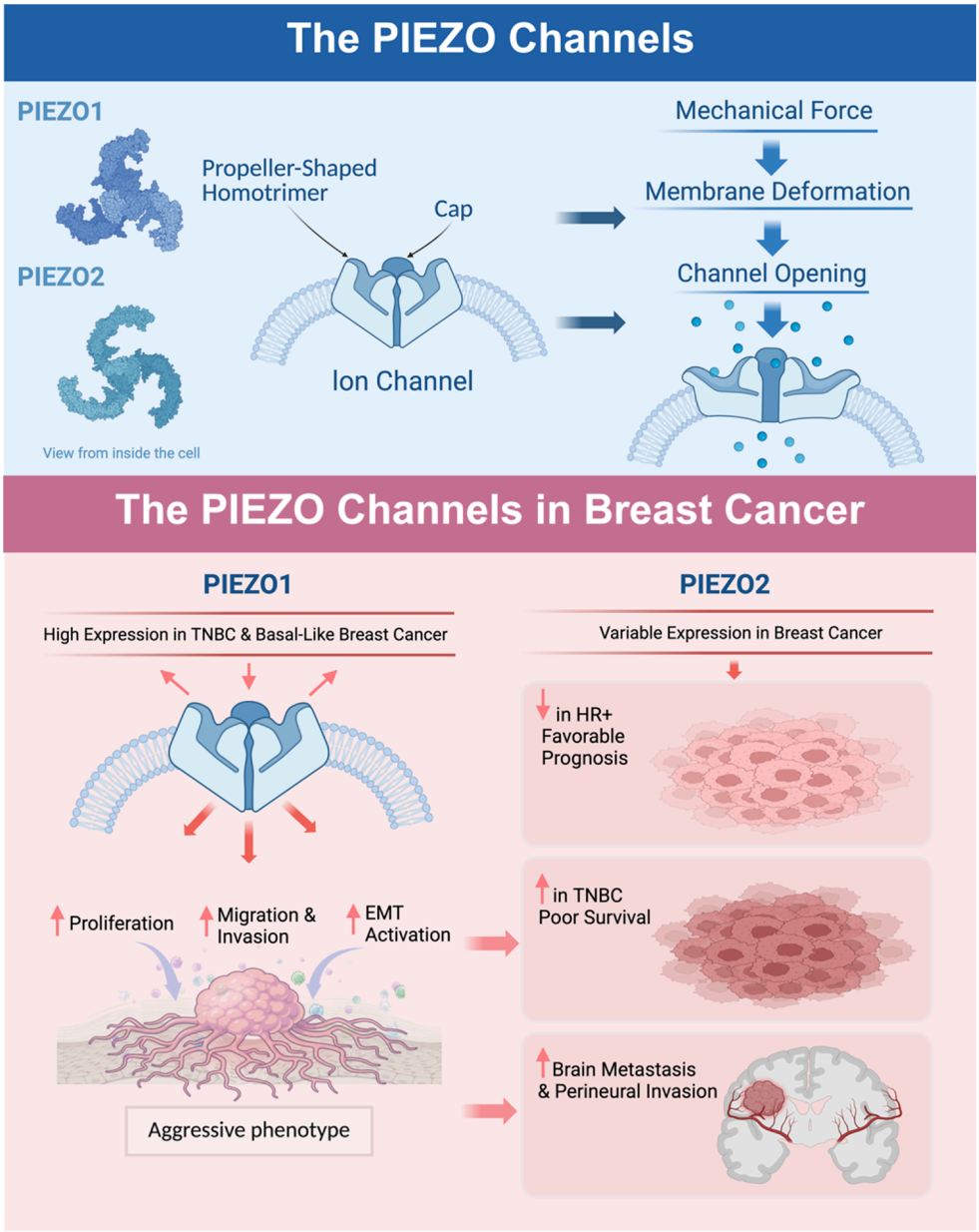


Figure 1. The PIEZO Channels in Breast Cancer. Schematic representation of the expression and functional roles of PIEZO channels in breast cancer. Mechanical stimuli from the tumor microenvironment, such as extracellular matrix stiffness, shear stress, and cell crowding, activate PIEZO channels, leading to calcium influx. This mechanotransduction regulates key cellular processes, including proliferation, migration, invasion, epithelial–mesenchymal transition (EMT), angiogenesis, and metastatic progression, thereby contributing to breast cancer development and aggressiveness.

PIEZO1 has versatile roles, including but not limited to vascular and lymphatic development [2,8], and red blood cell volume and blood pressure regulation [9–11], whereas PIEZO2 is the main sensor for sensory neurons and tissues, playing key roles in touch and proprioception [2,12]. Mutations in PIEZO1 are primarily linked to dehydrated hereditary

stomatocytosis/xerocytosis and generalized lymphatic dysplasia [13–15], while mutations in PIEZO2 are linked to Gordon syndrome/distal arthrogryposis, Marden-Walker syndrome, and disrupted proprioception and sensory neuropathy [16,17].

Recent evidence suggests both PIEZO channels play important roles in various cancer types including, but not limited to, gastric, colorectal, glioblastoma, osteosarcoma, bladder, lung, and breast. Much evidence suggests dysregulation of either channel contributes to various means of tumor development and progression, and may mediate therapeutic response through different mechanisms [18–21]. Since both channels are increasingly recognized as modulators of the tumor microenvironment (TME) and the tumor immune microenvironment (TIME) in breast cancer, we are here to review their diverse, context-dependent, and sometimes contradictory roles and functions in breast cancer tumor development, progression, and therapeutic implications. Given the limited number of breast cancer-specific mechanistic studies, this review distinguishes between direct evidence in breast cancer and mechanistic insights derived from other tumor types, which are discussed as hypothesis-generating frameworks.

2. The PIEZO Channels in Breast Cancer

Analyses of both breast cancer cell lines and patient-derived datasets revealed that PIEZO1 expression is elevated in tumor tissue [22,23] and various breast cancer cell lines [22–26] at both mRNA and protein levels, and as observed through the formation of functional PIEZO1 channels [25]. Furthermore, analyses of PIEZO1 expression between breast cancer subtypes indicate that PIEZO1 mRNA expression is significantly higher in hormone receptor (HR)-negative subtypes, particularly in triple-negative breast cancer (TNBC) [27] and basal-like subtypes [26]. Elevated PIEZO1 expression is associated with more aggressive phenotypes and poorer clinical outcomes, including worse relapse-free survival, overall survival, distant metastasis-free survival, and palliative performance status, as well as higher Scarff-Bloom-Richardson (SBR) grade and Nottingham Prognostic Index (NPI) scores [23,26,27]. Collectively, these findings indicate that PIEZO1 may serve as a prognostic biomarker, particularly in more aggressive breast cancer subtypes.

PIEZO1's contribution to breast cancer cell proliferation appears to be limited and highly context dependent. In unconfined in vitro conditions, PIEZO1 has no significant impact on the proliferation of TNBC MDA-MB-231 cells [24]. In contrast, compression-induced activation of PIEZO1 enhances proliferation in the same cell line, highlighting the importance of mechanical context in regulating PIEZO1-mediated effects [28]. Despite these limitations, there is much stronger evidence indicating that PIEZO1 has a direct impact on cell cycle progression and proliferation in several other cancer types, including melanoma, prostate, gastric, and ovarian cancers. In melanoma and prostate cancer, PIEZO1 knockdown or inhibition significantly attenuates cell viability and reduces proliferation through the blockage of AKT/mTOR pathway activation [29,30]. Whether a similar effect exists in breast cancer cells is unknown and warrants further investigation, as activation of this pathway contributes to breast cancer cell proliferation [31]. PIEZO1 knockdown also significantly suppresses gastric cancer cell proliferation by causing G0/G1 phase cell-cycle arrest, though the exact mechanism through which this occurs is still unknown [32]. In hepatocellular carcinoma (HCC), PIEZO1 knockdown significantly reduced cell proliferation; PIEZO1 activation and the subsequent calcium influx phosphorylate MAPK, in turn leading to nuclear YAP translocation, driving cell proliferation [33]. PIEZO1-dependent YAP signaling also drives oral squamous cell carcinoma (OSCC) cell proliferation [34]. These comparable findings indicate similar mechanisms may sustain breast cancer cell growth and survival; however, further studies are warranted.

Functionally, PIEZO1 has been consistently linked with enhanced migratory and invasive capabilities in breast cancer cells. Upon PIEZO1 inhibition with the inhibitor GsMTx-4, both motility and velocity of the cancerous MCF7 were significantly decreased, while the wild-type MCF10A maintained both. The observation indicates that only in the cancer context does PIEZO1 modulate cell movement, though the exact mechanism of this phenomenon is still unknown [25]. Interestingly, PIEZO1 seems partially responsible for the suppression of unconfined 2D cell migration in MDA-MB-231 cells [24], but knockdown significantly impairs invadopodia formation through a decrease in F-actin assembly and significantly decreases matrix metalloprotease (MMP) expression, though the detailed mechanism through which this occurs is still unknown [24]. Furthermore, when activated by compressive forces, such as those experienced by cancer cells within the tumor, the invasive capabilities of these cells increase significantly [28]. In a 3D in situ stiffening hydrogel system, the stiffening of the extracellular matrix (ECM) was found to activate β1 integrins and intracellular FAK signaling, which in turn led to the activation of Piezo1 to drive invasive capabilities in breast cancer cells [35]. Importantly, PIEZO activation is required for this process. Cytoskeletal remodeling/cell morphological changes characteristic of epithelial–mesenchymal-transition (EMT) induce PIEZO1 upregulation to form a positive feedback loop, in which these changes result in YAP1 nuclear translocation and the subsequent transcription of SERPINE1, a known marker associated with poor clinical outcomes, E-cadherin loss, and increased vimentin expression, further reinforcing EMT [36]. This suggests that PIEZO1 plays a central role in the ability of cancer cells to change or alter their shape for migratory purposes. Interestingly, PIEZO1 knockdown in MDA-MB-231 cells impairs their ability for mechanosensation and leads to a lack of directional migration on collagen matrices, suggesting PIEZO1 activation enables directional migration for force-informed metastasis from the tumor site [37,38].

Conversely, the function of PIEZO2 in breast cancer remains largely unexplored, but some evidence suggests it may also hold prognostic significance. First, PIEZO2 mRNA and protein expression in breast cancer cell lines is lower than that of normal mammary tissues [39,40]. Within breast cancers, PIEZO2 expression is higher in HR-positive subtypes than HER2-positive and TNBC subtypes, but high expression for all was associated with a favorable prognosis [40]. However, in TNBC, a previous study found that high PIEZO2 expression correlated with worse survival, greater migratory and invasive capacity, and enrichment of EMT-related gene signatures [41]. Given these opposing findings, further exploration of PIEZO2 expression and function in specific breast cancer subtypes is necessary for a greater understanding of the role it plays during tumor formation and progression. Furthermore, PIEZO2 activation is crucial for mechanosensing during metastasis to the brain, where calcium influx activates the downstream RhoA-mDia pathway to regulate actin fibers, focal adhesion, and YAP nuclear translocation to enhance invasion and survival within the metastatic niche [42], indicating that PIEZO2 may play an important role in breast cancer cell migration and metastasis (Figure 1). Interestingly, actively proliferating tumors had significantly higher PIEZO2 expression and evidence of perineural invasion [39]. These conflicting findings indicate that PIEZO2 may play a more complex, context-dependent role in breast cancer tumorigenesis and metastasis and warrants further investigation. As summarized in Table 1 of direct evidence linking PIEZO channels to breast cancer, the number of breast cancer–specific functional studies remains limited, highlighting the need for careful distinction between established findings and extrapolated mechanisms.

Table 1. Direct Evidence Linking PIEZO Channels to Breast Cancer.

Biological Process	Channel	Key Outcome	Evidence Type	Source
Expression Pattern, Association with Prognosis	PIEZO1	Expression elevated in tumor tissues/cell lines	Breast cancer-specific evidence from human data or breast cancer cell lines.	[23–27]
		Expression higher in HR negative and TNBC subtypes		
		Associated with poor clinical outcomes		
	PIEZO2	Expression lower in cancerous tissues/cell lines, higher PIEZO2 expression is generally associated with improved survival in most breast cancer subtypes.	Patient samples, human data and breast cancer cell lines (MCF-7, Bcap37, MDA-MB-468 and MDA-MB-231).	[39,40]
		High expression correlates with poor survival in TNBC.	Human data.	[41]
Cell Proliferation	PIEZO1	No significant impact in unconfined in vitro conditions	Breast cancer cell line: MDA-MB-231	[24,28]
		Compression increases proliferation		
		Knockdown and/or inhibition reduces proliferation	No direct evidence, extrapolated from other cancer models.	[29,30,32–34]
	PIEZO2	Ki67 staining increased with Piezo2 expression, indicative of greater cell proliferation within the tumor	Breast Tumors	[39]
Migration and Invasion	PIEZO1	Inhibition decreases motility and velocity	Breast Cell line: MCF7	[25]
		Suppresses 2D cell migration, but knockdown impairs invadopodia for movement and matrix degradation	Breast Cell line: MDA-MB-231	[24]
		Activation increases invasive capabilities		[28]
		Knockdown results in loss of directional migration		[37,38]
		Activation drives invasive phenotype	3D models of Breast acini using: MCF10A, MCF10DCIS.com, MCF7	[35]
	PIEZO2	Overexpression enhances migration and invasion	TNBC Breast Cell lines: MDA-MB-231, BT549	[41]
		Knockdown decreases migration and invasion	TNBC brain metastatic cells: MDA-MB-231-BrM2	[42]
EMT	PIEZO1	Upregulation enforces positive feedback loop with YAP1 and its targets to reinforce EMT	TNBC Breast Cell line: MDA-MB-468	[36]
	PIEZO2	Expression correlated with enrichment of EMT gene signatures	Human data.	[41]

3. The PIEZO Channels and Oncogenic Signaling Pathways

Direct mechanistic studies linking PIEZO channels to canonical oncogenic signaling pathways in breast cancer remain limited. Therefore, this section first summarizes available breast cancer data and then integrates mechanistic findings from other tumor types to propose testable hypotheses relevant to breast cancer. Mechanotransducers in breast cancer act as a bridge between the physical forces of the TME and the biochemical signaling pathways that drive malignancy [21]. In breast cancer, particularly in aggressive subtypes like TNBC, these channels are often overexpressed and "hijacked" to promote survival, invasion, and metastasis [41].

3.1. Regulation of PIEZO Channels in Breast Cancer

The activity and expression of PIEZO channels are not static; they are regulated by both the physical state of the tumor and specific molecular anchors (Figure 2). Breast tumors are characterized by high stiffness and increased interstitial fluid pressure. These external forces provide the constant "trigger" that keeps PIEZO channels in a sensitized or active state [28,43]. While much attention has focused on downstream intracellular signaling cascades triggered by PIEZO-mediated calcium influx, PIEZO channels also function as membrane-localized mechanosensory hubs that integrate structural and biochemical cues at the cell surface. PIEZO1 function was found to be dependent on the membrane composition and lateral organization of membrane cholesterol domains, and disruption of membrane cholesterol organization impairs the activity of PIEZO1 channel clusters [44]. PIEZO1 is often localized in caveolae, small indentations in the cell membrane. Regulation of caveolin-1 or membrane cholesterol levels directly impacts the ability of PIEZO1 to respond to mechanical stress in driving the invasive phenotype of breast cancer cells [28]. Recent evidence suggests important post-transcriptional control of the PIEZO channels in regulating their expression and function through miRNAs. Downregulation of the tumor suppressive miR-10b-5p leads to the upregulation of PIEZO1; consequently, various genes in the co-expressed purine metabolism pathway, including GUK1, POLD1, and APRT, are upregulated, promoting tumor progression [23]. Similarly, PIEZO2 is downregulated by five oncogenic microRNAs: miR-130b-3p, miR-196a-5p, miR-301a-3p, miR421 and miR-454-3p, leading to disruption of hedgehog signaling via decreased expression of CDON, thereby promoting tumor progression [40], suggesting PIEZO2 suppression facilitates tumorigenesis through the activation of developmental signaling programs. Additionally, other calcium-permeable channels such as ORAI1 and members of the TRP channel family are known to regulate breast cancer proliferation and migration [45–47]. Although direct interactions between PIEZO channels and these calcium channels have not been demonstrated in breast cancer, functional crosstalk between calcium influx pathways could amplify or fine-tune mechanotransduction responses. Elucidating membrane-localized interaction partners of PIEZO1 and PIEZO2 in breast cancer cells, including integrins, cytoskeletal adaptors, scaffold proteins, and other ion channels, represents an important and largely unexplored research direction.

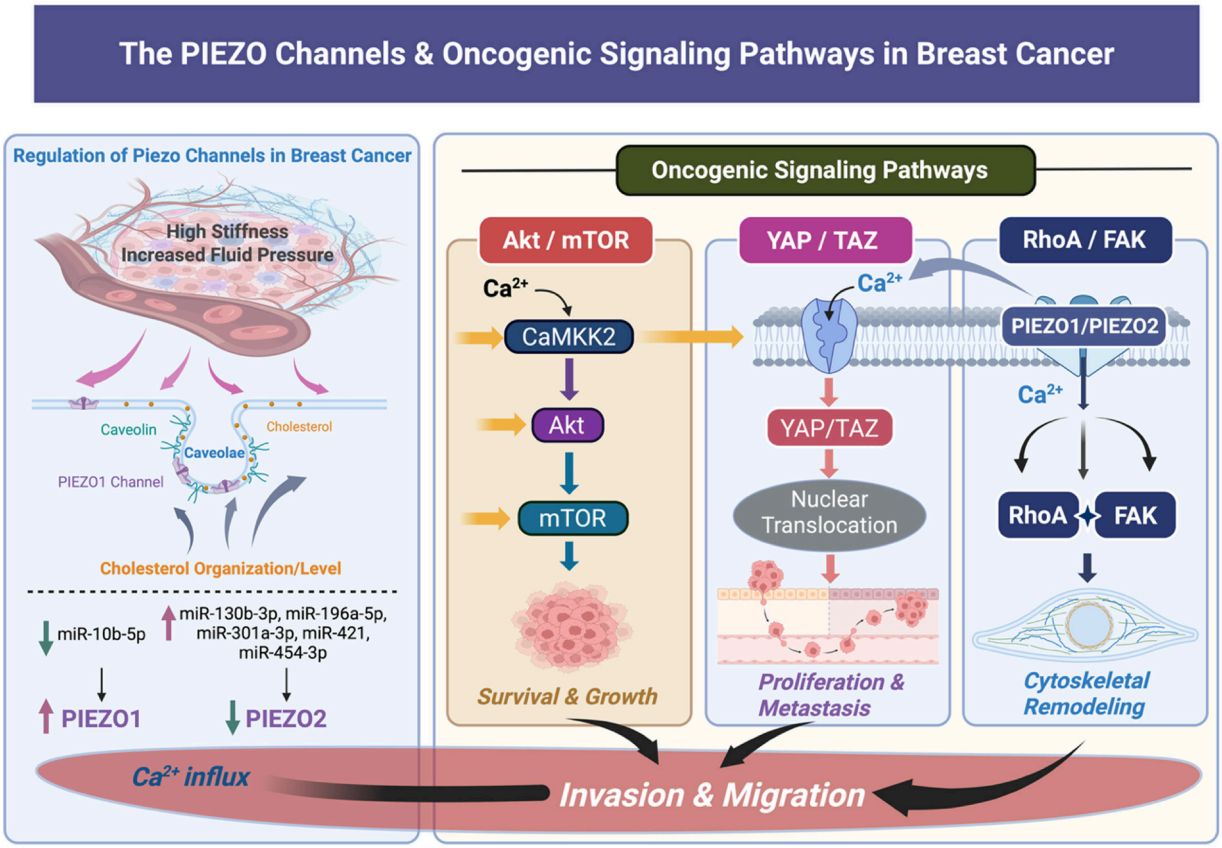


Figure 2. The PIEZO channels and oncogenic signaling pathways. Overview of oncogenic signaling pathways modulated by PIEZO channel-mediated calcium signaling in cancer cells. Activation of PIEZO channels triggers Ca^{2+} influx, which in turn influences multiple oncogenic pathways. Through these pathways, PIEZO channels regulate tumor cell survival, proliferation, mechanoadaptation, and metastasis.

3.2. Feed-Into Oncogenic Signaling

3.2.1. Akt/mTOR Pathway

The Akt/mTOR pathway is a frequently dysregulated oncogenic pathway in breast cancer [48,49]. Increasing evidence suggests calcium can modulate the activation/activity of this pathway. For example, in ovarian cancer cells, calcium-dependent intracellular Calmodulin-dependent protein kinase 2 (CaMKK2) resulted in Akt phosphorylation and activation [50]. In prostate and melanoma cancers, PIEZO1-mediated calcium influx has been found to activate Akt/mTOR signaling [29,30]. Furthermore, in HCC, PIEZO1 activation induced Akt pathway activation, resulting in increased CXCL8 secretion [51]. While there are no breast cancer-specific studies showing PIEZO1-mediated calcium influx results in Akt pathway activation, this could be a viable mechanism driving breast cancer cell proliferation and should be explored further. Interestingly, in breast cancer cells, the opposite was proposed: Akt pathway activation enhanced calcium influx, which was mediated through another calcium channel, ORAI1 [52]. Whether and how this phenomenon holds true for other calcium channels, the PIEZO family included, warrants further investigation, particularly regarding cell proliferation and metastasis. In breast cancer hepatic metastases, there is a significant enrichment of Akt pathway activation compared to other metastatic sites and primary tumors, though this was due in large part to PIK3CA activating mutations [53]. Whether this would, in turn, activate PIEZO1, which is already established to modulate the migratory capabilities of breast cancer cells [24,25,28,35–37], is another potential mecha-

nism for further investigation. Therefore, PIEZO1-Akt/mTOR coupling in breast cancer should currently be considered a testable hypothesis rather than an established mechanism.

Fewer studies assess the relationship between this pathway and PIEZO2. However, a previous study in TNBC reported that the overexpression of PIEZO2 enhances the phosphorylation of Akt, which subsequently phosphorylates and inactivates GSK-3β. Inactivated GSK-3β fails to phosphorylate SNAIL, preventing its degradation and leading to sustained stabilization and nuclear translocation. Nuclear SNAIL then upregulates the expression of vimentin and downregulates the expression of E-cadherin, thereby promoting metastasis [41,54–56].

3.2.2. YAP/TAZ Pathway

Although YAP/TAZ signaling is well established in breast cancer [57], direct linkage to PIEZO channels in breast cancer models has not yet been demonstrated. While mechanistic studies linking PIEZO channel activity with this pathway are lacking in breast cancer, several other studies have investigated this relationship in other cancers. PIEZO1 has been shown to both regulate and be regulated by this pathway. In squamous cell carcinomas, including cutaneous, oral, and lung cancers, increased matrix stiffness induces PIEZO1 upregulation, which in turn enhances YAP expression and activation via elevated *RCC2* gene expression. RCC2 has been implicated in the regulation of YAP transcription, although the precise molecular mechanisms underlying this pathway remain to be fully elucidated [58]. Another study in OSCC identified PIEZO1 as a transcriptional target of YAP and showed both were required for OSCC cell proliferation [34]. This suggests the two form a positive feedback loop in which stimuli inducing PIEZO1 activation result in downstream YAP activation, increasing the expression of PIEZO1 to further drive proliferation and invasion, warranting further investigation in the breast cancer context. In HCC, PIEZO1 activation with the selective agonist Yoda1 promoted YAP activation and nuclear translocation through activation of the MAPK pathway, specifically by modulating phosphorylation of JNK, ERK, and p38, for cell proliferation [33]. In bladder carcinoma (BLCA), stiffening of the ECM leads to the activation of PIEZO1 and the subsequent calcium influx induces YAP nuclear translocation for the expression of target genes *CTGF*, *α-SMA*, and *COL1A1* for collagen deposition, thereby forming a positive feedback loop for continual stiffening of the ECM and proliferation [59]. Interestingly, in kidney renal clear cell carcinoma, PIEZO1-mediated intracellular calcium influx increases calpain activity, which decreases YAP nuclear translocation through an unidentified mechanism [60]. Furthermore, in prostate cancer, PIEZO1 activation results in phosphorylation of Src, in turn influencing phosphorylation and nuclear translocation of YAP, though the exact mechanism by which PIEZO1 activation results in Src phosphorylation is still under investigation [61].

Despite a lack of direct evidence, one study in breast cancer examining the invasive characteristics of leader cells identified YAP as a critical driver of invasiveness; however, the study did not define any upstream regulators responsible for YAP activation, although PIEZO channels are implicated as potential contributors [62]. Overall, these data situate PIEZO1 as a key regulator of YAP to drive cell proliferation and invasive characteristics in various cancers, and further investigation assessing how the mechanically stiff breast cancer TME leads to YAP activation through PIEZO1 is warranted.

3.2.3. RhoA/FAK Pathway

In cervical cancer, PIEZO1 activation regulates F-actin expression and actin cytoskeleton organization through activation of the RhoA/Rock1 signaling pathway, thereby increasing levels of phosphatidylinositol 4,5-bisphosphate, a phospholipid, in the cell membrane, which may modulate various actin-binding proteins [63]. In gastric carcinogenesis, PIEZO1

knockdown significantly impaired cancer cell migratory and invasive capacity through modulation of the cytoskeleton; specifically, the cells formed lower numbers of protrusions with organized F-actin fibers [32]. This was likely the result of inhibition of GTP/GDP turnover from Rac1 and RhoA; with PIEZO1 knockdown, Rac1 remains bound to GTP and overactive, thereby preventing RhoA from being activated by the binding of GTP, in turn decreasing F-actin stress fibers, though the exact mechanism by which PIEZO1 mediates this process is unknown [32]. This should be investigated in breast cancer, as PIEZO1 knockdown is already established to impair invadopodia formation through decreasing F-actin assembly [24]. In HCC, the combined activation of PIEZO1 and β1 integrin activated RhoA and MLCK/MLC phosphorylation and activation for cytoskeletal remodeling; furthermore, both were essential for activation of FAK for downstream Src/Arg/cortactin signaling [64]. Both mechanisms were required for cytoskeletal remodeling and invadopodia formation for invasion [64]. Conversely, as mentioned previously, activation of FAK in a 3D model of the breast epithelium led to the activation of PIEZO1, thereby implying an intrinsic positive signaling between the two to induce migratory phenotypes [35]; however, detailed mapping of upstream–downstream RhoA/FAK signaling remains incomplete.

While PIEZO1 regulation of these pathways, and vice versa, is still under investigation in breast cancer, some studies implicate PIEZO2 regulation of these pathways regarding metastasis. For example, PIEZO2 expression is increased in breast cancer cells of a brain metastatic lineage, and in these cells, PIEZO2 knockdown significantly impairs the ability of the cell to generate traction forces for migration and invasion, and ability to sense stiffness; PIEZO2 knockdown blunts intracellular calcium influx, preventing the formation of focal adhesions and actin fibers, and preventing activation of RhoA for proper cytoskeletal reorganization [42].

The major PIEZO-regulated signaling axes discussed above (Akt/mTOR, YAP/TAZ, RhoA/FAK) are summarized in Figure 2 and serve as core mechanotransduction modules that may operate across multiple cellular compartments of the breast tumor ecosystem.

4. PIEZO Channels in the Tumor Microenvironment (TME)

The tumor microenvironment is the complex, non-cancer cell component of the local ecosystem. It is composed of tumor-infiltrating lymphocytes (TILs) or the immune microenvironment, and other stromal cell types, including fibroblasts, such as cancer-associated fibroblasts (CAFs), endothelial cells, and adipocytes [65]. The complex interactions between these cell types and cancer cells produce fibrotic regions and a hypoxic environment, and contribute to angiogenesis and lymphangiogenesis [65].

4.1. CAFs and Mechanical Remodeling

Fibroblasts, recruited to the site of the tumor, are referred to as CAFs. These CAFs serve two main purposes: they deposit ECM components for microenvironmental remodeling, and feed cancer cells by generating metabolites, namely lactate, through aerobic glycolysis [66,67]. In addition to depositing ECM components, CAFs are essential for the continual stiffening of the TME during tumor progression due to their expression of lysyl oxidase (LOX), which initiates collagen crosslinking [68].

The exceptionally stiff TME leads to the near constitutive activation of the PIEZO proteins, particularly PIEZO1 in the tumor cells [69]. Studies directly investigating how PIEZO1 signaling axes result in, or contribute to, CAF recruitment and activation in breast cancer are limited. Despite this, emerging evidence in other cancers suggests that PIEZO1 in tumor cells plays a critical role in this process. In non-small cell lung cancer, high PIEZO1 expression was correlated with increased CAF infiltration, leading to poor prognosis and immunotherapy resistance [70]. In *H. pylori* infection positive gastric cancer, NF-κB,

produced by *H. pylori*, can bind to PIEZO1 promoter to induce its expression, and when activated the calcium influx causes YAP1 nuclear translocation due to dephosphorylation of LATS1/2, thereby promoting CTGF expression for the recruitment of CAFs and facilitating tumor progression; this in turn leads to collagen deposition, stiffening the ECM and further activating PIEZO1 for a positive feedback loop [71]. These studies warrant further investigation into the mechanism regarding PIEZO1 modulation of CAF recruitment within the breast cancer TME. Beyond the cancer context, PIEZO1 has been implicated in fibroblast mechanosensing and fibrotic remodeling in non-malignant systems. In models of pulmonary and cardiac fibrosis, PIEZO1-mediated calcium influx has been shown to regulate fibroblast activation, cytoskeletal tension, and extracellular matrix deposition in response to mechanical stress [72,73]. Collectively, these findings suggest that PIEZO1 may influence CAF behavior through mechanosensitive regulation of matrix remodeling, although direct characterization of PIEZO1 expression and function in breast CAFs is currently limited.

PIEZO2's role in TME stromal remodeling through CAF recruitment and activation is under exploration. However, positive correlations between PIEZO2 and CAFs in colon cancer [74] have been reported. Further correlative and mechanistic studies should be conducted in breast and other cancers for more definitive data.

4.2. Hypoxia, HIF-1α Signaling, and Angiogenesis

Hypoxia is a well-established driver of breast cancer progression, therapeutic resistance, and metastatic dissemination, particularly in aggressive subtypes such as triple-negative breast cancer (TNBC) [75,76]. Hypoxia within the tumor leads to the stabilization of HIF-1α, enhancing glycolysis, EMT, and angiogenic signaling, further reinforcing invasive phenotypes [77]. Recent comprehensive reviews have highlighted the central role of HIF-1α-mediated transcriptional reprogramming in promoting angiogenesis, metabolic adaptation, and immune suppression in breast cancer [78,79]. Within this broader framework, PIEZO-mediated mechanotransduction may represent an additional layer of regulation influencing hypoxia-associated pathways.

In breast cancer, high PIEZO1 expression correlates with hypoxia gene signatures; however, mechanistic studies defining causality are lacking. A previous study showed that high PIEZO1 expression in HR-negative breast cancer also correlates with enrichment of hypoxia gene sets [27]. Despite this, direct evidence showing how hypoxia impacts PIEZO1, and vice versa, is still lacking in breast cancer. However, this relationship has been reported in other cancers. PIEZO1 expression is positively correlated with HIF-1α in hepatoblastoma, gastric cancers, HCC, and colon cancer [80–83]. In hepatoblastoma and omentum-metastasizing gastric cancers, PIEZO1 promotes migration through increasing expression and activation of HIF-1α, thereby increasing VEGF expression [80,81]. Though the exact mechanism of this remains under investigation, direct binding between PIEZO1 and HIF-1α was shown with immunoprecipitation. In HCC, calcium influx from stiffness-mediated PIEZO1 activation inhibits VHL, thereby preventing HIF-1α ubiquitination and degradation, leading to expression of downstream target genes, namely VEGF, to promote angiogenesis [82]. In colon cancer, PIEZO1 activation likely leads to HIF-1α expression and activation, potentially through mitochondrial calcium uniporter (MCU), though this mechanism requires further study [83]. Given these data, it is plausible that high PIEZO1 expression and activation in breast cancer can also be associated with HIF-1α expression and activation, either through regulatory or correlative mechanisms to promote angiogenesis.

As has been alluded to, PIEZO1 modulates angiogenesis through HIF-1α and downstream VEGF. Again, mechanistic evidence in breast cancer is lacking; however, it was demonstrated that in HR negative breast cancers, angiogenesis gene sets were highly enriched along with the elevated PIEZO1 expression [27]. As was previously mentioned,

PIEZO1 activation in HCC promotes angiogenesis [82]. Interestingly, in glioblastoma, the PIEZO1-VEGF axis that promotes angiogenesis appears to operate in reverse. Hypoxia-induced VEGF signaling activates Myc, which regulates the expression of myosin 1b; myosin 1b subsequently induces PIEZO1 expression and activation. The resulting PIEZO1-mediated calcium influx then drives sprouting angiogenesis [84]. PIEZO1 channel activation by its agonist Yoda1 has been shown to elicit pro-inflammatory responses in HCC cells, primarily through its downstream effector CXCL8. This effect is mediated by ERK1/2 and Akt signaling pathways, which upregulate CXCL8 expression at the transcriptional level. PIEZO1 activation enhances CXCL8 secretion, thereby facilitating immune cell trafficking, promoting angiogenesis, and crosstalk with the tumor microenvironment [51]. Tumor cells are able to produce and secrete sphingosine 1-phosphate (S1P) to stimulate angiogenesis when bound to its receptor on endothelial cells [85–87]. PIEZO1 in endothelial cells responds to shear stress and S1P to induce intracellular calcium influx, which ultimately results in MT1-MMP activation and translocation to the cell membrane for sprouting angiogenesis [88]. This suggests that PIEZO1 plays a critical role in endothelial cell response to tumor-secreted factors and shear stress in the process of angiogenic vessel sprouting.

To date, no direct evidence indicates that PIEZO2 mediates, or is activated or suppressed by, hypoxia-driven angiogenesis in breast cancer. Indeed, mechanistic links between PIEZO2 and angiogenesis remain limited across cancer types. Nevertheless, in glioma tumor endothelial cells, PIEZO2 has been shown to promote angiogenesis via calcium influx, which regulates the expression of Wnt11 and subsequently activates β-catenin signaling. Further studies are required to fully elucidate the underlying mechanisms [89].

In summary, available evidence suggests that PIEZO channels, particularly PIEZO1, may enable tumor cells to respond to hypoxia by enhancing HIF-1α and VEGF expression and activation, thereby promoting angiogenesis. Thus, while mechanistic links between PIEZO1 and HIF-1 signaling in breast cancer remain to be established, integration of mechanotransduction into hypoxia-focused therapeutic strategies represents a potential area for future investigation.

5. PIEZO Channels in the Tumor Immune Microenvironment (TIME)

The tumor immune microenvironment (TIME) is a dynamic ecosystem composed of immune cells, stromal elements, and soluble mediators that collectively influence tumor progression and therapeutic responsiveness [90–92]. In breast cancer, particularly in TNBC, immune infiltration and checkpoint signaling are clinically relevant determinants of response to immunotherapy. Although most studies describing PIEZO-mediated immune regulation have not been conducted in breast cancer models, emerging data from other tumor systems suggest that mechanosensitive signaling may modulate multiple immune cell populations within the TIME.

5.1. T Cells

PIEZO1 has been implicated in regulating T cell activation and mechanosensitive signaling. In $CD4^+$ and $CD8^+$ T cells, PIEZO1 facilitates T-cell receptor (TCR) activation and calcium-dependent cytoskeletal remodeling during immune synapse formation [93]. Pharmacologic inhibition or genetic deletion of PIEZO1 reduces TCR signaling responsiveness and alters actin organization [93]. In murine tumor models, PIEZO1 modulation influences cytotoxic T cell mechanics and tumor infiltration, with PIEZO1 inhibition enhancing T cell infiltration and limiting tumor growth in adoptive transfer settings [94]. PIEZO1 is critical in $CD4^+$ T cells for optimal cytokine secretion for the activation and expansion of cytotoxic $CD8^+$ T cells, and the generation of antitumor responses during immunogenic tumor challenge, though the exact mechanism of how PIEZO1 regulates this function of

$CD4^+$ T cells remains under investigation [95]. Using a cone-and-plate viscometer to apply defined levels of fluid shear stress, one such study demonstrated that mechanical forces could potentiate T cell activation in both Jurkat cells and primary human T cells. Fluid shear stress synergized with soluble or bead-bound CD3/CD28 stimulation to enhance activation of key signaling pathways, including ZAP70, NFAT, NF-κB, and AP-1, and to increase production of effector cytokines such as TNF-α, IL-2, and IFN-γ. This mechanically driven enhancement of T cell activation was shown to be calcium dependent and mediated by the mechanosensitive ion channel PIEZO1, as pharmacological inhibition or genetic deletion of PIEZO1 attenuated shear-induced ZAP70 phosphorylation [96]. PIEZO1 activation also inhibits SIRT3/OXPHOS mitochondrial metabolism, thereby inducing HIF-1α nuclear translocation, triggering IL-9 expression and differentiation into Th9 subsets for tumor suppression [97]. However, its role in effector $CD4^+$ T cells remains under investigation. Conflicting reports indicate that PIEZO1 does not directly modulate effector $CD4^+$ T cell function but may enhance TGF-β signaling and regulatory T (Treg) cell expansion, thereby suppressing inflammatory phenotypes in the experimental autoimmune encephalomyelitis (EAE) model [98]. In contrast, other studies using the same model report no effect on Treg expansion and instead show that Piezo1 promotes inflammatory responses and the differentiation of TH1 and TH17 cells [99]. Collectively, these findings suggest that PIEZO1 may influence pro-inflammatory T cell differentiation, although further investigation is required, particularly in cancer-specific contexts.

5.2. Macrophages

PIEZO1 plays a role in macrophage polarization in response to mechanical stiffness. Activation of PIEZO1 promotes pro-inflammatory M1 phenotypes through NF-κB signaling and cytoskeletal remodeling [100,101]. Furthermore, PIEZO1 activation in response to IFNγ/LPS stimulation and stiffness, and the subsequent calcium influx, enhances F-actin polymerization, which forms a positive feedback loop with PIEZO1 in which this cytoskeletal tension further activates PIEZO1, and modulates the inflammatory phenotype of macrophages through activation of NF-κB to upregulate various inflammatory markers, including iNOS, TNF-α, and IL-6 [102]. Other means of mechanical stimuli have also been evaluated regarding PIEZO1 activation and macrophage polarization. Cyclical mechanical force and PIEZO1 activation were found to be co-dependent with JUN phosphorylation, which in turn activates AP-1 and drives EDN1 expression and secretion in macrophages. When naïve macrophages were cultured in EDN1-conditioned medium, EDN1 signaling activated calcineurin, leading to dephosphorylation of RACK1. This process stabilized HIF-1α by preventing its degradation, thereby enhancing inflammatory phenotypes. Notably, while JUN phosphorylation depends on PIEZO1 activation, the precise mechanistic basis of this relationship remains undefined [103]. However, another study found that cyclic stretch was shown to downregulate PIEZO1, thereby blunting M1 macrophage inflammatory responses to IFNγ/LPS stimulation [104]. These seemingly contradictory findings indicate prolonged mechanical stimuli may lead to the desensitization of PIEZO1 to these stimuli, warranting further investigations into the function of PIEZO1 in various contexts. While this has not been explicitly studied in the breast cancer context, these findings seem to suggest that the mechanically stiff TME can polarize tumor-associated macrophages (TAMs) to M1 phenotypes [105].

5.3. Dendritic Cells and Myeloid-Derived Suppressor Cells

Mechanical stiffness has been found to regulate dendritic cell (DC) function, likely through PIEZO1-mediated signal transduction controlling metabolism [106]. PIEZO1 activation, either through mechanical stimuli or as an indirect effect of membrane stiffening in

response to inflammatory factors, in DCs leads to the simultaneous activation of SIRT1/HIF-1α/glycolysis pathways and calcineurin/NFAT to promote Th1 over Treg differentiation to promote pro-inflammatory effects in adenocarcinoma models [107]. PIEZO1 deletion in $CD11b^+$ DCs facilitates an anti-tumor response by increasing antigen uptake, processing, and presentation ability and enriches Major histocompatibility complex (MHC) class II for more effective cross-priming and activation of $CD8^+$ T cells in rhabdomyosarcoma models and slows local and metastatic tumor growth [108]. PIEZO2 expression is positively associated with dendritic cell infiltration as reported in previous studies [109,110]. In myeloid cells, PIEZO1 activation increases the expansion of myeloid-derived suppressor cell (MDSC) populations by upregulating HDAC2 to silence Rb1 to promote tumor growth in pancreatic ductal adenocarcinoma [111].

Collectively, these studies suggest that PIEZO channels may modulate immune cell activation, polarization, and tumor infiltration in response to mechanical cues. However, direct mechanistic studies in breast cancer remain limited. Given the clinical relevance of immune checkpoint blockade in TNBC, understanding whether PIEZO-mediated mechanotransduction influences immune infiltration or immunotherapy responsiveness represents an important area for future investigation.

6. The PIEZO Channels in Breast Cancer Stem and Stem-like Cells

Breast cancer stem cells (BCSCs) are a small subset of tumor cells that likely play a role in tumor initiation, progression, and metastasis due to their abilities to self-renew and differentiate. They are primarily identified through the surface expression of $CD44^+CD24^{-/low}$ and ALDH1 [112,113], though other markers can be used based on subtype. No study to date has directly evaluated PIEZO channel function in BCSC populations; this relationship has been established in other cancers and lineages.

In glioblastoma, the constraint from tumor confinement contributes to a stiff microenvironment in which PIEZO1 activation regulates various aspects of the cytoskeleton and its reorganization, such as RhoA activation to control focal adhesions, to translate mechanical stimuli for the distribution of CSCs in the periphery of the tumor, though further mechanistic studies are necessary [114]. Furthermore, PIEZO1 expression is significantly higher in colon cancer stem-like cells (CCSCs) compared to their non-CCSC counterparts and is important for their tumorigenicity and self-renewal properties through calcium-dependent NFAT1 stabilization and signaling; PIEZO1 knockdown significantly impaired these processes and decreased stemness in CCSC populations [115]. Given these findings, it is plausible that PIEZO1 functions through similar mechanisms in BCSCs: the mechanically stiff TME due to high ECM and collagen deposition, and the subsequent activation of PIEZO1 to control cytoskeletal arrangement, could modulate the distribution of BCSCs in these tumors as well. In fact, it is established that the mechanical force from the ECM increases stemness through activation of integrins and AIRE signals [116–119]. Though these findings were seemingly independent from PIEZO channel activity, their known ability to translate mechanical stimuli into intracellular signaling warrants further investigation in this context.

Intestinal stem cells (ISCs) require both PIEZO channels for proper ability to adapt and respond to the particularly stiff environment of the basement membrane. PIEZO channel activation and the subsequent calcium influx represses NOTCH signaling, leading to differentiation into secretory cell types, and regulates WNT signaling to maintain a balance between self-renewal and proliferation of the ISCs; knockout of both PIEZO channels led to the complete reversal of this phenotype that ultimately led to lethality [120]. Mechanical forces encountered during circulation can directly enhance metastatic potential. Constriction of melanoma cells during microcapillary transit induces rapid mechanotrans-

duction via the PIEZO1 channel, leading to calcium signaling, chromatin remodeling, and activation of metabolic and metastatic transcriptional programs. This process drives stable reprogramming toward a cancer stem cell–like state, characterized by increased stem cell marker expression, trans-endothelial invasion, and tumorigenicity. Inhibition or deletion of PIEZO1 abolishes this effect, while its activation is sufficient to induce stem-like features, highlighting vascular compression as a key regulator of metastatic competence [121].

Mesenchymal stem cells (MSCs), while still under investigation, play multifaceted roles in breast cancer. They promote proliferation, migration, and invasion, and may also contribute to immune evasion and therapeutic resistance [122,123]. Mechanosensitive PIEZO1 channels have been shown to regulate MSC migration through Ca^{2+}-dependent purinergic signaling. In human dental pulp-derived MSCs, PIEZO1 activation induces calcium influx and ATP release, which in turn stimulates P2 receptor signaling to promote cell migration via PYK2 and MEK/ERK pathways. These findings identify PIEZO1 as a key mechanotransducer linking mechanical cues to MSC motility and homing [124]. PIEZO1-mediated mechanosensing also plays a critical role in regulating the functional state of bone marrow-derived mesenchymal stem cells (BM-MSCs). Activation of PIEZO1 suppresses BM-MSC proliferation, osteogenic differentiation, and migration, while modulation of PIEZO1 activity alters self-renewal and lineage commitment. Mechanistically, shear stress-induced regulation of PIEZO1 influences Notch signaling and stemness-associated gene expression, highlighting the need for finely tuned PIEZO1 activity to maintain MSC function. Additionally, PIEZO1 modulates MSC interactions with hematopoietic and leukemia cells, impacting the chemoprotective niche, and underscoring its role in the bone marrow microenvironment [125].

7. PIEZO Channels in Breast Cancer Therapies

Therapeutic targeting of PIEZO channels remains at an early and predominantly preclinical stage. Although accumulating evidence has implicated PIEZO1 as a potential therapeutic target in breast cancer, particularly as a means to mediate migration and invasion of tumor cells [24,28], direct translational efforts in breast cancer are limited. To clarify the current state of the field, we distinguish below between (7.1) strategies that have been evaluated in breast cancer-relevant models and (7.2) conceptual approaches derived primarily from other tumor types that may inform future breast cancer research.

7.1. Strategies Evaluated in Breast Cancer Models

7.1.1. Mechanical Modulation and Metastatic Niche Targeting

Non-pharmacological mechanical stimulation represents one of the earliest explored approaches for modulating PIEZO1 activity in breast cancer-relevant systems. Electrical stimulation of MSCs has been proposed to activate PIEZO1, leading to downstream Akt phosphorylation and generation of induced tumor-suppressing cells (iTS) capable of secreting anti-tumor factors that reduce breast cancer cell proliferation, migration, and invasion in vitro [126]. Although indirect, this approach suggests that controlled mechanical activation of PIEZO1 in stromal cells may influence tumor behavior.

Similarly, low-magnitude high-frequency (LMHF) vibration of osteocytes inhibited breast cancer extravasation to the bone by 43%, suggesting activation of PIEZO1 in the metastatic niche could limit invasion in this area [127]. These findings indicate that electrical vibration as a means of mechanical stimuli to activate PIEZO1 may represent a non-pharmacological strategy to prevent metastasis; however, further investigations into the exact mechanisms of action and safety validation would be required.

7.1.2. Pharmacological Modulation in Breast Cancer Contexts

Yoda1, the most widely used small-molecule agonist of PIEZO1, has primarily served as a mechanistic probe rather than a therapeutic candidate. In breast cancer-relevant settings, Yoda1 has been evaluated in combination strategies. In the context of preventing or treating breast cancer metastasis to bone, in vitro studies have shown that combined Yoda1 treatment and LMHF vibration reduce tumor cell migration while enhancing osteocyte-mediated inhibition of osteoclastogenesis [128]. Consistent results have also been observed in preclinical studies using aged mouse models; however, these studies notably reported significant bone loss and cortical perforation in mice treated with Yoda1 alone [129]. These findings underscore the potential therapeutic benefits of combination strategies while also highlighting safety concerns that may limit the clinical application of Yoda1 as a monotherapy. The mechanisms by which Yoda1-induced PIEZO1 activation enhances osteocyte response to vibration and activity are still unclear. Additionally, in 4T1 murine breast cancer models, Yoda1 exacerbated hyperthermia-induced tumor cell injury by increasing reactive oxygen species production through NOX2 upregulation [130].

Yoda1 treatment sensitizes prostate adenocarcinoma PC3 cells to TRAIL-mediated apoptosis, likely through the activation of calpain and Bax, though this mechanism is still under investigation, ultimately resulting in mitochondrial outer membrane permeability (MOMP) [131]. Though this mechanism was not explored in breast cancer cells, MDA-MB-231 breast cancer cells were sensitive to this combination treatment [131], and, therefore, this strategy warrants further investigation. While these preliminary findings suggest Yoda1 may be a viable translational strategy, further investigations into safety and dosage are needed for clinical use. Yoda1 should be considered a pharmacological probe rather than a selective clinical PIEZO1 agonist based on current evidence. Development of more selective and tissue-specific modulators will be necessary before therapeutic translation can be realistically considered. The current pharmacological modulators of PIEZO channels are summarized in Table 2.

Table 2. Pharmacological Modulators of PIEZO Channels.

Name	Class	Specificity	Acting/Binding Site	Mechanism of Action	Key Functional Effect
Ruthenium Red	Noncompetitive Inhibitor	Nonspecific	Acidic residues in the intracellular C terminal domain	Blocks cationic pore	Inhibits calcium influx
Gadolinium	Noncompetitive Inhibitor	Nonspecific	Ion pore	Plugs channels	Inhibits calcium influx
GsMTx-4	Inhibitor	Nonspecific	Anionic phospholipids in the cell membrane	Changes local membrane tension	Prevents channel opening
Yoda1	Agonist	Specific for Piezo1	Transmembrane domains near pore that form allosteric binding pocket	Molecular wedge that stabilizes open conformation	Lowers threshold for activation
Dooku1	Selective antagonist (i.e., competitive inhibitor to Yoda1)	Specific for Yoda1 activated Piezo1	Transmembrane domains near pore that form allosteric binding pocket	Binds Yoda1 allosteric binding site on Piezo1	Blocks Yoda1 activation of Piezo1 channel

Table 2. *Cont.*

Name	Class	Specificity	Acting/Binding Site	Mechanism of Action	Key Functional Effect
Tubeimoside I	Selective antagonist (i.e., competitive inhibitor to Yoda1)	Specific for Yoda1 activated Piezo1	Likely the Yoda1 binding site	Likely binds Yoda1 allosteric binding site on Piezo1	Reduces Yoda1 induced calcium influx
Salvianolic acid B	Selective antagonist (i.e., competitive inhibitor to Yoda1)	Specific for Yoda1 activated Piezo1	Yoda1 binding site	Binds Yoda1 allosteric binding site on Piezo1	Blocks Yoda1 activation of Piezo1 channel
Jedi1 and Jedi2	Agonist	Specific for Piezo1	N-terminal fragment	Conformational change of the beam structures for allosteric gating (yet to be fully elucidated)	Lowers threshold for activation

Collectively, available breast cancer-relevant data suggest that PIEZO modulation may influence metastatic niche adaptation, apoptosis sensitivity in aggressive subtypes, and tumor–stromal mechanical interactions. However, robust in vivo validation, subtype stratification, and safety assessment remain major unmet needs.

7.2. Preclinical Concepts from Other Cancers: Hypothesis-Generating Strategies

Beyond breast cancer-specific studies, multiple investigations in other tumor types provide conceptual frameworks that may inspire future therapeutic exploration.

7.2.1. PIEZO Channel Modulation in Solid Tumors

Beyond breast cancer, PIEZO1 has been implicated as a therapeutic target in HCC [33,51,132,133], gliomas [134], prostate cancer [30], gastric cancer [32], renal clear cell carcinoma [135], cervical cancer [63], high-grade serous ovarian cancer [136], colon cancer [115], esophageal squamous cell carcinoma [137], non-small cell lung cancer liver metastasis [138], and squamous cell carcinoma [58]. PIEZO1 activation or inhibition has been shown to modulate proliferation, invasion, and angiogenesis through pathways such as Akt/mTOR, MAPK, YAP/TAZ, and HIF-1 signaling (see Section 3). In several models, pharmacologic activation or suppression of PIEZO1 altered tumor growth kinetics or metastatic behavior. PIEZO2's potential has been implicated in gastric cancer as a therapeutic target [110], but remains largely unexplored in breast and other cancers.

While these findings highlight PIEZO channel as a mechanotransduction node influencing tumor progression, none of these strategies have yet been systematically evaluated in breast cancer-specific in vivo models. Therefore, they should be interpreted as hypothesis-generating rather than directly translatable.

7.2.2. Nanoparticle-Based Mechanical Activation and Immune Modulation

In macrophages, PIEZO1 activation with nanoparticles and the subsequent calcium influx activate CAMK2A, which then phosphorylates and activates NF-κB, promoting M1 inflammatory phenotypes [139]. Furthermore, mesoporous silica nanoparticles (mSNs) of controllable stiffness targeting PIEZO1 in TAMs modulate M2 repolarization to M1 through upregulating CD80, and exosomes derived from these cells are able to induce T

cell activation through the secretion of TNF-α, IFN-γ, and granzyme B to generate effective antitumor responses [105].

Although these strategies have not been validated in breast cancer, they suggest that mechanical modulation of immune cells through PIEZO channels could potentially complement immunotherapy approaches in immunologically active subtypes such as TNBC.

7.2.3. PIEZO Channels and Immunotherapy Response

The PIEZO channels may also influence responses to immunotherapies. A previous study has suggested that high PIEZO1 expression in HR-negative breast cancers is associated with decreased levels of intratumoral $CD8^+$ T cells and activated $CD4^+$ memory T cells, suggesting impaired immune responses that contribute to the worse survival outcomes in these subtypes [27]. Despite this, studies directly investigating the role of PIEZO1 in immunotherapy efficacy in breast cancer are still lacking. Thus, whether PIEZO modulation could enhance or impair checkpoint blockade efficacy in breast cancer remains an open question. However, there is some documentation in other cancer types. In non-small cell lung cancer, PIEZO1 activation promotes YAP nuclear translocation, which then increases expression of PD-L1 and secretion of CXCL10, thereby enhancing anti-PD-1 efficacy [138].

As the role of PIEZO2 in breast and other cancers remains under exploration, so does its impact on immunotherapies. PIEZO2 expression was associated with poor immunotherapy responses in gastric cancer [110], melanoma, and bladder cancer, and T cell dysfunction in breast and endometrial cancers, but was associated with good responses in kidney cancer [109]. Tumor cell intrinsic PIEZO2 mediates $CD8^+$ T cell activity after radiation therapies by decreasing IL-15 production, thereby suppressing the JAK2/STAT1/IRF-1 pathway, leading to impaired immune responses, but the mechanism by which radiation activates and upregulates the expression of PIEZO2 remains unknown [140]. While this phenomenon has not been fully explored in the breast cancer context, it represents another means to fully elucidate and understand the complex role(s) PIEZO2 plays in breast cancer tumorigenesis and therapeutic response.

At present, therapeutic targeting of PIEZO channels in breast cancer remains exploratory. Nevertheless, as mechanobiology becomes increasingly integrated into cancer research, PIEZO channels represent intriguing modulators of tumor–mechanical crosstalk that warrant careful, breast cancer-specific investigation.

8. Summary and Outlook

Mechanotransduction has emerged as a fundamental regulator of cancer biology, and the mechanosensitive PIEZO channels are now recognized as central nodes linking mechanical cues to oncogenic signaling. In this review, we summarize accumulating evidence demonstrating that PIEZO1 and PIEZO2 play multifaceted, context-dependent roles in breast cancer development, progression, and therapeutic response. Through calcium-dependent activation of pathways such as AKT/mTOR, YAP/TAZ, RhoA-FAK, and HIF-1 signaling, PIEZO1 acts as a key mechanochemical transducer that amplifies malignant phenotypes and reinforces positive feedback loops within the tumor microenvironment. In contrast, the role of PIEZO2 in breast cancer remains less defined and more heterogeneous. While several datasets associate PIEZO2 expression with favorable prognosis in certain breast cancer subtypes, emerging mechanistic studies, particularly in TNBC and metastatic contexts, suggest that PIEZO2 can enhance tumor cell migration, invasion, and survival in mechanically challenging niches such as the brain. These seemingly contradictory findings underscore the importance of tumor subtype, metastatic site, and microenvironmental context in determining PIEZO2 function. Dissecting the distinct and potentially opposing roles

of PIEZO1 and PIEZO2, as well as their possible cooperative or compensatory interactions, represents a critical area for future investigation.

Beyond tumor cell-intrinsic effects, PIEZO channels also shape the TME. PIEZO1-mediated mechanosensing influences stromal remodeling, CAF recruitment, angiogenesis, and hypoxia-driven signaling, thereby contributing to the progressive stiffening and immune modulation of breast tumors. In immune cells, PIEZO1 regulates T cell activation, macrophage polarization, dendritic cell function, and myeloid-derived suppressor cell expansion, suggesting that mechanical signaling via PIEZO channels may profoundly affect antitumor immunity and responses to immunotherapy. Although breast cancer-specific studies remain limited, available evidence points to PIEZO channels as important determinants of immune composition, functional state, and therapeutic responsiveness within the TIME.

Therapeutically, PIEZO channels represent an intriguing but challenging class of targets. Pharmacologic modulation of PIEZO1 using small-molecule agonists or inhibitors, non-pharmacological mechanical stimulation strategies, and nanoparticle-based approaches have shown promise in preclinical models across multiple cancer types. A deeper understanding of cell-type-specific PIEZO signaling, mechanical thresholds for activation, and downstream pathway engagement will be essential for safe clinical translation. Moreover, PIEZO channels may ultimately be most effective as modulators of therapeutic response, sensitizing tumors to chemotherapy, radiotherapy, targeted agents, or immunotherapy rather than as standalone targets.

Looking forward, several key questions remain. How do mechanical cues dynamically regulate PIEZO channel expression and activity during different stages of breast cancer progression? What determines whether PIEZO-mediated signaling promotes tumor suppression versus tumor progression in distinct cellular contexts? How do PIEZO channels influence breast cancer stem and stem-like cell populations, metastatic organotropism, and therapy resistance? Is the PIEZO channel an intrinsic factor that influences the immunogenicity of tumor cells in the TME? Addressing these questions will require integrated approaches combining mechanobiology, single-cell and spatial profiling, advanced in vitro models that recapitulate tissue mechanics, and in vivo studies across clinically relevant subtypes.

In summary, PIEZO channels sit at the intersection of mechanics, signaling, and tumor ecology in breast cancer. Continued investigation into their complex biology promises not only to deepen our understanding of breast cancer mechanotransduction but also to uncover novel biomarkers and therapeutic strategies aimed at improving patient outcomes in this highly heterogeneous disease.

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Abbreviations

APCs	Antigen-presenting cells
BCSC	Breast cancer stem cell
BM-MSC	Bone marrow-derived mesenchymal stem cell
CAFs	Cancer-associated fibroblasts
CaMKK2	Calmodulin-dependent protein kinase 2
CCSC	Colon cancer stem-like cell
CSC	Cancer stem cell
DC	Dendritic cell
EAE	Experimental autoimmune encephalomyelitis
ECM	Extracellular matrix
EMT	Epithelial-to-mesenchymal transition
HCC	Hepatocellular carcinoma
HR	Hormone receptor
ISC	Intestinal stem cell
LMHF	low-magnitude, high-frequency
LOX	lysyl oxidase
MCU	mitochondrial calcium uniporter
MDSC	Myeloid-derived suppressor cell
MHC	Major histocompatibility complex
MMP	Matrix metalloprotease
MOMP	Mitochondrial outer membrane permeability
MSC	Mesenchymal stem cell
NPI	Nottingham Prognostic Index
OSCC	Oral squamous cell carcinoma
ROS	Reactive oxygen species
S1P	Sphingosine 1-phosphate
SBR	Scarff-Bloom-Richardson
TAM	Tumor-associated macrophage
TCR	T-cell receptor
THU	Transmembrane helical
TIME	Tumor immune microenvironment
TILs	Tumor-infiltrating lymphocytes
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
Treg cell	Regulatory T cell

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