Biomechanical Regulation of Therapeutic Resistance in Breast Cancer: Multiscale Mechanisms and Translational Opportunities

Yuqian Ji [1†], Qi Sun [2†], Bowen Wang [3], Ruijuan Liu [1,4,5*], Changgang Sun [1,3,4,5*]

[1] *College of First Clinical Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250014, China*

[2] *Department of Traditional Chinese Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China*

[3] *Faculty of Chinese Medicine, State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau 999078, China*

[4] *College of Traditional Chinese Medicine, Shandong Second Medical University, Weifang 261000, China*

[5] *Department of Oncology, Weifang Traditional Chinese Hospital, Weifang 261000, China*

[†]These authors contributed equally to this work.

[*]Corresponding authors: Ruijuan Liu, Changgang Sun; Email address: liuruijuan626@163.com (R.L), zyxyscg@sdsmu.edu.cn (C.S).

Abstract

Therapeutic resistance remains a major barrier to durable clinical benefit despite advances in breast cancer treatment. The biomechanical microenvironment contributes to the development and maintenance of resistance across treatment settings by influencing tissue transport, cellular adaptation, and antitumor immunity. This review examines matrix stiffness, solid stress, interstitial fluid pressure, and fluid

shear stress, highlighting their characteristics, distinctions, and interconnections. We describe how these factors affect vascular perfusion, drug distribution, and immune cell infiltration, and how they regulate damage responses, metabolic adaptation, phenotypic plasticity, and immune states through signal transduction. Stiff and soft matrices can support similar drug-resistant phenotypes through distinct mechanisms. In turn, therapy-induced cellular and matrix remodeling can alter the biomechanical microenvironment, creating dynamic feedback. This review proposes a framework linking tissue biomechanics, cellular states, and treatment responses, and compares shared resistance processes and treatment-specific mechanisms across different treatment contexts. Building on this framework, we discuss diagnostic, assessment, and therapeutic strategies based on tumor biomechanical characteristics. We aim to provide an integrative perspective on therapeutic resistance in breast cancer and highlight the translational potential of biomechanics for patient stratification and combination therapy.

Keywords: Breast cancer; Therapeutic resistance; Biomechanics; Mechanotransduction; Tumor microenvironment

1. Introduction

Breast cancer is one of the most common malignancies among women. Although an integrated treatment system has been established, encompassing surgery, radiotherapy, chemotherapy, endocrine therapy, antibody-drug conjugates (ADCs), and immunotherapy, therapeutic resistance, recurrence, and metastasis remain major causes of patient mortality. Data indicate that global deaths from breast cancer among women reached approximately 764,000 in 2023 and are projected to increase to approximately 1.37 million by 2050 [1]. Previous studies have elucidated the mechanisms underlying acquired resistance in breast cancer from the perspectives of genetic mutations, altered target expression, activation of bypass signaling, and epigenetic remodeling [2-4]. Non-genetic adaptation also enables some cancer cells to persist under treatment pressure, contributing to the maintenance of residual disease

and subsequent recurrence [5, 6]. These insights raise a broader question: why do therapies with different targets and mechanisms of action encounter some of the same functional limitations? By influencing therapeutic access, tissue oxygenation, and cellular adaptive states, the tumor microenvironment (TME) provides a starting point for understanding resistance mechanisms across treatment settings.

Biomechanics is an important dimension linking the TME to treatment responses. The breast comprises adipose, glandular, and fibrous connective tissues with distinct mechanical properties [7]. Its architecture and matrix state change dynamically during physiological processes, creating a mechanically adaptable environment [8, 9]. During breast cancer development and progression, extracellular matrix (ECM) deposition, crosslinking, and fiber alignment further alter local tissue architecture. These alterations interact with changes in solid stress, interstitial fluid pressure, and fluid shear stress, shaping distinct mechanical characteristics within and between lesions [10, 11]. These changes can affect drug transport and distribution, as well as immune cell trafficking and infiltration. Through cellular sensing and transduction of mechanical stimuli, they can also regulate the behavior of tumor, stromal, and immune cells, thereby contributing to the development and maintenance of therapeutic resistance. Previous studies have established an important conceptual foundation for these processes. The framework of the physical hallmarks of cancer links tissue architecture and biomechanics to tumor progression and therapeutic resistance [11]. Studies on remodeling the physical tumor microenvironment have explained how solid and fluid mechanics limit therapeutic delivery and have proposed vascular and ECM normalization as intervention strategies [12, 13]. More recently, research on mechanically driven drug resistance has further clarified the links among mechanotransduction, cellular adaptation, and the efficacy of anticancer therapies [14]. A recent review synthesized the mechanisms through which ECM stiffness contributes to therapeutic resistance in cancer and discussed the potential of targeting the ECM and its downstream signaling pathways [15]. Thus, the dual roles of biomechanics in creating physical barriers and regulating signaling have become fundamental to understanding its influence on treatment responses.

The biomechanical microenvironment of breast cancer varies with molecular subtype, disease stage, and spatial location. Higher matrix stiffness and greater mechanical heterogeneity have been observed in the invasive regions of HER2-positive breast cancer (HER2+ BC) and basal-like breast cancer than in luminal breast cancer [16]. Moreover, the relationship between biomechanics and therapeutic resistance cannot be reduced to a unidirectional effect of increasing stiffness. In specific breast cancer models, a soft microenvironment can promote tamoxifen resistance by enhancing autophagy and reducing estrogen receptor expression [17]. Another study showed that low-compression conditions associated with soft matrices can promote local immunosuppression through changes in tumor cell states and paracrine regulation [18]. These findings suggest that different mechanical conditions may confer similar survival advantages under specific treatment pressures through distinct adaptive programs. Similar resistance outcomes do not necessarily reflect the same signaling pathways or cellular states. Rather, they depend on the interplay among the biomechanical microenvironment, cellular states, and the mechanisms of therapeutic action.

Based on these insights, this review synthesizes evidence on functional constraints on treatment efficacy, including restricted therapeutic exposure, damage tolerance and evasion of cell death, metabolic adaptation, phenotypic plasticity, and immune evasion, to propose an integrative biomechanical framework for therapeutic resistance in breast cancer. This framework addresses three interrelated questions: which functional constraints are affected by different biomechanical conditions; how these constraints differ across breast cancer subtypes and treatment modalities; and whether they change during therapy-induced cellular and stromal remodeling. We also discuss how stiff and soft environments may support similar resistance outcomes through distinct adaptive pathways. Compared with previous studies, this review emphasizes shared resistance features and mechanistic differences across breast cancer treatment settings, providing a basis for further mechanistic validation and the exploration of therapeutic sensitization strategies.

2. The Biomechanical Niche of Therapeutic Resistance in Breast Cancer

Compared with normal breast tissue, breast cancer tissue exhibits increased matrix stiffness, excessive accumulation of solid stress, abnormal interstitial fluid pressure (IFP), and fluid shear stress (FSS) induced by irregular blood flow and interstitial fluid flow [11]. These biomechanical factors are interconnected through ECM remodeling, vascular function, and interstitial transport, jointly influencing therapeutic delivery and cellular responses (Table 2). Treatment can also alter stromal cell states and tissue mechanical architecture and properties, leading to continuous changes in the mechanical microenvironment during therapy. Thus, biomechanical regulation of treatment responses depends on the dynamic interplay among the initial mechanical state, tissue remodeling during treatment, and adaptive cellular behaviors.

2.1 Matrix Stiffness

Matrix stiffness reflects the resistance of the tumor ECM to deformation and is typically characterized by parameters such as the elastic modulus. Its measured value is influenced by factors including the measurement scale and material viscoelasticity. Collagen (COL) deposition, crosslinking, and fiber organization are key determinants of matrix stiffness in breast cancer [19]. Tumor cells and cancer-associated fibroblasts (CAFs) continuously modify ECM structure and mechanical properties by regulating collagen synthesis, lysyl oxidase (LOX)-mediated collagen crosslinking [20], and matrix metalloproteinases (MMPs)-mediated matrix degradation [21]. The resulting disruption of tensional homeostasis regulates tumor cell proliferation, migration, invasion, and therapeutic resistance and is closely associated with breast cancer metastasis and poor patient prognosis [14, 22]. Studies have shown that increased collagen crosslinking promotes integrin clustering and focal adhesion formation and enhances associated signaling activity. These findings provide a mechanistic basis for the contribution of matrix remodeling to breast cancer progression [23].

2.2 Solid Stress

Solid stress is the force per unit area borne by solid components, including tumor cells, stromal cells, and the ECM. It arises from tissue constraints on tumor growth,

cellular contraction, and matrix remodeling [24]. Unlike stiffness, which describes the response to deformation, solid stress reflects the actual mechanical load borne by tissue. Compressive stress generally predominates within the tumor, whereas tensile stress may occur at the periphery. The spatial distribution depends on tissue architecture and boundary constraints [25]. Some stress can persist after tumor excision and cause tissue deformation upon cutting or removal of constraints. Solid stress can therefore be estimated by combining measurements of displacement following stress release with mechanical models [24, 26].

Solid stress can alter perfusion and fluid drainage by compressing blood and lymphatic vessels. It also directly affects the deformation of cells and their surrounding matrix [27]. Under solid stress, collagen fibers are stretched and reorganized. Once strain exceeds a certain threshold, the fibers transition from a relaxed state to a highly stretched state, accompanied by a rapid increase in elastic modulus, thereby increasing ECM stiffness and reinforcing the local contractility of CAFs [28]. However, solid stress and matrix stiffness do not necessarily change in parallel. In the MMTV-M3C breast cancer model, measures of solid stress increased as tumors grew, whereas local matrix stiffness showed no significant change [26]. This finding indicates that matrix stiffness cannot serve as a direct surrogate for solid stress. Their respective roles in therapeutic delivery and cellular adaptation therefore require separate evaluation.

2.3 IFP

IFP refers to the local hydrostatic pressure of the interstitial fluid and is close to atmospheric pressure in normal tissues [11]. In breast cancer tissue, increased vascular permeability, elevated microvascular pressure, and impaired lymphatic drainage contribute to increased IFP. ECM stiffening further restricts fluid distribution and clearance, leading to interstitial fluid accumulation and hyaluronan (HA) swelling, which markedly increase IFP. Solid stress can promote these processes by compressing blood and lymphatic vessels. However, whether blood vessels become compressed also depends on local loading, vessel wall properties, and the balance

between intravascular and extravascular pressures [29].

The absolute level of IFP helps determine the pressure conditions for transvascular fluid exchange, whereas its spatial gradient acts together with local hydraulic permeability to influence interstitial fluid flow. In mouse models of breast cancer, IFP remains high and relatively uniform in the tumor center but decreases sharply at the periphery, creating a pronounced pressure gradient. High IFP reduces local therapeutic exposure by decreasing the hydrostatic pressure difference that favors transvascular transport. Interstitial fluid flow driven by the peripheral pressure gradient can alter the spatial distribution of drugs, nutrients, and immune cells. It also promotes the spread of tumor cells and growth factors into surrounding tissues, facilitating angiogenesis, tumor invasion, and metastasis [30, 31].

2.4 FSS

FSS is the tangential force per unit area exerted by fluid flowing along cell or matrix interfaces. Its magnitude depends on fluid viscosity, local velocity, and interface geometry [32]. FSS can contribute to CAF activation, vascular endothelial cell growth, and lymphangiogenesis [33]. It also promotes ECM degradation and remodeling by regulating MMP expression and activity.

The effects of FSS on breast cancer cells depend on anatomical location and disease stage. In primary tumors, vascular endothelial cells experience shear stress generated by intraluminal blood flow, whereas tumor and stromal cells are primarily exposed to local interstitial flow. Vascular compression, abnormal architecture, and pressure gradients between regions create highly heterogeneous flow patterns, resulting in substantial variation in FSS within primary tumors. In circulating tumor cells (CTCs) that have lost matrix anchorage, blood flow-induced shear stress, cellular deformation, and interactions with blood components jointly regulate cellular behavior and phenotype. In vitro circulation models have shown that FSS at physiological resting levels can enhance breast cancer cell invasiveness [34], whereas high shear stress causes cell damage and death [35]. These effects depend on shear magnitude, exposure duration, and cellular state. In metastatic microenvironments,

FSS can also indirectly influence tumor cell behavior through host cells. In a bone metastasis model, oscillatory FSS stimulated osteocytes and inhibited breast cancer cell extravasation through local intercellular communication [36].

2.5 Coupling of Biomechanical Characteristics

Matrix stiffness, solid stress, IFP, and FSS form an interconnected regulatory network through ECM architecture, vascular function, and interstitial transport (**Fig. 1**). ECM deposition, collagen crosslinking, and fiber alignment can increase matrix stiffness. Meanwhile, tumor cells, stromal cells, and the ECM collectively contribute to solid stress accumulation. Solid stress can promote matrix stiffening and further compress blood and lymphatic vessels, restricting perfusion, impairing lymphatic drainage, and causing interstitial fluid retention, thereby increasing IFP [24, 29]. Experiments using collagen networks have shown that compression-induced local densification can reduce matrix hydraulic permeability, providing direct evidence for the link between solid-phase deformation and fluid transport [28].

Biomechanical characteristics may become decoupled across disease stages and tumor regions, so a single parameter cannot capture the overall microenvironment. For example, during tumor growth, solid stress can continue to accumulate while matrix stiffness remains relatively stable [26] and intratumoral IFP remains high [37]. Fiber alignment, cell adhesion patterns, pore geometry, and stress transmission pathways can expose different cells within the same lesion to different mechanical loads. The biomechanical microenvironment also exhibits dynamic plasticity. A clinical study demonstrated that paclitaxel reduced tumor IFP and improved oxygenation in patients with breast cancer [38]. In mouse models, however, anthracycline or paclitaxel chemotherapy induced stromal COL IV deposition and promoted triple-negative breast cancer (TNBC) cell migration through FAK/Src signaling [39]. Given this complexity, the regulation of therapeutic resistance often involves multiple parallel or sequential processes. Clarifying these mechanisms requires combining selective perturbations with multiparametric measurements. This approach can distinguish the contributions of inadequate therapeutic exposure and increased intrinsic cellular tolerance to resistance, while tracking changes in the

biomechanical microenvironment during treatment. Biomaterials with independently tunable properties and microfluidic systems provide experimental platforms for examining these relationships. For example, hydrogels with independently adjustable stiffness, stress relaxation, and collagen density can help compare the independent and interactive effects of different ECM properties [40]. Microfluidic platforms operating under constant pressure gradients or constant flow rates have shown that breast cancer cells can remodel the ECM in response to IFP, thereby regulating fluid permeation through feedback [41]. Organoid or ex vivo tumor models can further recapitulate tumor cellular composition and tissue architecture to assess whether these mechanisms apply within tumor tissue. These approaches should also incorporate treatment-response endpoints, such as survival after drug exposure, damage responses, or regrowth after drug withdrawal, to determine the specific contribution of each mechanical variable to therapeutic resistance.

3. Cellular Decoding of Biomechanical Signals

Matrix stiffness, solid stress, IFP, and FSS generate biomechanical signals by altering forces at cell adhesion interfaces, membrane tension, and cellular deformation. These signals then regulate adaptive behaviors in breast cancer cells through a network encompassing sensing by membrane receptors, cytoplasmic signaling, and nuclear transcriptional reprogramming (**Fig. 2**).

3.1 Membrane Mechanosensors

Breast cancer cells sense and transduce biomechanical signals through adhesion complexes. Upon binding ECM ligands, integrins connect to the actin cytoskeleton through talin and kindlin, enabling cells to sense matrix resistance as they actively pull on it. Experiments have shown that mechanical stretching unfolds talin domains and exposes vinculin-binding sites, providing a molecular basis for mechanotransduction at adhesion sites [42]. In breast cancer models, increased collagen crosslinking is accompanied by integrin clustering, focal adhesion formation, and enhanced downstream signaling. These findings further support the role of adhesion in linking changes in the biomechanical microenvironment to cellular responses [23]. Cell-cell adhesion also contributes to mechanosensing. Within

cadherin-associated complexes, α-catenin undergoes tension-dependent conformational changes and recruits vinculin, converting changes in the biomechanical microenvironment into biochemical signals [43]. In addition, discoidin domain receptors (DDRs) bind directly to collagen and cooperate with integrins to regulate breast cancer cell responses to the matrix environment [44].

Mechanosensitive ion channels convert mechanical forces on the cell membrane into ionic signals. In MCF-7 cells, Piezo1 contributes to mechanically activated currents, providing direct evidence of its mechanosensing function [45]. Further studies have shown that compression activates Rho/ROCK through Piezo1-mediated signaling and enhances intracellular contractility. Piezo1 silencing blocks this signaling and inhibits compression-induced tumor progression [46]. In breast cancer cells, Piezo1 is also associated with caveolar membrane regions. Caveolin-1 knockdown or disruption of caveolar integrity reduces Piezo1 expression and compression-induced invasion [47]. In addition, Piezo2 loss markedly impairs traction generation and migration through confined spaces in brain-metastatic breast cancer cells by reducing RhoA activity and altering actin organization [48]. Transient receptor potential (TRP) channels regulate Ca^{2+} signaling and can amplify and sustain downstream Piezo signaling [49]. Under the regulation of tension and matrix stiffness, TRPV4 contributes to actin remodeling, cellular deformation, and transendothelial migration in breast cancer cells. It can also influence mammary epithelial cell differentiation and tissue architecture [50, 51]. G protein-coupled receptors can also sense biomechanical signals. An RNA interference screen in MDA-MB-231 cells identified a role for GPR68 in shear-induced intracellular Ca^{2+} transients [52]. Pannexin-1 (PANX1) links cellular deformation to extracellular nucleotide signaling. When CTCs become trapped in narrow microvessels, membrane stretch-associated PANX1 activation promotes ATP release and supports cell survival through purinergic signaling [53].

3.2 Cytoplasmic Signal Transduction

After biomechanical signals are sensed by membrane receptors, they are amplified and integrated through cytoplasmic response cascades, thereby coordinately

regulating downstream transcriptional outputs. In breast cancer cells, pathways including integrin/FAK/Src/integrin-linked kinase (ILK), Rho-ROCK, Wnt/β-catenin, and Hippo/YAP/TAZ are interconnected and convert mechanical stimuli into intracellular signaling networks associated with therapeutic resistance.

Focal adhesion kinase (FAK) is a key integrator of adhesion signaling. Integrin activation induces FAK autophosphorylation at tyrosine (Tyr) 397 and Src recruitment, forming a FAK/Src complex that engages downstream signaling cascades [54]. Mechanical stretching can relieve FAK autoinhibition, indicating that FAK functions in both mechanical responsiveness and signal amplification [55]. As an intracellular integrin-associated protein, ILK contributes to the transmission of ECM adhesion signals to the cytoskeleton and YAP [56]. Particularly in stiff ECM, ILK-mediated YAP activation can enhance drug resistance in breast cancer cells [57].

Rho/ROCK pathway converts adhesion signals into cytoskeletal tension and serves as an important signal amplifier. After upstream sensors such as integrins and Piezo channels activate RhoA-ROCK1/2 signaling, actomyosin contractility is enhanced and stress fiber formation is promoted [58]. This process not only regulates cell morphology, migration, and invasion, but also provides the basis for YAP/TAZ nuclear translocation. In breast cancer, this process promotes YAP/TAZ dephosphorylation and nuclear translocation through ROCK-dependent actin tension, driving the nuclear response to cytoplasmic signals [59] and accelerating therapeutic resistance.

YAP/TAZ function as both signaling convergence nodes and nuclear transcriptional coregulators, regulating gene expression through interactions with transcription factors such as TEAD. In addition to the canonical Hippo/LATS cascade, their responses are regulated by Rho activity and actomyosin tension [60]. Mechanical stimuli can also directly drive YAP nuclear translocation by reducing the mechanical restriction imposed by nuclear pores on molecular transport [61]. The functions of YAP/TAZ differ across breast cancer subtypes. Their activation can promote acquired trastuzumab resistance in HER2+ BC [62]. In ER-positive breast cancer (ER+ BC), however, nuclear YAP may suppress ERα target gene transcription by competing with

ERα for TEAD binding, thereby slowing tumor growth [63].

Other pathways, including PI3K/AKT and MAPK, integrate adhesion-related inputs with growth factor signaling, allowing the same mechanical conditions to elicit different responses in distinct cellular contexts [23, 64]. ULK1/2 phosphorylate the focal adhesion protein paxillin (PXN), counteracting FAK/Src-associated regulation and limiting focal adhesion assembly and breast cancer cell migration [65]. These interconnected pathways form multiple signaling cascades that collectively sustain breast cancer cell survival and proliferation, leading to therapeutic resistance.

3.3 Nuclear Signal Responses

After biomechanical signals are transduced through the cytoplasm, they are transmitted to the nucleus along the cytoskeleton and through the linker of nucleoskeleton and cytoskeleton (LINC) complex. Under the regulation of the nuclear lamina protein lamin A/C, these signals alter nuclear morphology and nuclear stiffness, thereby inducing chromatin remodeling and epigenetic modifications and ultimately regulating cellular behavior and state.

The LINC complex transmits mechanical signals across the nuclear envelope to the nuclear lamina and chromatin through SUN-KASH proteins [66]. In fibroblasts, LINC-associated proteins and lamin A/C contribute to the rapid response of perinuclear actin structures to fluid shear stress [67]. In breast cancer tissue, SUN1, SUN2, and nesprin-2 are often downregulated together with lamin A/C, suggesting remodeling of mechanical coupling between the nucleus and cytoplasm [68]. Matrix elasticity can also regulate lamin A/C phosphorylation and turnover through myosin activity, altering nuclear lamina properties and influencing cellular contractility through feedback [69]. Clinical studies have also associated lamin A/C downregulation or loss with high tumor grade, lymphovascular invasion, distant metastasis, and poorer survival in breast cancer [70].

Chromatin remodeling and epigenetic modifications are key steps in converting biomechanical signals into sustained transcriptional outputs. Matrix stiffening can substantially increase the number of open chromatin sites in mammary epithelial cells, reshape chromatin accessibility, and induce tumorigenic phenotypes [71]. In ER+ BC,

mechanical stimuli can also alter responses to endocrine therapy through H3K27me3-associated epigenetic regulation [72]. After the original mechanical conditions change or are removed, the induced chromatin alterations, transcriptional states, and cellular phenotypes may persist for a period, forming mechanical memory. In breast cancer cells, stiff matrices can promote chromatin opening at specific target gene loci through transcription factors such as RUNX2 and maintain this accessibility for 2-5 days [73]. Following acute compression, elevated histone H3K9 acetylation in breast cancer cells and ex vivo tissue can persist for at least 2 days. The associated modifications and tumor-promoting effects remain detectable in transplanted tumor tissue at week 4 [46].

Treatment itself can also reshape signaling response networks. In breast cancer models subjected to prolonged drug exposure, TRPC5-associated Ca^{2+} signaling is enhanced and contributes to proangiogenic responses [74]. In addition, X-ray irradiation can alter lamin A/C expression and YAP subcellular distribution in breast cancer cells, with effects varying by cell type, dose, and observation time [75]. Together, membrane-proximal sensing, cytoplasmic signal integration, and nuclear transcriptional regulation enable biomechanical signals to influence cellular behavior and ultimately shape breast cancer cell resistance phenotypes across multiple treatment modalities.

4. Biomechanics-Driven Core Mechanisms of Therapeutic Resistance

Although chemotherapy, radiotherapy, endocrine therapy, targeted therapy, ADCs, and immunotherapy differ in their therapeutic targets and effector mechanisms, their efficacy is influenced by similar factors, including local effective drug concentration, accumulation of treatment-induced damage, cell death, metabolic stress, cellular phenotype, and the intensity of antitumor immunity. Biomechanical signals, including matrix stiffness, solid stress, IFP, and FSS, regulate these processes and thereby establish shared mechanisms of resistance across therapeutic modalities.

4.1 Therapy Accessibility

Drug action requires vascular perfusion, transvascular transport, interstitial transport, and cellular uptake. The biomechanical microenvironment can influence

these processes by altering ECM architecture, vascular function, and cellular transport, thereby changing drug distribution within tissues and effective intracellular exposure (**Fig. 3**).

4.1.1 Physical Barriers

ECM composition and spatial architecture are major determinants of interstitial drug transport. Collagen deposition, crosslinking, and matrix densification can increase steric hindrance to molecular movement, limiting the distribution of macromolecular drugs and immune cells within tissues [76]. Studies have shown that IgG diffusivity is associated with collagen content and tissue stiffness, whereas collagenase treatment can improve its diffusion [77].

The biomechanical microenvironment also limits drug supply by affecting angiogenesis and effective perfusion. In animal models of breast cancer, reducing collagen and hyaluronan accumulation and alleviating solid stress can relieve vascular compression, improve perfusion and drug delivery, and enhance chemotherapy efficacy [78]. In three-dimensional breast cancer cell models, compressive stress can downregulate miR-9 through DNMT3A-dependent promoter methylation. This relieves miR-9-mediated repression of LAMC2, ITGA6, and EIF4E, increasing VEGFA expression [79]. Stiffness-induced MMP activation promotes angiogenesis, vascular invasion, and branching while disrupting the vascular barrier, leading to plasma and drug leakage [80]. CAFs support the formation of three-dimensional vascular networks through Rho/ROCK activation, promoting angiogenesis and exacerbating inadequate and uneven drug delivery [81]. High-affinity therapeutics, such as monoclonal antibodies, preferentially bind to densely expressed target antigens around blood vessels. This causes drugs to accumulate at the tumor periphery and limits penetration into the tumor, a phenomenon known as the “binding-site barrier” which is associated with ADC resistance in HER2+ BC [82]. Abnormal angiogenesis substantially promotes this process.

IFP and its spatial gradients further influence transvascular transport and interstitial flow. In normal tissues, the hydrostatic pressure gradient across the vascular wall is a key driving force for convective drug transport. However, in the

tumor core, IFP is often abnormally elevated and may even approximate microvascular pressure, forcing the predominant mode of transvascular transport for antibodies and macromolecular drugs to shift from efficient convection to less efficient diffusion [83]. More importantly, heterogeneous IFP elevation creates a pressure gradient from the tumor core toward the periphery [37]. This gradient drives outward interstitial fluid flow that washes drugs into surrounding tissues, further reducing local drug concentrations within the tumor [84].

4.1.2 Cell Membrane Transport

After drugs reach tumor tissue, their intracellular accumulation remains jointly regulated by membrane properties, endocytosis, and efflux activity. Drug-resistant breast cancer cells often exhibit tighter membrane lipid packing. This not only restricts drug penetration but also impedes the transmembrane transport and intracellular accumulation of anthracyclines, such as doxorubicin (DOX), through hydrophobic interactions [85]. Although studies have linked ECM alterations in breast cancer to AMPK-mediated metabolic adaptation [86, 87] and implicated these alterations in ER+ BC drug resistance through membrane transport [88], the precise regulatory relationships require further experimental evidence. Hypoxia resulting from impaired perfusion may also affect drug internalization. In HER2+ breast cancer cells, hypoxia induces the redistribution of phosphorylated caveolin-1 (Cav-1), reducing trastuzumab uptake and T-DM1 cytotoxicity without corresponding changes in HER2 expression or cellular sensitivity to DM1 [89].

The effects of the biomechanical microenvironment on intracellular drug exposure also involve the ATP-binding cassette (ABC) transporter family. ABC transporters reduce effective intracellular drug exposure through ATP-dependent drug efflux. ABCB1, ABCC1, and ABCG2 are key members involved in tumor multidrug resistance [90], with effects that depend on the transported substrate and cellular context [91]. In three-dimensional cultures, breast cancer cells under stiffer conditions showed greater resistance to DOX, accompanied by increased ABCB1 mRNA expression [92]. Another study using three-dimensional hydrogels with tunable

stiffness found that ABCB1 and YAP1 expression varied with culture conditions, supporting a link between biomechanical signals and efflux-associated phenotypes [93]. Conditions mimicking primary tumor stiffness (approximately 38 kPa) induced the strongest resistance phenotype in TNBC cells. This effect was mediated by the integrin-ILK-cytoskeletal axis, which inhibited Merlin/MST/LATS signaling and promoted YAP nuclear translocation and ABCB1 transcription [57]. Functional studies further showed that matrix stiffening enhances ABCC1 activity through cytoskeletal remodeling and changes in membrane tension, promoting vincristine efflux. Notably, MRP1-mediated vincristine efflux in MCF-7 cells was more sensitive to stiffness changes, indicating that the same mechanical input can elicit transport responses of different magnitudes across cellular contexts [94]. In addition to matrix stiffness, IFP can affect drug accumulation. In an in vitro microfluidic platform, MCF-7 and MDA-MB-231 cells cultured at 30 mmHg exhibited ABCC1 upregulation, reduced intracellular DOX concentrations, and increased drug resistance. Corresponding changes were also observed in ex vivo experiments using patient-derived CTCs [95].

Cell adhesion provides a more direct link between signal sensing and drug efflux. Breast cancer cell adhesion to COL1 enhances ABCB1-, ABCC1-, and ABCG2-associated efflux activity, accompanied by reduced intracellular accumulation of DOX and mitoxantrone [96]. This adhesion signaling primarily depends on the FAK/PI3K/AKT pathway in hormone receptor-positive breast cancer (HR+ BC), whereas it markedly activates MAPK/ERK signaling in TNBC. β1 integrin knockdown shifts signaling from PI3K/AKT to MAPK/ERK in MCF-7 cells, suggesting crosstalk and compensation between the two pathways. Both mechanisms, however, lead to CREB phosphorylation [97], making CREB a potential target for reversing drug efflux-associated therapeutic resistance.

4.2 Accumulation of Cellular Damage

Antitumor therapeutic effects depend on cellular damage and death; therefore, tumor cell repair, buffering, and evasion of damage are important causes of therapeutic resistance. Biomechanical factors can increase the resistance of breast

cancer cells to multiple therapeutic stresses by regulating DNA damage, apoptosis, and protective autophagy (**Fig. 4**).

4.2.1 DNA Damage

DNA double-strand breaks (DSBs) severely disrupt genomic integrity, constituting a core mechanism by which radiotherapy and genotoxic drugs kill tumor cells [98]. Matrix stiffness can influence DNA repair efficiency by regulating ubiquitination at DNA damage sites. Under low-stiffness conditions, activation of the RAP2-MAP4K4/6/7 kinase pathway induces ubiquitin phosphorylation at Thr66. This inhibits RNF8-mediated ubiquitin chain formation and the recruitment of BRCA1 and 53BP1, reducing the efficiency of homologous recombination and non-homologous end joining and impairing DNA repair. Conversely, a stiff ECM markedly enhances DNA damage repair efficiency in breast cancer cells, further supporting a biomechanics-dependent mechanism of resistance to genotoxic therapy [99].

Spatial confinement may affect nuclear energy supply through organelle reorganization. In cell models, including MDA-MB-231 cells, acute confinement induces actin-dependent reorganization of the endoplasmic reticulum and mitochondria, bringing mitochondria closer to the nucleus and increasing nuclear ATP levels. Disrupting mitochondrial ATP production or the associated cytoskeletal structures attenuates this response and affects chromatin states, DNA damage responses, and the recovery of proliferation [100]. Tissue analysis revealed more nucleus-associated mitochondria at the invasive front of breast tumors than in the main tumor mass, providing clinical tissue evidence consistent with this adaptive mechanism. However, the corresponding ATP changes, enhanced repair, and therapeutic resistance in breast cancer require further validation.

4.2.2 Autophagy and Apoptosis

The regulation of apoptosis and autophagy by matrix stiffness is intensity-dependent. In MDA-MB-231 cells, a soft matrix of 10 kPa can promote Bax translocation to mitochondria through the reactive oxygen species (ROS)/JNK pathway, inducing cell apoptosis. It also promotes Bcl-2 dissociation from Beclin-1

and the formation of the Beclin-1/Vps34/Atg14 complex to initiate protective autophagy, thereby partially counteracting apoptosis [101]. In a soft ECM mimicking lung metastatic lesions, breast cancer cells exhibit increased autophagy, reduced ERα expression, and acquired tamoxifen resistance. The same study found higher ILK expression in cells cultured on stiff matrices. Ectopic ILK expression in cells cultured on soft substrates reduced autophagosome abundance, suggesting that autophagic adaptation in soft environments involves cell-matrix adhesion and ILK regulation [17]. As tumors progress and the ECM stiffens, the β1 integrin/JNK pathway is persistently activated and engages in crosstalk with the ERK/p38 pathway, ultimately leading to sorafenib resistance in RAF-mutant TNBC [102]. In HER2+ BC, increased substrate stiffness attenuates the antiproliferative effects of lapatinib, whereas YAP/TAZ knockdown eliminates this stiffness-dependent difference [103]. Stiff ECM can also trigger the PI3K/AKT cascade through the integrin/FAK/Src pathway and activate survival signaling in tumor cells; compressive stress selectively induces PI3K overexpression, thereby playing an important role in biomechanics-dependent cell survival [104].

ECM adhesion can directly regulate the execution of apoptosis. In breast cancer models, binding of fibronectin (FN) to β1-integrin activates the PI3K/AKT cascade, suppresses mitochondrial cytochrome c release, and maintains Bcl-2 levels, thereby reducing paclitaxel- and vincristine-induced apoptosis [105]. FN adhesion can also upregulate survivin expression through the PI3K/AKT2 pathway, thereby diminishing the cytotoxicity of docetaxel [106]. The cytoskeleton represents another key node in the regulation of apoptosis. The actin-bundling protein fascin is influenced by ECM stiffness, and its high expression is associated with shorter disease-free survival in patients with breast cancer after chemotherapy [107]. Cell and xenograft models have confirmed an antiapoptotic role for fascin, potentially involving FAK/PI3K/AKT signaling [108].

FSS can elicit both adaptive protection and direct damage. For example, low FSS can suppress apoptosis in MCF-7 cells, whereas high FSS promotes apoptosis, inhibits migration, and induces G1-phase cell-cycle arrest in tumor cells [109]. In a

three-dimensional bioreactor mimicking flow conditions in the breast and pleural effusions, exposure to shear stress at 5.4 dyn/cm² for 72 h increased breast cancer cell resistance to paclitaxel, accompanied by elevated PLAU expression and urokinase activity [110]. Similarly, in a microfluidic platform mimicking in situ conditions, FSS activated AKT/mTORC1 signaling, suppressed hormone receptor expression in HR+ BC cells, thereby reducing their sensitivity to endocrine therapy [111]. By contrast, sustained exposure to shear stress at 60 dyn/cm² in an in vitro circulation model caused necrosis followed by apoptosis and reduced the viability of drug-resistant breast cancer cells [35]. In addition to the major mechanical factors described above, cyclic mechanical stretching also upregulates Bcl-2 expression and reduces the Bax/Bcl-2 ratio through multiple pathways, including PI3K, JAK, and YAP signaling, helping breast cancer cells survive chemotherapeutic pressure such as 5-fluorouracil [112].

4.3 Metabolic Stress and Adaptation

Metabolic reprogramming enables breast cancer cells to maintain energy supply, redox homeostasis, and biosynthesis under treatment pressure. The biomechanical microenvironment contributes to these processes by altering mitochondrial dynamics, nutrient utilization, and metabolic interactions between tumor and stromal cells (**Fig. 4**).

4.3.1 Redox Homeostasis

Oxidative stress responses and excessive accumulation of ROS are central mechanisms by which chemotherapy and radiotherapy kill tumor cells, but ROS can also act as signaling molecules that initiate adaptive protection. Drug-resistant cancer cells typically exhibit higher basal ROS levels and stronger antioxidant capacity [113]. The effects of the biomechanical microenvironment on treatment responses therefore depend on the relative changes in ROS production and clearance. In a simulated circulatory environment, arterial FSS enhanced the cytotoxicity of ROS-dependent drugs, including DOX and cisplatin, but had weaker sensitizing effects on paclitaxel and etoposide. These findings suggest a mechanically dependent mechanism of oxidative stress regulation [114].

Soft ECM can enhance oxidative stress adaptation in breast cancer by regulating mitochondria. Studies have shown that soft matrices promote perimitochondrial F-actin assembly involving Spire1C and Arp2/3, enhancing mitochondrial fission dependent on dynamin-related protein 1 (DRP1) and MIEF1/2. The subsequent increase in mitochondrial ROS specifically activates NRF2-associated antioxidant transcriptional programs, regulating cystine uptake and glutathione metabolism. This enhances breast cancer cell resistance to oxidative stress and ROS-associated chemotherapy-induced damage. In a mouse model of breast cancer lung metastasis, targeting DRP1- or NRF2-associated processes restored cisplatin sensitivity and limited the reactivation of dormant cells [115]. Ca^{2+} transfer from the endoplasmic reticulum to mitochondria is another important mechanism through which a soft ECM regulates mitochondrial dynamics. Soft ECM enhances endoplasmic reticulum calcium release and mitochondrial calcium uptake, promotes mitochondrial recruitment of DRP1 and phosphorylation at Ser616, and thereby induces excessive mitochondrial fission. Subsequently, cells initiate PINK1/Parkin-mediated mitophagy as a stress response, clearing damaged mitochondria and enhancing cellular antioxidant capacity. Inhibiting DRP1 activity increases tumor necrosis under soft ECM conditions [116].

Stiff ECM may induce antioxidant protection through mitohormesis. In mammary epithelial cell models, stiff ECM first activates the mechanosensitive ion exchanger SLC9A1 through integrin-ROCK signaling, causing mitochondrial Ca^{2+} overload and a transient increase in ROS levels. ROS then specifically activates heat shock factor 1 (HSF1), thereby upregulating target genes such as the mitochondrial protease YME1L1. These changes adjust mitochondrial architecture and respiratory function, promoting cellular tolerance to oxidative damage. Reduced matrix crosslinking in mouse mammary tumors was accompanied by decreased HSF1 nuclear localization, suggesting the potential relevance of this mechanism in breast cancer cells [117]. In addition to stiffness, ECM alignment can alter oxidative stress responses. A study mimicking aligned matrix architecture found that migrating breast cancer cell clusters activated AhR/CYP1 signaling through actin-mediated responses,

589 reducing ROS accumulation following DOX treatment. This induced DOX resistance
590 in TNBC and HR+ BC and promoted tamoxifen resistance in HR+ BC [118].
591 ***4.3.2 Glucose Metabolism***
592 Glucose metabolism is linked to redox homeostasis through energy production,
593 the supply of reducing equivalents, and the allocation of biosynthetic precursors [119].
594 Glycolysis generates ATP and NADH, whereas the conversion of pyruvate to lactate
595 regenerates NAD^+. NADPH required for antioxidant defense is supplied by pathways
596 such as the pentose phosphate pathway. Changes in mitochondrial function can also
597 contribute to shifts in glucose metabolism. In TNBC cells, mitochondrial uncoupling
598 and increased ROS promote HIF-1 α -associated signaling and upregulate
599 glycolysis-related molecules, including GLUT1 and LDHA, suggesting a feedback
600 mechanism between mitochondrial stress and glycolysis [120]. Lactate has been
601 shown to enhance G6PD activity through GSTP1-associated regulation, promoting
602 NADPH production and ROS tolerance under glucose-limited conditions. These
603 findings support a link between glucose metabolism and antioxidant defense in breast
604 cancer [121].
605 ECM architecture and stiffness can influence glucose utilization and metabolic
606 states. Microscopic imaging has shown that, compared with breast cancer cells
607 surrounded by randomly oriented collagen fibers, those encircled by directionally
608 aligned fibers exhibit markedly enhanced glycolytic activity [122]. Matrix stiffening
609 can also enhance glycolysis and glutamine metabolism in breast cancer cells,
610 accompanied by changes in the expression of molecules such as LDHA [123]. Stiff
611 ECM activates the FAK/PI3K/AKT/mTOR signaling cascade by stabilizing
612 integrin-ECM adhesion, directly upregulating glycolysis-related molecules such as
613 GLUT1, HK2, and PFKFB3, promoting glucose uptake and glycolytic flux.
614 Meanwhile, activated mTORC1 enhances protein, lipid, and nucleotide synthesis and
615 induces HIF-1α expression, further consolidating the glycolytic phenotype [124]. In
616 addition, stiffness can increase basal AKT and ERK activity by regulating CXCR4
617 internalization [125], and can upregulate miR-18a through the
618 integrin/β-catenin/MYC axis while suppressing PTEN, thereby continuously

amplifying PI3K/AKT signaling and driving glucose metabolic reprogramming [126]. In turn, glycolysis-associated ROS oxidatively inactivate PTEN, maintaining PI3K/AKT activation and favoring therapeutic resistance [127].

FSS can also induce metabolic reprogramming by regulating mitochondrial structure. Studies have shown that FSS exposure specifically downregulates the c-subunit of mitochondrial F1F0-ATP synthase, thereby reducing oxidative phosphorylation (OXPHOS) efficiency, inducing changes in mitochondrial membrane potential, and uncoupling oxygen consumption from ATP production. This process simultaneously facilitates a shift in cellular metabolism toward glycolysis, which enables rapid energy supply for tumors and accumulation of biosynthetic precursors. Overall, this metabolic transition reduces the dependence of tumor cells on mitochondrial function and enhances their resistance to oxidative stress-related mitochondrial damage, thereby promoting tumor cell survival during circulatory dissemination [128].

4.3.3 Biosynthetic Metabolism

Amino acid utilization and nucleotide synthesis link biomechanical signals to the survival requirements of cells under treatment pressure. YAP/TAZ serve as key transcriptional regulators in this connection. In HER2+ BC cell and mouse models, EphA2 activates YAP/TAZ-associated transcription to increase the expression of the glutamine transporter SLC1A5 and glutaminase (GLS), promoting glutamine uptake and metabolism [129]. Stiff ECM further upregulates the aspartate/glutamate transporter SLC1A3 through YAP/TAZ, driving metabolic crosstalk between cancer cells and CAFs. Specifically, CAF-derived aspartate provides precursors for nucleotide synthesis in cancer cells, whereas glutamate secreted by cancer cells helps CAFs maintain redox balance and enhance contractility, promoting ECM remodeling and thereby supporting the formation of a therapeutic resistance niche [123].

In nucleotide synthesis, YAP/TAZ can upregulate key enzymes, including ribonucleotide reductase subunit M2 (RRM2), expanding the deoxyribonucleotide triphosphate (dNTP) precursor pool. This not only provides sufficient substrates for DNA replication, accelerates tumor cell-cycle progression, and supports

anchorage-independent growth, but also attenuates DNA chain termination and replication stress induced by nucleoside analogs such as gemcitabine in tumor cells [130]. Clinical data further associate high RRM2 expression with resistance to therapies such as tamoxifen and palbociclib in patients with breast cancer [131, 132].

4.4 Phenotypic Plasticity

Phenotypic plasticity has been identified as the ninth hallmark of cancer [133]. Under therapeutic pressure, dynamic transitions between epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) phenotypes provide a celluar basis for therapeutic resistance [134]. The biomechanical microenvironment contributes to the formation of residual cell populations after treatment by regulating epithelial-mesenchymal plasticity, stemness maintenance, and transitions into and out of quiescence (**Fig. 5**).

4.4.1 Epithelial-Mesenchymal Plasticity

EMT refers to a reversible process in which cells lose polarity and adhesive function and acquire a mesenchymal phenotype. It is regulated by transcription factors such as ZEB1/2, Snail1/2, Slug, and Twist1/2 [135]. Breast cancer cells can transition along the continuum encompassing epithelial, partial EMT, namely hybrid E/M, and complete EMT phenotypes [136]. Hybrid E/M cells can exhibit enhanced self-renewal, sphere-forming capacity, and phenotypic plasticity and are associated with poorer survival in patients with breast cancer [137]. In mouse models of breast cancer, cells that have undergone EMT can resist cyclophosphamide through reduced proliferation, apoptosis tolerance, and altered expression of drug resistance-related genes. These cells also contribute to recurrent lung metastases after treatment [138]. Further lineage-tracing studies have shown that partial EMT cells contribute to lung metastasis and chemotherapy resistance. Although full EMT cells form lung metastases less frequently, they can become enriched in recurrent tumors after chemotherapy [139]. Epithelial-mesenchymal state transitions are also associated with tamoxifen resistance in ER+ BC [140].

Matrix stiffness can regulate transitions between epithelial and mesenchymal states. STIFMap analysis of breast cancer tissue revealed spatial associations of

higher matrix stiffness with biomechanical signaling activation and EMT-related markers, providing clinical evidence linking tissue mechanical heterogeneity to cellular phenotypes [141]. Mechanistically, stiff ECM can drive TWIST1 dissociation from its cytoplasmic anchoring protein G3BP2 and subsequent nuclear translocation, cooperating with TGF-β to induce EMT and invasion [142]. In MDA-MB-231 cells, stiff ECM can also promote YAP nuclear translocation and downregulate E-cadherin, inducing EMT and DOX resistance in a stiffness-dependent manner. However, MCF-7 cells did not exhibit stiffness-dependent drug resistance under the same conditions, indicating that the relationship between stiffness and EMT-associated phenotypes depends on cellular context [115]. Mammary epithelial cell models have further confirmed that EMT-inducing effects of TGF-β are regulated by the ECM. In stiff ECM, ILK-mediated strong cell-matrix adhesion and weak cell-cell adhesion enable cells to respond to TGF-β signaling and transition toward an EMT phenotype, thereby acquiring therapeutic resistance; by contrast, soft ECM can redirect TGF-β signaling toward apoptosis induction by strengthening cell-cell adhesion [143].

Fluid mechanical signals, including IFP and FSS, can also induce therapeutic resistance by promoting EMT. Studies have shown that the combined effects of IFP and FSS markedly reduce the sensitivity of breast cancer cells to DOX, accompanied by increased expression of Snail, MMP14, and HER2 and downregulation of cadherin-11, suggesting that fluid mechanics can shape the EMT phenotype [144]. During hematogenous metastasis, suspension conditions and FSS jointly promote cytoplasmic retention of YAP in CTCs and downregulate miR-29b. This relieves TGF-β inhibition and enhances associated EMT phenotypes [145].

In addition to stimuli derived from the TME, endogenous mechanical abnormalities arising during tumor evolution can also induce EMT-associated therapeutic resistance phenotypes. During progression from ductal carcinoma in situ to invasive ductal carcinoma, a RAB5A-mediated solid-to-fluid tissue transition can cause sustained nuclear deformation, reduced lamin B1 levels, DNA damage, and nuclear envelope rupture. Cytosolic double-stranded DNA can activate cGAS-STING signaling and induce a type I interferon (IFN-I) response [146]. In this breast cancer

model, genomic DNA released after nuclear envelope rupture activated a cGAS-STING-dependent transcriptional response, and this process is accompanied by an increase in mesenchymal features and reduced sensitivity to docetaxel and etoposide. Inhibition of cGAS or STING attenuates the expression of some EMT-associated genes [147]. In summary, the key feature of biomechanics-induced resistant phenotypes is not unidirectional promotion of EMT, but rather the maintenance of intermediate cellular states, which not only promotes residual disease, but can also drive metastasis and colonization through reverse mesenchymal-epithelial transition [148].

4.4.2 BCSCs

Breast cancer stem cells (BCSCs) are an important cellular subpopulation that drives post-treatment residual disease and recurrence, possessing self-renewal and tumor-initiating capacities, and are typically characterized by CD44+/CD24−/low and ALDH1+ phenotypes [149]. BCSCs exhibit intrinsic resistance to therapeutic modalities such as chemotherapy [150, 151] and can promote drug-resistant relapse by regulating cell death and crosstalk with immune cells [3, 152]. Notably, BCSCs can be dynamically induced by EMT [153, 154]and mechanical signals, thereby leading to resistance to multiple therapeutic modalities.

Matrix stiffening helps sustain BCSC-associated transcriptional programs. Clinical sample analyses have associated higher stiffness with BCSC enrichment, poorer responses to neoadjuvant chemotherapy, and unfavorable prognosis. Cell and animal experiments have shown that stiff matrices promote liquid-liquid phase separation of TAZ and NANOG, forming nuclear condensates that activate SOX2 and OCT4 transcription and enhance BCSC self-renewal and chemotherapy resistance. Targeting TAZ or NANOG reduces stem-like cell populations and improves chemotherapy sensitivity in vivo [155]. In drug-resistant breast cancer stem-like cell models, YAP/TAZ silencing also reduces SOX2 expression, disrupts mitochondrial homeostasis, and impairs sphere formation and survival [156]. Stemness maintenance is jointly regulated by other microenvironmental factors, including matrix composition. In ER+ BC models, high collagen density enriches an mTOR-dependent

BCSC population [157]. ECM stiffening and hypoxia can also synergistically activate integrin β1/ILK/PI3K/AKT signaling, enhancing stemness-associated gene expression and functions [158]. Unlike matrix stiffness, solid stress generated by spatial confinement can promote drug-resistant cell populations through local interface effects. In an MCF-7 spheroid model mimicking the tumor-host interface, hydrogel confinement promotes the emergence of CD44+/CD133+ cells at the spheroid periphery and enhances their resistance to DOX and tamoxifen [159]. Conversely, soft ECM promotes the maintenance of ALDH1+ BCSCs by inhibiting YAP nuclear translocation, thereby reducing breast cancer cell sensitivity to DOX and cisplatin [160].

Notably, stem-like cells can actively proliferate or enter a quiescent state while retaining the potential for reactivation. Stemness and quiescence are therefore related but distinct dimensions of cellular state. Specifically, low stiffness (approximately 45 Pa) supports breast cancer cell stemness and tumor-initiating capacity through β1/β3 integrin-cytoskeleton-AIRE signaling. Higher stiffness (approximately 450 Pa), by contrast, induces cell cycle arrest through the DDR2/STAT1/p27 pathway, driving BCSCs into dormancy. These cells can resume proliferation after three-dimensional confinement is removed [44]. Omics analyses further suggest that antiapoptotic and membrane transport-related processes may contribute to drug resistance in the quiescent state [88].

During metastatic dissemination through the circulation, FSS can also influence stem-like states through mechanisms including intercellular communication. In patient-derived breast cancer cell models, FSS induces ROS and nitric oxide (NO) production in CTCs and suppresses ERK/GSK3β signaling. This drives EMT and enriches ALDH1+CD133+CXCR4+ BCSCs, ultimately enhancing metastatic colonization [161]. FSS can also increase the release of miR-21-enriched extracellular vesicles (EVs) from breast cancer cells. Exposure to these vesicles markedly upregulates stemness-associated genes in MCF-7 cells and increases the proportion of CD44+/CD24- BCSCs [162].

4.5 Immune Microenvironment

An immunosuppressive microenvironment is a major barrier to antitumor immunotherapy. Fibrotic ECM not only constitutes a physical barrier that restricts immune cell infiltration, but also impairs the function of immune effector cells and enriches immunosuppressive cells [163], thereby reducing the efficacy of immunotherapy while affecting the establishment of antitumor immunity after chemotherapy, radiotherapy, and targeted therapy (**Fig. 6**).

4.5.1 Immune Exclusion and Effector Cell Inactivation

ECM collagen content and fiber alignment can influence T cell distribution within tumors. Computational models based on tumor-associated collagen architecture suggest that fiber density and alignment can alter tumor cell-T cell interactions and immune selection [164]. Analysis of TNBC tissue has directly linked higher collagen density to reduced CD8+ T cell infiltration. Three-dimensional culture experiments further showed that dense collagen suppresses T cell proliferation, downregulates cytotoxicity-related genes, and impairs the ability of infiltrating T cells to kill tumor cells [165]. The extracellular domain of DDR1 on mouse TNBC cells can also bind collagen and promote fiber alignment, restricting T cell entry into tumor nests. In corresponding human samples, DDR1 expression was inversely associated with antitumor T cell abundance, providing clinical correlative support for this mechanism [166]. Dense ECM can also induce a shift in T cell migration from "mesenchymal-like" mode to "amoeboid-like" mode, diverting T cells away from tumor cell clusters and thereby weakening immune cytotoxic efficacy [167].

Matrix stiffening can also impair immune effector cells through metabolic competition. In a stiffened and fibrotic TME, tumor-associated macrophages (TAMs) secrete and release TGF-β, activating collagen synthesis, while simultaneously consuming large amounts of arginine and secreting ornithine, resulting in arginine depletion and ornithine accumulation in the microenvironment. Persistent arginine deficiency can impair ATP synthesis and effector molecule expression in CD8+ T cells, whereas ornithine accumulation further inhibits arginine uptake. Together, these processes disrupt T cell metabolic homeostasis and ultimately suppress CD8+ T cell proliferation, activation, and tumor-killing capacity, thereby weakening the efficacy of

immune checkpoint blockade (ICB) [168].

By regulating immune checkpoints and intercellular communication, biomechanical signals further consolidate the immunosuppressive microenvironment. In cocultures of TNBC cells and cytokine-induced killer (CIK) cells, FAK knockdown or inhibition reduces tumor cell PD-L1 expression and enhances CIK-mediated killing [169]. Another study found that highly expressed CTLA-4 on breast cancer cells binds CD80 on antigen-presenting cells (APCs) and uses cellular traction forces to internalize CD80 through trans-endocytosis. This process deprives APCs of costimulatory signaling and markedly suppresses T cell activation within the TME [170].

4.5.2 Recruitment and regulation of immunosuppressive cells

The recruitment, polarization, and function of immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs), TAMs, and regulatory T cells (Tregs), are also regulated by biomechanical signals. ECM stiffness is an important factor influencing macrophage polarization [171]. Single-cell RNA sequencing has shown that the proportion of protumorigenic M2 macrophages is markedly increased in high-stiffness breast cancers. This may be related to the ability of stiff ECM to activate FAK and upregulate colony-stimulating factor 1 (CSF-1) expression, thereby recruiting macrophages and driving their M2 polarization [172]. Increased ECM collagen density may also promote Treg infiltration in TNBC [173]. In clinical samples and mouse models of high-grade breast cancer, tumors enriched in ECM-related expression signatures are associated with immunosuppressive Tregs. Mechanistic studies have shown that the matrix protein SPARC induces IL-23 release, which downregulates surface PD-1 expression on Tregs and contributes to immunosuppression [174].

Soft ECM and associated low compressive stress it generates can also induce the expression of immunosuppressive factors such as TGF-β and interleukin-10 (IL-10) by upregulating fibroblast growth factor 2 (FGF2) and prostaglandin E2, while promoting M2 macrophage polarization and exhaustion of CD8+ effector memory T cells. FGF2-enriched regions in primary tumor tissue likewise exhibit increased

M2-like macrophages and reduced T and B cell infiltration [18]. In addition, oscillatory stress can promote the release of PD-L1-enriched EVs from breast cancer cells, enhancing the immunosuppressive functions of MDSCs and M2 macrophages and reducing CD8+ T cell infiltration [175]. Studies have shown that activation of YAP/TAZ in tumor cells can participate in the recruitment or differentiation of M2 macrophages, Tregs, and MDSCs, and suppress natural killer (NK) cell function, thereby leading to immune evasion [176, 177]. YAP/TAZ may therefore serve as a signaling hub linking biomechanics to regulation of the immune microenvironment.

4.6 Context-dependent effects of matrix stiffness

The relationship between matrix stiffness and therapeutic resistance is not simply linear. Stiffer matrices can support tumor cell survival under treatment pressure by enhancing biomechanical signaling, maintaining stem-like states, and altering immune cell function. For example, matrix stiffening promotes TAZ- and NANOG-associated transcription and enhances chemotherapy resistance in breast cancer models [155]. Soft matrices can reduce tamoxifen sensitivity by enhancing autophagy [17] or support cisplatin resistance through mitochondrial fission and NRF2-associated antioxidant adaptation [178]. However, these differences cannot be reduced to stiff matrices promoting proliferation and soft matrices maintaining dormancy. In some breast cancer models, higher stiffness instead induces reversible quiescence, whereas softer environments support proliferative stem-like states. Stiffness effects also depend on cellular context, the mechanism of therapeutic action, and intervention duration. Different breast cancer cells can exhibit distinct drug responses under the same matrix conditions. Moreover, the definitions of "soft" and "stiff" are relative across studies. Differences in culture dimensionality, matrix composition, ligand density, and spatial confinement limit direct comparisons, precluding a universally applicable relationship between stiffness and drug resistance.

In summary, the biomechanical microenvironment contributes to therapeutic resistance in breast cancer by influencing therapeutic delivery, damage responses, metabolic adaptation, phenotypic plasticity, and immune function. Meanwhile, therapeutic pressure can alter tissue biomechanical properties and local mechanical

loads by regulating tumor cell behavior [39] and CAF function [179]. These changes modulate signaling responses and interactions between residual tumor cells and surrounding stromal cells, supporting the maintenance of tolerant states. Thus, the biomechanical microenvironment both contributes to pretreatment differences in sensitivity and forms part of post-treatment adaptation. The dominant mechanisms underlying this feedback may vary across breast cancer subtypes, lesion sites, and treatment stages, resulting in heterogeneous treatment responses.

5. Targeting Biomechanics: From Biomechanical Stratification to Combination Sensitization Therapy

The biomechanical microenvironment represents a shared basis for therapeutic resistance in breast cancer. Therefore, targeting biomechanics is not only an important sensitization strategy, but should also be incorporated into patient stratification and therapeutic regimen design.

5.1 Biomechanical Stratification Strategies

Imaging and tissue-based molecular assessments characterize the biomechanical microenvironment of breast cancer at different levels. Imaging methods noninvasively measure parameters such as stiffness and viscoelasticity and track their dynamic changes during treatment, whereas tissue and molecular methods reflect ECM architecture and mechanotransduction activity (Table 3). These measures can complement conventional pathological classification and inform risk assessment and treatment-response research.

5.1.1 Imaging-Based Assessment

Ultrasound elastography (UE) is an important method for biomechanical assessment in breast cancer. Strain elastography (SE) evaluates tissue mechanical properties based on deformation under compression, whereas shear wave elastography (SWE) uses shear wave propagation characteristics [180]. In addition to helping distinguish benign from malignant lesions [181], elastography parameters are associated with prognostic factors such as tumor size and histological grade [182]. A retrospective clinical study of neoadjuvant chemotherapy (NACT) found that the tumor tissue strain ratio after two chemotherapy cycles and its change from baseline

were associated with pathological complete response (pCR). Some pretreatment elastography measures may also provide prognostic information on recurrence-free survival [183].

Magnetic resonance elastography (MRE) analyzes mechanical wave propagation through tissue to obtain parameters such as stiffness and phase angle, which reflects viscoelastic properties [184]. A prospective clinical study showed that the ratio of the phase angle after the first chemotherapy cycle to its pretreatment value was associated with the final pathological response. The tumor stiffness ratio at the end of NACT was also associated with pCR. Combining this measure with dynamic contrast-enhanced MRI could improve the specificity of identifying patients with a complete response [185]. These findings suggest that baseline biomechanical characteristics and their changes during treatment can inform risk assessment and response monitoring, supporting their potential for further clinical validation and application.

5.1.2 Tissue-Molecular Assessment

Tissue and molecular techniques more directly characterize the structural features of breast cancer tissue. Second harmonic generation (SHG) imaging reveals the distribution, alignment, and associated microstructural features of fibrillar collagen and has prognostic value [186]. The forward-to-backward SHG scattering ratio in pretreatment biopsy specimens has also been explored as a marker of NACT response. At the tumor-stroma interface in HER2+ BC, this ratio was associated with residual tumor burden, whereas no comparable association was observed in the main tumor mass or in TNBC samples [187]. Thus, the performance of collagen structural measures may depend on molecular subtype and sampling location. Polarized light imaging, which infers tissue microarchitecture based on the propagation properties of polarized light, facilitates the differentiation of breast cancer molecular subtypes [188]and intraoperative margin assessment [189].

Gene expression analysis further links cellular states to clinical outcomes. The mechanical conditioning score (MeCo) is derived from gene expression signatures associated with mechanical conditions and reflects cellular transcriptional adaptation to the matrix environment [73]. A phase II clinical trial found that higher MeCo scores

were associated with a greater risk of recurrence. Exploratory analyses suggested that the score might help identify patients who could benefit from antifibrotic therapy [190]. Although current findings support the prognostic associations and predictive potential of MeCo, its utility in treatment selection requires validation in independent cohorts and prospective biomarker-stratified studies.

5.2 Biomechanics-Targeted Intervention Strategies

Based on the biomechanical features of the breast cancer microenvironment and the mechanistic networks through which they regulate therapeutic resistance, normalization of the biomechanical microenvironment, blockade of signal transduction, optimization of drug delivery, and mechanics-related physical interventions have emerged as important therapeutic strategies (**Fig. 7**).

5.2.1 Remodeling of Biomechanical Microenvironment

Remodeling the biomechanical microenvironment aims to reduce transport barriers by modulating ECM deposition and crosslinking, stromal cell function, and vascular status. Because microenvironments with different stiffness levels can support therapeutic resistance, the goal should not be continuous matrix softening. Instead, interventions should be tailored to vascular perfusion, drug distribution, and residual cell states.

Inhibiting collagen crosslinking is an important strategy for targeting the ECM. The LOX family contributes to matrix stiffening by catalyzing collagen and elastin crosslinking [191]. The pan-LOX inhibitor β-aminopropionitrile (β-APN) can not only prevent tissue fibrosis, reduce tumor incidence, and delay malignant progression in MMTV-Neu mice [23], but also synergize with DOX in the 4T1 model to control primary lesions [192]. However, long-term use of β-APN may cause adverse effects such as aortic injury. By contrast, the next-generation LOX inhibitor PXS-5505 has a favorable safety profile and has been shown to remodel collagen architecture and suppress tumor progression in ER+ BC and TNBC models [193]. Other agents with preclinical activity against breast cancer include the LOXL2-inhibitory antibody AB0023 [194], the small-molecule LOX inhibitor CCT365623 [195], and the LOXL2 inhibitors PXS-S1A and PXS-S2A [196].

Drug repurposing offers another antifibrotic strategy. The angiotensin receptor blocker losartan suppresses profibrotic signaling and reduces collagen and HA production. In breast cancer models, it alleviates solid stress and vascular compression, improves perfusion, and enhances chemotherapy efficacy [78]. It also reduces lung metastasis in mouse models of breast cancer [197]. Among antifibrotic agents, tranilast remodels the fibrotic matrix by inhibiting TGF-β-associated signaling, increases vascular perfusion [198], and improves the delivery and efficacy of chemotherapeutic drugs and nanoformulations [199]. Pirfenidone modulates breast cancer cell migration and EMT-associated phenotypes [200]. In HR+ BC models, it also inhibits CCL2-associated Treg chemotaxis induced by combined palbociclib and fulvestrant treatment, enhancing antitumor immunity [201]. Nintedanib has progressed to clinical investigation. In patients with luminal breast cancer, nintedanib combined with letrozole enhances antitumor activity, although prolonged use may cause toxicity [202]. In HER2-negative breast cancer (HER2- BC), nintedanib combined with paclitaxel reduced recurrence risk but did not significantly improve median event-free survival [190].

Relieving solid stress and IFP is likewise an important component of reversing therapeutic resistance. In breast cancer xenograft models, the Hedgehog pathway inhibitor vismodegib reduces activated CAFs and matrix components, alleviating solid and fluid pressures. This improves perfusion and enhances the efficacy of albumin-bound paclitaxel and DOX [203]. Hyaluronidases such as PEGPH20 degrade excessively accumulated HA, reduce IFP, and relieve transport barriers. These effects increase NK cell infiltration and enhance the antitumor activity of trastuzumab [204], while also facilitating nanomedicine delivery [205]. In addition, sunitinib-loaded lipid nanoparticles (Sun@PL) enable low-dose, sustained release of sunitinib, promote vascular normalization, and alleviate hypoxia, while synergizing with two-stage radiotherapy. The first irradiation softens the ECM and reduces vascular compression, amplifying the microenvironment-remodeling effects of Sun@PL; subsequent irradiation during the window of improved oxygenation then markedly enhances tumor radiosensitivity [206]. The selective MMP14 inhibitor DX-2400 also

suppresses TGF- β signaling, improves perfusion, and enhances radiotherapy efficacy in 4T1 model [207].

Multiple potential therapeutic targets remain within the breast cancer TME. COL4A2 can promote the ordered alignment of collagen fibers and activate YAP signaling; its knockdown not only softens and homogenizes the ECM and suppresses metastasis [208], but is also associated with cell-cycle arrest [209], providing mechanistic evidence for targeting matrix components. An antibody against GPR77 on CD10+GPR77+ CAFs has been shown to restore chemotherapy sensitivity in patient-derived xenograft models, supporting the feasibility of targeting specific stromal cell populations [210]. In addition, β-adrenergic receptors (β-ARs) [211] and copper depletion [212] are also associated with therapeutic resistance in breast cancer and warrant further investigation.

5.2.2 Modulating Signal Transduction

Modulation of signal transduction focuses on three levels: membrane mechanosensing, cytoplasmic signal transmission, and nuclear transcriptional regulation. It aims to weaken tumor cell adaptation to the biomechanical microenvironment and enhance sensitivity to existing treatments.

Integrins are important therapeutic targets linking the ECM to intracellular signaling. In tamoxifen-resistant breast cancer cells, the aryl hydrocarbon receptor ligand aminoflavone inhibits α6 integrin/Src/AKT signaling and enhances the response to tamoxifen [213]. The αvβ6-blocking antibody 264RAD, combined with trastuzumab, exhibits greater antitumor activity than either agent alone in HER2+ BC models and also shows activity in trastuzumab-resistant models [214]. In addition, αvβ3-CAR-T cells not only effectively kill primary and metastatic TNBC cells in preclinical models, but also promote the establishment of post-treatment antitumor immunity [215].

Mechanosensitive ion channels convert mechanical signals into biochemical signals. Ca^{2+} functions as a second messenger involved in resistance-related pathways [216]. The Piezo1 inhibitor GsMTx4 can reduce the migratory capacity of MCF-7 cells under stiff ECM conditions, thereby controlling metastasis [45]. The TRPV4

agonist GSK1016790A promotes vascular maturation and enhances cisplatin efficacy in mouse models of lung cancer [217]. In breast cancer cells with high TRPV4 expression, GSK1016790A instead induces cell death by activating this channel [218]. The calcium channel blocker lacidipine can activate effector T cells and suppress Treg function by regulating tryptophan metabolism, converting immunologically “cold” tumors into “hot” tumors [219], thereby enhancing sensitivity to immunotherapy.

Among cytoplasmic signaling nodes, FAK has a relatively extensive preclinical evidence base in breast cancer. PND-1186 selectively blocks phosphorylation of FAK at Tyr397, induces tumor cell apoptosis [220], and suppresses spontaneous lung metastasis in breast cancer models [221]. VS-4718 and VS-6063 preferentially target BCSC subpopulations, reduce chemotherapy-induced BCSC enrichment, and delay tumor regrowth after chemotherapy [222]. The ATP-competitive FAK inhibitor BI 853520 suppresses primary tumor growth in multiple mouse models of breast cancer and affects different stages of the metastatic cascade [223]. It has also shown preliminary evidence of safety and antitumor activity in a phase I trial in patients with advanced solid tumors [224]. Src, a kinase that cooperates with FAK, also contributes to therapeutic resistance in breast cancer. The representative Src/Abl inhibitor dasatinib can block BCSC enrichment and enhance the sensitivity of drug-resistant TNBC cells to paclitaxel [225]. Although its clinical activity as monotherapy is limited [226], its combination with trastuzumab and paclitaxel has shown favorable safety and an appreciable objective response rate in HER2+ BC [227], supporting its feasibility as a combination strategy to enhance treatment sensitivity.

Downstream of FAK/Src, RhoA/ROCK couples focal adhesion signaling to the actin cytoskeleton, thereby amplifying biomechanical signals. By disrupting stress fibers, the ROCK inhibitors Y-27632 [228] and fasudil [229] can effectively suppress breast cancer cell migration. RKI-1447 inhibits ROCK substrate phosphorylation and exhibits activity against invasion and anchorage-independent growth in breast cancer cell and mouse models [230]. These studies support the therapeutic tractability of Rho/ROCK signaling, but its ability to enhance sensitivity to specific treatments requires confirmation in direct combination studies.

Targeting YAP/TAZ-TEAD-mediated transcription provides another approach to limiting adaptive cellular behavior. In breast cancer models, verteporfin not only induces apoptosis and autophagy in paclitaxel-resistant TNBC cells and suppresses xenograft growth [231], but also reduces YAP-dependent glycolysis [232]and enhances the cytotoxicity of antitumor agents [233]. More importantly, verteporfin can selectively eliminate drug-resistant BCSCs by disrupting mitochondrial homeostasis and inducing oxidative stress and apoptosis, thereby reversing therapeutic resistance [156]. However, although verteporfin is FDA-approved for ophthalmic indications [234], its dosing and safety in breast cancer treatment remain unvalidated. VGLL4, an endogenous antagonist that binds TEAD, suppresses YAP/TAZ-dependent breast cancer growth [235]. Its mimetic peptide, super-TDU, has demonstrated antitumor potential in gastric cancer studies [236]. Studies of cooperative transcriptional regulation by YAP/TAZ and BRD4 have further shown that the BET inhibitors JQ1 and BAY-1238097 interfere with YAP/TAZ-mediated recruitment and activation of BRD4 and RNA polymerase II. This selectively suppresses YAP/TAZ-driven transcriptional output and effectively controls tumor progression in breast cancer models [237].

Targeting other biochemical signaling pathways is also a promising research direction. Combined JAK and SMO inhibition synergistically suppresses tumor growth and metastasis in models of TNBC and trastuzumab-resistant breast cancer [238]. However, despite evidence of target inhibition, the JAK inhibitor ruxolitinib failed to demonstrate clear efficacy in a phase II trial in TNBC [239]. Another study found that JAK inhibition may impair NK cell-mediated immune surveillance and increase metastatic burden [240]. The IL-6 receptor antibody tocilizumab, combined with cisplatin and docetaxel, has entered prospective phase I/II clinical investigation in TNBC. Larger clinical trials are still needed to establish its ability to enhance treatment sensitivity [241].

5.2.3 Optimizing Drug Delivery

Drug delivery optimization aims to improve delivery efficiency by modulating drug circulation, distribution, and release. Compared with conventional free drugs,

nanoparticles can improve drug stability and increase local tumor exposure [242], thereby attenuating the impact of biomechanical barriers on therapeutic efficacy.

Co-delivery of matrix-modulating agents and cytotoxic drugs can coordinate the alleviation of physical barriers with tumor cell killing. The pH-responsive DOX@CREKA/tPA-HP nanoparticles integrate the fibrin-targeting peptide CREKA, tissue plasminogen activator (tPA), and DOX. In the 4T1 mouse model, this system can degrade fibrin, reduce ECM stiffness and solid stress, relieve vascular compression, and ultimately increase intratumoral DOX accumulation. This strategy has demonstrated safe and efficient antitumor activity in TNBC model [243]. Targeted delivery can also reduce dose limitations imposed by systemic effects. TME-activated angiotensin receptor blocker nanoconjugates (TMA-ARBs) use acid-sensitive polymers for local drug delivery. In mouse models of breast cancer, they inhibit CAF-associated collagen deposition, improve delivery, and activate immune cells while avoiding systemic hypotension [244]. Cell membrane-fused liposomes, PFD/TAFsomes and DOX/CCMsomes, deliver pirfenidone and DOX to CAFs and tumor cells respectively. This coordinates antifibrotic and cytotoxic therapy and enhances anti-PD-L1 efficacy in TNBC models [245]. Delivery systems can also support interventions targeting biomechanical signaling. Niflumic acid prodrug-based polymeric micelles can encapsulate dasatinib, increasing tumor accumulation and enhancing tumor suppression [246].

Micellar encapsulation can enhance the effects of microenvironment-modulating agents, thereby improving sensitivity to combination therapy. Tranilast-loaded PEG-PBLG micelles (Tranilast/m) prolong drug circulation, increase tumor accumulation and CAF uptake, and suppress TGF-β-associated signaling in the 4T1 mouse tumor model. In E0771-bearing mice, daily intravenous administration of Tranilast/m at 2 mg/kg more effectively reduces tumor stiffness and IFP and improves vascular perfusion than daily oral administration of free tranilast at 200 mg/kg. Its antitumor efficacy in combination with epirubicin micelles was demonstrated in both models. With the addition of immune checkpoint blockade, E0771 rechallenge experiments supported the development of tumor-specific immune memory [247].

Another study encapsulated pirfenidone in micelles with pH-responsive release properties (Pirfenidone/m). In 4T1 model, intravenous Pirfenidone/m at 5-10 mg/kg reduced tumor stiffness and IFP and improved perfusion, at doses substantially lower than the 500 mg/kg used for orally administered free pirfenidone. Further experiments showed that Pirfenidone/m at 10 mg/kg combined with anti-PD-1 and anti-CTLA-4 antibodies increased T cell infiltration in 4T1 tumors, while E0771 rechallenge experiments also provided evidence of tumor-specific immune memory [248].

Nano-platforms can also enhance therapeutic efficacy by interfering with the signaling feedback loops between tumor cells and stromal cells. For example, the self-assembling lysosome-targeted chimera (LYTAC) nano-platform NanoCLY enhances the antitumor activity of paclitaxel in a TNBC model by degrading extracellular connective tissue growth factor (CTGF), thereby inhibiting the activation of inflammatory CAFs and disrupting CTGF-IL-6-mediated intercellular interactions [249]. As an emerging delivery system, lemon-derived vesicles can improve DOX tumor targeting and transcellular transport [250]. Local sustained-release platforms can also coordinate the timing of matrix modulation and anticancer drug activity. Through targeted delivery of losartan and oxaliplatin, LOS&FeOX@Gel reduces ECM deposition in breast tumors after chemotherapy and enhances chemotherapy-associated immune effects and subsequent immunotherapy efficacy [251]. These systems expand design options for targeted delivery and local controlled release. Integrating them with breast cancer biomechanical characteristics may enable more precise drug delivery in the future.

5.2.4 Mechanics-Related Physical Interventions

Physical therapies based on biomechanical features can enhance the sensitivity of breast cancer to radiotherapy, chemotherapy, targeted therapy, and immunotherapy by remodeling the ECM and improving vascular perfusion and the immune microenvironment.

Local hyperthermia combined with radiotherapy has a relatively substantial clinical evidence base. In locally recurrent breast cancer, radiotherapy combined with hyperthermia achieves a markedly higher complete response rate than radiotherapy

alone and retains radiosensitizing effects during re-irradiation [252]. Mechanistically, mild hyperthermia promotes BRCA2 degradation and inhibits homologous recombination repair, providing a basis for radiosensitization [253]. Focused ultrasound-microbubble radiosensitization further expands physical sensitization strategies. Microbubble cavitation can perturb tumor microvessels and activate endothelial cell apoptosis, thereby enhancing radiation-induced cytotoxicity. A phase I clinical trial showed that MR-guided focused ultrasound-microbubble therapy combined with radiotherapy has a favorable safety profile and showed preliminary evidence of an acceptable safety profile and promising complete response and local control rates [254]. For immunologically “cold” tumors such as TNBC, combining ultrasound with nanomaterials can integrate local stimulation, matrix remodeling, and immune activation into a single system. Under low-intensity focused ultrasound, R-I-LA NPs trigger ROS and NO production, leading to the formation of reactive nitrogen species (RNS). These effects degrade COL1, soften the matrix, improve vascular function, and alleviate hypoxia. Ultimately, this enhances sonodynamic therapeutic effects, induces immunogenic cell death and cytotoxic T cell infiltration, suppressing TNBC proliferation and lung metastasis [255].

The application of biomechanical signals can also extend to ex vivo immune cell manufacturing. Recent studies have shown that mechanical stimulation provided by three-dimensional fibrin gels can induce YAP phosphorylation through the β2 integrin-14-3-3ζ axis, and relieve YAP-mediated suppression of the transcription factor MafG. This decouples CAR-T cell proliferation from differentiation and generates stem cell-like CAR-T cells with stronger infiltrative capacity and more durable activity [256]. This strategy has demonstrated enhanced antitumor activity in mouse models of breast cancer. Although still at the preclinical stage, it offers a direction for applying biomechanical signals and may help overcome barriers to immunotherapy in solid tumors.

Biomechanics provides a theoretical framework for patient assessment and sensitization therapy in breast cancer. Mechanical assessment can help identify TME features such as matrix stiffening, providing a basis for patient stratification and

therapeutic response prediction. Remodeling the biomechanical microenvironment, modulating signal transduction, optimizing drug delivery, and applying physical therapies can improve therapeutic efficacy by relieving delivery barriers, attenuating resistance-associated signaling, enabling responsive drug delivery, and activating antitumor effects. Despite substantial preclinical evidence, several factors constrain the clinical translation of strategies targeting the biomechanical microenvironment. Many relevant pathways also support normal vascular and immune functions, so the systemic effects of inhibitors may narrow the therapeutic window. For example, early clinical investigation of the ROCK/AKT inhibitor AT13148 was limited by adverse effects, including hypotension [257]. Biomechanical heterogeneity across breast cancer subtypes and tumor regions further complicates treatment [16], while compensatory signaling may weaken the effects of inhibiting a single node [258]. Simplified matrix models also cannot fully recapitulate the multicellular composition and biomechanical coupling of tumor tissue. Moreover, treatment-induced cellular and ECM remodeling can continuously alter the conditions under which interventions act, limiting the applicability of preclinical findings [251]. Future studies should therefore integrate mechanical assessment with drug distribution, cellular function, and clinical endpoints. They should also avoid excessive matrix depletion and use dynamic assessments to determine intervention intensity and the timing and sequencing of combination treatments, helping translate mechanistic evidence into clinical benefit.

6. Conclusion and Future Perspectives

Biomechanics contributes to the development and maintenance of therapeutic resistance in breast cancer by linking tissue architecture, cellular states, and treatment responses. This review synthesizes evidence on matrix stiffness, solid stress, interstitial fluid pressure, and fluid shear stress to establish an integrative framework for understanding shared resistance mechanisms across treatment modalities. Biomechanical characteristics, including increased matrix stiffness, accumulated solid stress, abnormal IFP, and altered FSS, are coupled. They can alter therapeutic exposure by affecting tissue transport and drug distribution, while also regulating

damage responses, metabolic adaptation, phenotypic plasticity, and immune states through signal transduction. Notably, stiff and soft matrices can support similar resistance phenotypes through distinct cellular adaptation processes across experimental conditions and breast cancer subtypes. The effects of FSS likewise depend on its magnitude and the stage of metastasis. Treatment itself can also induce tumor cell and stromal remodeling, altering tissue mechanical properties and cellular mechanical responses and further contributing to adaptive resistance. Thus, the effects of the biomechanical microenvironment depend on breast cancer subtype, lesion site, cellular state, and the mechanism of therapeutic action.

Although existing studies provide an important basis for understanding therapeutic resistance in breast cancer, translation remains constrained by differences in experimental models, measurement scales, and clinical validation. Existing studies have largely focused on individual mechanical features or signaling pathways, and a multiscale evaluation system integrating matrix stiffness, solid stress, IFP, and FSS has not yet been established. Commonly used two- and three-dimensional culture systems, microfluidic platforms, organoids, and animal tumors do not reproduce equivalent mechanical conditions. Matrix composition, dimensionality, stiffness range, spatial confinement, shear magnitude, and exposure duration can all influence cellular responses, limiting comparisons across studies and the establishment of thresholds. Manipulating stiffness may also alter collagen density, pore architecture, and molecular transport, making it difficult to isolate the effects of individual biomechanical factors. Subtype differences, spatial heterogeneity, and dynamic remodeling during treatment further limit the generalizability of findings. More importantly, most current evidence remains at the preclinical stage, and some interventions have failed to demonstrate clinical benefit. Further clinical data are therefore needed to validate the regulatory mechanisms of the biomechanical microenvironment across lesion sites and disease stages and to carefully define the contexts in which these interventions may be applicable.

Future research should focus on the effects of the biomechanical microenvironment, its dynamic changes during treatment, and its value in clinical

decision-making. Biomechanical biomarkers can be used for risk assessment and prediction of therapeutic efficacy. Integrating direct measurements from elastography and SHG imaging with tissue architecture, spatial omics, and cellular functional analyses would support longitudinal assessment before and during treatment and at the residual or recurrent disease stage. This approach could establish a dynamic biomechanical atlas of breast cancer spanning molecular subtypes, disease stages, and lesion sites, providing a basis for identifying intervention windows. Experimental systems with independently tunable properties, together with organoids and ex vivo tissue models, can help distinguish the independent and interactive effects of biomechanical characteristics. They can also clarify crosstalk and compensatory mechanisms within the native TME and improve comparability across studies. Despite extensive research on targeted interventions, their efficacy and practical value still require validation in controlled clinical studies. Clinical studies could incorporate imaging assessments, collagen structural features, and signaling pathway activity into eligibility criteria, stratification schemes, and outcome measures. Corresponding primary interventions could then be evaluated in patients with different biomechanical characteristics. Such stratified designs account for TME heterogeneity and dynamic changes while providing evidence for context-dependent mechanisms of therapeutic resistance.

Biomechanics offers an integrative perspective on shared resistance processes across breast cancer treatment settings. It helps explain how tissue transport, cellular adaptation, and immune evasion interact under treatment pressure and produce distinct treatment responses across breast cancer subtypes, disease stages, and anatomical sites. Defining the conditions, effects, and evidentiary limits of these relationships can guide the development of testable combination strategies and provide a basis for improving treatment responses.

Abbreviations

ADC: Antibody-Drug Conjugate; AKT: Protein kinase B; BCSC: Breast Cancer Stem Cell; CAF: Cancer-Associated Fibroblast; cGAS-STING: Cyclic GMP-AMP Synthase-Stimulator of

Interferon Genes; COL: Collagen; CXCR4: C-X-C Motif Chemokine Receptor 4; DDR: Discoidin Domain Receptor; DRP1: Dynamin-related Protein 1; ECM: Extracellular Matrix; EMT: Epithelial-Mesenchymal Transition; ER+ BC: Estrogen Receptor-Positive Breast Cancer; ERK: Extracellular Signal-Regulated Kinase; F-Actin: Filamentous Actin; FAK: Focal Adhesion Kinase; FN: Fibronectin; FSS: Fluid Shear Stress; GPR: G Protein-Coupled Receptor; HA: Hyaluronic Acid; HER2+ BC: Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer; HIF-1α: Hypoxia-Inducible Factor-1α; IFN-I: Type I interferon; IFP: Interstitial Fluid Pressure; ILK: Integrin-Linked Kinase; JAK: Janus Kinase; JNK: c-Jun N-terminal Kinase; LATS: Large Tumor Suppressor Kinase; LINC: Linker of Nucleoskeleton and Cytoskeleton; LOX: Lysyl oxidase; MAPK: Mitogen-Activated Protein Kinase; MMP: Matrix Metalloproteinase; mTORC1: Mechanistic Target of Rapamycin Complex 1; NF-κB: Nuclear Factor Kappa-B; OXPHOS: Oxidative Phosphorylation; PD-1: Programmed Cell Death Protein 1; PD-L1: Programmed Death-Ligand 1; PI3K: Phosphoinositide 3-Kinase; Piezo: Piezo-type Mechanosensitive Ion Channel; PTEN: Phosphatase and Tensin Homolog; Rho: Ras Homologous GTPase; ROCK: Rho-Associated Coiled-Coil-Containing Protein Kinase; ROS: Reactive Oxygen Species; Src: proto-oncogene tyrosine-protein kinase Src ; STAT : Signal Transducer and Activator of Transcription; TACS-3: Tumor-Associated Collagen Signature-3; TAM: Tumor-Associated Macrophage; TAZ: Transcriptional Coactivator with PDZ-Binding Motif; TEAD: Domain TEA domain transcription factor; TGF-β: Transforming Growth Factor-Beta; TNBC: Triple-Negative Breast Cancer; TRP: Transient Receptor Potential Channel; VEGF: Vascular Endothelial Growth Factor; Wnt: Wingless/Int-1; YAP: Yes-associated protein; β-APN: Beta-Aminopropionitrile.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors have declared no competing interests exists.

Funding

This work was supported by the Innovative Drug Research and Development National Science and Technology Major Project (Grant No. 2025ZD1800603), the Key Support Projects of the Joint Fund for Regional Innovation and Development of the National Natural Science Foundation of China (Grant No. U25A20169), the Key Program of the National Natural Science Foundation of China (Grant No. 82430123), the Science and Technology Co-construction Project of the Science and Technology Department of the State Administration of Traditional Chinese Medicine (Grant No. GZY-KJS-SD-2024-017), the Clinical Research Project of the "Jingyi Research Fund Phase II" of the Beijing Weiai Public Welfare Foundation (Grant No. JVII2024-0051216011).

Authors' contributions

Y.J and Q.S conceptualized and designed the study. Y.J, Q.S and B.W drafted the manuscript. R.L and C.S provided supervision. All authors reviewed and edited the final manuscript.

Acknowledgements

Thanks to BioRender (www.biorender.com) for the drawing materials.

Reference

1. Collaborators GBC. Global, regional, and national burden of breast cancer among females, 1990-2023, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2023. Lancet Oncol. 2026; 27: 302-26.
2. Hanker AB, Sudhan DR, Arteaga CL. Overcoming Endocrine Resistance in Breast Cancer. Cancer Cell. 2020; 37: 496-513.
3. Zhang H, Sun Y, Liu R, Hamdy H, Shi Z, Jiang D, et al. The role of tumor microenvironment and signaling pathways in regulating breast cancer stem cells: Implications for therapy resistance and tumor recurrence. Drug Resist Updat. 2026; 84: 101315.
4. Garcia-Martinez L, Zhang Y, Nakata Y, Chan HL, Morey L. Epigenetic mechanisms in breast cancer therapy and resistance. Nat Commun. 2021; 12: 1786.
5. Russo M, Chen M, Mariella E, Peng H, Rehman SK, Sancho E, et al. Cancer drug-tolerant persister

cells: from biological questions to clinical opportunities. Nat Rev Cancer. 2024; 24: 694-717.
6. Wang Z, Wang M, Dong B, Wang Y, Ding Z, Shen S. Drug-tolerant persister cells in cancer: bridging the gaps between bench and bedside. Nat Commun. 2025; 16: 10048.
7. Buchholz MB, Scheerman DI, Levato R, Wehrens EJ, Rios AC. Human breast tissue engineering in health and disease. EMBO Mol Med. 2024; 16: 2299-321.
8. Need EF, Atashgaran V, Ingman WV, Dasari P. Hormonal regulation of the immune microenvironment in the mammary gland. J Mammary Gland Biol Neoplasia. 2014; 19: 229-39.
9. Fornili M, Perduca V, Fournier A, Jérolon A, Boutron-Ruault MC, Maskarinec G, et al. Association between menopausal hormone therapy, mammographic density and breast cancer risk: results from the E3N cohort study. Breast Cancer Res. 2021; 23: 47.
10. Gerasimova-Chechkina E, Toner BC, Batchelder KA, White B, Freynd G, Antipev I, et al. Loss of Mammographic Tissue Homeostasis in Invasive Lobular and Ductal Breast Carcinomas vs. Benign Lesions. Front Physiol. 2021; 12: 660883.
11. Nia HT, Munn LL, Jain RK. Physical traits of cancer. Science. 2020; 370.
12. Jain RK, Martin JD, Stylianopoulos T. The role of mechanical forces in tumor growth and therapy. Annu Rev Biomed Eng. 2014; 16: 321-46.
13. Stylianopoulos T, Munn LL, Jain RK. Reengineering the Physical Microenvironment of Tumors to Improve Drug Delivery and Efficacy: From Mathematical Modeling to Bench to Bedside. Trends Cancer. 2018; 4: 292-319.
14. Kalli M, Poskus MD, Stylianopoulos T, Zervantonakis IK. Beyond matrix stiffness: targeting force-induced cancer drug resistance. Trends Cancer. 2023; 9: 937-54.
15. Song Y, Huang C, Han J, Wang S, Liu H, Li Y, et al. Extracellular matrix stiffness and mechanotransduction in cancer drug resistance. Drug Resist Updat. 2026; 89: 101470.
16. Acerbi I, Cassereau L, Dean I, Shi Q, Au A, Park C, et al. Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. Integr Biol (Camb). 2015; 7: 1120-34.
17. Anlaş AA, Nelson CM. Soft Microenvironments Induce Chemoresistance by Increasing Autophagy Downstream of Integrin-Linked Kinase. Cancer Res. 2020; 80: 4103-13.
18. Peura A, Turpin R, Liu R, Heilala M, Salmela M, Aung J, et al. Soft matrix promotes immunosuppression in tumor-resident immune cells via COX-FGF2 signaling. Nat Commun. 2025; 16: 4908.
19. Lepucki A, Orlińska K, Mielczarek-Palacz A, Kabut J, Olczyk P, Komosińska-Vassev K. The Role of Extracellular Matrix Proteins in Breast Cancer. J Clin Med. 2022; 11.
20. Piersma B, Hayward MK, Weaver VM. Fibrosis and cancer: A strained relationship. Biochim Biophys Acta Rev Cancer. 2020; 1873: 188356.
21. Casey T, Bond J, Tighe S, Hunter T, Lintault L, Patel O, et al. Molecular signatures suggest a major role for stromal cells in development of invasive breast cancer. Breast Cancer Res Treat. 2009; 114: 47-62.
22. Kaushik S, Pickup MW, Weaver VM. From transformation to metastasis: deconstructing the extracellular matrix in breast cancer. Cancer Metastasis Rev. 2016; 35: 655-67.
23. Levental KR, Yu H, Kass L, Lakins JN, Egeblad M, Erler JT, et al. Matrix crosslinking forces tumor progression by enhancing integrin signaling. Cell. 2009; 139: 891-906.
24. Stylianopoulos T, Martin JD, Chauhan VP, Jain SR, Diop-Frimpong B, Bardeesy N, et al. Causes, consequences, and remedies for growth-induced solid stress in murine and human tumors. Proc Natl

Acad Sci U S A. 2012; 109: 15101-8.
25. Kalli M, Stylianopoulos T. Defining the Role of Solid Stress and Matrix Stiffness in Cancer Cell Proliferation and Metastasis. Front Oncol. 2018; 8: 55.
26. Nia HT, Liu H, Seano G, Datta M, Jones D, Rahbari N, et al. Solid stress and elastic energy as measures of tumour mechanopathology. Nat Biomed Eng. 2016; 1.
27. Wen Q, Janmey PA. Effects of non-linearity on cell-ECM interactions. Exp Cell Res. 2013; 319: 2481-9.
28. Ferruzzi J, Sun M, Gkousioudi A, Pilvar A, Roblyer D, Zhang Y, et al. Compressive Remodeling Alters Fluid Transport Properties of Collagen Networks - Implications for Tumor Growth. Sci Rep. 2019; 9: 17151.
29. Stylianopoulos T, Martin JD, Snuderl M, Mpekris F, Jain SR, Jain RK. Coevolution of solid stress and interstitial fluid pressure in tumors during progression: implications for vascular collapse. Cancer Res. 2013; 73: 3833-41.
30. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol. 2013; 31: 2205-18.
31. Song JW, Munn LL. Fluid forces control endothelial sprouting. Proc Natl Acad Sci U S A. 2011; 108: 15342-7.
32. Wirtz D, Konstantopoulos K, Searson PC. The physics of cancer: the role of physical interactions and mechanical forces in metastasis. Nat Rev Cancer. 2011; 11: 512-22.
33. Swartz MA, Lund AW. Lymphatic and interstitial flow in the tumour microenvironment: linking mechanobiology with immunity. Nat Rev Cancer. 2012; 12: 210-9.
34. Ma S, Fu A, Chiew GG, Luo KQ. Hemodynamic shear stress stimulates migration and extravasation of tumor cells by elevating cellular oxidative level. Cancer Lett. 2017; 388: 239-48.
35. Regmi S, Fu A, Luo KQ. High Shear Stresses under Exercise Condition Destroy Circulating Tumor Cells in a Microfluidic System. Sci Rep. 2017; 7: 39975.
36. Mei X, Middleton K, Shim D, Wan Q, Xu L, Ma YV, et al. Microfluidic platform for studying osteocyte mechanoregulation of breast cancer bone metastasis. Integr Biol (Camb). 2019; 11: 119-29.
37. Boucher Y, Baxter LT, Jain RK. Interstitial pressure gradients in tissue-isolated and subcutaneous tumors: implications for therapy. Cancer Res. 1990; 50: 4478-84.
38. Taghian AG, Abi-Raad R, Assaad SI, Casty A, Ancukiewicz M, Yeh E, et al. Paclitaxel decreases the interstitial fluid pressure and improves oxygenation in breast cancers in patients treated with neoadjuvant chemotherapy: clinical implications. J Clin Oncol. 2005; 23: 1951-61.
39. Fatherree JP, Guarin JR, McGinn RA, Naber SP, Oudin MJ. Chemotherapy-Induced Collagen IV Drives Cancer Cell Motility through Activation of Src and Focal Adhesion Kinase. Cancer Res. 2022; 82: 2031-44.
40. Sharma A, Steger RF, Li JM, Fong SY, Saxena N, Baude JA, et al. Sp1 mechanotransduction regulates breast cancer cell invasion in engineered viscoelastic extracellular matrices. Biomaterials. 2026; 327: 123755.
41. Wang H, Lu J, Rathod M, Aw WY, Huang SA, Polacheck WJ. A facile fluid pressure system reveals differential cellular response to interstitial pressure gradients and flow. Biomicrofluidics. 2023; 17: 054103.
42. del Rio A, Perez-Jimenez R, Liu R, Roca-Cusachs P, Fernandez JM, Sheetz MP. Stretching single talin rod molecules activates vinculin binding. Science. 2009; 323: 638-41.
43. Yonemura S, Wada Y, Watanabe T, Nagafuchi A, Shibata M. alpha-Catenin as a tension transducer

1399 that induces adherens junction development. Nat Cell Biol. 2010; 12: 533-42.
1400 44. Li C, Qiu S, Liu X, Guo F, Zhai J, Li Z, et al. Extracellular matrix-derived mechanical force governs
1401 breast cancer cell stemness and quiescence transition through integrin-DDR signaling. Signal Transduct
1402 Target Ther. 2023; 8: 247.
1403 45. Li C, Rezania S, Kammerer S, Sokolowski A, Devaney T, Gorischek A, et al. Piezo1 forms
1404 mechanosensitive ion channels in the human MCF-7 breast cancer cell line. Sci Rep. 2015; 5: 8364.
1405 46. Boyle ST, Gallego-Ortega D, Buckley EJ, Cognard E, Johan MZ, Esmaeili Z, et al. Compressive
1406 stress-driven Piezo1 activation and Rho-ROCK mechanotransduction promote tumor progression via
1407 epigenetic mechanical memory. Sci Adv. 2026; 12: eaeb1271.
1408 47. Luo M, Cai G, Ho KKY, Wen K, Tong Z, Deng L, et al. Compression enhances invasive phenotype
1409 and matrix degradation of breast Cancer cells via Piezo1 activation. BMC Mol Cell Biol. 2022; 23: 1.
1410 48. Pardo-Pastor C, Rubio-Moscardo F, Vogel-González M, Serra SA, Afthinos A, Mrkonjic S, et al.
1411 Piezo2 channel regulates RhoA and actin cytoskeleton to promote cell mechanobiological responses.
1412 Proc Natl Acad Sci U S A. 2018; 115: 1925-30.
1413 49. Cox CD, Poole K, Martinac B. Re-evaluating TRP channel mechanosensitivity. Trends Biochem Sci.
1414 2024; 49: 693-702.
1415 50. Lee WH, Choong LY, Mon NN, Lu S, Lin Q, Pang B, et al. TRPV4 Regulates Breast Cancer Cell
1416 Extravasation, Stiffness and Actin Cortex. Sci Rep. 2016; 6: 27903.
1417 51. Tytti K, Sanna K, Carla G, Jonatan P, Kaisa R, Sari T. Mechanosensitive TRPV4 channel guides
1418 maturation and organization of the bilayered mammary epithelium. Sci Rep. 2024; 14: 6774.
1419 52. Xu J, Mathur J, Vessières E, Hammack S, Nonomura K, Favre J, et al. GPR68 Senses Flow and Is
1420 Essential for Vascular Physiology. Cell. 2018; 173: 762-75.e16.
1421 53. Furlow PW, Zhang S, Soong TD, Halberg N, Goodarzi H, Mangrum C, et al. Mechanosensitive
1422 pannexin-1 channels mediate microvascular metastatic cell survival. Nat Cell Biol. 2015; 17: 943-52.
1423 54. Hamidi H, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. Nat Rev
1424 Cancer. 2018; 18: 533-48.
1425 55. Bauer MS, Baumann F, Daday C, Redondo P, Durner E, Jobst MA, et al. Structural and mechanistic
1426 insights into mechanoactivation of focal adhesion kinase. Proc Natl Acad Sci U S A. 2019; 116:
1427 6766-74.
1428 56. Wu C, Dedhar S. Integrin-linked kinase (ILK) and its interactors: a new paradigm for the coupling
1429 of extracellular matrix to actin cytoskeleton and signaling complexes. J Cell Biol. 2001; 155: 505-10.
1430 57. Qin X, Lv X, Li P, Yang R, Xia Q, Chen Y, et al. Matrix stiffness modulates ILK-mediated YAP
1431 activation to control the drug resistance of breast cancer cells. Biochim Biophys Acta Mol Basis Dis.
1432 2020; 1866: 165625.
1433 58. Xie N, Xiao C, Shu Q, Cheng B, Wang Z, Xue R, et al. Cell response to mechanical
1434 microenvironment cues via Rho signaling: From mechanobiology to mechanomedicine. Acta Biomater.
1435 2023; 159: 1-20.
1436 59. Pascual-Vargas P, Cooper S, Sero J, Bousgouni V, Arias-Garcia M, Bakal C. RNAi screens for Rho
1437 GTPase regulators of cell shape and YAP/TAZ localisation in triple negative breast cancer. Sci Data.
1438 2017; 4: 170018.
1439 60. Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, et al. Role of YAP/TAZ in
1440 mechanotransduction. Nature. 2011; 474: 179-83.
1441 61. Elosegui-Artola A, Andreu I, Beedle AEM, Lezamiz A, Uroz M, Kosmalska AJ, et al. Force Triggers
1442 YAP Nuclear Entry by Regulating Transport across Nuclear Pores. Cell. 2017; 171: 1397-410.e14.

62. González-Alonso P, Zazo S, Martín-Aparicio E, Luque M, Chamizo C, Sanz-Álvarez M, et al. The Hippo Pathway Transducers YAP1/TEAD Induce Acquired Resistance to Trastuzumab in HER2-Positive Breast Cancer. Cancers (Basel). 2020; 12.
63. Li X, Zhuo S, Zhuang T, Cho YS, Wu G, Liu Y, et al. YAP inhibits ERα and ER(+) breast cancer growth by disrupting a TEAD-ERα signaling axis. Nat Commun. 2022; 13: 3075.
64. Provenzano PP, Inman DR, Eliceiri KW, Keely PJ. Matrix density-induced mechanoregulation of breast cell phenotype, signaling and gene expression through a FAK-ERK linkage. Oncogene. 2009; 28: 4326-43.
65. Liang P, Zhang J, Wu Y, Zheng S, Xu Z, Yang S, et al. An ULK1/2-PXN mechanotransduction pathway suppresses breast cancer cell migration. EMBO Rep. 2023; 24: e56850.
66. Bougaran P, Bautch VL. Life at the crossroads: the nuclear LINC complex and vascular mechanotransduction. Front Physiol. 2024; 15: 1411995.
67. Chambliss AB, Khatau SB, Erdenberger N, Robinson DK, Hodzic D, Longmore GD, et al. The LINC-anchored actin cap connects the extracellular milieu to the nucleus for ultrafast mechanotransduction. Sci Rep. 2013; 3: 1087.
68. Matsumoto A, Hieda M, Yokoyama Y, Nishioka Y, Yoshidome K, Tsujimoto M, et al. Global loss of a nuclear lamina component, lamin A/C, and LINC complex components SUN1, SUN2, and nesprin-2 in breast cancer. Cancer Med. 2015; 4: 1547-57.
69. Buxboim A, Swift J, Irianto J, Spinler KR, Dingal PC, Athirasala A, et al. Matrix elasticity regulates lamin-A,C phosphorylation and turnover with feedback to actomyosin. Curr Biol. 2014; 24: 1909-17.
70. Alhudiri IM, Nolan CC, Ellis IO, Elzagheid A, Rakha EA, Green AR, et al. Expression of Lamin A/C in early-stage breast cancer and its prognostic value. Breast Cancer Res Treat. 2019; 174: 661-8.
71. Stowers RS, Shcherbina A, Israeli J, Gruber JJ, Chang J, Nam S, et al. Matrix stiffness induces a tumorigenic phenotype in mammary epithelium through changes in chromatin accessibility. Nat Biomed Eng. 2019; 3: 1009-19.
72. Munne PM, Martikainen L, Räty I, Bertula K, Nonappa, Ruuska J, et al. Compressive stress-mediated p38 activation required for ERα + phenotype in breast cancer. Nat Commun. 2021; 12: 6967.
73. Watson AW, Grant AD, Parker SS, Hill S, Whalen MB, Chakrabarti J, et al. Breast tumor stiffness instructs bone metastasis via maintenance of mechanical conditioning. Cell Rep. 2021; 35: 109293.
74. Zhu Y, Pan Q, Meng H, Jiang Y, Mao A, Wang T, et al. Enhancement of vascular endothelial growth factor release in long-term drug-treated breast cancer via transient receptor potential channel 5-Ca(2+)-hypoxia-inducible factor 1α pathway. Pharmacol Res. 2015; 93: 36-42.
75. La Verde G, Artiola V, Pugliese M, La Commara M, Arrichiello C, Muto P, et al. Radiation therapy affects YAP expression and intracellular localization by modulating lamin A/C levels in breast cancer. Front Bioeng Biotechnol. 2022; 10: 969004.
76. Feng X, Cao F, Wu X, Xie W, Wang P, Jiang H. Targeting extracellular matrix stiffness for cancer therapy. Front Immunol. 2024; 15: 1467602.
77. Netti PA, Berk DA, Swartz MA, Grodzinsky AJ, Jain RK. Role of extracellular matrix assembly in interstitial transport in solid tumors. Cancer Res. 2000; 60: 2497-503.
78. Chauhan VP, Martin JD, Liu H, Lacorre DA, Jain SR, Kozin SV, et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. Nat Commun. 2013; 4: 2516.
79. Kim BG, Gao MQ, Kang S, Choi YP, Lee JH, Kim JE, et al. Mechanical compression induces VEGFA

overexpression in breast cancer via DNMT3A-dependent miR-9 downregulation. Cell Death Dis. 2017; 8: e2646.
80. Bordeleau F, Mason BN, Lollis EM, Mazzola M, Zanotelli MR, Somasegar S, et al. Matrix stiffening promotes a tumor vasculature phenotype. Proc Natl Acad Sci U S A. 2017; 114: 492-7.
81. Sewell-Loftin MK, Bayer SVH, Crist E, Hughes T, Joison SM, Longmore GD, et al. Cancer-associated fibroblasts support vascular growth through mechanical force. Sci Rep. 2017; 7: 12574.
82. Fujimori K, Covell DG, Fletcher JE, Weinstein JN. A modeling analysis of monoclonal antibody percolation through tumors: a binding-site barrier. J Nucl Med. 1990; 31: 1191-8.
83. Jain RK, Baxter LT. Mechanisms of heterogeneous distribution of monoclonal antibodies and other macromolecules in tumors: significance of elevated interstitial pressure. Cancer Res. 1988; 48: 7022-32.
84. Wu M, Frieboes HB, Chaplain MA, McDougall SR, Cristini V, Lowengrub JS. The effect of interstitial pressure on therapeutic agent transport: coupling with the tumor blood and lymphatic vascular systems. J Theor Biol. 2014; 355: 194-207.
85. Peetla C, Bhave R, Vijayaraghavalu S, Stine A, Kooijman E, Labhasetwar V. Drug resistance in breast cancer cells: biophysical characterization of and doxorubicin interactions with membrane lipids. Mol Pharm. 2010; 7: 2334-48.
86. Saha M, Kumar S, Bukhari S, Balaji SA, Kumar P, Hindupur SK, et al. AMPK-Akt Double-Negative Feedback Loop in Breast Cancer Cells Regulates Their Adaptation to Matrix Deprivation. Cancer Res. 2018; 78: 1497-510.
87. Endo H, Owada S, Inagaki Y, Shida Y, Tatemichi M. Metabolic reprogramming sustains cancer cell survival following extracellular matrix detachment. Redox Biol. 2020; 36: 101643.
88. Han R, Sun X, Wu Y, Yang YH, Wang QC, Zhang XT, et al. Proteomic and Phosphoproteomic Profiling of Matrix Stiffness-Induced Stemness-Dormancy State Transition in Breast Cancer Cells. J Proteome Res. 2024; 23: 4658-73.
89. Indira Chandran V, Månsson AS, Barbachowska M, Cerezo-Magaña M, Nodin B, Joshi B, et al. Hypoxia Attenuates Trastuzumab Uptake and Trastuzumab-Emtansine (T-DM1) Cytotoxicity through Redistribution of Phosphorylated Caveolin-1. Mol Cancer Res. 2020; 18: 644-56.
90. Modi A, Roy D, Sharma S, Vishnoi JR, Pareek P, Elhence P, et al. ABC transporters in breast cancer: their roles in multidrug resistance and beyond. J Drug Target. 2022; 30: 927-47.
91. Fletcher JI, Williams RT, Henderson MJ, Norris MD, Haber M. ABC transporters as mediators of drug resistance and contributors to cancer cell biology. Drug Resist Updat. 2016; 26: 1-9.
92. Zeng T, Chen H, Yoshitomi T, Kawazoe N, Yang Y, Chen G. Effect of Hydrogel Stiffness on Chemoresistance of Breast Cancer Cells in 3D Culture. Gels. 2024; 10.
93. Chen Y, Xue D, Huang D, Li X, Duan Y, Chen B. Biofabrication of Tunable 3D Hydrogel for Investigating the Matrix Stiffness Impact on Breast Cancer Chemotherapy Resistance. ACS Biomater Sci Eng. 2025; 11: 1417-31.
94. Kuermanbayi S, Yang Y, Zhao Y, Li Y, Wang L, Yang J, et al. In situ monitoring of functional activity of extracellular matrix stiffness-dependent multidrug resistance protein 1 using scanning electrochemical microscopy. Chem Sci. 2022; 13: 10349-60.
95. Shang M, Lim SB, Jiang K, Yap YS, Khoo BL, Han J, et al. Microfluidic studies of hydrostatic pressure-enhanced doxorubicin resistance in human breast cancer cells. Lab Chip. 2021; 21: 746-54.
96. Baltes F, Pfeifer V, Silbermann K, Caspers J, Wantoch von Rekowski K, Schlesinger M, et al. β(1)-Integrin binding to collagen type 1 transmits breast cancer cells into chemoresistance by

activating ABC efflux transporters. Biochim Biophys Acta Mol Cell Res. 2020; 1867: 118663.
97. Jakubzig B, Baltes F, Henze S, Schlesinger M, Bendas G. Mechanisms of Matrix-Induced Chemoresistance of Breast Cancer Cells-Deciphering Novel Potential Targets for a Cell Sensitization. Cancers (Basel). 2018; 10.
98. Lacombe J, Zenhausern F. Effect of mechanical forces on cellular response to radiation. Radiother Oncol. 2022; 176: 187-98.
99. Deng M, Lin J, Nowsheen S, Liu T, Zhao Y, Villalta PW, et al. Extracellular matrix stiffness determines DNA repair efficiency and cellular sensitivity to genotoxic agents. Sci Adv. 2020; 6.
100. Ghose R, Pezzano F, Badia R, Kourtis S, Sheraj I, Das S, et al. Mitochondria-derived nuclear ATP surge protects against confinement-induced proliferation defects. Nat Commun. 2025; 16: 6613.
101. Chen Y, Li P, Peng Y, Xie X, Zhang Y, Jiang Y, et al. Protective autophagy attenuates soft substrate-induced apoptosis through ROS/JNK signaling pathway in breast cancer cells. Free Radic Biol Med. 2021; 172: 590-603.
102. Nguyen TV, Sleiman M, Moriarty T, Herrick WG, Peyton SR. Sorafenib resistance and JNK signaling in carcinoma during extracellular matrix stiffening. Biomaterials. 2014; 35: 5749-59.
103. Lin CH, Pelissier FA, Zhang H, Lakins J, Weaver VM, Park C, et al. Microenvironment rigidity modulates responses to the HER2 receptor tyrosine kinase inhibitor lapatinib via YAP and TAZ transcription factors. Mol Biol Cell. 2015; 26: 3946-53.
104. Di-Luoffo M, Schmitter C, Barrere EC, Therville N, Chaouki M, D'Angelo R, et al. Mechanical compressive forces increase PI3K output signaling in breast and pancreatic cancer cells. Life Sci Alliance. 2025; 8.
105. Aoudjit F, Vuori K. Integrin signaling inhibits paclitaxel-induced apoptosis in breast cancer cells. Oncogene. 2001; 20: 4995-5004.
106. Xing H, Weng D, Chen G, Tao W, Zhu T, Yang X, et al. Activation of fibronectin/PI-3K/Akt2 leads to chemoresistance to docetaxel by regulating survivin protein expression in ovarian and breast cancer cells. Cancer Lett. 2008; 261: 108-19.
107. Al-Alwan M, Olabi S, Ghebeh H, Barhoush E, Tulbah A, Al-Tweigeri T, et al. Fascin is a key regulator of breast cancer invasion that acts via the modification of metastasis-associated molecules. PLoS One. 2011; 6: e27339.
108. Ghebeh H, Al-Khaldi S, Olabi S, Al-Dhfyan A, Al-Mohanna F, Barnawi R, et al. Fascin is involved in the chemotherapeutic resistance of breast cancer cells predominantly via the PI3K/Akt pathway. Br J Cancer. 2014; 111: 1552-61.
109. Alamro AA, AlSuwaidi OA, Alghamdi AA, Abdi S, Alshammari AH, Alotaibi RN. Fluid Shear Stress Modulates Inflammation in Breast Cancer Microenvironment. Diseases. 2025; 13.
110. Novak CM, Horst EN, Taylor CC, Liu CZ, Mehta G. Fluid shear stress stimulates breast cancer cells to display invasive and chemoresistant phenotypes while upregulating PLAU in a 3D bioreactor. Biotechnol Bioeng. 2019; 116: 3084-97.
111. Cuccia J, Ortega Quesada BA, Littlefield EP, Ham AM, Burow ME, Melvin AT, et al. Loss of Hormone Receptor Expression after Exposure to Fluid Shear Stress in Breast Cancer Cell Lines. Int J Mol Sci. 2024; 25.
112. Spencer A, Sligar AD, Chavarria D, Lee J, Choksi D, Patil NP, et al. Biomechanical regulation of breast cancer metastasis and progression. Sci Rep. 2021; 11: 9838.
113. Cui Q, Wang JQ, Assaraf YG, Ren L, Gupta P, Wei L, et al. Modulating ROS to overcome multidrug resistance in cancer. Drug Resist Updat. 2018; 41: 1-25.

114. Regmi S, Fung TS, Lim S, Luo KQ. Fluidic shear stress increases the anti-cancer effects of ROS-generating drugs in circulating tumor cells. Breast Cancer Res Treat. 2018; 172: 297-312.
115. Romani P, Nirchio N, Arboit M, Barbieri V, Tosi A, Michielin F, et al. Mitochondrial fission links ECM mechanotransduction to metabolic redox homeostasis and metastatic chemotherapy resistance. Nat Cell Biol. 2022; 24: 168-80.
116. Chen Y, Li P, Chen X, Yan R, Zhang Y, Wang M, et al. Endoplasmic reticulum-mitochondrial calcium transport contributes to soft extracellular matrix-triggered mitochondrial dynamics and mitophagy in breast carcinoma cells. Acta Biomater. 2023; 169: 192-208.
117. Tharp KM, Higuchi-Sanabria R, Timblin GA, Ford B, Garzon-Coral C, Schneider C, et al. Adhesion-mediated mechanosignaling forces mitohormesis. Cell Metab. 2021; 33: 1322-41.e13.
118. Su CY, Wu A, Dong Z, Miller CP, Suarez A, Ewald AJ, et al. Tumor stromal topography promotes chemoresistance in migrating breast cancer cell clusters. Biomaterials. 2023; 298: 122128.
119. Wang Y, He J, Lian S, Zeng Y, He S, Xu J, et al. Targeting Metabolic-Redox Nexus to Regulate Drug Resistance: From Mechanism to Tumor Therapy. Antioxidants (Basel). 2024; 13.
120. Lu Y, Wang L, Ding W, Wang D, Wang X, Luo Q, et al. Ammonia mediates mitochondrial uncoupling and promotes glycolysis via HIF-1 activation in human breast cancer MDA-MB-231 cells. Biochem Biophys Res Commun. 2019; 519: 153-9.
121. Sun Y, He Q, Li J, Yang Z, Ahmad M, Lin Y, et al. A GSTP1-mediated lactic acid signaling promotes tumorigenesis through the PPP oxidative branch. Cell Death Dis. 2023; 14: 463.
122. Pickett MR, Chen YI, Kamra M, Kumar S, Kalkunte N, Sugerman GP, et al. Assessing the impact of extracellular matrix fiber orientation on breast cancer cellular metabolism. Cancer Cell Int. 2024; 24: 199.
123. Bertero T, Oldham WM, Grasset EM, Bourget I, Boulter E, Pisano S, et al. Tumor-Stroma Mechanics Coordinate Amino Acid Availability to Sustain Tumor Growth and Malignancy. Cell Metab. 2019; 29: 124-40.e10.
124. Fontana F, Giannitti G, Marchesi S, Limonta P. The PI3K/Akt Pathway and Glucose Metabolism: A Dangerous Liaison in Cancer. Int J Biol Sci. 2024; 20: 3113-25.
125. Ho KKY, Buschhaus JM, Zhang A, Cutter AC, Humphries BA, Luker GD. Substrate stiffness regulates triple-negative breast cancer signaling through CXCR4 receptor dynamics. Sci Rep. 2025; 15: 29621.
126. Mouw JK, Yui Y, Damiano L, Bainer RO, Lakins JN, Acerbi I, et al. Tissue mechanics modulate microRNA-dependent PTEN expression to regulate malignant progression. Nat Med. 2014; 20: 360-7.
127. Trinh VH, Nguyen Huu T, Sah DK, Choi JM, Yoon HJ, Park SC, et al. Redox Regulation of PTEN by Reactive Oxygen Species: Its Role in Physiological Processes. Antioxidants (Basel). 2024; 13.
128. McKinnon G, Davidson M, De Jersey J, Shanley B, Ward L. Effects of acetaldehyde on polymerization of microtubule proteins. Brain Res. 1987; 416: 90-9.
129. Edwards DN, Ngwa VM, Wang S, Shiuan E, Brantley-Sieders DM, Kim LC, et al. The receptor tyrosine kinase EphA2 promotes glutamine metabolism in tumors by activating the transcriptional coactivators YAP and TAZ. Sci Signal. 2017; 10.
130. Santinon G, Brian I, Pocaterra A, Romani P, Franzolin E, Rampazzo C, et al. dNTP metabolism links mechanical cues and YAP/TAZ to cell growth and oncogene-induced senescence. Embo j. 2018; 37.
131. Putluri N, Maity S, Kommagani R, Creighton CJ, Putluri V, Chen F, et al. Pathway-centric integrative analysis identifies RRM2 as a prognostic marker in breast cancer associated with poor survival and tamoxifen resistance. Neoplasia. 2014; 16: 390-402.
132. Sultana N, Elford HL, Faridi JS. Targeting the Cell Cycle, RRM2 and NF-κB for the Treatment of

Breast Cancers. Cancers (Basel). 2024; 16.
133. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022; 12: 31-46.
134. Pan G, Liu Y, Shang L, Zhou F, Yang S. EMT-associated microRNAs and their roles in cancer stemness and drug resistance. Cancer Commun (Lond). 2021; 41: 199-217.
135. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2014; 15: 178-96.
136. De Las Rivas J, Brozovic A, Izraely S, Casas-Pais A, Witz IP, Figueroa A. Cancer drug resistance induced by EMT: novel therapeutic strategies. Arch Toxicol. 2021; 95: 2279-97.
137. Grosse-Wilde A, Fouquier d'Hérouël A, McIntosh E, Ertaylan G, Skupin A, Kuestner RE, et al. Stemness of the hybrid Epithelial/Mesenchymal State in Breast Cancer and Its Association with Poor Survival. PLoS One. 2015; 10: e0126522.
138. Fischer KR, Durrans A, Lee S, Sheng J, Li F, Wong ST, et al. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. Nature. 2015; 527: 472-6.
139. Lüönd F, Sugiyama N, Bill R, Bornes L, Hager C, Tang F, et al. Distinct contributions of partial and full EMT to breast cancer malignancy. Dev Cell. 2021; 56: 3203-21.e11.
140. Sahoo S, Mishra A, Kaur H, Hari K, Muralidharan S, Mandal S, et al. A mechanistic model captures the emergence and implications of non-genetic heterogeneity and reversible drug resistance in ER+ breast cancer cells. NAR Cancer. 2021; 3: zcab027.
141. Stashko C, Hayward MK, Northey JJ, Pearson N, Ironside AJ, Lakins JN, et al. A convolutional neural network STIFMap reveals associations between stromal stiffness and EMT in breast cancer. Nat Commun. 2023; 14: 3561.
142. Wei SC, Fattet L, Tsai JH, Guo Y, Pai VH, Majeski HE, et al. Matrix stiffness drives epithelial-mesenchymal transition and tumour metastasis through a TWIST1-G3BP2 mechanotransduction pathway. Nat Cell Biol. 2015; 17: 678-88.
143. Kilinc AN, Han S, Barrett LA, Anandasivam N, Nelson CM. Integrin-linked kinase tunes cell-cell and cell-matrix adhesions to regulate the switch between apoptosis and EMT downstream of TGFβ1. Mol Biol Cell. 2021; 32: 402-12.
144. Azimi T, Loizidou M, Dwek MV. Cancer cells grown in 3D under fluid flow exhibit an aggressive phenotype and reduced responsiveness to the anti-cancer treatment doxorubicin. Sci Rep. 2020; 10: 12020.
145. Zhao B, Lv Y. Suspension state and shear stress enhance breast tumor cells EMT through YAP by microRNA-29b. Cell Biol Toxicol. 2023; 39: 1037-52.
146. Wang Q, Yu Y, Zhuang J, Liu R, Sun C. Demystifying the cGAS-STING pathway: precision regulation in the tumor immune microenvironment. Mol Cancer. 2025; 24: 178.
147. Frittoli E, Palamidessi A, Iannelli F, Zanardi F, Villa S, Barzaghi L, et al. Tissue fluidification promotes a cGAS-STING cytosolic DNA response in invasive breast cancer. Nat Mater. 2023; 22: 644-55.
148. Gunasinghe NP, Wells A, Thompson EW, Hugo HJ. Mesenchymal-epithelial transition (MET) as a mechanism for metastatic colonisation in breast cancer. Cancer Metastasis Rev. 2012; 31: 469-78.
149. Bai X, Ni J, Beretov J, Graham P, Li Y. Cancer stem cell in breast cancer therapeutic resistance. Cancer Treat Rev. 2018; 69: 152-63.
150. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. Nat Rev Cancer. 2005; 5: 275-84.
151. Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, et al. Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. J Natl Cancer Inst. 2008; 100: 672-9.

152. Bayik D, Lathia JD. Cancer stem cell-immune cell crosstalk in tumour progression. Nat Rev Cancer. 2021; 21: 526-36.
153. May CD, Sphyris N, Evans KW, Werden SJ, Guo W, Mani SA. Epithelial-mesenchymal transition and cancer stem cells: a dangerously dynamic duo in breast cancer progression. Breast Cancer Res. 2011; 13: 202.
154. Khan AQ, Hasan A, Mir SS, Rashid K, Uddin S, Steinhoff M. Exploiting transcription factors to target EMT and cancer stem cells for tumor modulation and therapy. Semin Cancer Biol. 2024; 100: 1-16.
155. Liu X, Ye Y, Zhu L, Xiao X, Zhou B, Gu Y, et al. Niche stiffness sustains cancer stemness via TAZ and NANOG phase separation. Nat Commun. 2023; 14: 238.
156. Talukdar PD, Pramanik K, Gatti P, Mukherjee P, Ghosh D, Roy H, et al. Precise targeting of transcriptional co-activators YAP/TAZ annihilates chemoresistant brCSCs by alteration of their mitochondrial homeostasis. Signal Transduct Target Ther. 2025; 10: 61.
157. Shea MP, O'Leary KA, Wegner KA, Vezina CM, Schuler LA. High collagen density augments mTOR-dependent cancer stem cells in ERα+ mammary carcinomas, and increases mTOR-independent lung metastases. Cancer Lett. 2018; 433: 1-9.
158. Pang MF, Siedlik MJ, Han S, Stallings-Mann M, Radisky DC, Nelson CM. Tissue Stiffness and Hypoxia Modulate the Integrin-Linked Kinase ILK to Control Breast Cancer Stem-like Cells. Cancer Res. 2016; 76: 5277-87.
159. Soliman BG, Tian P, Cui J, Kilian KA, Gooding JJ. Interfacial Stress Regulates Plasticity and Drug Resistance at the Breast Cancer-Host Interface. Adv Sci (Weinh). 2025; 12: e09361.
160. Li Y, Randriantsilefisoa R, Chen J, Cuellar-Camacho JL, Liang W, Li W. Matrix Stiffness Regulates Chemosensitivity, Stemness Characteristics, and Autophagy in Breast Cancer Cells. ACS Appl Bio Mater. 2020; 3: 4474-85.
161. Choi HY, Yang GM, Dayem AA, Saha SK, Kim K, Yoo Y, et al. Hydrodynamic shear stress promotes epithelial-mesenchymal transition by downregulating ERK and GSK3β activities. Breast Cancer Res. 2019; 21: 6.
162. Brown SR, Radcliffe ME, Danner JT, Andújar Cruz WJ, Lackey KH, Park HA, et al. Extracellular Vesicle-Mediated Modulation of Stem-like Phenotype in Breast Cancer Cells under Fluid Shear Stress. Biomolecules. 2024; 14.
163. Zhang T, Jia Y, Yu Y, Zhang B, Xu F, Guo H. Targeting the tumor biophysical microenvironment to reduce resistance to immunotherapy. Adv Drug Deliv Rev. 2022; 186: 114319.
164. Fan Y, George JT. Distinct evolutionary patterns of tumour-immune escape and elimination determined by extracellular matrix architectures. J R Soc Interface. 2025; 22: 20250116.
165. Kuczek DE, Larsen AMH, Thorseth ML, Carretta M, Kalvisa A, Siersbæk MS, et al. Collagen density regulates the activity of tumor-infiltrating T cells. J Immunother Cancer. 2019; 7: 68.
166. Sun X, Wu B, Chiang HC, Deng H, Zhang X, Xiong W, et al. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature. 2021; 599: 673-8.
167. Hyun J, Kim SJ, Cho SD, Kim HW. Mechano-modulation of T cells for cancer immunotherapy. Biomaterials. 2023; 297: 122101.
168. Tharp KM, Kersten K, Maller O, Timblin GA, Stashko C, Canale FP, et al. Tumor-associated macrophages restrict CD8(+) T cell function through collagen deposition and metabolic reprogramming of the breast cancer microenvironment. Nat Cancer. 2024; 5: 1045-62.
169. Pan MR, Wu CC, Kan JY, Li QL, Chang SJ, Wu CC, et al. Impact of FAK Expression on the Cytotoxic

Effects of CIK Therapy in Triple-Negative Breast Cancer. Cancers (Basel). 2019; 12.
170. Park S, Shi Y, Kim BC, Jo MH, Cruz LO, Gou Z, et al. Force-dependent trans-endocytosis by breast cancer cells depletes costimulatory receptor CD80 and attenuates T cell activation. Biosens Bioelectron. 2020; 165: 112389.
171. Atcha H, Jairaman A, Holt JR, Meli VS, Nagalla RR, Veerasubramanian PK, et al. Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. Nat Commun. 2021; 12: 3256.
172. Taufalele PV, Wang W, Simmons AJ, Southard-Smith AN, Chen B, Greenlee JD, et al. Matrix stiffness enhances cancer-macrophage interactions and M2-like macrophage accumulation in the breast tumor microenvironment. Acta Biomater. 2023; 163: 365-77.
173. Gao H, Tian Q, Zhou Y, Zhu L, Lu Y, Ma Y, et al. 3D Collagen Fiber Concentration Regulates Treg Cell Infiltration in Triple Negative Breast Cancer. Front Immunol. 2022; 13: 904418.
174. Talarico G, Lecchi M, Zanichelli A, Portararo P, Botti L, Cappelletti V, et al. ECM-Induced IL-23 Drives Immune Suppression in Breast Cancer via Regulating PD-1 on Tregs. J Exp Clin Cancer Res. 2025; 44: 264.
175. Wang Y, Goliwas KF, Severino PE, Hough KP, Van Vessem D, Wang H, et al. Mechanical strain induces phenotypic changes in breast cancer cells and promotes immunosuppression in the tumor microenvironment. Lab Invest. 2020; 100: 1503-16.
176. Ni X, Tao J, Barbi J, Chen Q, Park BV, Li Z, et al. YAP Is Essential for Treg-Mediated Suppression of Antitumor Immunity. Cancer Discov. 2018; 8: 1026-43.
177. Shibata M, Ham K, Hoque MO. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. Int J Cancer. 2018; 143: 2133-44.
178. Joyce MH, Lu C, James ER, Hegab R, Allen SC, Suggs LJ, et al. Phenotypic Basis for Matrix Stiffness-Dependent Chemoresistance of Breast Cancer Cells to Doxorubicin. Front Oncol. 2018; 8: 337.
179. Raaijmakers K, Adema GJ, Bussink J, Ansems M. Cancer-associated fibroblasts, tumor and radiotherapy: interactions in the tumor micro-environment. J Exp Clin Cancer Res. 2024; 43: 323.
180. Youk JH, Gweon HM, Son EJ. Shear-wave elastography in breast ultrasonography: the state of the art. Ultrasonography. 2017; 36: 300-9.
181. Barr RG, Destounis S, Lackey LB, 2nd, Svensson WE, Balleyguier C, Smith C. Evaluation of breast lesions using sonographic elasticity imaging: a multicenter trial. J Ultrasound Med. 2012; 31: 281-7.
182. Evans A, Whelehan P, Thomson K, McLean D, Brauer K, Purdie C, et al. Invasive breast cancer: relationship between shear-wave elastographic findings and histologic prognostic factors. Radiology. 2012; 263: 673-7.
183. Wan C, Zhou L, Jin Y, Li F, Wang L, Yin W, et al. Strain ultrasonic elastography imaging features of locally advanced breast cancer: association with response to neoadjuvant chemotherapy and recurrence-free survival. BMC Med Imaging. 2023; 23: 216.
184. Pepin KM, Ehman RL, McGee KP. Magnetic resonance elastography (MRE) in cancer: Technique, analysis, and applications. Prog Nucl Magn Reson Spectrosc. 2015; 90-91: 32-48.
185. Sinha AP, Jurrius P, van Schelt AS, Darwish O, Shifa B, Annio G, et al. Tumor Biomechanics Quantified Using MR Elastography to Predict Response to Neoadjuvant Chemotherapy in Individuals with Breast Cancer. Radiol Imaging Cancer. 2025; 7: e240138.
186. Conklin MW, Eickhoff JC, Riching KM, Pehlke CA, Eliceiri KW, Provenzano PP, et al. Aligned collagen is a prognostic signature for survival in human breast carcinoma. Am J Pathol. 2011; 178:

1221-32.
187. Desa DE, Bhanote M, Hill RL, Majeski JB, Buscaglia B, D'Aguiar M, et al. Second-harmonic generation directionality is associated with neoadjuvant chemotherapy response in breast cancer core needle biopsies. J Biomed Opt. 2019; 24: 1-9.
188. Tumanova K, Khorasani M, Nofech-Mozes S, Vitkin A. Machine learning-based prediction of luminal breast cancer subtypes using polarised light microscopy. Br J Cancer. 2025; 133: 1916-25.
189. Suzuki M, Shimizu T, Nishizawa N, Sakamoto M, Noda K, Sasaki T, et al. Acquisition of full Mueller matrix distribution of cancer tissue with near-infrared polarization-probe polarization-imaging and search for its optimal polarization conditions. Opt Express. 2025; 33: 18214-24.
190. Quintela-Fandino M, Bermejo B, Zamora E, Moreno F, García-Saenz J, Pernas S, et al. High Mechanical Conditioning by Tumor Extracellular Matrix Stiffness Is a Predictive Biomarker for Antifibrotic Therapy in HER2-Negative Breast Cancer. Clin Cancer Res. 2024; 30: 5094-104.
191. Siegel RC. Biosynthesis of collagen crosslinks: increased activity of purified lysyl oxidase with reconstituted collagen fibrils. Proc Natl Acad Sci U S A. 1974; 71: 4826-30.
192. Rossow L, Veitl S, Vorlová S, Wax JK, Kuhn AE, Maltzahn V, et al. LOX-catalyzed collagen stabilization is a proximal cause for intrinsic resistance to chemotherapy. Oncogene. 2018; 37: 4921-40.
193. Flaherty RL, Hughes F, Sflomos G, Ronchi C, Kemp H, Roumeliotis TI, et al. LOX Inhibition Disrupts a Collagen-Integrin-MYC Axis to Suppress Progression of Invasive Lobular Carcinoma. Cancer Res. 2026; 86: 2487-507.
194. Barry-Hamilton V, Spangler R, Marshall D, McCauley S, Rodriguez HM, Oyasu M, et al. Allosteric inhibition of lysyl oxidase-like-2 impedes the development of a pathologic microenvironment. Nat Med. 2010; 16: 1009-17.
195. Leung L, Niculescu-Duvaz D, Smithen D, Lopes F, Callens C, McLeary R, et al. Anti-metastatic Inhibitors of Lysyl Oxidase (LOX): Design and Structure-Activity Relationships. J Med Chem. 2019; 62: 5863-84.
196. Chang J, Lucas MC, Leonte LE, Garcia-Montolio M, Singh LB, Findlay AD, et al. Pre-clinical evaluation of small molecule LOXL2 inhibitors in breast cancer. Oncotarget. 2017; 8: 26066-78.
197. Zhang L, Wang Y, Xia T, Yu Q, Zhang Q, Yang Y, et al. Suppression for lung metastasis by depletion of collagen I and lysyl oxidase via losartan assisted with paclitaxel-loaded pH-sensitive liposomes in breast cancer. Drug Deliv. 2016; 23: 2970-9.
198. Mpekris F, Panagi M, Voutouri C, Martin JD, Samuel R, Takahashi S, et al. Normalizing the Microenvironment Overcomes Vessel Compression and Resistance to Nano-immunotherapy in Breast Cancer Lung Metastasis. Adv Sci (Weinh). 2021; 8: 2001917.
199. Papageorgis P, Polydorou C, Mpekris F, Voutouri C, Agathokleous E, Kapnissi-Christodoulou CP, et al. Tranilast-induced stress alleviation in solid tumors improves the efficacy of chemo- and nanotherapeutics in a size-independent manner. Sci Rep. 2017; 7: 46140.
200. Es HA, Cox TR, Sarafraz-Yazdi E, Thiery JP, Warkiani ME. Pirfenidone Reduces Epithelial-Mesenchymal Transition and Spheroid Formation in Breast Carcinoma through Targeting Cancer-Associated Fibroblasts (CAFs). Cancers (Basel). 2021; 13.
201. Li S, Zhang X, Pang D. Pirfenidone inhibits CCL2-mediated Treg chemotaxis induced by palbociclib and fulvestrant in HR+/HER2- breast cancer. Int Immunopharmacol. 2024; 142: 113059.
202. Quintela-Fandino M, Apala JV, Malon D, Mouron S, Hornedo J, Gonzalez-Cortijo L, et al. Nintedanib plus letrozole in early breast cancer: a phase 0/I pharmacodynamic, pharmacokinetic, and

safety clinical trial of combined FGFR1 and aromatase inhibition. Breast Cancer Res. 2019; 21: 69.
203. Mpekris F, Papageorgis P, Polydorou C, Voutouri C, Kalli M, Pirentis AP, et al. Sonic-hedgehog pathway inhibition normalizes desmoplastic tumor microenvironment to improve chemo- and nanotherapy. J Control Release. 2017; 261: 105-12.
204. Singha NC, Nekoroski T, Zhao C, Symons R, Jiang P, Frost GI, et al. Tumor-associated hyaluronan limits efficacy of monoclonal antibody therapy. Mol Cancer Ther. 2015; 14: 523-32.
205. Brundel DH, Feeney OM, Nowell CJ, Suys EJ, Gracia G, Kaminskas LM, et al. Depolymerization of hyaluronan using PEGylated human recombinant hyaluronidase promotes nanoparticle tumor penetration. Nanomedicine (Lond). 2021; 16: 275-92.
206. Li P, Dong Z, Jiang Q, Yu C, Liu Y, Yuan R, et al. Sunitinib lipid nanoparticles remodel tumor vasculature to synergize with two-stage radiotherapy for enhanced radiosensitivity in breast Cancer. J Control Release. 2026; 389: 114406.
207. Ager EI, Kozin SV, Kirkpatrick ND, Seano G, Kodack DP, Askoxylakis V, et al. Blockade of MMP14 activity in murine breast carcinomas: implications for macrophages, vessels, and radiotherapy. J Natl Cancer Inst. 2015; 107.
208. Peng J, Zhu W, Zhang C, Yin S, Ye J, Mao H, et al. COL4A2 drives ECM remodeling and stiffness increasing to promote breast cancer metastasis via YAP signaling pathway in dECM induced models. Biomater Adv. 2025; 177: 214430.
209. Egorova A, Pyankov I, Maretina M, Baranov V, Kiselev A. Peptide Nanoparticle-Mediated Combinatorial Delivery of Cancer-Related siRNAs for Synergistic Anti-Proliferative Activity in Triple Negative Breast Cancer Cells. Pharmaceuticals (Basel). 2021; 14.
210. Su S, Chen J, Yao H, Liu J, Yu S, Lao L, et al. CD10(+)GPR77(+) Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness. Cell. 2018; 172: 841-56.e16.
211. Kim TH, Tran Le MT, Oh M, Vazquez-Hidalgo E, Chavez B, Lamkin DM, et al. β-adrenergic signaling modulates breast cancer cell mechanical behaviors through a RhoA-ROCK-myosin II axis. iScience. 2025; 28: 112676.
212. Chan N, Willis A, Kornhauser N, Ward MM, Lee SB, Nackos E, et al. Influencing the Tumor Microenvironment: A Phase II Study of Copper Depletion Using Tetrathiomolybdate in Patients with Breast Cancer at High Risk for Recurrence and in Preclinical Models of Lung Metastases. Clin Cancer Res. 2017; 23: 666-76.
213. Campbell PS, Mavingire N, Khan S, Rowland LK, Wooten JV, Opoku-Agyeman A, et al. AhR ligand aminoflavone suppresses α6-integrin-Src-Akt signaling to attenuate tamoxifen resistance in breast cancer cells. J Cell Physiol. 2018; 234: 108-21.
214. Moore KM, Thomas GJ, Duffy SW, Warwick J, Gabe R, Chou P, et al. Therapeutic targeting of integrin αvβ6 in breast cancer. J Natl Cancer Inst. 2014; 106.
215. Wallstabe L, Mades A, Frenz S, Einsele H, Rader C, Hudecek M. CAR T cells targeting α(v)β(3) integrin are effective against advanced cancer in preclinical models. Adv Cell Gene Ther. 2018; 1.
216. Cui C, Merritt R, Fu L, Pan Z. Targeting calcium signaling in cancer therapy. Acta Pharm Sin B. 2017; 7: 3-17.
217. Adapala RK, Thoppil RJ, Ghosh K, Cappelli HC, Dudley AC, Paruchuri S, et al. Activation of mechanosensitive ion channel TRPV4 normalizes tumor vasculature and improves cancer therapy. Oncogene. 2016; 35: 314-22.
218. Peters AA, Jamaludin SYN, Yapa K, Chalmers S, Wiegmans AP, Lim HF, et al. Oncosis and apoptosis

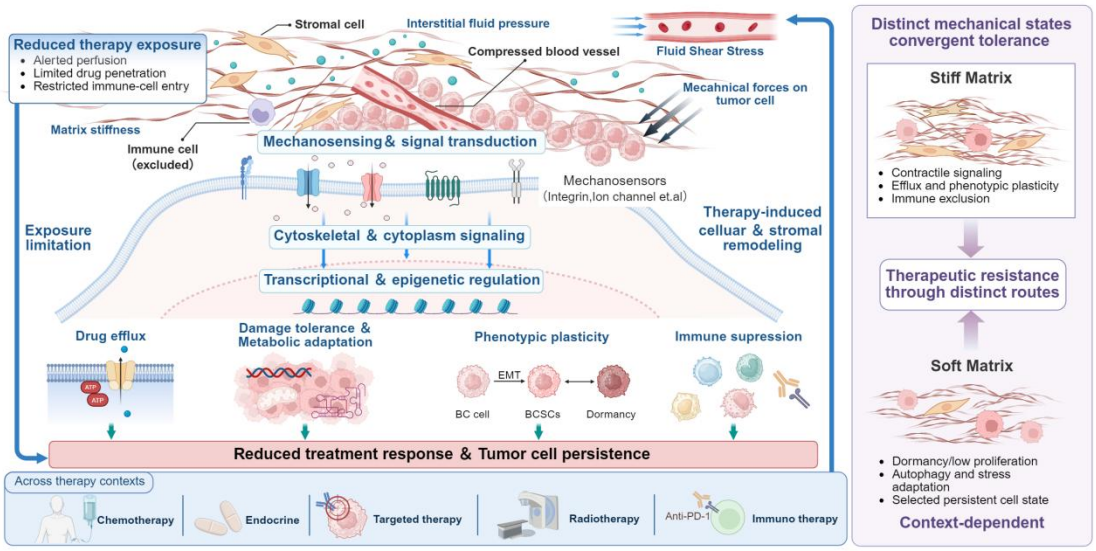
induction by activation of an overexpressed ion channel in breast cancer cells. Oncogene. 2017; 36: 6490-500.
219. Sheng Y, Qiao C, Zhang Z, Shi X, Yang L, Xi R, et al. Calcium Channel Blocker Lacidipine Promotes Antitumor Immunity by Reprogramming Tryptophan Metabolism. Adv Sci (Weinh). 2025; 12: e2409310.
220. Tanjoni I, Walsh C, Uryu S, Tomar A, Nam JO, Mielgo A, et al. PND-1186 FAK inhibitor selectively promotes tumor cell apoptosis in three-dimensional environments. Cancer Biol Ther. 2010; 9: 764-77.
221. Walsh C, Tanjoni I, Uryu S, Tomar A, Nam JO, Luo H, et al. Oral delivery of PND-1186 FAK inhibitor decreases tumor growth and spontaneous breast to lung metastasis in pre-clinical models. Cancer Biol Ther. 2010; 9: 778-90.
222. Kolev VN, Tam WF, Wright QG, McDermott SP, Vidal CM, Shapiro IM, et al. Inhibition of FAK kinase activity preferentially targets cancer stem cells. Oncotarget. 2017; 8: 51733-47.
223. Tiede S, Meyer-Schaller N, Kalathur RKR, Ivanek R, Fagiani E, Schmassmann P, et al. The FAK inhibitor BI 853520 exerts anti-tumor effects in breast cancer. Oncogenesis. 2018; 7: 73.
224. Doi T, Yang JC, Shitara K, Naito Y, Cheng AL, Sarashina A, et al. Phase I Study of the Focal Adhesion Kinase Inhibitor BI 853520 in Japanese and Taiwanese Patients with Advanced or Metastatic Solid Tumors. Target Oncol. 2019; 14: 57-65.
225. Tian J, Raffa FA, Dai M, Moamer A, Khadang B, Hachim IY, et al. Dasatinib sensitises triple negative breast cancer cells to chemotherapy by targeting breast cancer stem cells. Br J Cancer. 2018; 119: 1495-507.
226. Finn RS, Bengala C, Ibrahim N, Roché H, Sparano J, Strauss LC, et al. Dasatinib as a single agent in triple-negative breast cancer: results of an open-label phase 2 study. Clin Cancer Res. 2011; 17: 6905-13.
227. Ocana A, Gil-Martin M, Antolín S, Atienza M, Montaño Á, Ribelles N, et al. Efficacy and safety of dasatinib with trastuzumab and paclitaxel in first line HER2-positive metastatic breast cancer: results from the phase II GEICAM/2010-04 study. Breast Cancer Res Treat. 2019; 174: 693-701.
228. Cascione M, De Matteis V, Toma CC, Pellegrino P, Leporatti S, Rinaldi R. Morphomechanical and structural changes induced by ROCK inhibitor in breast cancer cells. Exp Cell Res. 2017; 360: 303-9.
229. Guerra FS, Oliveira RG, Fraga CAM, Mermelstein CDS, Fernandes PD. ROCK inhibition with Fasudil induces beta-catenin nuclear translocation and inhibits cell migration of MDA-MB 231 human breast cancer cells. Sci Rep. 2017; 7: 13723.
230. Patel RA, Forinash KD, Pireddu R, Sun Y, Sun N, Martin MP, et al. RKI-1447 is a potent inhibitor of the Rho-associated ROCK kinases with anti-invasive and antitumor activities in breast cancer. Cancer Res. 2012; 72: 5025-34.
231. Li Y, Wang S, Wei X, Zhang S, Song Z, Chen X, et al. Role of inhibitor of yes-associated protein 1 in triple-negative breast cancer with taxol-based chemoresistance. Cancer Sci. 2019; 110: 561-7.
232. Chen H, Zhang LF, Miao Y, Xi Y, Li X, Liu MF, et al. Verteporfin Suppresses YAP-Induced Glycolysis in Breast Cancer Cells. J Invest Surg. 2023; 36: 2266732.
233. Fu J, Liu W, Liu S, Zhao R, Hayashi T, Zhao H, et al. Inhibition of YAP/TAZ pathway contributes to the cytotoxicity of silibinin in MCF-7 and MDA-MB-231 human breast cancer cells. Cell Signal. 2024; 119: 111186.
234. Liu-Chittenden Y, Huang B, Shim JS, Chen Q, Lee SJ, Anders RA, et al. Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. Genes Dev. 2012; 26: 1300-5.

235. Zhang Y, Shen H, Withers HG, Yang N, Denson KE, Mussell AL, et al. VGLL4 Selectively Represses YAP-Dependent Gene Induction and Tumorigenic Phenotypes in Breast Cancer. Sci Rep. 2017; 7: 6190.
236. Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, et al. A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. Cancer Cell. 2014; 25: 166-80.
237. Zanconato F, Battilana G, Forcato M, Filippi L, Azzolin L, Manfrin A, et al. Transcriptional addiction in cancer cells is mediated by YAP/TAZ through BRD4. Nat Med. 2018; 24: 1599-610.
238. Doheny D, Sirkisoon S, Carpenter RL, Aguayo NR, Regua AT, Anguelov M, et al. Combined inhibition of JAK2-STAT3 and SMO-GLI1/tGLI1 pathways suppresses breast cancer stem cells, tumor growth, and metastasis. Oncogene. 2020; 39: 6589-605.
239. Stover DG, Gil Del Alcazar CR, Brock J, Guo H, Overmoyer B, Balko J, et al. Phase II study of ruxolitinib, a selective JAK1/2 inhibitor, in patients with metastatic triple-negative breast cancer. NPJ Breast Cancer. 2018; 4: 10.
240. Bottos A, Gotthardt D, Gill JW, Gattelli A, Frei A, Tzankov A, et al. Decreased NK-cell tumour immunosurveillance consequent to JAK inhibition enhances metastasis in breast cancer models. Nat Commun. 2016; 7: 12258.
241. Al-Tweigeri T, Tulbah A, Akhtar S, Alzahrani M, Najjar S, El Hassan T, et al. Safety and preliminary efficacy of adding tocilizumab to cisplatin/docetaxel for the treatment of locally advanced triple-negative breast cancer patients: prospective phase 1/2 clinical trial. Sci Rep. 2026; 16: 7029.
242. Singh SK, Singh S, Lillard JW, Jr., Singh R. Drug delivery approaches for breast cancer. Int J Nanomedicine. 2017; 12: 6205-18.
243. Chen J, Zhang Z, Li Y, Zeng H, Li Z, Wang C, et al. Precise fibrin decomposition and tumor mechanics modulation with hydroxyethyl starch-based smart nanomedicine for enhanced antitumor efficacy. J Mater Chem B. 2022; 10: 8193-210.
244. Chauhan VP, Chen IX, Tong R, Ng MR, Martin JD, Naxerova K, et al. Reprogramming the microenvironment with tumor-selective angiotensin blockers enhances cancer immunotherapy. Proc Natl Acad Sci U S A. 2019; 116: 10674-80.
245. Jia N, Wang Q, Li W, Chen D, Hu H. Membrane Fusion Liposomes Deliver Antifibrotic and Chemotherapeutic Drugs Sequentially to Enhance Tumor Treatment Efficacy by Reshaping Tumor Microenvironment. Adv Healthc Mater. 2024; 13: e2400219.
246. Zhang Z, Luo Z, Huang H, Huang Y, Xu J, Liu XY, et al. YAP/TAZ Inhibitor-Based Drug Delivery System for Selective Tumor Accumulation and Cancer Combination Therapy. Biomacromolecules. 2025; 26: 266-78.
247. Panagi M, Mpekris F, Chen P, Voutouri C, Nakagawa Y, Martin JD, et al. Polymeric micelles effectively reprogram the tumor microenvironment to potentiate nano-immunotherapy in mouse breast cancer models. Nat Commun. 2022; 13: 7165.
248. Mpekris F, Papaphilippou PC, Panagi M, Voutouri C, Michael C, Charalambous A, et al. Pirfenidone-Loaded Polymeric Micelles as an Effective Mechanotherapeutic to Potentiate Immunotherapy in Mouse Tumor Models. ACS Nano. 2023; 17: 24654-67.
249. Lin JY, Wu Y, Liang XH, Tang M, Sun X, Lu SX, et al. A Self-Assembling LYTAC Mediates CTGF Degradation and Remodels Inflammatory Tumor Microenvironment for Triple-Negative Breast Cancer Therapy. Adv Sci (Weinh). 2025; 12: e2500311.
250. Yang LY, Liang GW, Cai BJ, Xu KM, Zhao YJ, Xie XT, et al. Enhanced tumor self-targeting of lemon-derived extracellular vesicles by embedding homotypic cancer cell membranes for efficient drug delivery. J Nanobiotechnology. 2025; 23: 74.

251. Hou X, Shen Y, Huang B, Li Q, Li S, Jiang T, et al. Losartan-based nanocomposite hydrogel overcomes chemo-immunotherapy resistance by remodeling tumor mechanical microenvironment. J Nanobiotechnology. 2024; 22: 667.
252. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016; 94: 1073-87.
253. Krawczyk PM, Eppink B, Essers J, Stap J, Rodermond H, Odijk H, et al. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. Proc Natl Acad Sci U S A. 2011; 108: 9851-6.
254. Moore-Palhares D, Dasgupta A, Saifuddin M, Anzola Pena ML, Prasla S, Ho L, et al. Radiation enhancement using focussed ultrasound-stimulated microbubbles for breast cancer: A Phase 1 clinical trial. PLoS Med. 2024; 21: e1004408.
255. Hu Y, Cheng L, Guo X, Zheng M, Zhang W, Wang X, et al. Sono-Gas-Mediated Precise Stiffness Remodeling for Triple-Negative Breast Cancer Mechanical Immunotherapy. Biomater Res. 2025; 29: 0207.
256. Lv J, Si T, Wang D, Zhang C, Zhou Y, Yu J, et al. Mechanical signaling via β2 integrin decouples T cell proliferation and differentiation for generating stem cell-like CAR T cells. Immunity. 2025; 58: 2289-304.e10.
257. McLeod R, Kumar R, Papadatos-Pastos D, Mateo J, Brown JS, Garces AHI, et al. First-in-Human Study of AT13148, a Dual ROCK-AKT Inhibitor in Patients with Solid Tumors. Clin Cancer Res. 2020; 26: 4777-84.
258. Marlowe TA, Lenzo FL, Figel SA, Grapes AT, Cance WG. Oncogenic Receptor Tyrosine Kinases Directly Phosphorylate Focal Adhesion Kinase (FAK) as a Resistance Mechanism to FAK-Kinase Inhibitors. Mol Cancer Ther. 2016; 15: 3028-39.
259. Evans A, Whelehan P, Thomson K, Brauer K, Jordan L, Purdie C, et al. Differentiating benign from malignant solid breast masses: value of shear wave elastography according to lesion stiffness combined with greyscale ultrasound according to BI-RADS classification. Br J Cancer. 2012; 107: 224-9.
260. Nathanson SD, Nelson L. Interstitial fluid pressure in breast cancer, benign breast conditions, and breast parenchyma. Ann Surg Oncol. 1994; 1: 333-8.
261. Barr RG, Nakashima K, Amy D, Cosgrove D, Farrokh A, Schafer F, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 2: breast. Ultrasound Med Biol. 2015; 41: 1148-60.
262. Ding Y, Sun C, Zhou Q, Cheng C, Yan C, Wang B. Use of Palpation Imaging in Diagnosis of Breast Diseases: A Way to Improve the Detection Rate. Med Sci Monit. 2020; 26: e927553.
263. Liu Y, Hossain MM, Li XJ, Konofagou EE. Amplitude-Modulation Frequency Optimization for Enhancing Harmonic Motion Imaging Performance of Breast Tumors in the Clinic. Ultrasound Med Biol. 2025; 51: 169-79.
264. Fang Q, Sanderson RW, Zilkens R, Boman I, Foo KY, Lakhiani DD, et al. Diagnostic feasibility study of stereoscopic optical palpation for breast tumour margin assessment. BMC Cancer. 2025; 25: 1793.

Figure Legends

Graphical abstract



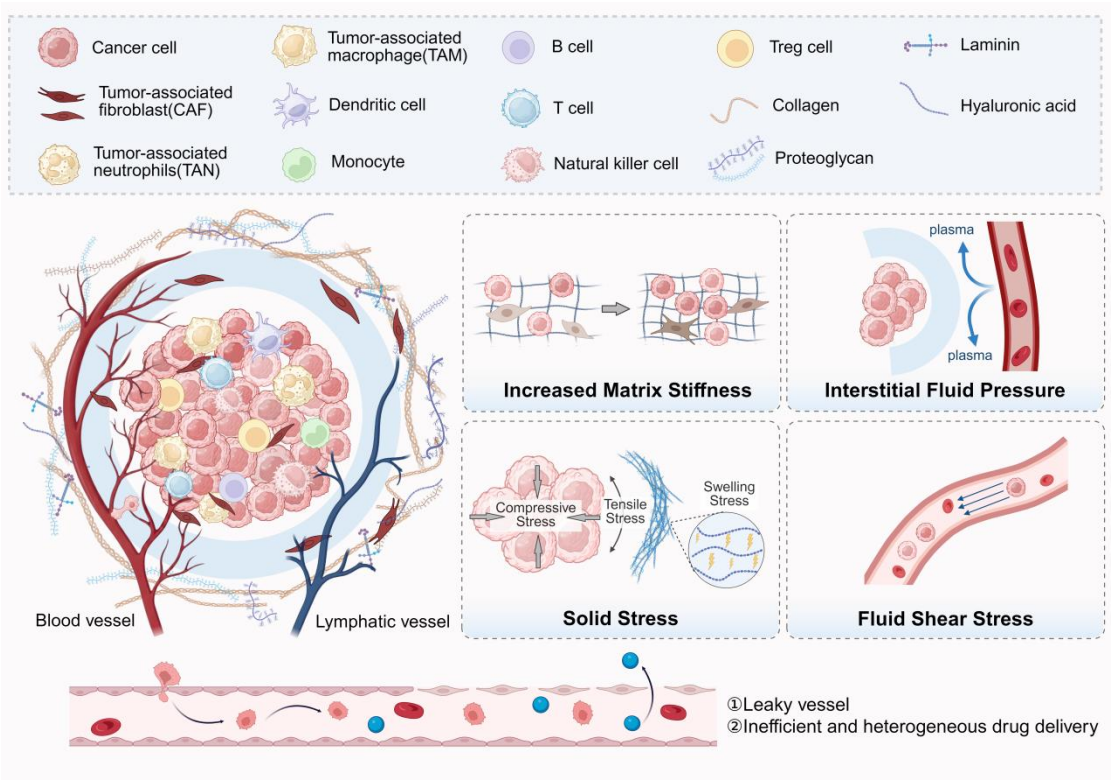


Fig. 1. Biomechanical features of the breast cancer microenvironment. Increased matrix stiffness is associated with collagen deposition and fiber crosslinking and is regulated by tumor cells and cancer-associated fibroblasts; solid stress arises from the accumulation of forces generated by cellular proliferation, matrix deposition, and compression of surrounding tissues by the tumor; abnormal interstitial fluid pressure is related to vascular leakage, vascular compression, and impaired lymphatic drainage; and heterogeneity in fluid shear stress originates from aberrant hemodynamics and vascular endothelial cell function.

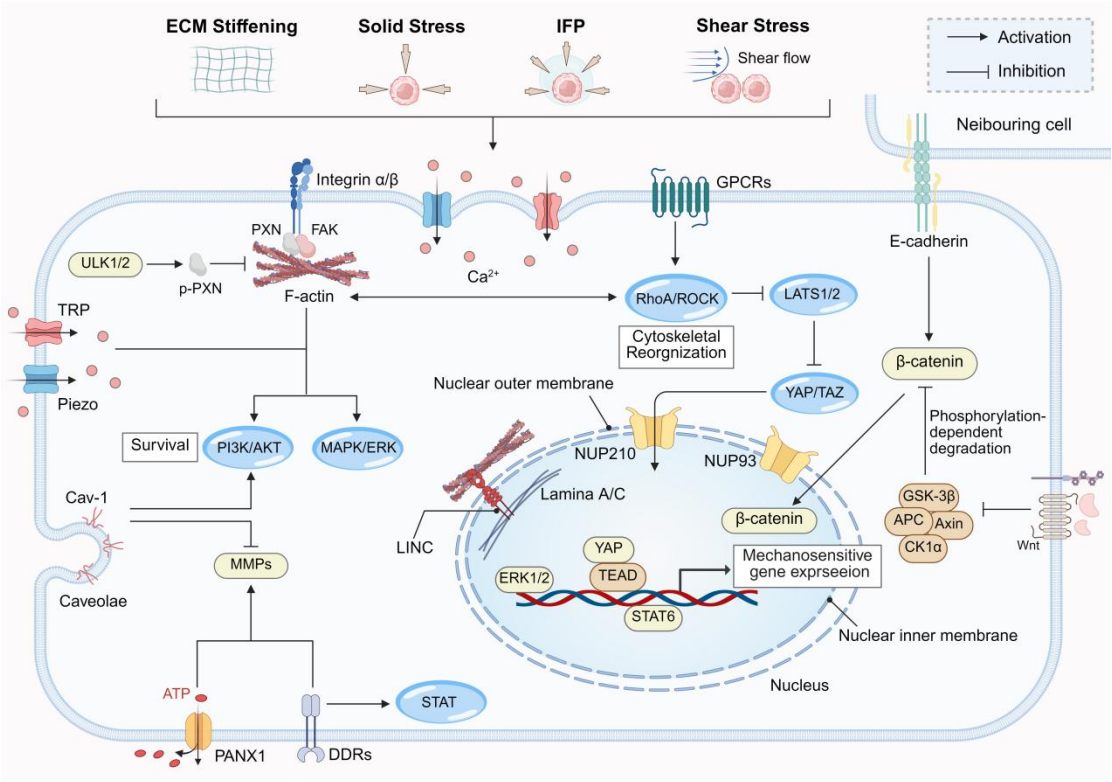


Fig. 2. Sensing and transduction of biomechanical signals. The principal mechanosensors on the surface of breast cancer cells include adhesion proteins represented by integrins, calcium ion channels, and G protein-coupled receptors. After these signals are transmitted into the cell, they activate downstream cascades such as FAK/Src, Rho/ROCK, and Hippo/YAP/TAZ signaling. Among these pathways, YAP/TAZ plays a central role in the biomechanical signal response cascade; upon nuclear translocation, YAP/TAZ binds to TEAD family transcription factors and initiates relevant gene transcriptional programs. Finally, the linker of nucleoskeleton and cytoskeleton complex can also directly participate in chromatin remodeling and the maintenance of mechanical memory.

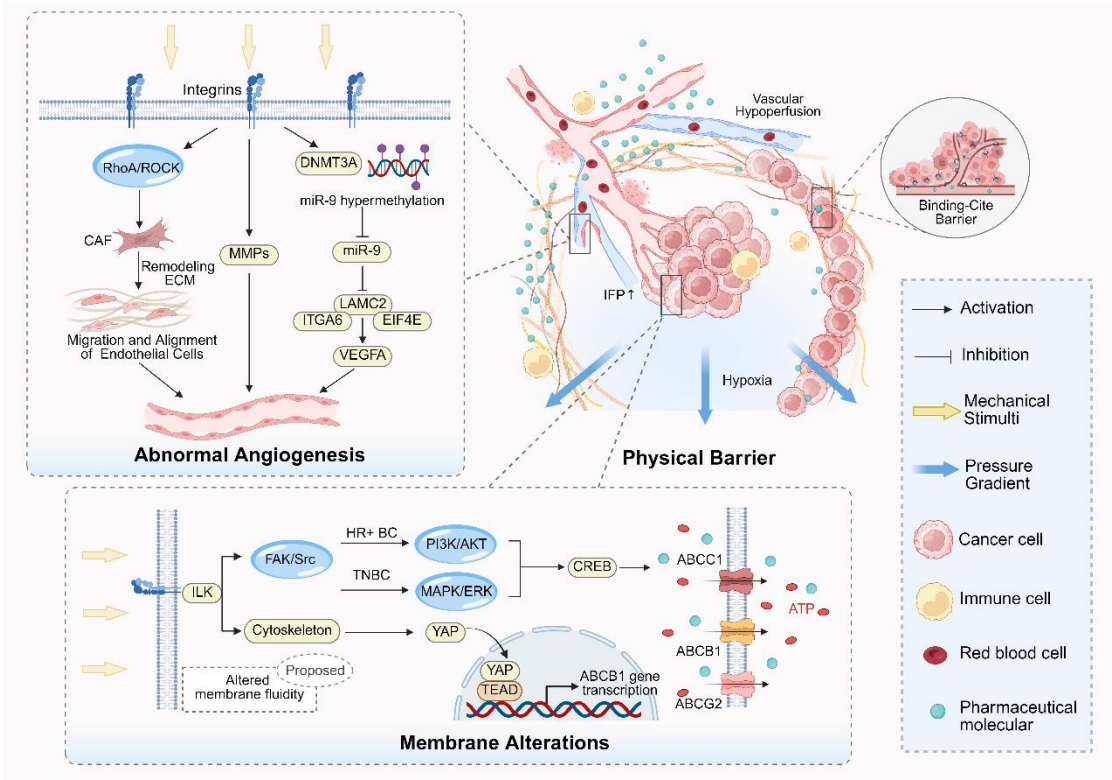


Fig. 3. Biomechanical regulation of drug delivery. Dense matrix first forms a physical barrier and compresses blood and lymphatic vessels, leading to increased intratumoral interstitial fluid pressure and the formation of pressure gradients, thereby restricting drug transport. In addition, biomechanics induces aberrant tumor angiogenesis, affecting drug infiltration and homogeneous distribution. The perivascular "binding-site barrier" impedes the penetration of high-affinity drugs, such as monoclonal antibodies, into the tumor center, thereby limiting therapeutic efficacy. Meanwhile, biomechanical signals can upregulate ABC transporter expression to enhance drug efflux and may also affect transmembrane drug transport by altering the lipid composition of the cell membrane, ultimately accelerating treatment failure and recurrence in breast cancer.

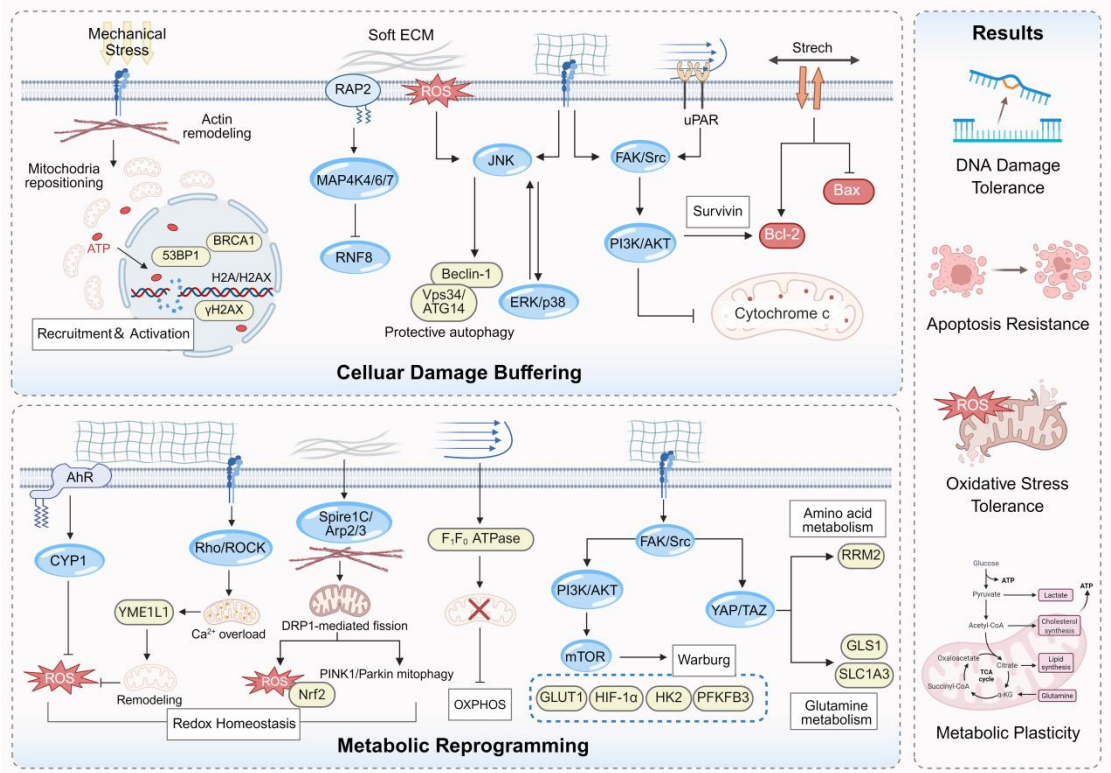


Fig. 4. Biomechanical signals promote cellular damage repair and metabolic adaptation. At the levels of DNA repair and cell death, biomechanical signals can support the recruitment of DNA repair proteins by promoting perinuclear mitochondrial accumulation and increasing intranuclear ATP. They also regulate protective autophagy through multiple pathways and counteract apoptosis. At the metabolic level, biomechanical signals help maintain cellular redox homeostasis by regulating the AhR/CYP1 pathway and mitochondria, and reprogram glycolysis through F1F0-ATP synthase and the FAK/Src–PI3K/AKT–mTOR axis. In addition, YAP/TAZ participates in the regulation of nucleotide, amino acid, and glutamine metabolism.

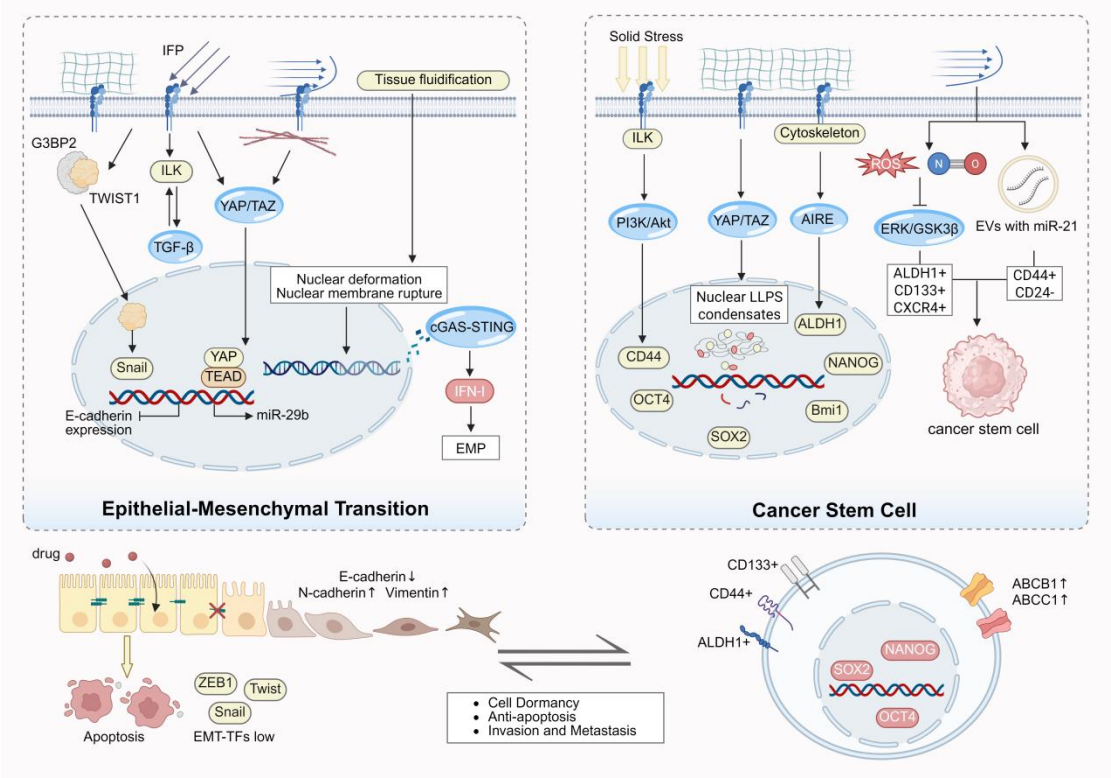


Fig. 5. Biomechanically induced phenotypic transition. Matrix stiffness, solid stress, interstitial fluid pressure, and fluid shear stress can induce the EMT phenotype in tumors through pathways such as ILK/TGF-β, YAP/TAZ, TWIST1, and cGAS-STING-IFN-I signaling, ultimately promoting breast cancer cell survival. Meanwhile, biomechanical signals can enrich BCSCs and maintain their dormant state through signaling pathways such as ILK-PI3K/AKT, YAP/TAZ, the AIRE-ALDH1 axis, and FSS-induced miR-21 and ROS/NO signaling, thereby reducing treatment-induced damage. More importantly, EMT and CSCs phenotypes in tumor cells can undergo dynamic interconversion, facilitating invasion, metastasis, and therapeutic resistance under different microenvironmental conditions.

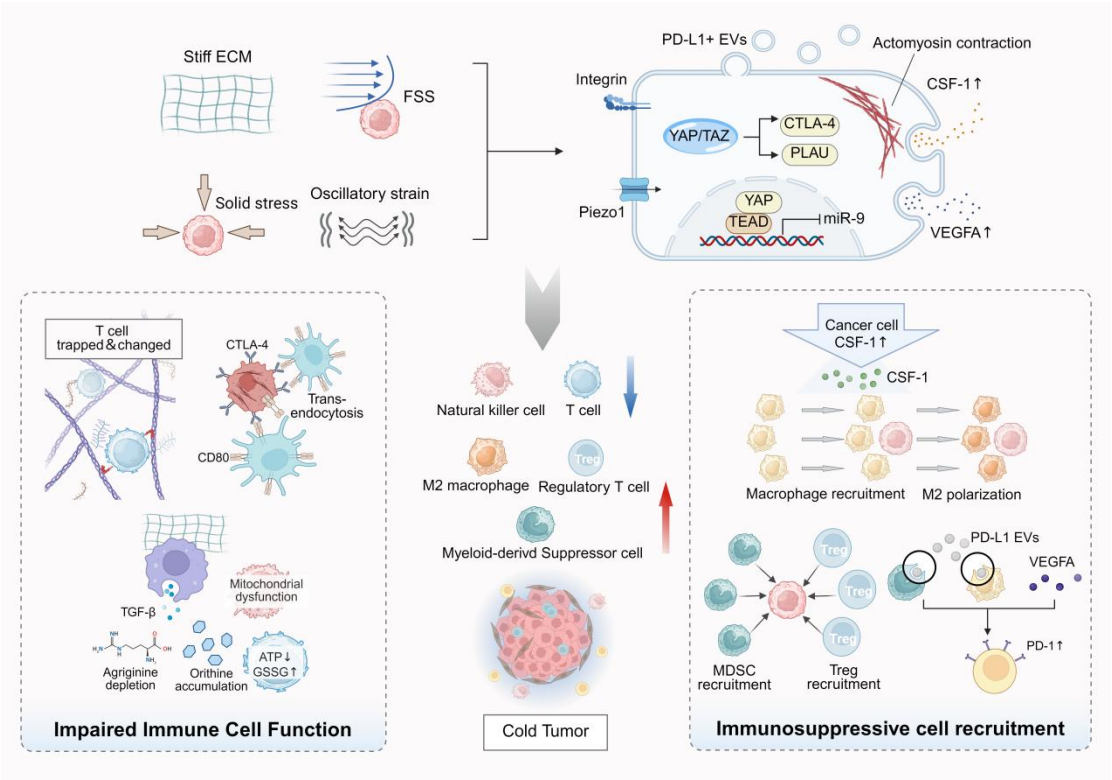


Fig. 6. Biomechanically mediated tumor immune escape. Dense ECM not only alters T-cell migration patterns and restricts T-cell infiltration, but also impairs T-cell and NK-cell function through metabolic reprogramming. Meanwhile, biomechanical forces induce T-cell exhaustion through PD-L1, CTLA-4, and VEGFA-related signaling. Mechanically induced CSF-1 and YAP/TAZ can also promote M2 macrophage polarization and recruit MDSCs and Tregs, ultimately establishing an immunosuppressive microenvironment and reducing responses to immunotherapy.

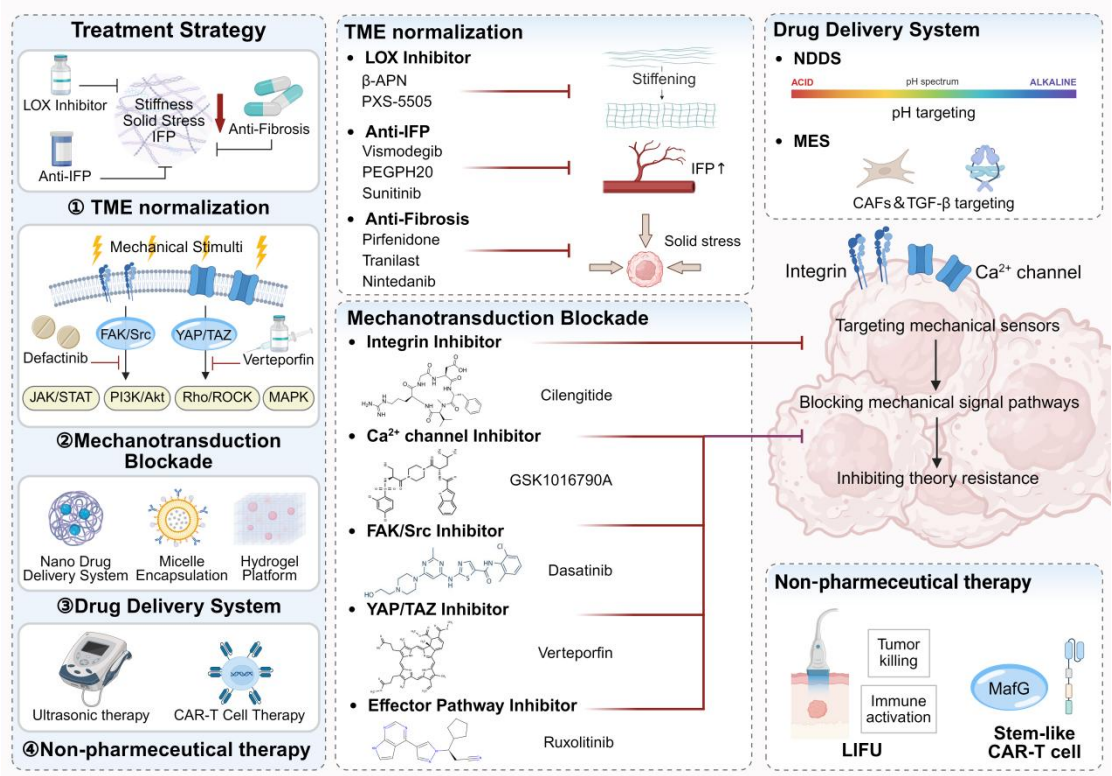


Fig. 7. Therapeutic strategies targeting breast cancer biomechanics. Normalization of the biomechanical microenvironment: inhibition of collagen crosslinking and fibrosis, reduction of solid stress and elevated interstitial fluid pressure, and alleviation of vascular compression to improve drug perfusion and penetration. Blockade of mechanotransduction: targeting key pathways such as integrin/FAK/Src, RhoA/ROCK, and YAP/TAZ to suppress adaptive changes in tumor cells. Optimization of drug delivery systems: increasing delivery specificity through mechanically responsive delivery systems to promote drug transport and homogeneous distribution. Mechanics-related physical therapies: using hyperthermia or ultrasound therapy to regulate cellular activity and sensitize tumors to conventional treatment.

Table 1

Comparison of the present review with representative frameworks for biomechanical regulation of therapeutic resistance

Previous conceptual framework	Main focus	Key contribution	Novelty of the present review	Reference
Physical hallmarks of cancer	Physical abnormalities in tumors, including solid stress, interstitial fluid pressure, material properties, and tissue microarchitecture.	Links the origins and consequences of tumor physical properties to progression and resistance, complementing biological hallmarks.	Uses recurrent resistance functions to link tumor physical properties with breast cancer treatment responses.	[11]
Normalization of the tumor mechanical microenvironment	Interactions among tumor mechanics, vascular function, tissue transport, and therapeutic delivery.	Explains how solid and fluid mechanics affect cell behavior and treatment outcomes, supporting vascular and ECM normalization.	Examines insufficient therapeutic exposure alongside cellular adaptation, distinguishing transport barriers from survival mechanisms under treatment pressure.	[12, 13]
Mechanically driven drug resistance in cancer	Mechanical abnormalities, mechanotransduction pathways, and resistance-associated cellular programs across cancer types.	Integrates mechanical effects on proliferation, survival, apoptosis, and phenotypic transitions, and discusses microenvironment- or mechanotransduction-targeted interventions.	Organizes breast cancer evidence around shared resistance functions, distinguishing similar outcomes from distinct mechanisms and treatment contexts.	[14]
ECM stiffness and resistance-associated mechanotransduction	Regulation of ECM stiffness, mechanosensing, downstream signaling, and therapeutic resistance.	Summarizes how stiff ECM restricts drug delivery and activates resistance signaling, and discusses ECM- and pathway-targeted strategies.	Integrates matrix stiffness, solid stress, interstitial fluid pressure, and fluid shear stress to explain similar resistance outcomes arising through distinct adaptations under different mechanical conditions.	[15]

Table 2

Characteristics and significance of the principal biomechanical forces in the breast cancer microenvironment

Biomechanical features	Representative value	Measurement subject and context	Pathological significance	Level of evidence	Reference
Matrix Stiffness	14-288 kPa	Human breast cancer tissue; in vivo shear wave elastography	Aids differentiation between benign and malignant lesions	Human correlative study	[259]
Solid Stress	2-19 kPa	Human breast cancer tissue; estimation using an ex vivo model	Intratumoral residual stress accumulation; vascular compression	Human correlative study; animal model study	[24]
Interstitial Fluid Pressure	29 ± 3 mmHg (mean ± SEM)	Human breast cancer tissue; intraoperative pressure measurement under local anesthesia	Vascular compression	Human correlative study	[260]
Fluid shear stress	Approximately 5.4 dyn/cm²	Three-dimensional breast cancer cell culture; pulsatile flow and finite element calculations	Invasion and drug resistance	Controlled perturbation experiment	[110]

Table 3

Assessment of Biomechanical Features in Breast Cancer

Detection technique	Spatial scale and invasiveness	Measured parameters and output	Standardization and reproducibility	Application scope	Level of evidence	Reference
Strain elastography (SE)	Lesion and peritumoral tissue; noninvasive in vivo	Relative strain, strain ratio, and elasticity score; qualitative/semiquantitative	Operational recommendations available; acquisition and interpretation are operator-dependent	Diagnosis; prognosis; treatment-response prediction and monitoring	Multicenter clinical studies	[183]
Shear wave elastography (SWE)	Lesion and peritumoral tissue; noninvasive in vivo	Shear wave velocity, model-derived elastic modulus, and corresponding ratios; quantitative	Operational recommendations and multicenter reproducibility validation available; cross-device consistency requires validation	Diagnosis; treatment-response prediction and monitoring	Multicenter clinical studies	[261]
Magnetic resonance elastography (MRE)	Lesion and peritumoral tissue; noninvasive in vivo	Stiffness, phase angle, and their ratios relative to baseline; quantitative	Within-study reproducibility validated; cross-platform consistency requires validation	Treatment-response prediction and monitoring	Small prospective studies	[185]
Breast tactile imaging	Local breast regions and lesions; noninvasive in vivo	Pressure distribution, stiffness-related features, and composite scores; quantitative	Device-specific scoring protocols available; cross-device consistency and reproducibility require validation	Diagnosis	Single-center clinical studies	[262]
Harmonic motion imaging (HMI)	Lesion and peritumoral tissue; noninvasive in vivo	Oscillatory displacement amplitude and displacement ratio, reflecting relative mechanical responses; quantitative	Phantom-based parameter optimization performed; clinical reproducibility requires validation	Lesion characterization; treatment-response prediction and monitoring	Small feasibility studies	[263]

Stereoscopic optical palpation	Tissue surfaces and surgical margins; ex vivo assessment of surgical specimens	Surface contact stress distribution under external compression; quantitative	Calibration protocols established; multicenter reproducibility requires validation	Diagnosis; margin identification	Clinical specimen studies	[264]
Second harmonic generation (SHG) imaging	Local tissue microstructure; ex vivo assessment of sampled tissue	Collagen alignment, tumor-associated collagen signature (TACS) features, and forward-to-backward scattering ratio (F/B); qualitative/semiquantitative/quantitative	Research acquisition and analysis protocols established; cross-platform consistency requires validation	Prognosis; treatment-response prediction	Clinical specimen studies	[186]
Polarized light imaging	Tissue sections and local microstructure; ex vivo assessment of sampled tissue	Mueller matrix elements and derived parameters, including phase retardance and depolarization; quantitative	System calibration protocols established; multicenter consistency requires validation	Diagnosis; adjunctive subtyping	Clinical specimen studies	[188]
Mechanical conditioning score (MeCo)	Tissue transcriptional profiles; ex vivo assessment of sampled tissue	Mechanical conditioning-related gene expression; molecular score	Research computational workflow established; cross-platform score consistency requires validation	Prognosis; prediction of therapeutic benefit and assessment of drug effects	Clinical specimen studies	[73]

2046