Unveiling the potential of biomechanics in pioneering innovative strategies for cancer therapy

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Abstract

Mechanical force transmission is pivotal in tumor biology, profoundly affecting cancer cell behaviors such as proliferation, metastasis, and resistance to therapy. To explore novel biomechanical-based therapeutic strategies for cancer treatment, this paper deciphers the advances in biomechanical measurement approaches and the impact of biomechanical signals on fundamental oncological processes such as tumor microenvironment remodeling, angiogenesis, metastasis, and drug resistance. Then, the mechanisms of biomechanical signal transduction of tumor cells are demonstrated to identify novel targets for tumor therapy. Additionally, this study proposes a novel tumor treatment strategy, the biomechanical regulation tumor nanotherapeutics, including smart biomaterials designed to disturb mechanical signaling pathways and innovative nanodrugs that interfere transduction of biomechanical signals to improve tumor therapeutic outcomes. These methods mark a departure from conventional pharmacological therapies to novel strategies that utilize mechanical forces to impede tumor progression and enhance tumor responsiveness to treatment. In general, this review highlights the critical role of biomechanical signals in cancer biology from a holistic perspective and underscores the potential of biomechanical interventions as a transformative class of therapeutics. By integrating mechanobiology into the development of cancer treatments, this paper paves the way for more precise and effective strategies that leverage the inherent physical properties of the tumor microenvironment.

Keywords: biomechanics, cancer, mechanosensors, mechanosignaling proteins, nanotherapeutics

61 **Graphical abstract**
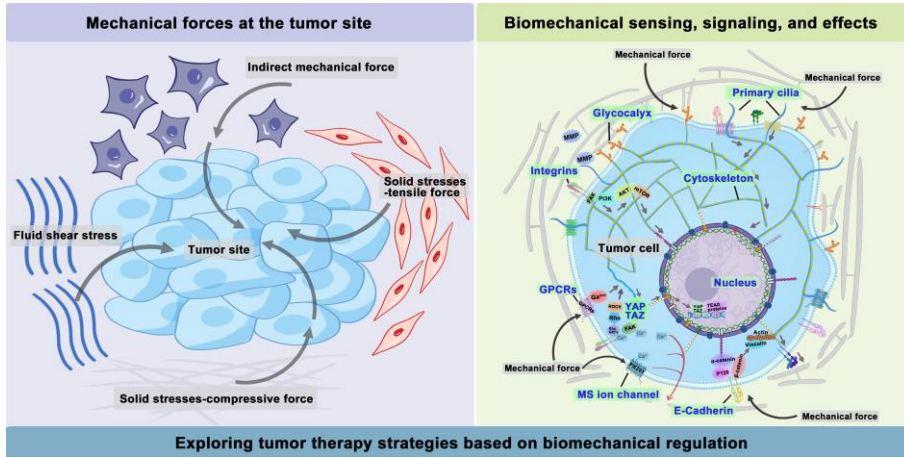
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Mechanical forces at the tumor site

Indirect mechanical force

Solid stresses -tensile force

Fluid shear stress

Tumor site

Solid stresses-compressive force

Biomechanical sensing, signaling, and effects

Mechanical force

Mechanical force

Glycocalyx

Primary cilia

Integrins

Cytoskeleton

Tumor cell

Nucleus

GPCRs

YAP TAZ

Mechanical force

MS ion channel

E-Cadherin

Mechanical force

Exploring tumor therapy strategies based on biomechanical regulation

63 (Graphics parameters,12 cm (width) × 6 cm (height), 1000 dpi)

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1. Introduction

Despite significant advancements in anti-cancer drug development, diagnostic methods, and treatment approaches, cancer continues to be the leading cause of mortality worldwide. Cancer has traditionally been understood as primarily stemming from genetic abnormalities, which trigger epigenetic changes and result in abnormal cellular behaviors [1]. However, the role of cellular physical properties in cancer initiation and progression has recently attracted scientific attention. Biomechanics, especially the mechanical microenvironment of tumors, plays an important role in cancer prediction, diagnosis, and treatment. Tumor cells inhabit abnormal mechanical microenvironments, including altered solid tumor stress, extracellular matrix (ECM) stiffness, and hydrostatic pressure [2]. Tumor cells sense and convert these mechanical signals into biochemical signals through mechanosensors, which include glycocalyx, primary cilia, cytoskeleton, and nucleus. Any disturbance to this mechanotransduction may result in tumor progression. Many biophysicists can predict cellular activities such as division, proliferation, metastasis, and drug resistance through the physical characteristics of tumor cells accurately [3, 4]. Therefore, integrating theoretical and experimental approaches from mechanics and biology into tumor biomechanics allows for a detailed investigation of the complex mechanical dynamics underlying cancer [5].

To achieve the transition from specific mechanosensitive (MS) molecules to tumor mechanomedicine, this article elucidates how the tumor mechanical environment impacts their growth and progression, from molecular and subcellular to cellular, tissue, organ, and even whole-body scales perspective. Firstly, this paper elucidates the biomechanical measurement approaches, biomechanical characteristics of tumor tissue, and how biomechanics promote tumor progression. Then, the manuscript decodes the biomechanical signaling mechanisms of cancer cells. The cellular mechanosensors in tumor cells, like glycocalyx and primary cilia, are responsible for sensing mechanical signals in the tumor microenvironment. After that, diverse mechanosignaling proteins are responsible for transmitting biomechanical signals inside tumor cells to achieve better survival. During the above process, this article summarizes a series of potential or clinically studied anti-tumor small molecule drugs that interfere with mechanical signal reception or conduction (**Table 1**). Based on the published research, this paper summarizes a novel

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103   tumor treatment strategy: the biomechanical regulation tumor nanotherapeutics, which

104   aims to achieve tumor treatment by blocking the biomechanical signal transduction through

105   the nanosystems. By adopting a holistic, interdisciplinary, rigorous investigation into the

106   biomechanics of cancer, there exists a substantial opportunity to transform established

107   therapeutic strategies. This could significantly boost cancer treatment efficacy, ultimately

108   elevating survival rates and enriching the life quality of patients.

109   *2. Biomechanical measurement approaches*

110   Accurate measurement of mechanical properties is crucial for studying tumor

111   mechanobiology. Based on the spatial and temporal scales, as well as the force sensitivity

112   characteristics of tumor tissue, various biophysical techniques, such as atomic force

113   microscopy (AFM), micropipette aspiration (MPA), and traction force microscopy (TFM),

114   have been developed to measure stiffness, viscoelasticity, or deformability, shedding light

115   on the mechanics of tumor cells [5]. To fully understand the biomechanical landscape of

116   cancer, it is important to integrate multiple techniques, each tailored to specific research

117   needs. AFM is a widely used method due to its high spatial resolution and ability to measure

118   forces at the nanoscale. It can assess mechanical properties such as Young's modulus,

119   viscosity, surface tension, and adhesion forces in both normal and pathological tissues [6,

120   7]. However, AFM is low-throughput, requires technical expertise, and has limitations

121   related to scan quality and time. MPA involves pulling a cell into a micropipette using

122   negative pressure, with the resulting deformation measured to determine properties such

123   as Young's modulus, surface tension, and intracellular pressure [5, 8]. While inexpensive,

124   MPA has low spatial and temporal resolution, and the quality of the seal between the cell

125   and the pipette can significantly affect the results [9]. Optical tweezers use focused laser

126   beams to manipulate small objects and apply forces in the femtonewton to piconewton

127   range. This technique is ideal for molecular force analysis, as it allows for precise control

128   of low forces. It is useful for studying mechanical compliance, adhesion forces, and surface

129   tension at the molecular level [5]. However, it is inherently low-throughput, as each object

130   is manipulated individually [10]. TFM measures the forces of cells exert on an elastic

131   surface. By analyzing the deformation of the substrate, the forces exerted by the cells can

132   be quantified. This technique does not require chemical perturbations, allowing for natural

133   quantification of cellular stresses. However, it requires accurate imaging of cell-substrate

134   interactions and computational methods to analyze the data [5].

135   Although these methods yield valuable insights into mechanical properties, they are

136   constrained by limitations such as spatial resolution, throughput, and the requirement for

137   direct physical contact with the sample. To overcome these issues, non-contact optical

138   techniques, such as brillouin microscopy, have emerged. Additionally, ultrasound [11] and

139   magnetic resonance imaging [12] have been used to collect mechanical data non-

140   invasively. While these methods are non-invasive, they have lower spatial resolution

141   compared to other techniques, making them less effective for cellular and subcellular

142   analysis. Furthermore, mechanical properties differ across cell types [13]. For instance,

143   varying collagen/GAG compositions in different cartilage types result in distinct mechanical

144   characteristics [14]. In summary, while current techniques provide valuable information

145   about the mechanical properties of cells and tissues, each has its strengths and limitations.

146   ***3. The role of biomechanics in tumor progression***

147   ***3.1 Biomechanical modulation of the tumor microenvironment***

148   The tumor microenvironment (TME) composed of interstitial cells and ECM is

149   characterized by a complex interaction between cells. The ECM is primarily composed of

150   intercellular matrix and basement membrane, while the interstitial cells include fibroblasts

151   and immune cells (**Figure 1**). The intercellular matrix, which includes components such as

152   collagen, fibronectins, integrins, laminins, and matrix metalloproteinases (MMPs), plays a

153   crucial role in mediating mechanical properties and is a key element of the mechanical

154   signaling pathway [15]. Unlike normal tissues, tumor tissues have a unique

155   microenvironment characterized by abnormal structures of blood and lymphatic vessels,

156   increased stromal pressure, and a dense interstitial matrix. Recent studies indicate that, in

157   addition to biochemical cues, physical signals from the microenvironment can play a crucial

158   role in influencing cellular behaviors, including growth, metastatic potential, and drug

159   resistance [2]. These physical signals mainly include solid stresses, fluid shear stresses,

160   and indirect mechanical forces (**Figure 1**).

161   Solid stress accumulates in tumors as proliferating cancer cells exert strain on the

162   surrounding structural elements of both tumor and normal tissues [16]. Solid stresses are

163   produced by mechanisms such as cell infiltration, proliferation, matrix deposition, osmotic

164   swelling of glycosaminoglycans like hyaluronic acid (HA), and actomyosin-mediated cell

165 contractions [17]. A portion of this stress arises from reciprocal forces imposed by adjacent

166 normal tissue, while the remainder is stored within the cells and matrix components of the

167 tumor. This residual stress, also known as growth-induced solid stress, persists even after

168 tumor excision and the removal of external forces [16, 18]. Elevated solid stresses within

169 tumors compress blood vessels, reducing blood flow. Concurrently, the excessive

170 deposition and cross-linking of ECM components, such as collagen, lead to ECM

171 remodeling and thus increased stiffness [19]. Therefore, tumors are always appreciably

172 stiffer than normal tissue [20].

173 Interstitial fluid, composed of water and solutes such as soluble carbohydrates and

174 plasma proteins, exists alongside a solid phase formed by the extracellular matrix. The

175 hydrostatic pressure of this interstitial fluid is referred to as interstitial fluid pressure (IFP)

176 or interstitial hydraulic pressure. Fluid shear stresses encompass microvascular and IFP

177 alongside shear forces exerted by blood and lymphatic flow on vessel walls and by

178 interstitial flow on cancer and stromal cells [21]. Elevated IFP, a distinctive feature of solid

179 tumors, results from both solid stress and fluid buildup in the interstitial space [22],

180 potentially influencing tumor cell migration through autocrine C-C chemokine receptor 7

181 signaling [23]. Additionally, IFP in the TME can guide cell movement and promote tumor

182 development. Research by Hyler *et al.* from Virginia Tech - Wake Forest University

183 highlights that even low, continuous fluid shear stress can variably impact adherent

184 epithelial ovarian cancer cells at distinct progression stages [24].

185 The growth and expansion of cells within the TME, especially local pressure variation,

186 also contributed to generating indirect mechanical forces. These forces are mediated by

187 cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs). They

188 are transmitted to mechanosensors, such as integrins, and play pivotal roles in shaping

189 the mechanical microenvironment of tumors [25].

190 ### 3.2 Biomechanics and tumor angiogenesis

191 ### 3.2.1 The effect of ECM stiffness on tumor angiogenesis

192 Solid stress from tumor cell growth leads to increased ECM stiffness and

193 compositional changes [26]. ECM stiffening enhances integrin-mediated Rho/ROCK

194 activity and contraction in tumor epithelial and endothelial cells (ECs) [27]. The

195 dysregulation of mechanical force sensing contributes to aberrant behaviors in tumor ECs,

196   resulting in abnormal structure and mechanosensitivity [27]. An *in vitro* study demonstrated

197   that elevating collagen stiffness—without altering the matrix architecture—boosted

198   angiogenic outgrowth and increased vascular branching density in endothelial cell

199   spheroids, thereby facilitating the formation of tumor vascular networks [28].

200   Increased matrix stiffness impacts the function of ECs by impairing vascular barrier

201   integrity, altering VE-Cadherin localization, enhancing permeability, and causing

202   morphological changes in tumor vessels (**Figure 2A**) [29]. Stiffness also disrupts the

203   expression of MS ion channels which regulate tumor angiogenesis. Moreover, the

204   response of ECs to growth factor signaling is closely related to ECM stiffness. In

205   hepatocellular carcinoma (HCC) cells, ECM stiffness up-regulates VEGF expression *via*

206   the integrin $\beta 1$/PI3K/Akt pathway and VEGFR2 expression in ECs through the integrin

207    $\alpha_v\beta_5$/Akt/Sp1 pathway, thus promoting angiogenesis in tumors [30, 31]. Bevacizumab, a

208   well-studied antiangiogenic agent, blocks VEGFA binding to its receptors, thereby inhibiting

209   neovascularization and signal transduction activation [32].

210   ***3.2.2 The effect of solid stress on tumor angiogenesis***

211   The accumulation of solid stress also impairs vascular flow in tumors by compressing

212   the more fragile outflow vessels, such as veins and lymphatics, thereby contributing to the

213   increased IFP (**Figure 2B**). Consequently, relieving solid stress can help decompress both

214   blood and lymphatic vessels, leading to improved perfusion and normalization of IFP levels

215   [33]. Recent studies indicate the rising solid stress can reduce vascular patency, resulting

216   in heightened tumor hypoxia [33, 34]. This initiates a harmful feedback loop [34]: tumor

217   growth induces solid stress, which in turn causes hypoxia and prompting collagen

218   remodeling. This remodeling affects angiogenesis and tumor cell invasion, thereby

219   accelerating tumor progression. Solid stresses are primarily generated within matrix

220   components, and many associated complications can be mitigated through drugs that

221   target the degradation of these matrix elements and reduce fibrosis [33]. For instance,

222   losartan, an angiotensin receptor 1 blocker, has been shown to decrease collagen I and

223   hyaluronic acid levels by inhibiting TGF-β signaling [35]. In preclinical models of pancreatic

224   ductal adenocarcinoma (PDAC), losartan alleviates solid stress and decompresses blood

225 vessels, thereby improving the efficacy of chemotherapy and extending overall survival

226 [35].

3.2.3 The effect of fluid stress on tumor angiogenesis

228 The abnormal blood and lymphatic vessel structures of tumor leads to increased

229 interstitial fluid pressure and heightened permeability of blood vessels, which allows large

230 molecules, such as plasma proteins, to cross the vascular wall and enter the tumor stroma,

231 thereby elevating the osmotic pressure within the interstitium [36]. The rapid growth of

232 tumor cells in a confined space generates internal stress, which compresses intratumoral

233 lymphatic vessels, thus leading to lymphatic dysfunction and fluid retention [37]. Fluid

234 stress within the TME increases viscous and geometric resistance to blood flow, thus

235 resulting in hypoperfusion and insufficient delivery of oxygen and nutrients [29]. This

236 process ultimately results in hypoxia and a decrease in pH levels, and tumor hypoxia

237 subsequently promotes angiogenesis [38, 39]. Elevated IFP in tumors, ranging from 4

238 mmHg to up to 60 mmHg, facilitates the outward flow of interstitial fluid from the tumor core

239 to its periphery.

240 The shear stress within tumor vessels, which is influenced by blood viscosity and

241 shear rate, is impacted by the immature and abnormal structure of these vessels [40]. The

242 endothelial lining of the vascular network demonstrates discontinuities, lacks a complete

243 basement membrane, and shows inadequate pericyte coverage. These structural

244 abnormalities lead to large pores that increase blood plasma leakage into the interstitial

245 space, thereby increasing hemoconcentration and blood viscosity [41]. In tumors, the

246 elevated IFP often surpasses microvascular pressure (MVP), which will restrict perfusion

247 and alter flow dynamics (**Figure 2C-D**). Additionally, tumor vessels may become dilated

248 and tortuous, potentially forming vascular shunts [42]. Solid stress compresses both blood

249 and lymphatic vessels, contributing to increased geometric resistance and significantly

250 reducing blood flow velocity, which can be markedly lower than that in normal vessels [43,

251 44]. This reduced shear stress in intratumoral vessels affects angiogenesis regulation and

252 contributes to abnormalities in the tumor vascular network. Fluid shear stresses specifically

253 influence VEGFR conformational shifts, tubule formation, and barrier integrity, ultimately

254 directing endothelial morphogenesis and sprouting [45].

255 In ECs, transient receptor potential vanilloid 4 serves as a mechanosensor for both

shear stress and vascular deformation, affecting tumor angiogenesis and vessel maturation. Shear stress and increased membrane tension also activate G protein-coupled receptors (GPCRs), thus triggering angiogenesis-related signaling pathways such as RhoA, PI3K, MAPK, and Akt [46]. Additionally, pharmacological activation or overexpression of transient receptor potential vanilloid 4 can normalize tumor vasculature and inhibit GPCRs, thereby reducing tumor progression and enhancing the effectiveness of cancer therapies. Tyrosine kinase inhibitors like Anlotinib target these pathways, effectively suppressing angiogenesis by blocking critical phosphorylation events within ECs. Consequently, this leads to the suppression of angiogenesis. Tumors experience a combination of mechanical forces that lead to the development of dysfunctional and leaky tumor vasculature characterized by impaired barrier function and endothelial defects [47]. The effective and consistent systemic delivery of cancer therapeutics remains a significant challenge in cancer treatment. To improve therapeutic delivery and efficacy, our group previously reviewed the clinical drugs aimed at normalizing tumor vasculature [48], including Sunitinib, Lenvatinib, and Nintedanib, which have been utilized in combination with chemotherapy to enhance the survival rates of cancer patients.

3.3 Biomechanical regulation of tumor metastasis

Tumor metastasis is primarily a mechanical process [49], in which alterations in cellular biophysical properties, matrix rigidity, and the TME play crucial roles in facilitating cancer invasion and dissemination [50]. The mechanical properties of cellular subcomponents are inherently associated with cancer tissues [5]. For instance, in breast cancer, disruptions in the actomyosin and microtubule cytoskeletons result in a disordered network, correlating with softer and more aggressive cancer cells [51]. In ovarian malignancy, reduced actomyosin contractility results in softer malignant cells, enhancing their migratory capability and aggressiveness [52]. The prevailing view is that cancer cells become softer as they acquire greater aggressiveness and revert to a stiffer state when their aggressive behavior is reduced, typically through pharmacological interventions or genetic silencing of oncogenic factors across various cancers [5]. However, it is important to recognize that this pattern is not universal. For instance, studies in pancreatic cancer have observed that tumors can become stiffer as they grow more aggressive due to the formation of an extensive and dense ECM [53, 54]. Therefore, generalizations about

287 changes in tumor stiffness should be made cautiously, given the considerable variability

288 across different cancer types.

289   Tumor growth intensifies solid stress due to increased cellular density and ECM

290 deposition, thus enhancing the invasiveness of cancer cells [15]. At the onset of tumor

291 metastasis, epithelial cells undergo a transition to a mesenchymal phenotype, thereby

292 resulting in reduced cell-cell adhesion. This process enables tumor cells to breach the

293 basement membrane and basal lamina of the primary tumor, ultimately allowing infiltration

294 into the surrounding tumor microenvironment (**Figure 3A**). After entering the tumor

295 microenvironment, metastatic tumor cells sense vascular and lymphatic endothelial cells.

296 Then, tumor cells disrupt endothelial intercellular junctions, thus facilitating their entry into

297 blood and lymphatic vessels (**Figure 3B**), through which they spread *via* the circulatory

298 system to distant organs. Several factors influence metastatic efficiency of tumor cells,

299 including shear forces and vascular architecture. Hydrodynamic shear stress is known to

300 induce the conversion of circulating tumor cells (CTCs) to less rigid cancer stem cells,

301 enhancing their ability to mimic ECs during the metastatic processes of infiltration and

302 extravasation, thereby facilitating tumor metastasis [2]. The shear forces determine how

303 long CTCs stay adhered to the vessel walls in larger vessels, potentially remaining dormant

304 and increasing their chances of extravasation (**Figure 3C**) [15]. Tumor cells increase

305 intracellular pressure to facilitate nuclear passage through constrictions, such as matrix

306 pores and intercellular gaps between endothelial cells [55, 56]. During this process, the

307 reorganization of the cytoskeleton can influence cellular stiffness and cell shape [57], thus

308 influencing the capacity of cell to penetrate complex tumor stroma or vascular walls (**Figure**

309 **3D**). Additionally, maintaining optimal tumor cell stiffness allows the tumor cells to withstand

310 high shear forces in the bloodstream while crossing endothelial junctions without incurring

311 fatal nuclear damage. At the site of vascular extravasation, the MMP secreted by tumor

312 cells can degrade ECM, reduce the solid pressure and resistance around tumor cells, and

313 thus enable tumor cells to pass through the vascular basement membrane and move

314 closer to the implantation site (**Figure 3E**). Upon reaching a favorable site, tumor cells

315 adhere to the inner lining of blood or lymphatic vessels through integrin or other adhesion

316 ligands (**Figure 3F**), thus forming secondary tumors within the lumen or extravasating

317 through the endothelium to establish secondary growths in surrounding tissues (**Figure**

318   **3G**).

319   Scientists are developing therapeutic strategies aimed at inhibiting tumor metastasis

320   through biomechanical regulation. Paclitaxel and vincristine are commonly used

321   therapeutic drugs for tumors (including ovarian, breast, and brain tumors) in clinical

322   practice, based on the mechanical mechanisms of stable or depolymerized microtubules

323   (MT), indicating that the clinical application of biomechanical therapy is becoming mature

324   [58, 59]. As our understanding of biomechanical influences deepens, it is anticipated that

325   a greater array of novel anti-tumor drugs will be integrated into clinical practice to improve

326   the management of tumor metastasis.

327   *3.4 Biomechanical regulation of tumor drug resistance*

328   Growing evidence indicates that the biomechanical microenvironment and the

329   physical properties of tumor cells are crucial in promoting tumor resistance [60]. For

330   instance, the composition, stiffness, and structure of the ECM are critical determinants

331   influencing the response of cancer cells to therapeutic agents [61]. Adhesion of cancer

332   cells to ECM components, such as collagen and fibronectin, or their growth in a stiff matrix,

333   drives resistance to chemotherapy. When the ECM is stiff, ATP-binding cassette (ABC)

334   transporters are less active and less effective at removing drugs from cells. Conversely,

335   when the ECM is more compliant or soft, ABC transporters are more active, which can

336   enhance drug clearance [62]. Hypoxia and acidity are key characteristics of tumor

337   metabolism that greatly enhance tumor resistance to radiation therapy, chemotherapy, and

338   other treatment modalities [63]. In the TME, hypoxia triggers stiffening of the ECM, further

339   enhancing the drug resistance of tumor cells [64, 65].

340   High interstitial pressure and shear stress within the tumor can alter the morphology

341   and behavior of tumor cells, thus enhancing the remodeling and adhesion capabilities of

342   the cytoskeleton [5]. This mechanical stress can activate multiple signaling pathways,

343   including yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif

344   (TAZ), which promote the survival and resistance of tumor cells [66]. Further, the stiffness

345   of the ECM can impede drug penetration into tumors. Studies on breast cancer cells have

346   demonstrated that their response to chemotherapeutic agents significantly varies with

347   substrate stiffness. While the cells cultured on substrates with increased rigidity have been

348   observed to demonstrate a heightened resistance to specific chemotherapeutic agents [67].

349   This resistance is further supported by the high deposition of collagen proteins, which bind

350   to proteoglycans and stabilize ECM components, thus enhancing its stiffness (**Figure 4A**).

351   Notably, treatment with collagenase has been shown to increase IgG diffusion to tumor

352   sites in penetration-resistant tumors [68]. In all, targeting the stiffness of the ECM could

353   offer new strategies to overcome chemoresistance.

354   Other evidence indicates that ECM stiffness modulates the activation of YAP, which is

355   significantly associated with drug resistance across various human cancer cell lines [66,

356   69]. Upon activation, the nuclear translocation of YAP may contribute to drug resistance by

357   regulating anti-apoptotic gene transcription and interacting with the MAPK and PI3K-AKT

358   signaling pathways [66]. CAFs are primary contributors to ECM stiffness during tumor

359   development. Within the TME, CAFs interact with cancer and immune cells, reshaping the

360   ECM to promote tumor progression (**Figure 4B**) [70]. Additionally, CAFs influence cancer

361   cell behavior and response to treatments through ECM remodeling [71].

362   In addition to the tumor microenvironment, drug-resistant tumor cells exhibit distinct

363   lipid metabolism from that of sensitive cells to reduce the damage caused by chemotherapy,

364   thus resulting in different lipid compositions and membrane characteristics [72]. For

365   example, drug-resistant ovarian cancer cells increase the uptake of extracellular

366   cholesterol [73], and enhance cholesterol synthesis [74], thereby elevating cholesterol

367   levels in their membranes. The high cholesterol content in the membranes of drug-resistant

368   ovarian cancer cells leads to thicker and more rigid membranes, resulting in reduced drug

369   permeability, which is one of the significant reasons for the development of drug resistance

370   in tumor cells (**Figure 4C**) [75, 76]. Moreover, the increased cholesterol and sphingolipid

371   content in the lipid rafts of drug-resistant tumor cells enhances the expression, recycling,

372   and bioactivity of multidrug resistance transporters (such as ABC transporters)

373   concentrated in these regions [77, 78]. Cholesterol can alter the rigidity and fluidity of lipid

374   rafts, thereby modifying the spatial conformation of multidrug resistance proteins within

375   their domains, making it easier for these proteins to bind and transport intracellular

376   chemotherapy drugs (**Figure 4D**) [79]. Maintaining high levels of cholesterol within the lipid

377   rafts of resistant cells is crucial for supporting the bioactivity of P-glycoprotein located

378   therein [80]. A study has shown that depleting cholesterol-enriched sphingolipid lipid rafts

379   with small-molecule drugs can successfully reverse tumor resistance [81]. In general,

380 targeting the mechanical properties of tumor cells offers a promising strategy to overcome

381 drug resistance.

382

4. Decoding biomechanical signaling mechanisms of cancer cells

4.1 Tumor cellular mechanosensors

385   The study of tumor cellular mechanosensors opens a crucial pathway for

386 understanding the intricate mechanisms through which cancer cells perceive and react to

387 biomechanical forces within their microenvironment. Tumor cellular mechanosensors

388 primarily consist of the glycocalyx, primary cilium, cytoskeleton, and nucleus. Glycocalyx

389 is the sugar and glycoprotein covering layer on the outside of the cell membrane. Primary

390 cilium is a tiny protrusion on the cell membrane, and the cell membrane is the base of

391 glycocalyx and primary cilium. The cytoskeleton is intricately linked to the cell membrane

392 and the basal body of the primary cilium, which offers essential structural support for both.

393 It not only senses mechanical signals but also plays an important role in transmitting these

394 signals.

4.1.1 Glycocalyx

396   Glycoproteins and proteoglycans represent the predominant glycan categories within

397 the glycocalyx (GCX) [82]. Proteoglycans are composed of core proteins attached to

398 glycosaminoglycan (GAG) chains, including heparan sulfate (HS) and HA, as well as

399 sialoglycoproteins. The GCX, interfacing directly with the ECM, plays an essential role in

400 mediating integrin adhesions to the ECM and in responding mechanically to environmental

401 stiffness (**Figure 5A**) [83]. Furthermore, the specific composition and size of the GCX

402 influence the extent of mechanosensing experienced by cell-bound integrins upon

403 contacting the ECM [84]. Notably, bulky cancer-associated glycoproteins like MUC1 are

404 known to facilitate integrin clustering and enhance mechanosensing capabilities [85].

405 Research indicated that overexpressing MUC13 in Panc-1 cells typically reduced their

406 modulus and diminishes adhesion. Conversely, knocking down MUC13 in HPAF-II cells

407 leads to increased modulus and enhanced adhesion [86]. Therefore, it is speculated that

408 tumor cell-cell adhesion can be enhanced and invasiveness can be reduced by reducing

409 the volume or directly knockdown of the expression of GCX.

410   The GCX on cancer cells is notably dense, aiding in integrin clustering, growth factor

signaling, and mechanotransduction of elevated interstitial flow shear stress within tumors. This process subsequently promotes release of MMPs, which will enhance cell motility and metastasis [82]. Research by Qazi *et al*. from City University of New York indicated that such interstitial flow notably increased migration in SN12L1 cells (high metastatic potential) of human kidney carcinoma lines, unlike in SN12C cells (low metastatic potential) [87]. Specifically, the expression of MMP-1, MMP-2, CD44, and α3 integrin were upregulated by interstitial flow in SN12L1 cells, while it remained unchanged in SN12C cells. Moreover, enzymatic cleavage of GCX components, such as HS or HA, inhibited flow-induced migration and MMP expression in SN12L1 cells. This suggests that the GCX in cancer cells serves as a mechanosensor for interstitial flow shear stress, coordinating the expression of MMP-1, MMP-2, CD44, and α3 integrin to control cell migration and metastasis. Additionally, 4-Methylumbelliferone inhibits HA synthesis by downregulating HA receptors and the phosphatidylinositol 3-kinase/CD44 complex [88]. The anti-CD44 monoclonal antibody A6 has been shown to inhibit tumor cell migration, invasion, and metastasis by blocking CD44-mediated signaling pathways [89].

Understanding the MS and transductive functions of the GCX on tumor cells have paved the way for innovative cancer therapeutic strategies. First, modulating GCX mechanotransduction will block GCX-mediated adhesive interactions, which will reduce tumor cell extravasation, potentially halting metastasis and improving patient survival rates [90]. Second, reducing the thickness of the GCX enhances immune recognition by natural killer cells, which can be achieved by degrading the GCX, thereby augmenting the cytotoxicity of these immune cells [91]. Lastly, editing the composition of the GCX through self-executed feedback loops presents a novel and manageable approach to cancer treatment [92].

4.1.2 Primary cilia

Primary cilia (PC) consist of a microtubule-based core, called the axoneme, which extends from a specialized centriole known as the basal body and is enclosed by a lipid bilayer continuous with the cell membrane (**Figure 5B**). Despite their small size, PC constitutes approximately 1/200 total surface area of the cell. The PC are critical for both development and homeostasis of the body. These structures are densely packed with receptors, ion channels, and downstream signaling molecules critical for numerous

442   pathways, such as Hedgehog and GPCR signaling. The absence of this antenna-like

443   structure results in improper signaling activation. Consequently, mutations that disrupt the

444   assembly, structure, or function of cilia impair the transmission of mechanical signals,

445   resulting in ciliopathies—a diverse group of over 30 human diseases and syndromes

446   affecting various organs and tissues, including the eye, heart, kidney, brain, liver, and bone

447   [93].

448   Under fluid flow stimulation, PC deflect, transmitting mechanical strains *via* the

449   cytoskeleton to critical cytoplasmic organelles like the Golgi complex, which governs the

450   response of cell to mechanical stimuli. Modifying the length and rigidity of PC can influence

451   this cellular mechanosensitivity [94]. Notably, primary cilia are frequently absent in various

452   cancers [95], including glioblastoma, melanoma, pancreatic, prostate, ovarian, colon,

453   breast, medulloblastoma, and renal cancers, as opposed to their presence in normal tissue

454   [96]. In cholangiocarcinoma cases without primary cilia, inhibiting histone deacetylase 6, a

455   protein involved in cilia disassembly, has been shown to restore cilia formation and

456   suppress tumor growth [97].

457   Approximately 25% of tumors in patients with PDAC exhibit PC. The presence of PC

458   is associated with an increased incidence of lymph node metastasis [98]. Research by

459   Martínez-Hernández et al. from Spain demonstrated a marked elevation in PC levels in

460   pituitary neuroendocrine tumors (PitNETs), which was associated with increased tumor

461   invasiveness and higher recurrence rates[99]. Additionally, molecular analysis revealed the

462   dysregulation of 123 cilia-associated genes, including doublecortin domain containing

463   protein 2, syntaxin-3, and centriolar coiled-coil protein 110 in PitNETs. Moreover, an

464   increase in both the formation and length of primary cilia has been observed in cancer cells

465   that exhibit resistance to anti-cancer drug kinase inhibitors [100]. Thus, regarding a clear

466   link between PC and tumorigenesis, the impact of PC on cancer progression may differ

467   depending on the specific type and stage of the cancer. Regulating the expression and

468   mechanical properties of PC holds the potential to unveil new therapeutic strategies, given

469   their pivotal role in biomechanical signal transduction and resistance to chemotherapy in

470   cancer cells. Future investigations might focus on accurately modulating these structures

471   to enhance therapeutic outcomes and curtail tumor progression.

472   **4.1.3 Cytoskeleton**

473   The primary components of cytoskeleton include MTs, actin filaments, and

474   intermediate filaments. It not only senses and transduces mechanical stress but is also

475   influenced by external forces from the ECM (**Figure 5C**) [101]. When mechanical forces

476   are applied to cancer cells, actin filaments act as mechanosensors that detect these forces

477   [102]. These filaments generate contractile forces through interactions with myosin II and

478   through polymerization, which drives the forward movement of the plasma membrane [103].

479   MTs are essential in aligning chromosomes and organizing the spindle in response to

480   mechanical forces during mitosis [104]. In tumor cell migration, MTs facilitate pseudopodia

481   formation, which reacts to mechanical signals from the TME [105]. Intermediate filaments,

482   recognized for their stability and durability, are critical in sensing the magnitude and

483   direction of mechanical forces encountered by cancer cells. As tumors progress, the

484   cytoskeleton undergoes continual remodeling, allowing tumor cells to develop distinctive

485   mechanical properties and adapt to the dynamic shifts within their microenvironment [106].

486   During tumor progression, tumor cells actively remodel their cytoskeletal structures and

487   decrease cellular stiffness [107]. As tumor cells enter and exit the vascular system, they

488   experience significant shape alterations facilitated by cytoskeletal remodeling, which

489   enable them to traverse endothelial cell-cell junctions [108]. Research by Liu *et al*. from

490   Chengdu Medical College has shown that low shear stress markedly enhances both the

491   percentage and length of filopodia, which are vital for cancer cell mobility and can trigger

492   migration[109]. However, shear stress may also influence tumor progression through

493   synergistic interactions with chemical factors like chemokines or growth factors, and

494   mechanical factors such as matrix stiffness. Further research is needed to elucidate the

495   complex tumor microenvironment's impact. Recent findings indicate that the cytoskeletal

496   structure and biophysical characteristics of breast cancer subgroups are linked to their

497   metastatic preference, regarding the gene expression profiles and mechanoadaptation

498   capacities [110]. Therefore, by increasing the shear stress and inhibiting Cdc42, filopodia

499   is greatly reduced, thereby reducing tumor metastasis.

500   Modulating the mechanical properties of the cytoskeleton is a promising strategy for

501   tumor therapy. A research obstacle is to develop equipments capable of measuring and

502   applying forces. Future studies should focus on integrating mechanotransduction research

503   with therapeutic interventions by identifying key molecules that promote cell health or treat

504　diseased cells. Additionally, it is important to understand how cellular mechanosensors

505　interact with the tumor microenvironment to activate cytoskeletal movements. This will

506　require a multidisciplinary approach to model mechano-responses and develop treatments

507　that can reverse cancer pathologies.

508　***4.1.4 Cell nucleus***

509　　　The nucleus, notable for being both the largest and stiffest organelle, is also highly

510　dynamic, capable of sensing external mechanical cues and adapting rapidly [111, 112]. The

511　nucleus plays an integral role in mechanoregulation, which encompasses both

512　mechanosensing and mechanotransduction processes (**Figure 5D**). Surface

513　mechanoreceptors detect these cues and transmit signals to the nucleus, influencing

514　cytoskeletal integrity and tension. This leads to adjustments in gene expression related to

515　mechanical stimulation [113]. Changes in nuclear mechanics, such as those induced by

516　the ECM, can influence the morphology of nucleus and localization of transcription factors

517　[114]. Cellular adaptations to matrix tension involve alterations in lamin A phosphorylation

518　and nuclear positioning, which are regulated *via* the mechanotransduction pathways of

519　YAP and retinoic acid receptor (RAR), ensuring cytoskeletal equilibrium [45]. Cells adapt

520　to matrix tension by modifying lamin A phosphorylation and nuclear positioning, and

521　maintain cytoskeletal balance through the mechanosignaling routes of YAP and RAR [114].

522　　　Cell spreading and nuclear stretching activate MS calcium channels on the nuclear

523　membrane, leading to an increase in nuclear calcium levels. This increase causes elevated

524　levels of the transcription factor CREB, which is vital for regulating gene transcription,

525　protein import, apoptosis, and subsequent mechanosignaling processes [115, 116]. The

526　phosphorylation of Lamin A/C and Emerin within the nucleus responds to mechanical

527　stimulation by altering nuclear stiffness and nucleo-cytoskeletal coupling [114]. Further,

528　changes in chromatin organization, condensation, and modification are influenced by the

529　actin cytoskeleton and the linker of nucleoskeleton and cytoskeleton complex [117, 118].

530　　　Cytoskeletal contraction also triggers adenosine triphosphate (ATP) release and

531　calcium signaling, which facilitate the nuclear import and activation of histone modifiers,

532　such as enhancer of zeste homolog 2 and histone deacetylase [117, 118]. These processes

533　drive cancer-related gene silencing and transcriptional regulation through alterations in

534　histone methylation [119] and acetylation [120]. Furthermore, polymerization of nuclear

18

actin adjusts nuclear structure and transcription factor functionality, influencing gene expression through enhanced nuclear transport mechanisms [121]. Softer nuclei, characterized by reduced levels of lamin A/C, are more susceptible to rupture and subsequent DNA damage during migration [122]. In contrast, cells with stiffer nuclei, induced by progerin, also exhibit increased DNA damage [123]. This paradox highlights the complex role of nuclear mechanics in cellular health. The research conducted by Nava *et al.* from University of Helsinki demonstrated that mechanical stretching of the nucleus induced a calcium-dependent softening mediated by chromatin alterations, and inability to initiate the nuclear MS response led to DNA damage [124]. Subsequent DNA damage response reorganizes the nucleus, altering chromatin structure to facilitate more efficient DNA repair, which may inadvertently contribute to chemotherapeutic resistance [125].

4.2 Mechanosignaling proteins

In addition to cellular mechanosensors, a range of mechanical signals are perceived and relayed to cells *via* the activation of surface mechanosignaling proteins like integrins [83], YAP/TAZ [126], transient receptor potential (TRP) ion channels [127], GPCRs [128], and Piezo channels [129]. The mechanosignaling proteins transmit these cues to cellular internal components, thus influencing the behavior of tumor cells.

4.2.1 Integrins

Integrins, which are transmembrane proteins, bind to diverse ECM proteins and play a pivotal role in detecting changes in the extracellular environment (**Figure 5E**). These proteins are critical for cell adhesion and signal transduction. They facilitate the detection of the mechanical properties within the ECM and relay these signals to focal adhesion kinase (FAK). This interaction strengthens focal adhesions and triggers subsequent intracellular signaling pathways [130]. In the TME, FAK influences both cancer and stromal cells, enhancing tumor progression and metastatic potential [131].

Integrin-mediated adhesions engage with the ECM and respond to its rigidity, consequently influencing cellular activities including motility and migration [132]. Integrin interactions with specific ECM components trigger outside-in signaling that regulates the cytoskeleton. Concurrently, mechanical forces generated by the cytoskeleton are transmitted back to integrin-ECM interactions, promoting cancer metastasis [133]. Several clinical studies have linked high integrin expression to poor cancer survival [106]. Integrin-

566 mediated mechanotransduction reciprocally affects the mechanical properties of the TME.

567 In non-small cell lung carcinoma cells, the absence of integrin α11 is associated with

568 reduced collagen reorganization and lower tissue stiffness, which in turn inhibits cell growth

569 and metastatic potential [134]. This phenomenon highlights the pivotal role of stromal

570 integrin α11 expression in collagen cross-linking. In colon cancer cells, integrins are

571 responsive to mechanical stimuli, particularly shear stress, which leads to the

572 downregulation of integrin β1-FAK signaling, subsequently enhancing the cytotoxic effects

573 of radiation [135]. The deregulation of integrin signaling, facilitated by alterations in the

574 ECM and integrin diversity, allows cancer cells to rapid cell proliferation, invade tissues,

575 and adapt to different environments [136]. As a result of dynamic remodeling of the ECM,

576 tumor cells change in density, hardness, or tissue composition. For instance, the

577 progression of breast cancer is associated with elevated mechanosignaling and increased

578 tissue birefringence, suggesting that ECM hardness promotes malignancy and increases

579 tumor aggressiveness [137]. Moreover, hypoxia-inducible factor 1 upregulates the

580 expression of lysyl oxidase which enhances the crosslinking of collagen fibers. This

581 process increases the stiffness of the TME, which in turn enhances integrin-mediated

582 signaling and promotes cell proliferation [138].

583   During the early stages of tumorigenesis, neoplastic conversion significantly impacts

584 the expression levels of specific integrins, resulting in changes to the integrin profile on

585 cancer cells. It triggers modifications in integrin signaling pathways that facilitate the

586 advancement of neoplastic transformation [139]. Oncogenic signaling plays an important

587 role in driving these alterations. For example, in terms of ovarian cancer, mutant p53

588 operates via integrin $\alpha_5\beta_1$ to enhance the expression of the epithelial-mesenchymal

589 transition (EMT) transcription factor TWIST1. This process promotes the formation of tumor

590 cell clusters that penetrate the mesothelium and subsequently proliferate into peritoneal

591 tumors [140]. However, certain integrins, like $\alpha_2\beta_1$, may impede tumor progression,

592 highlighting the complex and variable roles of integrins in cancer [141]. Given their

593 overlapping functions in adhesion and signaling, it is challenging to develop specific

594 inhibitors and sensitive biomarkers. Over the past 30 years, many drug discovery projects

595 and clinical studies have focused on integrins. However, the approved anti-cancer drugs

596 targeting integrins are limited [142]. Therefore, a comprehensive investigation into integrin

597 dependency across various cancer types, coupled with biomarker development using

598 genetically engineered and patient-derived xenograft models, is essential for advancing

599 integrin-targeted cancer therapies.

600 ***4.2.2 Cadherins***

601 Cadherins, such as E-, VE-, N-, R-, P-, and K-cadherin, are transmembrane proteins

602 that function as cell-cell interaction receptors and enable calcium-dependent adhesion

603 [143]. In tumors, cadherins act as critical mechanosensors that detect and convey

604 mechanical signals from neighboring cells (**Figure 5F**). The cadherin cytodomain connects

605 to the actin cytoskeleton through β-catenin and α-catenin, thereby regulating

606 mechanotransduction [144]. Among the classical family of cadherins, E-cadherin plays a

607 central role as a mechanosensor by both sensing and facilitating the transmission of

608 mechanical forces [145]. The force transduction mediated by E-cadherin influences various

609 cellular functions. It activates signaling *via* the epidermal growth factor receptor (EGFR),

610 which governs local cytoskeletal restructuring and promotes cellular proliferation [146]. E-

611 cadherin is identified as a tumor suppressor protein, and its decreased expression

612 associated with the EMT is a common occurrence in the process of tumor metastasis. By

613 enhancing E-cadherin expression, α-solanine (a glycoalkaloid extract of Solanum nigrum

614 Linn) inhibited endothelial cell transformation and exhibited potent anti-carcinogenic

615 properties [147].

616 Moreover, the internalization of E-cadherin in response to blood flow may represent

617 an adaptive metastatic mechanism that enhances cellular motility and invasion [148].

618 Concurrently, a stiffer ECM elevates N-cadherin expression on endothelial cells, enhancing

619 their interaction with tumor cells and vascular endothelium to facilitate metastasis [149].

620 Additionally, E-cadherin affects the activity of transcriptional coregulators such as catenins

621 and YAP. Under biaxial mechanical stretch conditions, YAP and β-catenin, which are

622 components of the cadherin complex, promote cell cycle progression in an E-cadherin-

623 dependent manner [150]. The modulation of actin cytoskeleton rigidity influences the

624 interaction between APC and β-catenin, thereby affecting the localization of β-catenin

625 within the nucleus or cytoplasm. The suppression of β-catenin–mediated transcription

626 impeded the progression of the cell cycle from the G1 phase to the S phase [150]. Moreover,

627 the cadherin-mediated mechanical force transmission, especially *via* the N/E-cadherin

628 complex, is key to tumor cell migration and invasion. Inhibiting this complex can reduce

629 interactions between mesenchymal-like and epithelial-like cancer cells, thus decreasing

630 tumor aggressiveness [151]. Overall, the cell-cell interaction mediated by cadherin is

631 crucial for the migration, survival, and proliferation of cancer cells. However, the specific

632 impact of cadherin-driven mechanotransduction on tumor progression *in vivo* warrants

633 further exploration.

634 ### *4.2.3 Mechanosensitive ion channels*

635 During tumor progression, mechanical cues activated by MS ion channels influence

636 both the cancer cells and their surrounding microenvironment. These mechanical signals

637 are converted into cellular responses, including proliferation (**Figure 5G**) [152]. MS ion

638 channels, including epithelial sodium channels, TRP channels, two-pore domain potassium

639 channels, and Piezo channels, convert mechanical stimuli at the cell membrane into

640 biochemical signals *via* mechanotransduction [5, 153].

641 Piezo1 and Piezo2, the primary mechanosensors in mammals, facilitate cellular

642 adaptations to mechanical forces [153]. Their upregulation is linked to increased

643 proliferation, migration, and invasion in tumor cells, suggesting their potential as

644 therapeutic targets in cancer [154, 155]. Changes in the matrix microenvironment may

645 result in the overexpression of certain MS ion channels, including Piezo1. Specifically, the

646 study by Chen *et al*. from hospital for sick children in Canada demonstrated that Piezo1

647 activation could initiate integrin-FAK signaling, influence ECM composition, and contribute

648 to tissue stiffening. Meanwhile, the stiffer environment increased the expression of Piezo1,

649 inducing glioma aggression [156]. Thus, targeting Piezo1 offers a potential strategy to

650 interrupt the harmful feedback loop between the mechanotransduction of tumor and

651 abnormal tissue mechanics [156]. Mechanical stimuli, including stretch and compression,

652 activate Piezo1 and its associated signaling pathways, such as the Akt/mTOR pathway in

653 prostate cancer [106], thereby promoting cell cycle progression and enhancing tumor cell

654 invasion as well as matrix degradation. Additionally, Piezo1-mediated calcium influx

655 induced by circulatory shear stress increases susceptibility of cancer cells towards TRAIL-

656 induced apoptosis [157], underscoring the potential of targeting Piezo1/2 in cancer therapy.

657 As cationic channels, TRP proteins could be activated by physicochemical stimuli to

658 regulate diverse sensory capabilities which are associated with various cancers[158].

Among them, transient receptor potential melastatin 7 (TRPM7) is a MS TRP ion channel, whose expression is notably altered in various cancers [159]. High TRPM7 levels are linked to EMT pathway activation and are associated with reduced disease-free and overall survival in ovarian cancer cells [160]. Additionally, TRPM7 is essential for activating Notch and JAK/STAT3 pathways in glioblastoma, increasing the levels of cancer stem cell marker ALDH1 [159]. Above all, these insights underscore the potential of MS ion channels as key targets in the development of novel cancer therapies, leveraging their MS properties to counteract tumor progression.

4.2.4 G protein-coupled receptors

GPCRs constitute the largest family of membrane receptors, characterized by diverse intracellular signaling properties that originate from the activity of G-protein subunits [161]. GPCRs have been postulated independently to mediate mechanotransduction [162] and to facilitate changes in cell shape (**Figure 5H**) [163]. Recently, the function of GPCRs as mechanosensors in cancer cells has been progressively demonstrated [106]. Yang *et al*. [164] from first affiliated hospital of Xi'an Jiaotong University showed a member of the GPCR family, C-X-C chemokine receptor type 4 (CXCR4), acted as a crucial intracellular signal transducer to regulate mechano-sensitive cellular activities through YAP signaling pathway mediated by ubiquitin domain-containing protein 1. Their study demonstrated that the expression of CXCR4 was significantly upregulated in HCC cells as matrix stiffness increased, driving cell growth, EMT, and cancer cell stemness. Notably, luteolin, a natural compound, was found to suppress the effects induced by matrix stiffness and block the CXCR4-driven YAP signaling pathway within HCC cells [164].

Evidence suggested that targeting GPCR function could effectively slow or prevent the progression and metastasis of various cancers [165]. GPCRs, such as those responsive to chemokines, thrombin, and neuropeptides, represent promising targets for pharmacological interventions in cancer prevention and therapy [165]. Studies by Liu *et al*. from Kunming University of Science and Technology have demonstrated that GRPR-specific inhibitors could significantly reduce tumor growth and angiogenesis, highlighting their potential in clinical cancer management [166]. Despite GPCRs being crucial drug targets, their exploitation as cancer targets is limited, with few anti-cancer compounds that modulate GPCR-mediated signaling currently in clinical use [166]. Maraviroc, an FDA-

approved antagonist of the C-C chemokine receptor 5 (CCR5), showcases the potential of small molecules in inhibiting GPCRs [167, 168]. A phase I trial confirmed the anti-tumor effects of a CCR5 antagonist in patients with advanced, refractory colorectal cancer and liver metastases [169]. In general, GPCRs play a crucial role in transducing mechanical signals within tumor cells. Moreover, combinatorial immunotherapies that target GPCRs are emerging with promising effects for cancer treatment, highlighting the potential of GPCRs in mechanotransduction and cancer cell behavior [170].

4.2.5 YAP/TAZ

YAP and the transcriptional coactivator TAZ function as mechanosensors and mechanotransducers, responding to ECM stiffness, cell morphology, and cytoskeletal tension, which are essential for nuclear localization (**Figure 5I**) [171]. YAP/TAZ activity is closely linked to the structure of the actin cytoskeleton, which reinforces membrane-cytoskeleton integrity and supports cancer cell viability during metastasis [172]. These proteins are central to tumor morphogenesis by reshaping the TME to promote growth and evade immune surveillance, influencing not only tumor cells but also surrounding fibroblasts, immune, and endothelial cells [69].

YAP/TAZ are frequently deregulated in cancer due to alterations in mechanotransduction, inflammation, oncogenic signaling, and inhibition of the Hippo pathway [173]. This deregulation enhances force transmission between oncogene-expressing cells and the ECM, facilitating tumorigenesis through YAP/TAZ mechanotransduction [174]. YAP additionally stimulates the expression of cytoskeletal regulators, which allows fibroblasts to increase matrix stiffness and facilitate cancer cell invasion [175].

Targeting YAP/TAZ could be a viable cancer treatment strategy. IAG933, an inhibitor developed by Novartis targeting YAP/TAZ-mediated transcription, is currently undergoing a phase I clinical trial for tumors with YAP/TAZ gene fusions (NCT04857372) [69]. Similarly, VT3989 from Vivace Therapeutics is undergoing a Phase I trial for solid tumors and mesotheliomas with NF2 mutations (NCT04665206) [69]. Drugs like dasatinib, targeting SRC family members, also show potential in inhibiting YAP/TAZ activity in both laboratory and clinical settings [176]. However, the clinical efficacy of these treatments has been variable, indicating a need for continued research into effective YAP/TAZ inhibitors [176].

While research is still in its early stages, these studies are expected to be crucial for developing new anti-tumor drugs and treatment strategies in the future.

4.2.6 Other mechanosignaling proteins

Rho GTPases, a family of small G proteins, are essential regulators of cytoskeletal dynamics, cell polarity, motility, vesicular transport, cell cycle progression, differentiation, and gene expression [177]. Activation of growth factor receptors and integrins promotes the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP) on Rho proteins, allowing GTP-bound Rho proteins to interact with effectors that regulate their activity and localization [178]. In humans, around 20 kinds of Rho GTPases have been identified, with RhoA, Rac, and Cdc42 being the most extensively studied. These proteins are key in remodeling actin-rich cytoskeletal structures and regulating cell contractility, influencing many cellular processes [179]. In cancer, Rho GTPases are typically overexpressed [177]. The overexpression of active RhoA, RAC1 [180], or Cdc42 [181] in rodent fibroblasts enhances anchorage-independent growth and tumorigenesis. Furthermore, effectors such as Rho-associated coiled-coil-containing protein kinase (ROCK) and p21-activated kinases (PAKs) play an important role in cellular transformation; elevated levels of ROCK2 have been associated with high-risk neuroblastoma and adverse patient outcomes, indicating that ROCK inhibitors could offer therapeutic benefits [182]. Targeting these regulators, either alone or combined with MAPK or SRC therapies, may offer effective treatment options. Recently, small-molecule inhibitors of Rho GTPases have shown promise *in vitro* and *in vivo* [183]. For example, AZA1, a specific inhibitor of Cdc42/RAC1, effectively suppresses prostate cancer growth *in vivo* and improves survival in mouse models [184].

Research has demonstrated that forces applied to the cell surface can transmit to chromatin *via* the cytoskeleton and nuclear proteins, leading to chromatin stretching and activation of gene expression [15]. Nuclear proteins primarily regulate gene expression, translation, and related processes [185]. Abnormal expression of certain nuclear proteins is associated with tumorigenesis, drug resistance, and metastasis [186, 187]. Notably, mutations in these proteins can affect nuclear mechanics and cytoskeletal organization, influencing various cellular functions [188]. For example, mutations in nuclear envelope proteins disrupt mechanotransduction signaling and force transmission [189]. Poh *et al*.

from University of Illinois at Urbana-Champaign [190] found that applying excessive force led to rapid and irreversible dissociation of survival of motor neuron from coilin in the Cajal body of HeLa nuclei [190]. This dissociation was sensitive to substrate stiffness, suggesting that sufficient cytoskeletal tension is essential for transmitting forces to the nucleus and inducing deformations [191]. Since Cajal body interact directly with chromatin, these results indicate that force-induced dissociation of nuclear proteins can alter gene expression. Further studies are necessary to determine the functional consequences and longevity of these transcriptional changes [192].

In general, mechanosignaling proteins are being recognized for their pivotal roles in the occurrence and progression of tumors [5]. Additionally, these proteins that influence the mechanosensitivity and mechanotransduction of cancer cells represent potential therapeutic targets. Numerous agents that block mechanosignal transduction have already entered clinical trials (**Table 1**). As research advances, biomechanical regulation strategies are expected to pioneer new avenues for cancer therapy.

5. Biomechanical regulation tumor nanotherapeutic strategies

Nanotechnologies offer transformative potential in biomechanical regulation for tumor therapy by targeting the mechanical characteristics of TME and cancer cells. Such technologies enable precise control over cellular biomechanics, which is crucial for developing effective therapies. For example, the unique enhanced permeability and retention (EPR) effect of tumor tissue can retain more nano-sized systems, thereby achieving passive drug enrichment in the tumor site; targeted drug delivery systems can selectively interact with primary cilia or cytoskeletal components, thus enhancing the therapeutic efficacy on tumor; advances in molecular self-assembly technologies and mechanical modulation of the ECM hold promise for disrupting tumor progression and improving treatment outcomes [193]. In this context, we delineate innovative therapeutic approaches leveraging nanotechnology to modulate the perception and transduction of tumor biomechanical signals. These strategies are designated as biomechanical regulation tumor nanotherapeutic strategies (**Table 2**).

5.1 Interfering primary ciliary biomechanical function

Primary cilia play a role in sensing chemical and mechanical signals. Compounds that

regulate cilia length can enhance mechanosensitivity [194]. In glioblastoma, primary cilia formation is reduced. Loskutov et al. from Virginia University School of Medicine [195] reported that lysophosphatidic acid receptor 1 (LPAR1) accumulates in cilia, where it binds lysophosphatidic acid (LPA) to promote cell proliferation. When cilia are lost, LPAR1 moves to the plasma membrane, driving tumor cell proliferation. The small molecule Ki16425 inhibits LPA signaling and suppresses glioblastoma growth. In a mouse model, Ki16425-loaded nanoplatforms significantly reduced tumor progression, suggesting a potential therapeutic strategy for glioblastoma.

Primary cilia are cell organelles that expose themselves to the extracellular lumen, providing an important access to target the cilia. With a diameter of about 250 nm, primary cilia make nano-sized particles promising vehicles for drug delivery. In a study, Pala *et al*. from University of California Irvine reported a kind of cilia-targeted (CT) nanoparticles for the precise delivery of the therapeutic drug (fenoldopam), termed CT-Fe_2O_3-NPs (**Figure 6A-B**) [196]. High-resolution differential interference contrast imaging was used to locate cilia and assess the selectivity and specificity of CT-Fe_2O_3-NPs. Results indicated that both control CT-Fe_2O_3-NPs without fenoldopam (cCT-Fe_2O_3-NPs) and CT-Fe_2O_3-NPs exhibited specific CT delivery; however, only CT-Fe_2O_3-NPs containing fenoldopam significantly increased cilia length (**Figure 6C-D**). Notably, CT-Fe_2O_3-NPs also enabled remote manipulation of cilia movement and function *via* an external magnetic field (**Figure 6E**). Cilia function was assessed by monitoring changes in cytosolic Ca^{2+} concentrations. Application of a magnetic field caused significant cilia bending and a sustained rise in Ca^{2+} signaling within both the cilioplasm and cytoplasm in cells treated with cilia-targeted nanoplatforms, compared to controls (**Figure 6F**). In the *in vivo* study, localization of CT-Fe_2O_3-NPs in the vascular endothelium was confirmed at 24 h and 72 h post-injection. Cilia length was notably increased in mice treated with CT-Fe_2O_3-NPs or CT-M-Fe_2O_3-NPs (under magnetic field exposure) but not in those receiving a 30-min fenoldopam infusion (**Figure 6G**). The results in this section demonstrated that controlling ciliary movement to block the conduction of mechanical signals can achieve efficient tumor treatment.

5.2 Interfering protein biomechanical sensing-transduction function

The oncogenic activity of YAP is controlled by the Hippo kinase cascade and mechanical-force-induced actin remodeling. Li *et al*. from Okinawa Institute of Science and

814   Technology Graduate University developed molecular self-assembly technology to

815   selectively inhibit cancer cell proliferation by inactivating YAP (**Figure 7A**) [193]. In this

816   study, a ruthenium-complex-peptide precursor molecule was engineered to self-assemble

817   into nanostructures under alkaline phosphatase action (**Figure 7B**). These nanostructures

818   were designed to stabilize the lipid rafts of ovarian cancer cells. Upon stabilization, they

819   trigger actin cytoskeleton remodeling (**Figure 7C**), with a particular focus on disrupting F-

820   actin. This actin reorganization subsequently activates LATS, promoting YAP

821   phosphorylation through Hippo signaling. To confirm YAP inactivation, time-lapse

822   immunofluorescence staining of YAP in SKOV3 cells was conducted following 3a

823   incubation, revealing clear inhibition of YAP nuclear translocation after 12 h (**Figure 7D**).

824   Enhanced YAP phosphorylation deactivates YAP, suppressing TEAD-mediated target

825   genes such as connective tissue growth factor (CTGF) and CYR61 (**Figure 7E**), ultimately

826   inhibiting cancer cell proliferation *in vitro* and reducing ovarian tumor growth *in vivo*.

827   Molecular self-assembly technology has demonstrated strong anti-proliferative effects

828   in various cancer cell lines and mouse xenograft models. In SKOV3-Luc xenograft mice,

829   untreated tumors continued to grow throughout the 24-day observation period, while 3a-

830   treated mice showed dose-dependent tumor suppression as early as 4 days post-injection.

831   A 25 mg/kg dose of 3a reduced mean tumor volume by about 60% by day 16 compared to

832   controls. By day 24, tumor volume was reduced by 45% and 60% in groups receiving 25

833   mg/kg and 50 mg/kg doses, respectively (**Figure 7F-G**). In summary, this strategy, which

834   inhibits tumor growth by modulating YAP activity, offers a promising biomechanical

835   regulatory approach to tumor nanotherapeutic strategy.

836   ***5.3 Interfering cytoskeletal biomechanical sensing-transduction function***

837   ***5.3.1 Electrostimulation disrupts cytoskeletal structure and function***

838   Based on the literature, it has been observed that tumor cells exhibit a comparatively

839   higher susceptibility to external stimulation than normal cells, particularly with regards to

840   their cytoskeletal structure [197]. For instance, Jin's group from State Key Laboratory of

841   Electroanalytical Chemistry of Chinese Academy of Sciences [198] demonstrated that

842   electrostimulation (ES) significantly inhibits glucose and energy metabolism in cancer cells,

843   resulting in rapid cell death (**Figure 8A-C**). From a mechanical perspective, ES leads to

844   cytoskeletal disruption (**Figure 8D**), which reduces the Young's modulus of MCF-7 cell

membranes (**Figure 8E**) due to the depolymerization of F-actin and the down regulation

and irregular distribution of glucose transporter 1 (GLUT1) (**Figure 8F**). This effect

highlights the potential of ES as a highly effective approach for clinical cancer treatments.

Experiments reveal that high frequencies and cyclic pressures are primarily responsible

for the disruption of actin fibers. Particularly, higher frequency and negative pressures in

the latter half of the cycle induce greater tensile strain and deformation, leading to the

breakdown of F-actin fibers and increased fluidization.

5.3.2 Low-intensity ultrasound disrupts cytoskeletal structure and function

As for another external stimulation, low-intensity ultrasound (LIUS) is widely used in

medicine due to its non-invasive nature, safety, and ability to precisely target and

manipulate biological tissues. The ultrasonic cavitation effect of LIUS involves the dynamic

expansion and collapse of submicron air pockets, also known as cavitation nuclei, within a

fluid when the sound pressure surpasses a certain threshold [199]. The impact of LIUS on

the cytoskeleton is pronounced, especially in tumor cells. Recently, Song *et al.* [200]

discovered that Piezo1 plays a role in the apoptosis of pancreatic cancer cells when

subjected to ultrasound (US) combined with microbubbles (MBs). However, since MBs

used in this study are micron-sized, their ideal application *in vivo* presents certain

challenges. Following treatment with US and MBs, tumors displayed slower growth rates;

however, the growth rate remained higher in the US + MBs + Lv-siPiezo1 group compared

to the US + MBs + Lv-NC group. This research emphasized the potential of using

ultrasound alongside microbubbles as a non-invasive approach for treating pancreatic

ductal adenocarcinoma through mechanotransduction. Additionally, other studies have

shown that this combination can effectively disrupt the cytoskeletal structure of tumor cells

by generating intense mechanical forces [201, 202]. However, the micrometer size of MBs

may limit their *in vivo* application, and achieving Piezo1 overexpression *in vivo* is

challenging due to its high molecular weight. Overcoming these challenges will be crucial

for future clinical applications.

5.4 Interfering ECM-cellular membrane biomechanical sensing-transduction function

5.4.1 Interfering the mechanical properties of ECM

The TME exhibits increased stiffness due to an abundance of ECM, which amplifies

its intrinsic mechanical properties [203]. These 'inside-out' tensile forces are primarily mediated through integrin-dependent cell adhesions involving FAK activation [204]. Consequently, targeting FAK in tumor tissue can modulate the mechanical properties of tumor and stromal cells as well as the tumor ECM. CRISPR/Cas genome editing offers substantial potential for cancer treatment by enabling precise inactivation or repair of cancer-related genes. A study developed multiplexed nanoparticles designed to deliver siFAK to disrupt the ECM, Cas9 mRNA to express Cas protein, and targeted sgRNA to knockout specific cancer genes [205]. FAK inhibition was shown to reduce tumor cell contractility and membrane tension, along with ECM stiffness, thereby enhancing CRISPR gene editing efficiency in tumor cells both *in vitro* and *in vivo* by promoting lipid nanoparticles (LNPs) endocytosis and tumor penetration. *In vivo* results further demonstrated that siFAK + CRISPR-LNPs decreased metastatic potential in an ovarian cancer mouse model, improved outcomes in a tumor xenograft mouse model, and extended survival in an aggressive MYC-driven liver cancer model, highlighting significant anti-tumor effects across different cancer types.

5.4.2 Disrupting cellular membrane integrity

The cellular membrane, composed of a lipid bilayer and cell surface receptors, detects mechanical signals from the environment and transmits this information to the intracellular cytoskeletal machinery. Thus, membrane-disruptive macromolecules can weaken membrane integrity, interfere with biomechanical signaling, and reduce the ability of cells to adhere to the stroma or neighboring cells. Yang's group from University of Science and Technology of China [206] demonstrated the feasibility of acid-responsive nanoparticles composed solely of membrane-disruptive molecules for treating pancreatic cancer with dense stromal barriers (**Figure 9A**). Using a pH-sensitive micelle derived from a polymeric mimic of host defense peptides as the core of the nanoplatform, the acid-activatable nanoparticle (M-14K) showed selective cytotoxicity toward BxPC-3 pancreatic cancer and NIH-3T3 fibroblast cells under mildly acidic conditions (**Figure 9B-C**). These nanoparticles dissociate at the weakly acidic pH of the TME (pH 6.5−6.8) but remain stable at physiological pH (7.4). In a BxPC-3@NIH-3T3 spheroid model, M-14K effectively penetrated the fibroblast layer to target cancer cells at pH 6.8 over 24 h (**Figure 9D**). Intravenous administration in mouse models with BxPC-3 xenograft tumors showed higher

uptake of M-14K compared to its pH-insensitive counterpart (M-35K) (**Figure 9E**), with delivery efficiency 12.3 times that of M-35K (0.74% vs. 0.06%) (**Figure 9F**). Throughout the observation period, M-14K treatment significantly delayed tumor growth (**Figure 9G**) without causing off-target effects. Overall, this strategy provides a promising translational approach for improving pancreatic cancer treatment by disrupting cellular membrane integrity, permeating the stromal barrier, and interfering with biomechanical signaling. Although these pH-sensitive nanoplatforms show promise in treating pancreatic cancer, their non-biodegradability, limited cell selectivity, and model limitations remain significant drawbacks that must be addressed in future research.

5.5 Interfering TME-biomechanical sensing-transduction function

In photodynamic therapy (PDT), the solid stress in stroma-rich tumors can hinder photosensitizer delivery. To address this, Chen *et al*. from Huazhong University of Science and Technology [207] proposed a strategy to enhance PDT efficacy by combining hydroxyethyl starch–chlorin e6 conjugate nanoparticles (HES–Ce6 NPs) with the TGF-β inhibitor LY2157299 (LY) (**Figure 10A**). Prior to PDT, LY administered intragastrically downregulated TGF-β signaling and ECM-related mRNA expression (**Figure 10B**), reduced collagen deposition (**Figure 10C**), alleviated solid stress (**Figure 10D**), and decompressed tumor blood vessels. This pretreatment significantly promoted HES–Ce6 NP penetration in tumors (**Figure 10E**), allowing the restructured tumor microenvironment to improve the accumulation and penetration of HES–Ce6 NPs, ultimately enhancing the anti-tumor efficacy of PDT (**Figure 10F**).

In a separate study, Cong *et al.* from Yanshan University [208] developed a "nano-lymphatic" system (DOX/g-C$_3$N$_4$/luminol@cytomembrane, DCL@M) aimed at addressing the elevated tumor IFP resulting from lymphatic insufficiency. In this system, lactic acid serves as a sacrificial agent, while DCL@M facilitates photocatalytic water splitting to reduce the volume of interstitial fluid, thereby mitigating the resistance to transfer caused by high tumor interstitial fluid pressure. The *in vivo* experiments demonstrated a significant 62.11% reduction in tumor IFP within the tumor tissue, which subsequently improved blood perfusion. The accumulation of the "nano-lymphatic" system (16.73%) in the tumor was found to be 15.9 times and 3.31 times greater than that of free doxorubicin hydrochloride (DOX, 1.05%) and DOX/g- C$_3$N$_4$@cytomembrane (DC@M, 3.03%), respectively. This

938   indicates that the "nano-lymphatic" approach offers a novel strategy for enabling

939   nanodrugs to navigate biological barriers and enhance therapeutic efficacy. Overall, these

940   innovative strategies hold promise for advancing cancer treatments by overcoming the

941   physical and mechanical challenges present within the tumor microenvironment. Although

942   this research has highlighted the significant potential of the 'nano-lymphatic' system in

943   tumor treatment, its clinical translation remains challenging. Issues such as biological

944   safety, large-scale production difficulties, and individual patient variability can impact the

945   efficacy of the 'nano-lymphatic' system, necessitating the integration of personalized

946   treatment plans and precision medicine.

947 ***6. Conclusions, challenges and prospectives***

948   Tumors and tumor microenvironments complement each other, jointly promoting the

949   growth, invasion, metastasis, and drug resistance of tumor cells. Therefore, effective tumor

950   treatment strategies should regulate the tumor microenvironment simultaneously.

951   Compared with chemical drugs, macromolecular drugs, and cell therapy, the main

952   advantage of biomechanical based cancer treatment strategies is that: i) biomechanics can

953   macroscopically regulate the function of cell secondary structures, such as primary cilia,

954   cytoskeleton, etc., rather than targeting a single target or a specific type of cell. Therefore,

955   the scope of regulation based on biomechanics is broad and has multiple impacts on tumor

956   progression. For example, the regulation of the cytoskeleton can simultaneously affect

957   DNA damage repair, metastasis, and drug resistance in tumor cells. This widespread effect

958   makes the tumor suppressive effect stronger and less likely to develop tolerance. ii) The

959   biomechanical regulation methods have the characteristic of diversity, which can be small

960   molecule drugs or mechanical effects applied *in vitro*, such as low-intensity focused

961   ultrasound, ultrasound cavitation, etc. Regulating tumor cells through physical means

962   rather than chemically active biomolecules can significantly reduce common toxic side

963   effects in tumor treatment, such as nausea, immune system suppression, and organ

964   damage. However, the investigation of how biomechanics affect the onset and progression

965   of cancer remains relatively underexplored. Mechanical imbalance is a significant feature

966   of malignant tumor tissues, suggesting that disruptions in mechanical homeostasis may

967   precede tumorigenesis and tumor advancement. A deeper exploration of biomechanics

968   could facilitate earlier and more precise detection of cancer development and tumor

969 formation, while also expanding the conversation about the various factors that contribute

970 to cancer progression. This review presents a thorough overview of the known mechanical

971 properties linked to malignant tumors. By synthesizing the molecular and mechanical

972 characteristics at both cellular and tissue levels across different cancers, researchers can

973 better focus on applying mechanobiology to the study of malignant conditions.

974   This paper analyzed the impact of the tumor mechanical environment on the

975 occurrence and development of tumor angiogenesis, tumor drug resistance, and tumor

976 metastasis. Mechanoreceptors initially detect mechanical signals from the TME and

977 subsequently interact with mechanosignaling proteins to transduce these mechanical

978 signals into biological signals, thereby modulating cellular responses, gene expression,

979 and tumor microenvironment. The multidimensional mechanical forces experienced by

980 tumors create abnormal tumor vasculature and morphological structures, leading to

981 specific therapies such as nanodrug-mediated embolization treatment and tumor

982 vasculature normalization induction strategies. All proteins acting as mechanosensors and

983 the involved signaling networks have provided new therapeutic targets and challenges in

984 overcoming tumor metastasis and drug resistance mechanisms.

985   Innovative bioengineering technologies and novel therapeutic strategies for

986 biomechanical regulation offer transformative potential in tumor therapy by addressing the

987 mechanical properties of cancer cells and their microenvironment. These technologies,

988 such as targeted drug delivery systems and molecular self-assembly, enable precise

989 control over cellular biomechanics, crucial for effective treatment. For instance, primary

990 cilia-targeted nanoparticles enhance drug delivery and therapeutic efficacy by specifically

991 targeting and modulating cilia functions. Additionally, advancements in

992 mechanotransduction, such as using small molecules to inhibit key signaling pathways or

993 employing low-intensity ultrasound to disrupt cytoskeletal structures, demonstrate

994 significant promise in altering tumor progression and enhancing treatment outcomes. The

995 integration of nanotechnology into biomechanical regulation strategies holds immense

996 potential for revolutionizing cancer treatment. Ultimately, expanding research into

997 mechanical properties and their impact on tumor behavior will enhance our understanding

998 of cancer and lead to more effective, personalized therapies.

999   Nevertheless, the main challenge of biomechanical tumor treatment strategies lies in

the translation of mechanobiological principles into clinical practice. Firstly, current research lacks simplifying and standardizing methods for measuring mechanical properties. The complexity of current technologies requires advancements to make them more accessible for clinical use. Secondly, while analyzing the adaptation of tumors to the surrounding mechanical environment, we also realize the significant gaps remain in our understanding of the complex interactions between mechanoreceptors, mechanosensors, and tumor progression. Current experimental models often fail to capture the dynamic mechanical interactions within tumors, highlighting the need for more sophisticated models. Thirdly, current research focuses on the therapeutic effect on tumors, while ignoring the safety of strategies based on mechanical signal interference. Subsequent research must further enhance the tumor targeting of therapeutic agents to reduce crosstalk with biomechanical signals of normal tissues. Finally, the therapeutic effects of combined treatment approaches based on tumor biomechanical regulation remain to be developed. For instance, prior to chemotherapy, physical methods like low-intensity ultrasound or electrical stimulation can be employed to disrupt the cytoskeletal structure of tumor cells, thereby reducing their drug resistance and enhancing the permeability and efficacy of chemotherapeutic agents. Similarly, inhibiting integrin-mediated cell-matrix adhesion signaling can decrease the adhesion force between tumor cells and the ECM, diminishing their ability to colonize other tissues. With the increasing attention and the continuous breakthrough of technical barriers, more patients will benefit from biomechanical regulation tumor therapeutic strategies.

Abbreviations

ECM, extracellular matrix; MS, mechanosensitive; AFM, atomic force microscopy; MPA, micropipette aspiration; TFM, traction force microscopy; TME, tumor microenvironment; MMPs, matrix metalloproteinases; HA, hyaluronic acid; IFP, interstitial fluid pressure; CAFs, cancer-associated fibroblasts; TAMs, tumor-associated macrophages; ECs, endothelial cells; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; MVP, microvascular pressure; GPCRs, G protein-coupled receptors; CTCs, circulating tumor cells; MTs, microtubules; ABC, ATP-binding cassette; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; GCX, glycocalyx; GAG,

glycosaminoglycan; HS, heparan sulfate; PC, primary cilia; PDAC, pancreatic ductal adenocarcinoma; PitNETs, pituitary neuroendocrine tumors; RAR, retinoic acid receptor; CREB, cAMP-response element binding protein; ATP, adenosine triphosphate; TRP, transient receptor potential; TRPM7, transient receptor potential melastatin 7; FAK, focal adhesion kinase; EMT, epithelial-mesenchymal transition; EGFR, epidermal growth factor receptor; CXCR4, C-X-C chemokine receptor type 4; CCR5, C-C chemokine receptor 5; GDP, guanosine diphosphate; GTP, guanosine triphosphate; ROCK, rho-associated coiled-coil-containing protein kinase; PAKs, p21-activated kinases; EPR, enhanced permeability and retention; LPAR1, lysophosphatidic acid receptor 1; LPA, lysophosphatidic acid; CT, cilia-targeted; GCX, glycocalyx; GAG, glycosaminoglycan; CTGF, connective tissue growth factor; ES, electrostimulation; GLUT1, glucose transporter 1; LIUS, low-intensity ultrasound; US, ultrasound; MBs, microbubbles; LNPs, lipid nanoparticles; M-14K, acid-activatable nanoparticle; PDT, photodynamic therapy; HES– Ce6 NPs, hydroxyethyl starch–chlorin e6 conjugate nanoparticles; LY, TGF-β inhibitor LY2157299; DCL@M, DOX/g-C_3N_4/luminol@cytomembrane; DOX, doxorubicin hydrochloride; DC@M, DOX/g- C_3N_4@cytomembrane; TGF-β, transforming growth factor-β; DP, guanosine diphosphate; GLUT1, glucose transporter 1; GO, graphene oxide.

Competing Interests

The authors have declared that no competing interest exists.

Author contributions

Figures

Figure 1. Mechanical forces at the tumor site. Solid stresses encompass both tensile and
compressive forces. Increased fluid and hydrostatic pressure result from fluid extravasation
from blood vessels and secretions from stromal cells. Indirect mechanical forces are
relayed by CAFs and TAMs to mechanosensors. Abbreviations: CAFs, cancer-associated
fibroblasts; TAMs, tumor-associated macrophages. (Adapted with permission from Ref.
[163]. Copyright 2020 Ivyspring International Publisher)
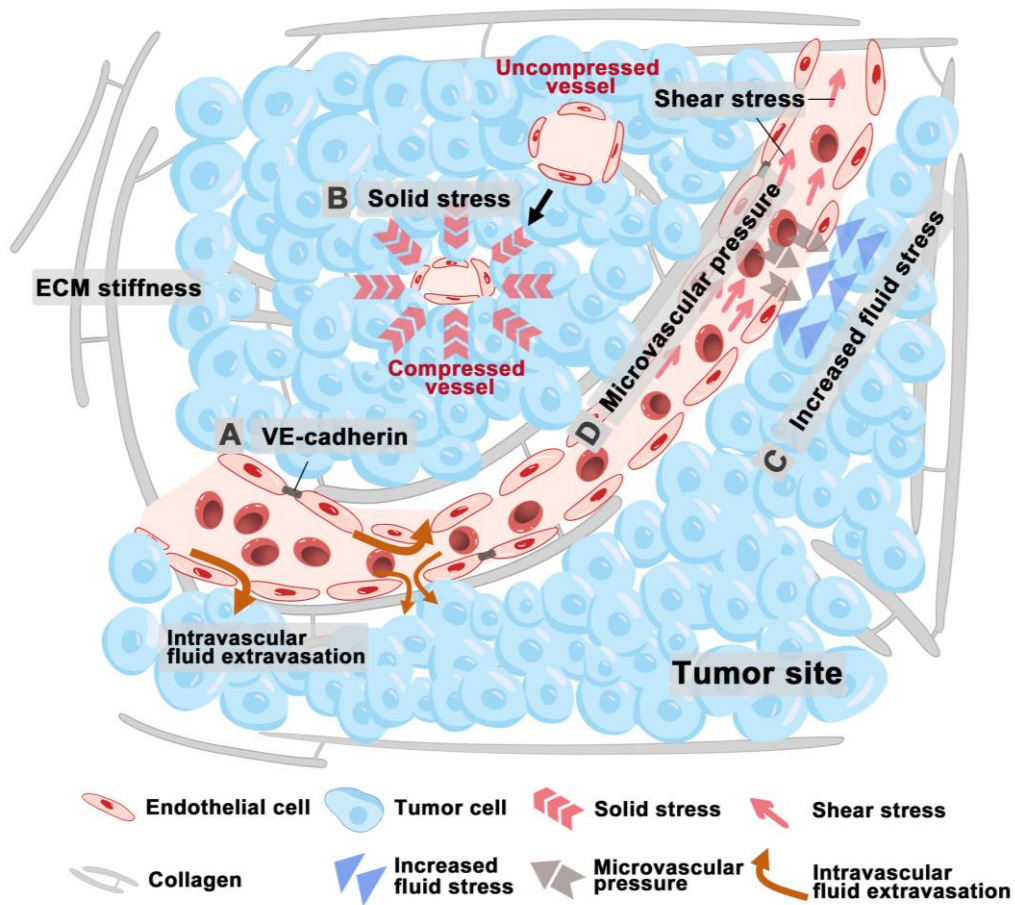
Figure 2. Mechanical forces within the tumor microenvironment impact tumor angiogenesis. (A) ECM stiffening alters cell-cell junctions and the positioning of VE-cadherin, thus disrupting barrier integrity and increasing permeability. (B) Solid stress compresses tumor vessels. (C) Increased fluid stress results in abnormal vascular development and inadequate tissue perfusion. (D) Elevated IFP within tumors often surpasses MVP, thereby limiting perfusion and disturbing flow patterns. Abbreviations: ECM, extracellular matrix; IFP, interstitial fluid pressure; MVP, microvascular pressure.
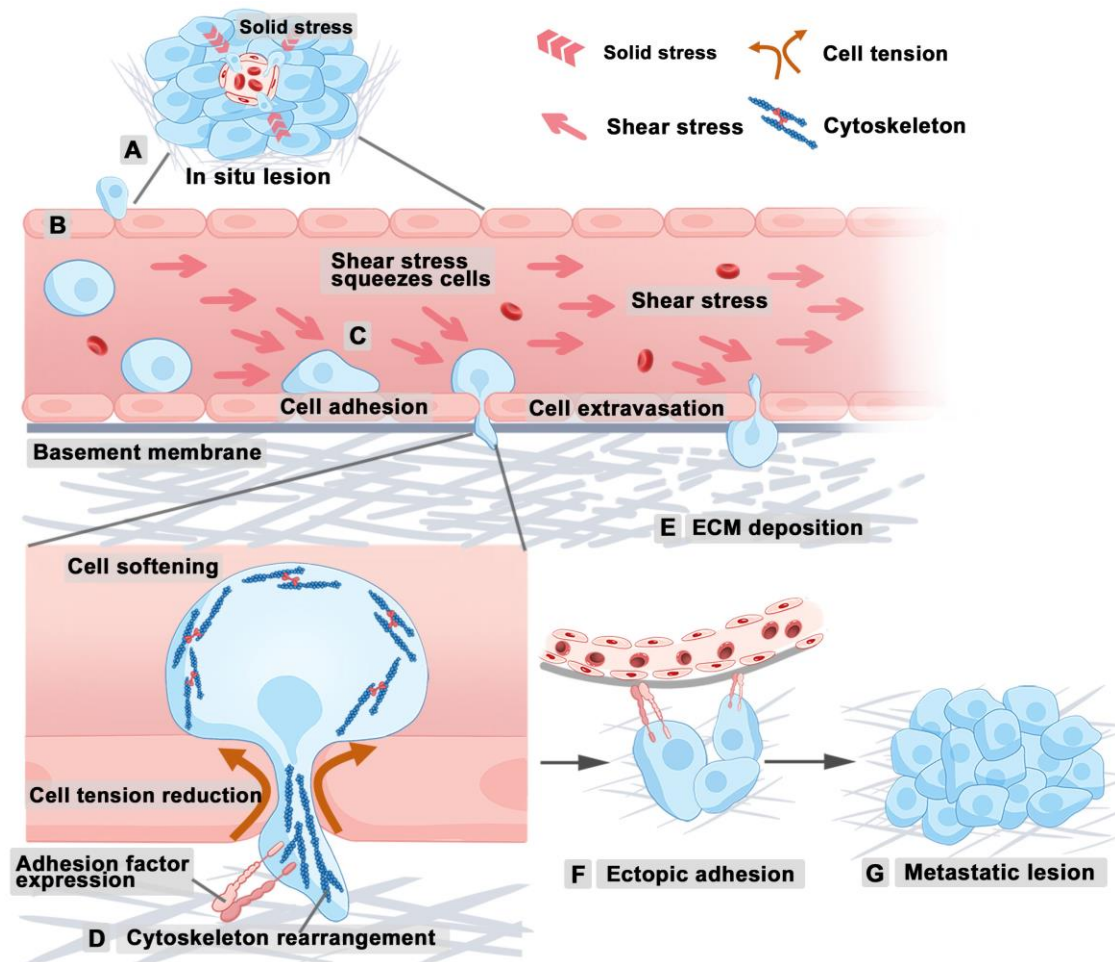
Figure 3. Tumor cell metastasis under biomechanical influence. (A) Tumor cells lose adhesion and detach from tumor tissue. (B) Tumor cells disrupt endothelial junctions, enabling entry into blood vessels. (C) Hydrodynamic shear stress converts CTCs into flexible cancer stem cells, enhancing their mimicry of ECs and promoting metastasis. (D) The cytoskeleton regulates tumor cell stiffness and penetration. (E) MMPs degrade the ECM, facilitating tumor cell passage through the vascular basement membrane. (F) Tumor cells adhere to blood or lymphatic vessels. (G) Metastatic tumor forms. Abbreviations: ECM, extracellular matrix; CTCs, circulating tumor cells; ECs, endothelial cells; MMPs, matrix metalloproteinases. (Adapted with permission from Ref. [209]. Copyright 2024 Springer Nature)
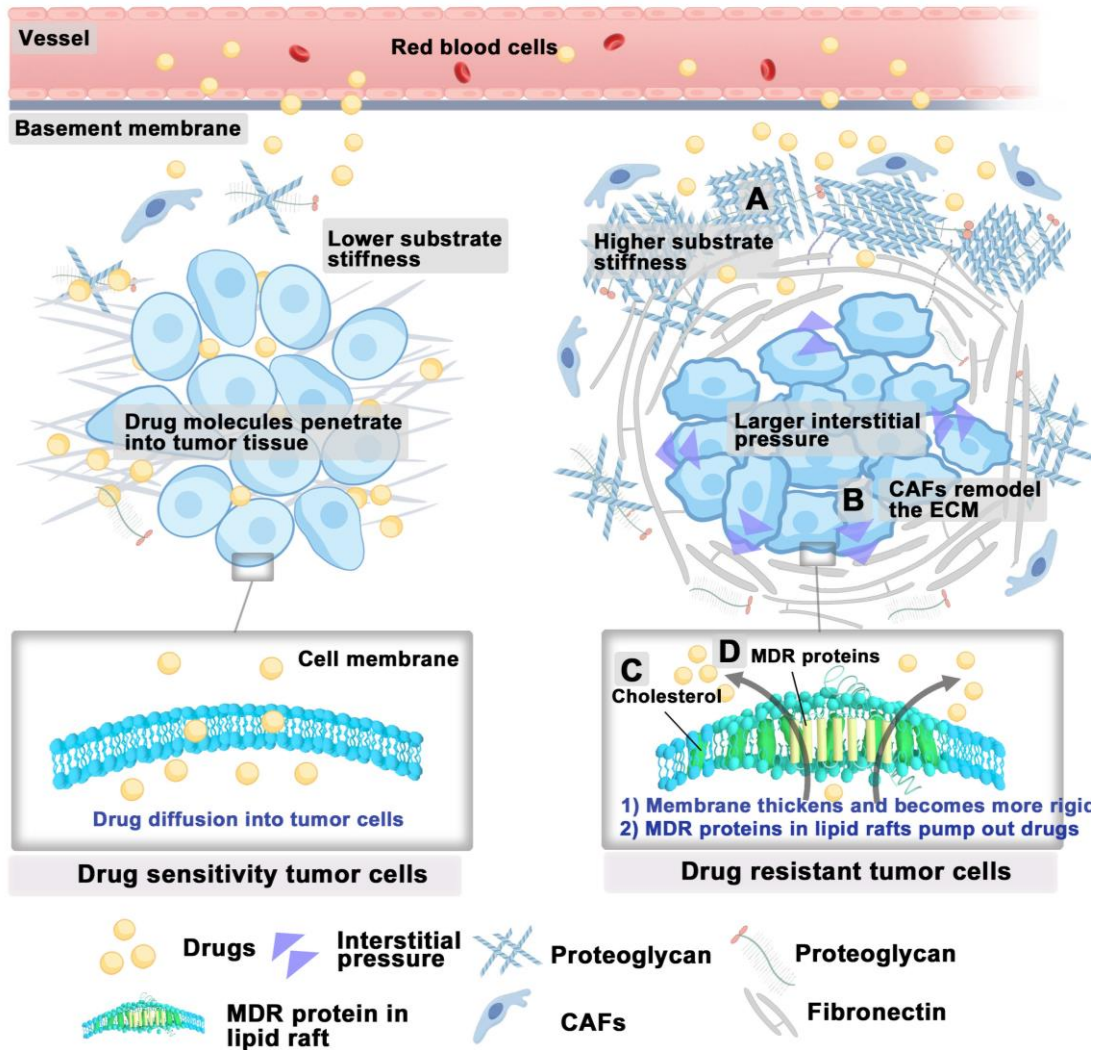
Figure 4. The biomechanical environment of drug-resistant tumor cells. (A) High collagen deposition in the ECM increases stiffness, contributing to drug resistance. (B) CAFs modify the ECM, promoting drug tolerance. (C) Elevated cholesterol levels in cancer cells, leading to thicker membranes that reduce drug permeability. (D) Increased cholesterol in lipid rafts enhances the function of multidrug resistance transporters, facilitating drug transport and contributing to drug resistance. Abbreviations: ECM, extracellular matrix; CAFs, cancer-associated fibroblasts.
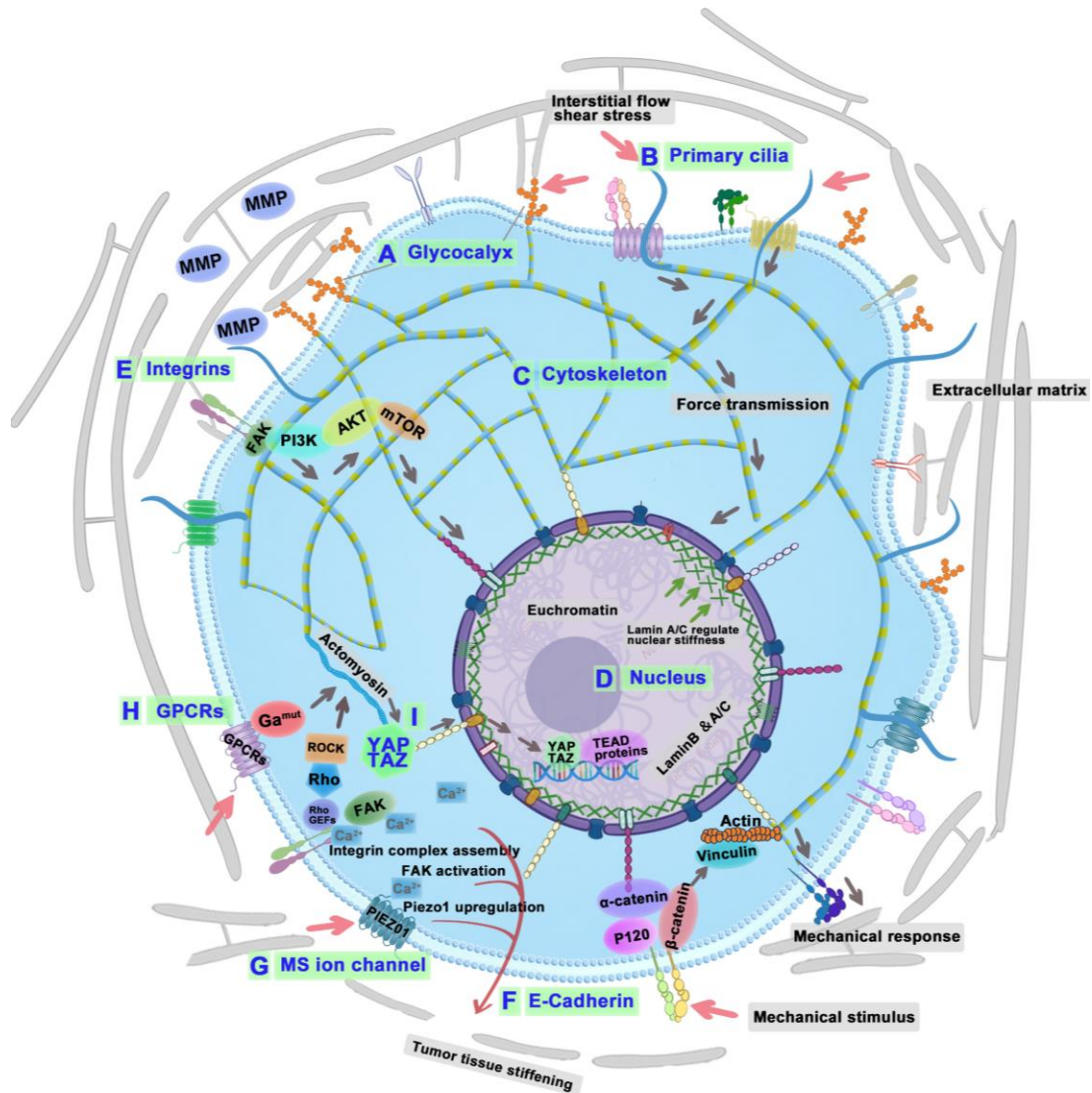
Figure 5. Diagram of tumor cell biomechanical perception, conduction, and effect mechanism. The GCX (A), primary cilium (B), cytoskeletonm (C), and nucleus (D) of tumor cells sense the surrounding mechanical signals; integrins (E), cadherins (F), MS ion channels (G), GPCRs (H), and YAP/TAZ (I) convert physical signals into biological signals. Decoding biomechanical signaling mechanisms of cancer cells: GCX senses shear stress and helps integrin clustering-MMP expression-tumor metastasis; PC senses fluid flow-influence cilia assembly-tumorigenesis and tumor progression; Cytoskeleton senses and transduces mechanical stresses-cytoskeletal remodeling-tumor metastasis; Nucleus senses mechanical cues-calcium channels regulation-DNA repair-tumor therapy resistance; Nucleus regulate lamin A-YAP and RAR-cytoskeleton regulation; Integrins interact with ECM components-regulates cytoskeleton-tumor metastasis; Cadherins convey mechanical signals-EGFR, catenins, and YAP-tumor proliferation, migration, and

invasion; GPCRs mediate mechanotransduction-YAP signaling pathway-tumor progression and metastasis; MS ion channels convert biochemical signals-Piezo1 initiate integrin-FAK signaling-tumor invasion; TRPM7-activate EMT pathway-tumor metastasis; YAP/TAZ convert mechanical signal-matrix stiffness-tumor invasion.

Abbreviations: GCX, glycocalyx; PC, primary cilia; YAP, yes-associated protein; RAR, retinoic acid receptor；ECM, extracellular matrix; EGFR, epidermal growth factor receptor; GPCRs, G protein-coupled receptors; EMT, epithelial-mesenchymal transition; MS, Mechanosensitive; TRPM7, transient receptor potential melastatin 7; YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif.

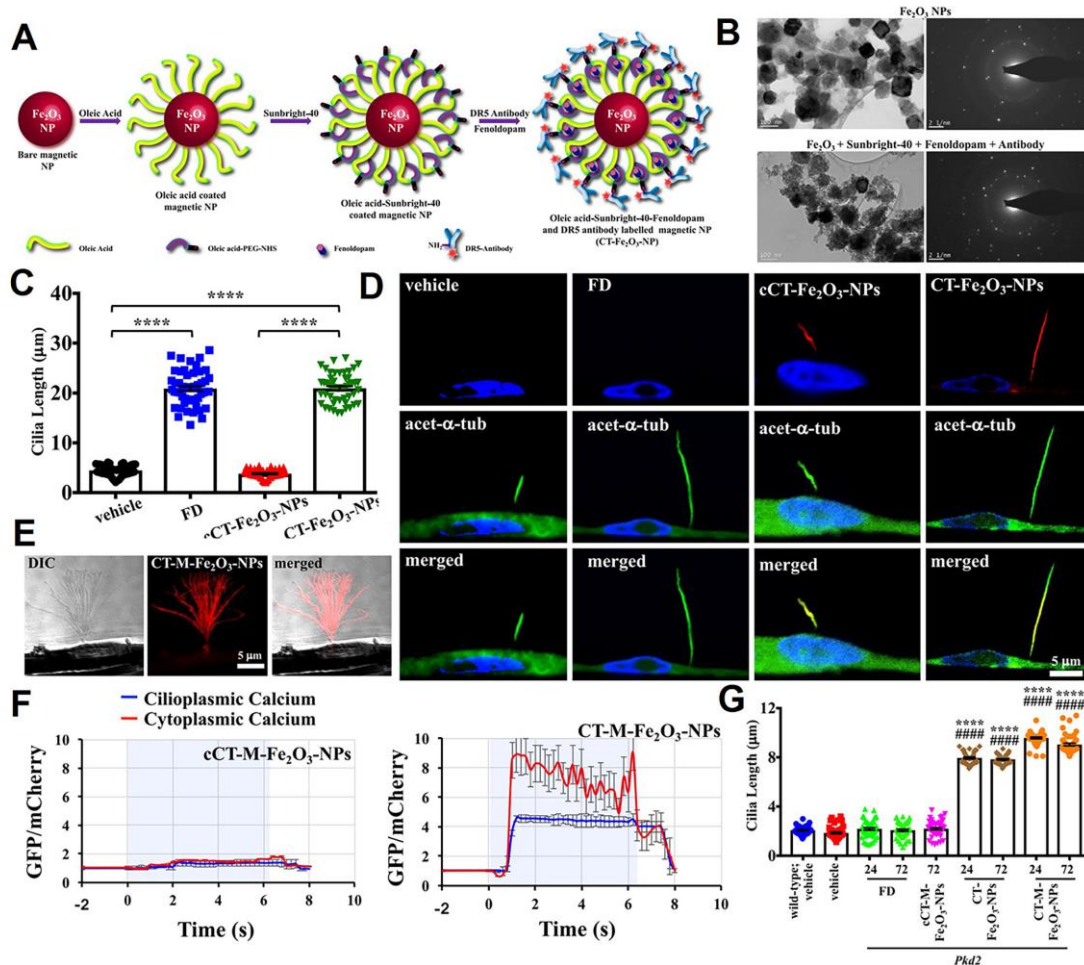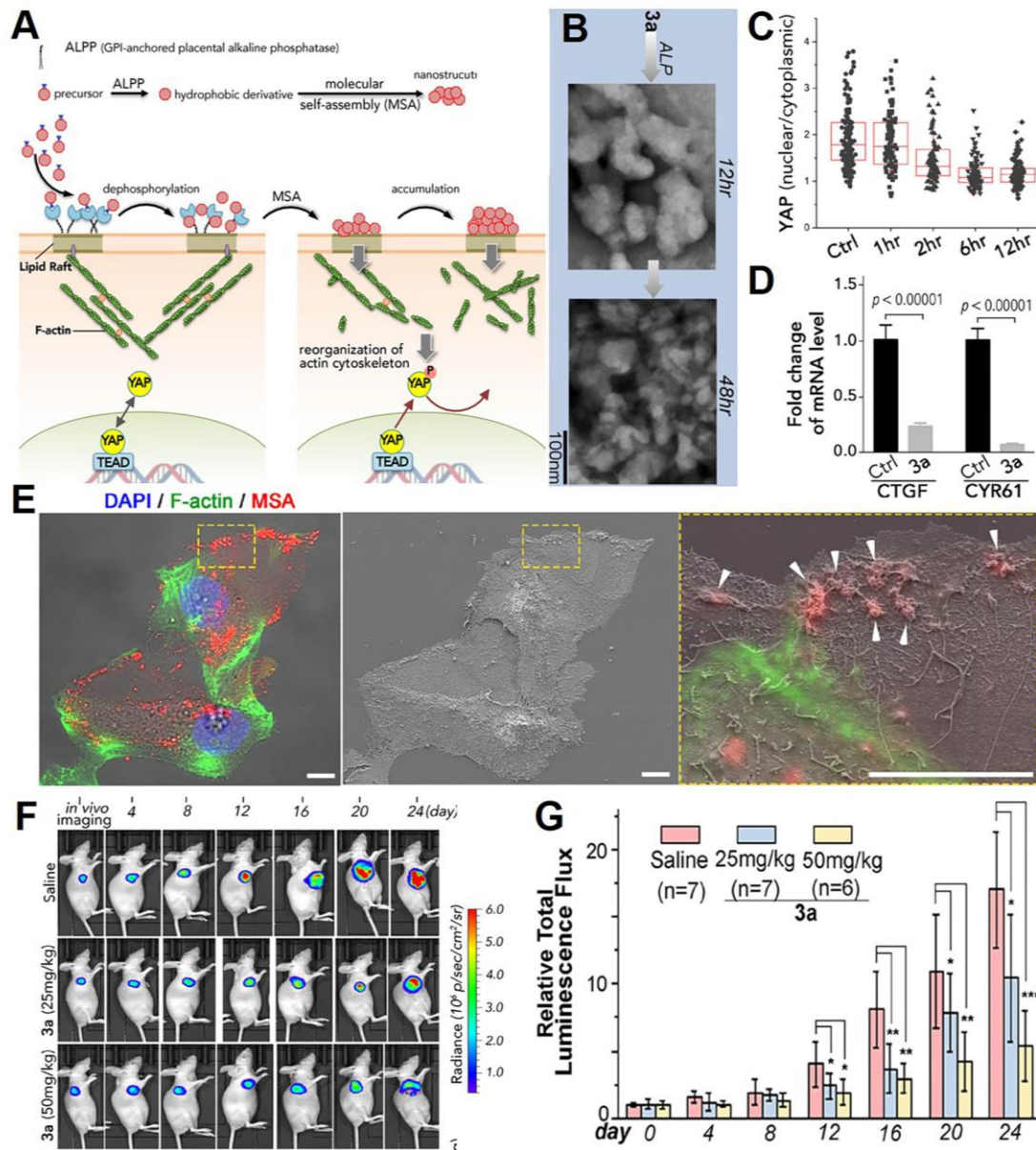**Figure 6.** Design nanoplatforms for interfering with the biomechanical function of primary cilia. (A) Synthesis and surface functionalization of CT-Fe$_2$O$_3$-NPs. (B) TEM and selected area electron diffraction images of bare Fe$_2$O$_3$-NPs and CT-M-Fe$_2$O$_3$-NPs. (C) A representative dot-plotted bar graph displaying the ciliary lengths measured in cells subjected to various treatments. (D) Fluorescence images illustrating that both fenoldopam and CT-Fe$_2$O$_3$-NPs (red) resulted in increased cilia length. (E) An external magnetic field applied to CT-M-Fe$_2$O$_3$-NPs induced passive movements of the cilia. (F) Line graphs depicting average cytosolic (red) and cilioplasmic (blue) Ca^{2+} levels (in arbitrary units). (G) Dot-plotted bar graphs showing cilia lengths in vascular endothelial cells. (Adapted with permission from Ref. [196]. Copyright 2019 American Chemical Society)
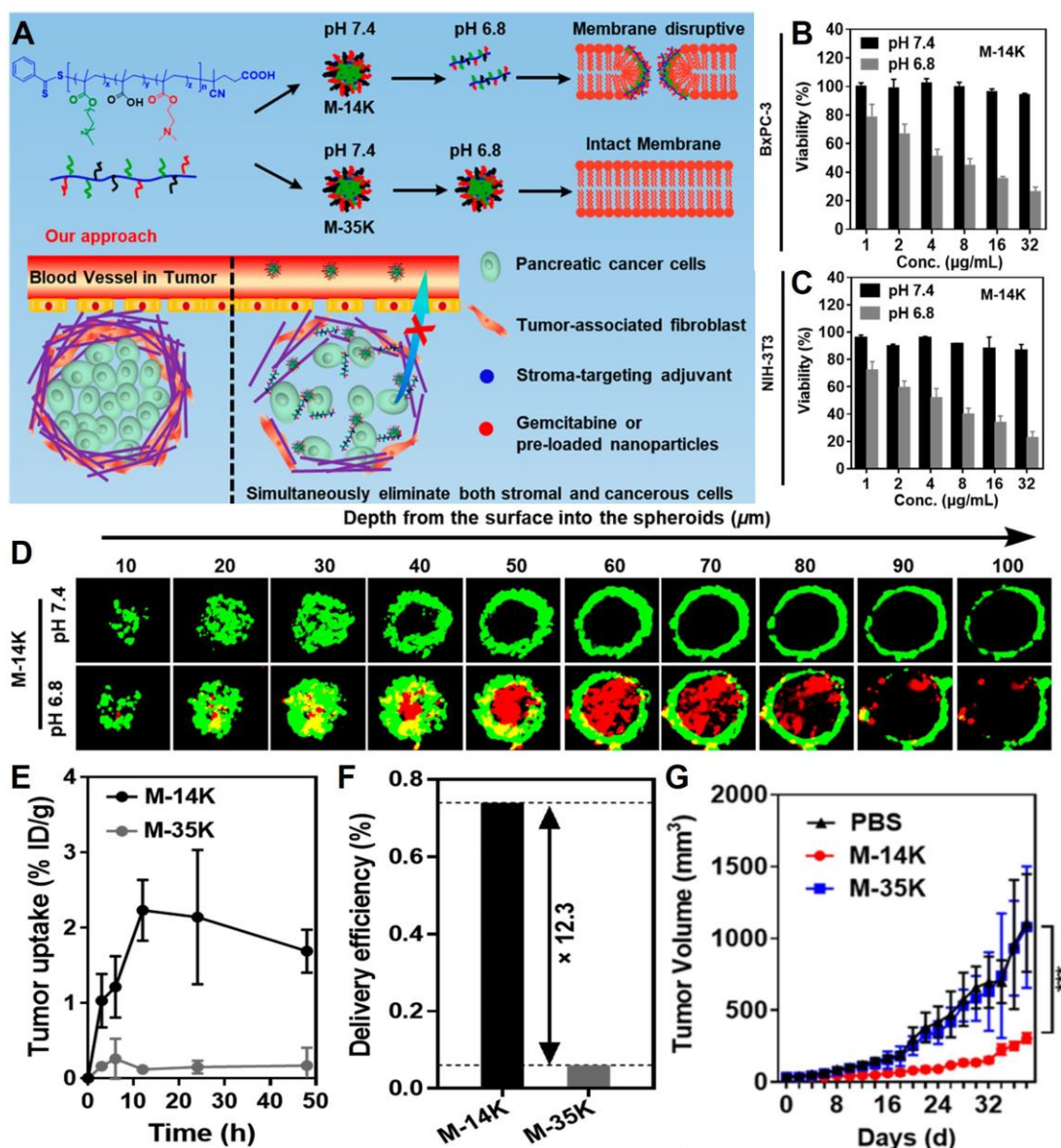
Figure 7. Design nanotherapeutics for interfering with the biomechanical transduction function of YAP. (A) Schematic illustrating the mechanisms of lipid-raft-targeted nanoplatforms for disturbing the YAP through actin cytoskeleton disruption. (B) Alkaline phosphatase dephosphorylation of 3a initiates molecular self-assembly at varying time points, forming diverse nanostructures. (C) Quantification of YAP intensity ratio between the nucleus and cytoplasm in SKOV3 cells at 60-70% confluence after incubation with 3a over different time periods. (D) The qPCR analysis of YAP target genes CTGF and CYR61 in untreated and 3a-treated SKOV3 cells. (E) Correlative light-electron microscopy of HeLa cells following incubation with 3a. Tumor growth was monitored (F) and analyzed (G) using bioluminescence detection. (Adapted with permission from Ref. [193]. Copyright 2021

American Chemical Society)
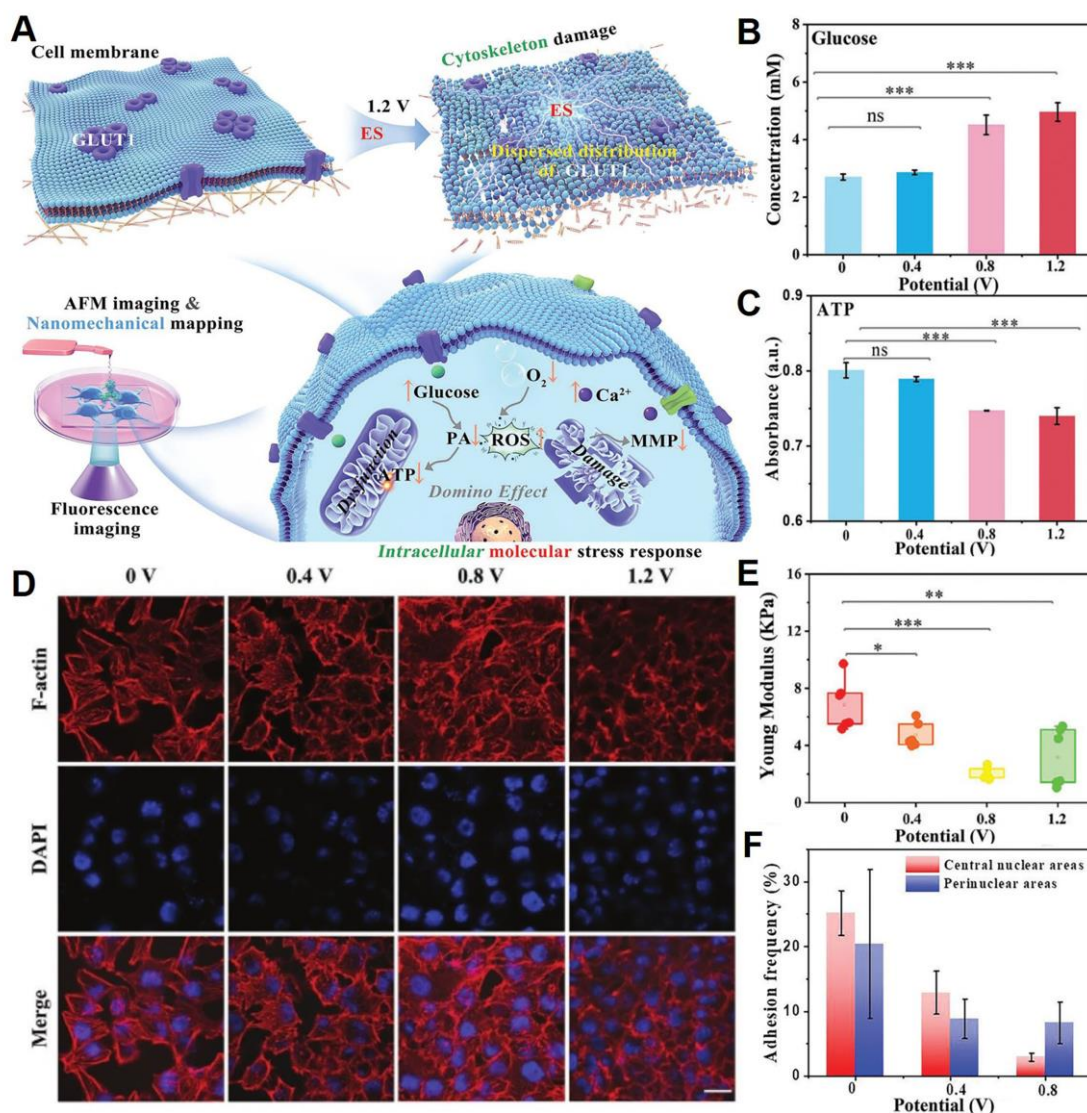
Figure 8. Electrostimulation disrupts the structure and function of the cytoskeleton. (A) Schematic representation of the molecular and nanomechanical insights into how ES inhibits energy metabolism and causes cytoskeletal damage in cancer cells. (B) Glucose concentration within MCF-7 cells measured using under different voltage conditions for 5 min. (C) ATP content in MCF-7 cells treated for 5 min at varying voltages. (D) Fluorescence imaging of MCF-7 cells subjected to different voltages for 5 min, showing F-actin (Cy3, red) and cell nuclei (DAPI, blue). (E) Statistical analysis of perinuclear Young's modulus (fitted using the Cone Sphere model) from MCF-7 cells exposed to different voltages for 5 min. (F) Probability statistics of GLUT1 recognition in the nuclear and perinuclear regions of MCF-7 cells after ES treatment at different voltages for 5 min. (Adapted with permission from Ref. [198]. Copyright 2023 Wiley-VCH)

Figure 9. Design nanotherapeutics for disrupting the integrity of the cellular membrane. (A) Schematic of acid-activatable, membrane-disruptive nanomicelles (M-14K) designed to target both cancer and stromal cells. (B-C) Viability assays for BxPC-3 cancer cells and activated NIH-3T3 fibroblasts. (D) Images of three-dimensional BxPC-3@NIH-3T3 spheroids, showing a fibroblast shell (green) surrounding a core of cancer cells post-M-14K treatment; propidium iodide (red) stains the dead cells. (E) Tumor uptake of DiD-labeled M-14K and M-35K, and (F) comparison of calculated tumor-targeting efficiency between M-14K and M-35K in BxPC-3 tumor-bearing mouse models. (G) Tumor volume measurements during treatment. (Adapted with permission from Ref. [206]. Copyright 2021 American Chemical Society)
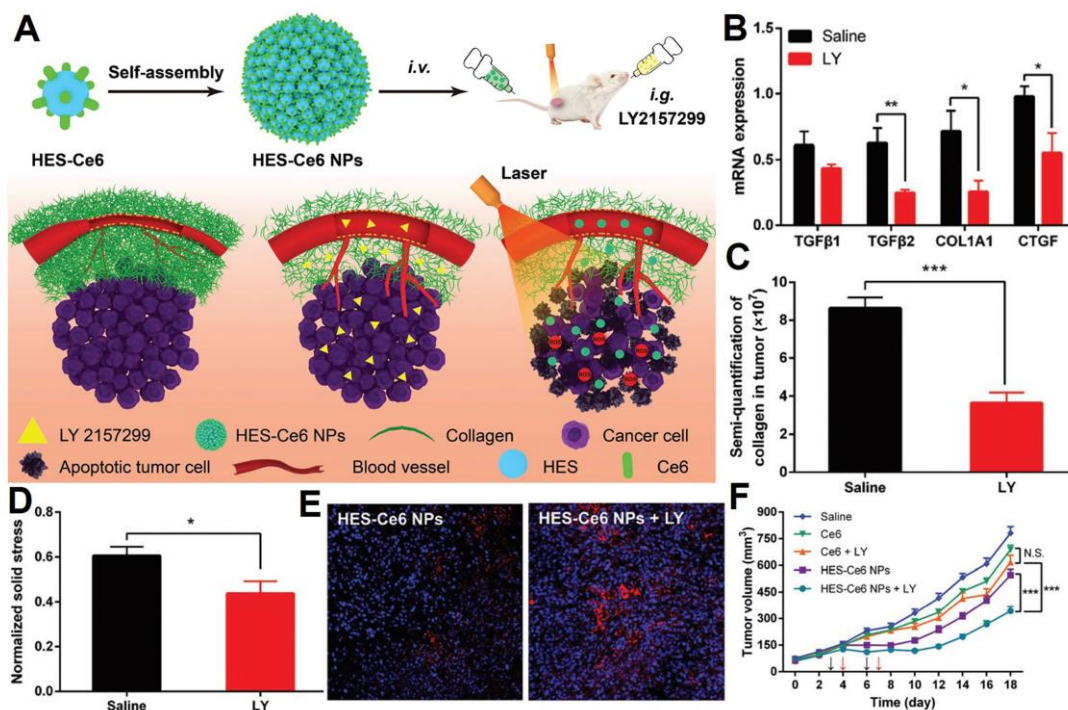
Figure 10. Design nanoplatforms for interfering with the biomechanical transduction function of the tumor microenvironment. (A) Schematic of HES–Ce6 NPs combined with TGFβ inhibitors to enhance PDT. (B) The mRNA expression levels of TGF-β1, TGF-β2, COL1A1, and CTGF in tumor tissues. (C) Semi-quantitative analysis of collagen in tumors using Masson staining. (D) Normalized solid stress measured as the ratio of tumor opening to tumor height. (E) Representative images of drug penetration in tumors (blue: DAPI, red: Ce6). (F) Tumor growth in 4T1 tumor-bearing mice. (Adapted with permission from Ref. [207]. Copyright 2021 Royal Society of Chemistry)

47

1221 **Table 1.** Clinically used drug on mechanical forces of tumor treatment.

Drugs	Signaling pathway	Functional mechanism	Ref
PEGPH20	HA-tumor solid stress	Degrade HA and decrease solid stresses, enhance perfusion and drug delivery in pancreatic ductile adenocarcinomas	[210]
4-MU	HA-tumor solid stress	Inhibits HA synthesis by down-regulating HA receptors and the phosphatidylinositol 3-kinase/CD44 complex	[88]
A6	A6-CD44-HA	CD44 is a receptor for HA while A6 binds to CD44, resulting in the inhibition of the modulation of CD44-mediated cell signaling including HA	[89]
Bevacizumab	VEGFA-tumor angiogenesis	Prevents VEGFA from binding to receptors, hinders neovascularization and the activation of signal transduction cascades	[32]
Anlotinib	Tyrosine kinase inhibitors	Inhibit VEGFR, fbroblast growth factor receptors, platelet-derived growth factor receptors, c-Kit and Ret, resulting in inhibiting tumor angiogenesis and growth	[211]
α-solanine	EMT and MMPs	Blocking EMT and MMPs expression	[212]
Microtubule-destabilizing agents	Microtubule-cytoskeleton-mechanical forces	Inhibit microtubule polymerization at high concentrations, modulation of microtubule dynamics influence cytoskeleton	[213]
Microtubule-stabilizing agents	Microtubule	Promote microtubule polymerization	[213]

Mycalolide B	Actin-cytoskeleton	Inhibiting G-actin polymerization and severing F-actin by binding to barbed end of actin leads to a rapid collapse of the actin cytoskeleton, impairing cancer cell motility and invasion by blocking invadopodia-mediated ECM degradation	[214]
Collagenase	Collagen protein-stiffness of ECM	Decrease collagen proteins, reduce the stiffness of ECM, increase IgG diffusion to tumor sites in penetration-resistant tumors	[68]
GsMTx4	Piezo1	Inhibit the Ca^{2+} concentration, and alter EMT-correlated markers expression in response to mechanical stretch, influence the morphology and migration	[215]
shPTK2/PND1186	FAK	Represses YAP activation by inhibiting p-YAP^{Y357}, leading to decreased YAP nuclear localization and activation, suppresses tumor initiation and progression	[216]
AZA1	Cdc42/RAC1 GTPase	Blocking Rac1/Cdc42-dependent cell cycle progression, cancer cell migration, and increase of cancer cell apoptosis involving down-regulation of the AKT and PAK signaling pathway	[184]
Pirfenidone	Antifibrotic	Restore biomechanical abnormalities of the tumor microenvironment, related to increased stiffness and hypo-perfusion	[217]

Tranilast	Antifibrotic	Reduce stiffness and mechanical forces, improve tumor perfusion and significantly enhance the efficacy of chemotherapy and nanomedicine by affecting CAFs.	[218]
Ketotifen	Antifibrotic	Suppressed CAFs proliferation and stiffness of the extracellular matrix accompanied by an increase in vessel perfusion in fibrosarcoma and osteosarcoma	[219]
Losartan	Angiotensin inhibition	Reduces solid stress in tumours, resulting in increased vascular perfusion. [35] And improves drug and oxygen delivery to tumours, thereby potentiating chemotherapy and reducing hypoxia in breast and pancreatic cancer models.	

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1223   **Table 2.** The classification and mechanisms of mechanobiology perturbing tumor nanotherapeutics.

Classification	Therapeutic mechanisms	Functional nanoplatform	Cargoes	Cancer type	Ref.
Interfering tumor microenvironment	Improve tumor blood vessel perfusion functionality	PEGylated liposomal	Tranilast and Doxil	Breast cancer	[220]
	Decrease collagen deposition, alleviated solid stress	Hydroxyethyl starch– Ce6 conjugate self-assembled nanoparticles	Ce6 and LY2157299	Breast cancer	[207]

	Decrease the volume of the tumor interstitial fluid to ameliorate the transfer resistance derived from the high tumor interstitial fluid pressure	Graphitic carbon nitride nanosheets	DOX and luminol	Cervical carcinoma	[208]
	Reduce mechanical stresses to decompress tumor vessels and improve perfusion and chemotherapy	Pegylated liposomal	DOX	Breast cancer	[221]
Interfering cell membrane	Decrease membrane tension and increase LNP endocytosis and tumor penetration.	Lipid nanoparticles	siRNA, mRNA, and targeted sgRNA	Ovarian cancer, and lung adenocarcinoma	[205]
	Acid-activatable disrupt cellular membrane integrity	Host defense peptides polymeric mimetic micelle	/	Pancreatic cancer	[206]
Interfering cytoskeletal	Reduce cell stiffness and inhibit cell migration through the graphene oxide nanosheets-mediated disruption of the intracellular cytoskeleton	Graphene oxide nanosheets	/	Breast cancer	[222]
	Softening cells enhances nanoparticle uptake through activating clathrin- and caveolae-	Nitrogen-doped graphene quantum dots	DOX	Breast cancer	[223]

	mediated endocytosis				
Interfering glycocalyx	Dynamic stretch forces combined with stiffness changes in the interstitium alter glycocalyx gene expression, thus change the cell uptake efficiency	Liposomal nanoparticles	Dil or DiO	Lung adenocarcino ma	[224]
Interfering primary ciliary	Inhibit primary cilia related signal lysophosphatidic acid signaling	PEG-PLGA nanoparticles	Ki16425	Glioblastoma	[195]
	Control the movement and function of a cilium with an external magnetic field, and improved cardiac function	CT-Fe$_2$O$_3$-NPs	Fenoldopam	LLC-PK1	[196]
Interfering mechanotransduction proteins	Inactivate Yes-associated protein and regulate Hippo signaling pathway	Ruthenium-complex-peptide / precursor molecule		Ovarian cancer	[193]

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1225 **Table 3.** Clinical trials based on mechanical forces for tumor treatment.

Drugs	Cancer type	Indication	Tips	Ref
IAG933	Mesothelioma	NF2/LATS1/LATS2 mutated tumors and tumors with functional YAP/TAZ fusions	NCT04857372, Phase I, Recruiting	[62]

VT3989	Mesothelioma	Metastatic solid tumors that are resistant or refractory to standard therapy or for which no effective standard therapy	NCT04665206, Phase I, Recruiting	[62]
ION537	Advanced solid tumors	Molecularly selected advanced solid tumors	NCT04659096, Phase I, Completed	[225]
IK-930	Solid tumors	Malignant pleural mesothelioma, epithelioid hemangioendothelioma, NF2 deficient solid tumors, and solid tumors with YAP1/TAZ fusion genes	NCT05228015, Phase I, Terminated	[226]
VS-6063	Pancreatic Ductal adenocarcinoma	Resectable pancreatic ductal adenocarcinoma	NCT03727880, Phase II, Recruiting	[227]
VS-6766	Non-small cell lung cancer	Recurrent KRAS-mutant and BRAF-mutant non-small cell lung cancer	NCT04620330, Phase II, Completed	[228]
ADH-1	Melanoma	Advanced in-transit malignant melanoma	NCT00421811, Phase II, Completed	[229]
ADH-1	Solid tumors	Incurable solid tumors expressing N-cadherin	NCT00265057, Phase II, Completed	[229]
TG-0054	Hematological tumors	Multiple myeloma, and non-hodgkin lymphoma	NCT01458288, Phase II, Completed	[230]
PF-03732010	Solid tumors	Advanced solid tumors	NCT00557505, Phase I, Completed	[231]
CHM-2101	Advanced gastrointestinal cancer	Advanced gastrointestinal cancers resistant to at least one standard treatment in the metastatic or locally advanced setting.	NCT06055439, Phase I/II, Recruiting	[232]

Maraviroc	Colorectal cancer	Advanced colorectal cancer patients with hepatic liver metastases	NCT01736813	[169]
MBQ-167	Breast cancer	Breast cancer stage IV	NCT06075810, Phase I, Recruiting	[233]
SST0001	Multiple myeloma	Advanced refractory multiple myeloma	NCT01764880, Phase I, Completed	[234]

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