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# The application of nanomaterials in tumor therapy based on the regulation of mechanical properties

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Mechanical properties, as crucial physical properties, have a significant impact on the occurrence, development, and metastasis of tumors. Regulating the mechanical properties of tumors to enhance their sensitivity to radiotherapy and chemotherapy has become an important strategy in the field of cancer treatment. Over the past few decades, nanomaterials have made remarkable progress in cancer therapy, either based on their intrinsic properties or as drug delivery carriers. However, the investigation of nanomaterials of mechanical regulation in tumor therapy is currently in its initial stages. The mechanical properties of nanomaterials themselves, drug carrier targeting, and regulation of the mechanical environment of tumor tissue have far-reaching effects on the efficient uptake of drugs and clinical tumor treatment. Therefore, this review aims to comprehensively summarize the applications and research progress of nanomaterials in tumor therapy based on the regulation of mechanical properties, in order to provide strong support for further research and the development of treatment strategies in this field.

## 1 Introduction

The global incidence and mortality rates of cancer continue to escalate annually, positioning it as a preeminent cause of mortality worldwide.[1] Cancer cells are universally acknowledged as a highly heterogeneous population, possessing not only the capacity for indefinite proliferation but also re-engineer their extracellular matrix (ECM), thereby crafting a distinct tumor microenvironment (TME) that fosters their growth, proliferation, and metastasis.[2] Investigating the intrinsic properties of cancer cells and their surrounding microenvironment, as well as developing therapeutic interventions targeting these aspects, constitutes a pivotal approach against cancer. Hanahan and Weinberg have delineated eight hallmarks of cancer which include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, evading immune destruction, and reprogramming energy metabolism. Subsequent research has elucidated that the biological functions of cancer cells undergo significant alterations throughout tumor progression.

Tumor mechanics, a pivotal characteristic of neoplasms, reveals that cancer cells and their ECM exhibit distinct mechanical properties when compared to their normal tissue counterparts. Despite potential morphological similarities to normal cells, cancer cells can be differentiated by mechanical properties through various analytical techniques.[3] Current methodologies for mechanical analysis encompass optical, magnetic, and acoustic tweezers, as well as sensing platforms employing biomaterials and micro-nanotechnology. Among these, the Atomic Force Microscope (AFM) is capable of imaging biological samples with nanometer-scale spatial resolution and collecting force spectroscopy information under near-physiological conditions, rendering it an indispensable tool in the study of tumor cell biomechanics.[4–6] Each technique offers unique advantages and is suited for specific applications.[7] The Young's modulus, a measure of elastic modulus which quantifies the ratio of stress to strain and describes a material's resistance to elastic deformation under load, is the most frequently cited mechanical parameter.[8] Empirical evidence suggests that cancer cells exhibit a lower Young's modulus compared to healthy cells from the same tissue type, indicative of decreased cellular stiffness. This diminution in stiffness correlates with disease progression,[9] with "softer" cancer cells often displaying enhanced metastatic potential.[10]

Cancer cells exhibit marked deviations from their normal cellular counterparts, necessitating alterations to the ECM to accommodate their growth and proliferation.[2] The TME is an intricate network primarily composed of tumor-associated macrophages (TAMs), lymphocytes, cancer-associated fibroblasts (CAFs), extracellular vesicles, a plethora of cytokines,

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and the ECM. It is characterized by a densely packed ECM, enrichment of CAFs, vascular anomalies, hypoxia, acidic pH shifts, TAM infiltration, and an immune-tolerant milieu.[11] The progression of many solid tumors is accompanied by an increase in structural components-most notably the ECM density and the proliferation of cancer cells and stromal cells —leading to a stiffening of the tumor. This stiffening results in elevated solid stress within the TME. Concurrently, impaired lymphatic drainage and retention of tissue fluid elevate the interstitial fluid pressure within the TME above that of normal tissues. Furthermore, the dense ECM can impede angiogenesis within tumors. Consequently, these unique mechanical properties of the TME create a formidable physical barrier that obstructs the efficacious delivery and potency of anticancer therapeutics.[12] Investigating these mechanical properties within tumor cells and their microenvironment offers novel insights and strategies for cancer treatment (Fig. 1).

In conclusion, this review will concentrate on the mechanical properties, encompassing the modulation of mechanical characteristics in cancer cells and the TME by nanomaterials, as well as the inherent mechanical properties of the nanomaterials themselves. The objective is to elucidate the role of nanomaterials in oncological therapeutics and to explore novel strategies for cancer treatment through the lens of physical properties.

## 2 Modulation of cancer cell mechanics by nanomaterials

Normal cells exhibit pronounced differences in mechanical properties when compared to cancer cells, which are typically softer and exhibit a reduced perception of stiffness. Hsi-Hui Lin and colleagues observed that in response to varying substrate stiffness, normal cells dynamically adjust their own stiffness, whereas cancer cells display a notable insensitivity to such environmental cues.[13] This insensitivity potentially contributes to their unregulated proliferation and metastatic behavior.[13] Cancer cells are also softer compared to normal cells. Nanomaterials can leverage this characteristic by preferentially targeting the softer mechanical profile of cancer cells for efficient nanoparticle internalization.[14] For example, Arventh Velusamy *et al.* designed and constructed a "DNA mechanocapsule" for targeting cells with specific mechanical properties. This capsule can recognize piconewton-level differences in mechanical force and selectively deliver therapeutic drugs to target cells with specific biophysical phenotypes in a force-selective manner.[15] Moreover, by modulating the mechanical properties of cancer cells, nanomaterials can enhance drug susceptibility, facilitate drug internalization through endocytosis, and suppress the metastatic potential of these cells.[16]

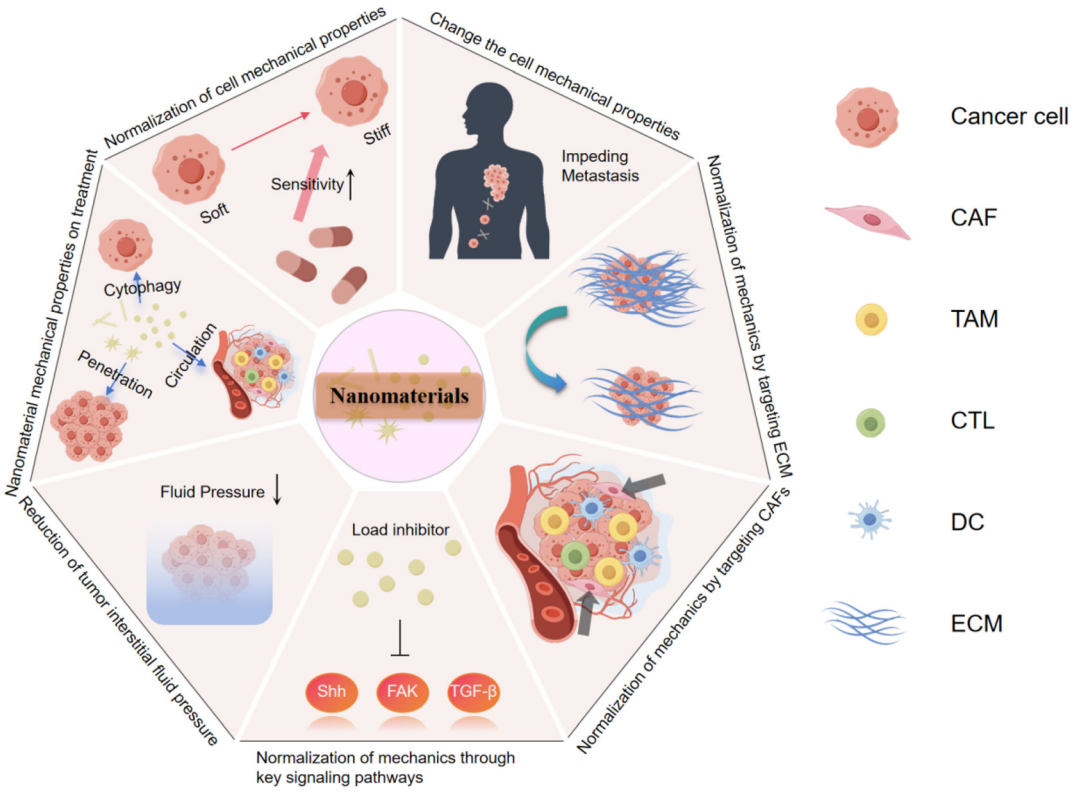


**Fig. 1** Mechanical properties in nanomaterials for tumor therapy (by Figdraw).

### 2.1 Enhancing treatment sensitivity through alteration of cancer cell mechanics by nanomaterials

The phenomenon of drug resistance in cancer cells presents a formidable challenge in oncological therapeutics. It has been postulated that the unique mechanical properties of cancer cells may contribute to their resistance to pharmacological interventions. Consequently, altering the mechanical properties of cancer cells to mirror those of normal cells could enhance their responsiveness to treatment. This concept paves the way for the innovative application of nanomaterials in cancer therapy, potentially improving treatment outcomes by modulating cellular mechanics.

Self-assembling nanomaterials are capable of forming nanofibers within cancer cells in response to the heterogenous enzymes these cells express. This process enhances the mechanical tension within the cancer cells, thereby increasing their susceptibility to chemotherapeutic agents. Jie Li and colleagues engineered a small peptide precursor incorporating a carboxylesterase-sensitive substrate.[17] Upon cellular uptake by cancer cells, this precursor is cleaved by carboxylesterase, triggering self-assembly into nanofibers (Fig. 2a). This innovative approach has been shown to heighten the sensitivity of drug-resistant ovarian cancer cells to cisplatin, a commonly used chemotherapy drug, without exacerbating systemic toxicity.[17] Self-assembled nanomaterials offer the dual functionality of enzyme-guided assembly within cells and morphological transitions for efficient drug delivery. Xiaotong Cheng and colleagues developed a deformable nanoparticle, Nap-AZD-Yp, which is equipped with self-loading peptide chains. Within the cancer cell milieu, Nap-AZD-Yp undergoes a morphological transition from nanospheres to nanofibers under the sequential catalysis of alkaline phosphatase and carboxylesterase, culminating in the release of an encapsulated autophagy inducer (Fig. 2b).[18] In its initial state, the peptide conjugate Nap-AZD-Yp self-assembles into spherical nanoparticles in solution, which then preferentially accumulate within tumor tissue *via* the bloodstream, leveraging the Enhanced Permeability and Retention (EPR) effect. Upon cellular uptake through endocytosis, these nanoparticles encounter an overexpression of alkaline phosphatase on cancer cell membranes leading to dephosphorylation, followed by a carboxylesterase-mediated transformation into nanofibers. This sequential reaction not only augments intracellular accumulation but also induces an increase in mechanical tension within cancer cells. These studies further demonstrate that this heightened mechanical tension can facilitate drug endocytosis and concurrently impede cancer cell migration.[18] Valeria De Matteis *et al.* have substantiated that nanomaterials possess the capability to alter cytoskeletal structure and Young's modulus, consequently inducing phenotypic alterations in cancer cells.[19] In essence, modulating the mechanical characteristics of cancer cells *via* nanomaterials presents a novel approach to addressing drug resistance, thereby offering a fresh perspective for constructing nanocarrier-based drug platforms and enhancing drug delivery efficacy.

In contrast to self-assembled nanoparticles, which provide gentle support to cancer cells, enhancing their chemotherapy sensitivity by increasing mechanical tension, deformable nanoparticles apply a penetrating force directly on cancer cells or their organelles, leading to cell destruction and enabling effective cancer treatment. Through their research, Xuelin

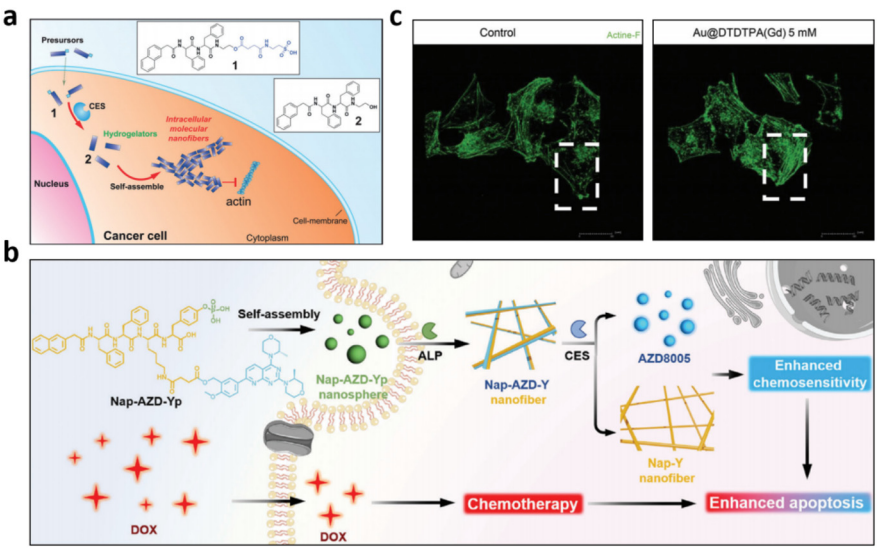


**Fig. 2** (a) Enzymatic transformation of the precursor (1) asasubstrate of carboxylesterase (CES) to the corresponding hydrogelator (2) for intracellular self-assembly. Reproduced from ref. 17 with permission from John Wiley and Sons, copyright 2015. (b) Schematic illustration of Nap-AZD-Yp working mechanism in enhancing the chemotherapeutic efficacy of DOX through synergetic actions of cancer-specific intracellular nanofiber formation and autophagy inducer release. Reproduced from ref. 18 with permission from John Wiley and Sons, copyright 2022. (c) Representative *z*-stack images of the F-actin cytoskeleton (Alexa Fluor™ 488 Phalloidin) obtained by confocal microscopy. Reproduced from ref. 25 with permission from Royal Society of Chemistry, copyright 2021.

 

Wang *et al.* observed significant morphological changes in membrane-encapsulated gallium nanospheres when exposed to low temperatures.[20] Transmission electron microscopy revealed the formation of cactus-like structures at low temperatures, causing physical and mechanical disruption of endosomal membranes.[20] This phenomenon enhances drug escape from endosomes, facilitating efficient drug payload release from gallium nanospheres, thereby augmenting chemotherapy sensitivity and enhancing the efficacy of tumor cryoablation treatment.[20] Consequently, applying force to the organelles of cancer cells, or even directly to cancer cells themselves, to induce rupture represents a novel approach to cancer therapy.

### 2.2 Impeding metastasis *via* nanomaterial-induced changes in cancer cell mechanic

The metastatic spread of cancer cells is a hallmark of malignancy, often resulting in the emergence of secondary tumors at sites distant from the primary lesion.[21] This characteristic significantly contributes to the complexity and challenge of achieving a cure for cancer. Throughout tumorigenesis, cancer cells undergo alterations not only in their stiffness but also in their motility, adhesion, and contractility. Typically, these transformed cells exhibit reduced stiffness, increased propensity for deformation, and diminished adhesion to neighboring cells, collectively enhancing their proliferative capacity.[9] Consequently, the mechanical stiffness of cancer cells is a determinant that can influence the efficacy of their migration.

Gold nanoparticles (AuNPs) have been extensively investigated for their significant contributions to the suppression of tumor proliferation and the inhibition of metastasis. These nanoparticles not only promote the normalization of tumor vasculature and counteract the epithelial–mesenchymal transition (EMT) in cancer cells, thereby modulating the ECM,[22,23] but they also have been documented to impair cell viability through their interactions with actin.[24] Research by Maxime Durand *et al.* revealed that ultrasmall gadolinium-chelated gold nanoparticles (Au@DTDTPA(Gd)), when employed in image-guided radiotherapy for brain tumors, are capable of localizing within glioma cells. These nanoparticles reorganize the actin cytoskeleton and cellular adhesion structures, leading to an elevation in cellular Young's modulus and a subsequent attenuation of cell migration (Fig. 2c).[25] In contrast, Ahmad Sohrabi Kashani *et al.* reported that upon exposure to gold nanospheres, human lung cancer cells (A549) experienced a marked reduction in stiffness and adhesion properties, but this was paradoxically associated with a decrease in their migratory potential.[26] In a similar vein, Hefang Xiao *et al.* discovered that silver nanoparticles inflict structural damage on the cytoskeleton and cell membrane, augment membrane roughness, and diminish both adhesion and membrane stiffness.[27] Benoit Toubhans *et al.* conducted an evaluation of the anticancer efficacy of protein (BSA) and carbohydrate (chitosan) coated inorganic selenium nanoparticles (SeNPs) on two serous ovarian cancer cell lines, OVCAR-3 and SKOV-3, observing a decline in cellular activity with divergent effects on mechanical properties.[28] The reduction in surface roughness and membrane stiffness observed in OVCAR-3 cells may be indicative of an enhanced susceptibility to apoptosis or autophagy. Conversely, SKOV-3 cells exhibited an increase in membrane surface roughness and stiffness coupled with diminished motility.[28]

In conclusion, it appears that cancer cells exhibit optimal migratory efficiency at a specific cellular stiffness; deviations from this optimal state—whether towards increased rigidity or pliability—result in reduced migration efficiency. Thus, by modulating the mechanical properties of cancer cells through nanomaterials intervention, it is feasible to effectively hinder cancer metastasis. This approach heralds a promising new direction for therapeutic strategies targeting cancer dissemination.

## 3 Modulation of tumor microenvironment by nanomaterials

A rigid TME not only facilitates tumor progression but also poses obstacles to drug delivery. As a result, the normalization of TME by modifying its mechanical properties has surfaced as a crucial strategy in cancer therapeutics. In this context, nanomaterials exhibit substantial potential; they can bolster the efficacy of tumor therapy by modulating the mechanical properties inherent to the tumor microenvironment.

### 3.1 Normalization of tumor microenvironment mechanics by targeting extracellular matrix components

The ECM, a physical barrier primarily composed of collagen, elastin, laminin, hyaluronic acid, and other constituents,[29] poses a significant challenge to the delivery of nanomaterials. Conventional strategies have centered on the use of proteases to degrade the ECM, thereby enhancing the permeability of nanomedicine. For instance, Liu and colleagues engineered a coordination polymer (NCP) using $Mn^{2+}$ and benzoimide to encapsulate collagenase (CLG), which was subsequently modified with polyethylene glycol (PEG) to create a pH-responsive nanoparticle drug delivery system (CLG@NCP-PEG).[30] In the acidic TME, the NCP structure disassembles and releases CLG that specifically degrades collagen components in the TME, thereby loosening the ECM structure and facilitating drug penetration (Fig. 3a).[30] In another study, Ting Yin *et al.* conjugated CLG with human serum albumin (HSA) and further coated it with iron prophyrin (FeP) and molecular oxygen to develop a novel nano-acoustic sensitizing agent ($FePO_2$@HC) (Fig. 3b).[31] In tumors where reducing glutathione (GSH) is overexpressed, HSA disintegrates, leading to the release of components in $FePO_2$@HC. The released CLG degrades collagen fibers in the tumor, disrupting tumor tissue and resulting in $FePO_2$ accumulation within the tumor. In hypoxic conditions, $FePO_2$ releases oxygen molecules to mitigate tumor hypoxia. Upon ultrasound irradiation, acoustic sensitizing agent FeP activates surrounding $O_2$ molecules producing singlet oxygen that exhibits cytotoxic effects on cancer cells.[31] The reduction of collagen levels also decreases ECM pressure,

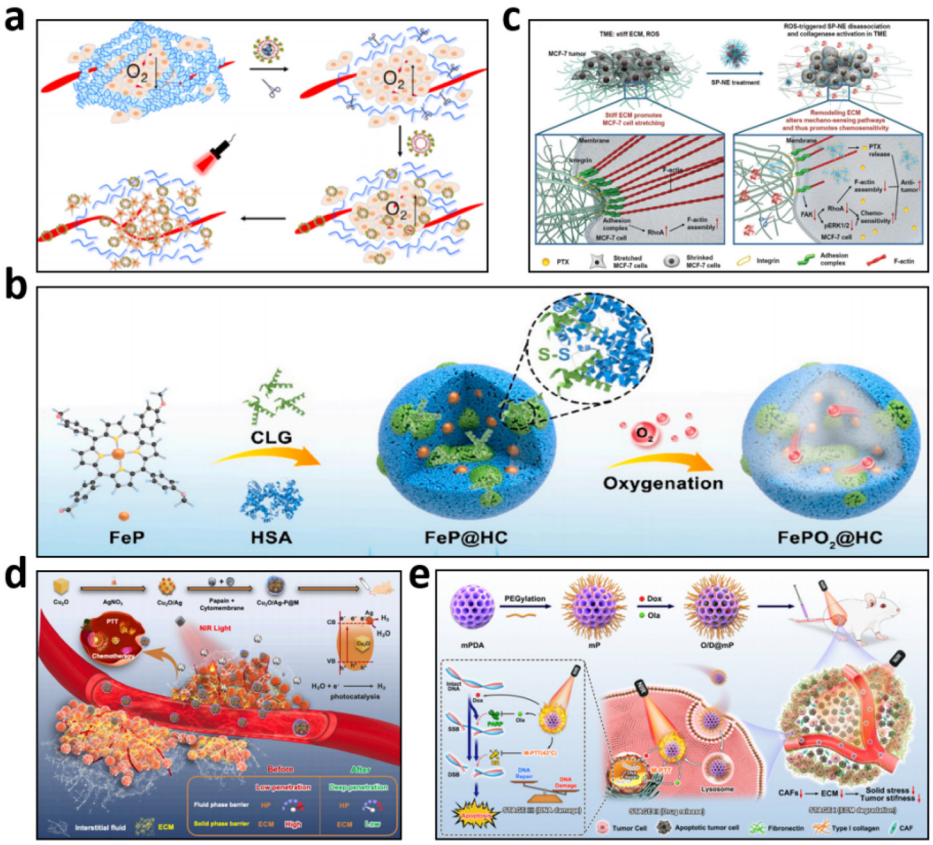


**Fig. 3** (a) Schematic representation of the modulation of the tumor microenvironment and photodynamic therapy mediated by CLG@NCP-PEG. Reproduced from ref. 30 with permission from American Chemical Society, copyright 2018. (b) The design of $FePO_2$@HC. FeP was first prepared and then encapsulated with CLG and HSA, constructing the multifunctional nanoparticles (FeP@HC). The $FePO_2$@HC were obtained after oxygenation. Reproduced from ref. 31 with permission from Elsevier, copyright 2023. (c) The proposed mechanism of SP-NE-modulated mechanical remodeling of ECM to enhance MCF-7 cells' susceptibility toward chemotherapy: in the presence of ROS in TME, SP-NE is disassociated, resulting in release of collagenase for ECM softening and PTX prodrug for chemotherapy within cells; the dramatically relieved ECM stiffness compromises the mechanical signaling events of integrin-FAK-RhoA involved in enhancing F-actin assembly dynamics and integrin-FAK-pERK 1/2 mediating mitosis, leading to an unfavorable state of cells with shrinked morphologies and dampened cytoskeleton, and improved chemosensitivity. Reproduced from ref. 32 with permission from John Wiley and Sons, copyright 2020. (d) Schematic illustration of the $Cu_2O$/Ag-P@M for overcoming the barriers of tumor interstitial solid and fluid phases to boost the tumor penetration and therapeutic efficacy. Reproduced from ref. 33 with permission from Elsevier, copyright 2022. (e) The preparation of O/D@mP nanomedicine and its action mechanism. Reproduced from ref. 35 with permission from Elsevier, copyright 2023.

which can enhance chemotherapy sensitivity. For instance, Yinan Zhong *et al.* combined collagenase and paclitaxel (PTX) to construct an active oxygen-activated nanase (SP-NE) based on a dendritic polyglycerol scaffold.[32] Upon encountering abundant reactive oxygen species in the TME, the nanase decouples due to the cleavage of terminal diacetylenic oxalic acid crosslinkers, and the release of collagenase alleviates ECM pressure. This process facilitates the release of the PTX prodrug for efficient delivery into tumor cells (Fig. 3c).[32] In a human mammary gland MCF-7 tumor-bearing mouse model, this nanosystem demonstrated a significant reduction in ECM pressure from 4300 to 1200 Pa, and the tumor growth inhibition rate reached 87.1% under low dose PTX administration,[32] thereby enhancing chemotherapy drug sensitivity.

Nevertheless, the protein degradation strategy is not without limitations. The degradation products of the ECM, namely amino acids and peptides, may increase the osmotic pressure within the tumor interstitium. This pressure differential may cause water to flow into this space, which is unfavorable for drug delivery. Moreover, an increase in interstitial fluid pressure can also impede drug penetration. Consequently, Zining Hao and colleagues proposed a strategy in which papain was incorporated into a homologous tumor cell membrane and coated with a $Cu_2O$/Ag nanoparticle photocatalyst.[33] Near-infrared light stimulation induced $Cu_2O$/Ag to generate heat, promoting ECM enzymatic digestion by papain and eliminating solid barriers within the tumor interstitium. Simultaneously, $Cu_2O$/Ag was excited to produce photoelectrons and holes that could decompose water, thereby reducing fluid volume in the tumor interstitium and decreasing hydrostatic pressure accordingly (Fig. 3d).[33] This method enables synchronous decomposition of both solid and liquid

 

phases of the tumor interstitium, enhancing the targeting, penetration, and therapeutic efficacy of nanomaterials.[33]

Nanomaterials can also reduce ECM stiffness through their inherent properties, in addition to drug loading capabilities. Photothermal therapy (PTT) has emerged as a novel method for precise cancer treatment due to its advantages of localized treatment, non-invasiveness, and temperature control.[34] Nanomaterials with broad spectral absorption and excellent photothermal conversion properties are preferred for PTT applications. For instance, Yuxuan Xiong *et al.* co-loaded Olaparib (Ola) and Doxorubicin (Dox) into polyethylene glycol mesoporous polydopamine (mPDA) nanoparticles (O/D@mP). The PDA nanoparticles exhibited photothermal conversion characteristics.[35] Upon near-infrared light irradiation, the temperature within the tumor increased, leading to ECM degradation and normalization of the mechanical properties of the TME, thereby enhancing drug penetration (Fig. 3e).[35] Studies have demonstrated that local mild photothermal therapy (M-PTT) can significantly reduce the content of collagen fibers, type I collagen, and fibronectin. Post M-PTT treatment, the content of collagen fibers, type I collagen, and fibronectin decreased by 37.8%, 77.1%, and 36.7% respectively, and there was a significant reduction in the tumor's Young's modulus. Furthermore, tumor vascular distortion was reduced, which is beneficial for drug delivery and penetration.[35]

In conclusion, by targeting ECM components within tumors, nanomaterials can effectively alter the mechanical properties of the tumor microenvironment and normalize it. This leads to an improvement in drug permeability and therapeutic efficacy.

### 3.2 Normalization of tumor microenvironment mechanics *via* modulation of cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) are one of the primary stromal cells within the tumor microenvironment. They not only foster tumor growth[36,37] and metastasis,[38,39] hinder drug penetration,[40] but also aid tumor cells in evading immune surveillance.[41] CAFs generate high contractility through the secretion of matrix proteins and the expression of α-SMA. This, in conjunction with excessive ECM deposition, amplifies local microenvironmental stiffness.[42] Consequently, CAFs are a significant source of solid pressure within tumors, and directly targeting CAFs emerges as a viable strategy for cancer treatment. For instance, Tianjiao Ji *et al.* developed a peptide nanoparticle (PNP-D-mAb) that was loaded with the anti-cancer drug doxorubicin (Dox) and electrostatically modified with a mouse monoclonal antibody (mAb) targeting human fibroblast-activating protein-α (FAP-α) on the particle surface.[43] This construct can specifically target CAFs and accumulate within tumor tissues. Once at the tumor site, PNP-D-mAb interacts with FAP-α expressed on the cell membrane of CAFs through surface-attached anti-FAP mAb. This interaction facilitates binding to CAFs and depletes them, thereby disrupting the TME barrier and enhancing Dox penetration within tumor tissues.[43]

CAFs constitute the most abundant ECM population. Upon nanoparticle injection into tumors, fibroblasts are first encountered by these particles. Alba Nicolas-Boluda *et al.* discovered that even without any CAF-targeting agents and in a competitive environment, CAFs can preferentially uptake multifunctional iron oxide nanoflowers (GIONF) modified with gold nanoparticles over cancer cells.[44] Therefore, GIONF-mediated photothermal therapy can be utilized to deplete CAFs. GIONF comprises ultra-small gold nanoparticles (Au@DTDTPA) with a 2–3 nm gold core coated with dithiodylenetriamine pentaacetic acid and affixed to a flower-like single crystal structure (IONF) composed of small iron oxide nanoparticles. This structure retains its photothermal effects even after cellular internalization.[44] The quantity of GIONF internalized by fibroblasts was five times higher than that by macrophages. To further simulate tumor progression, EGI-1 (human bile duct cancer cells) and hTERT-HSC (human liver fibroblasts) were co-cultured at a 1 : 1 ratio. The results post GIONF incubation demonstrated that, even in a competitive environment, CAFs preferentially consumed GIONF.[44] Therefore, although dense ECM may induce off-target effects of cytotoxic drugs and form a protective barrier for cancer cells, this effect can be harnessed to directly target CAFs, thereby reducing TME stiffness and enhancing the therapeutic effect on tumor cells.

In addition to reducing tumor solid pressure by targeting and eliminating CAFs, inactivating CAFs is also an effective strategy for remodeling the TME. CXCL12, directly secreted by CAFs, not only activates various TME responses but also maintains the pro-tumor phenotype of CAFs. Therefore, downregulating CXCL12 is an effective method to inactivate CAFs.[45] Jiayan Lang *et al.* developed a nanoparticle system based on cell-penetrating peptides to deliver CXCL12 silencing siRNA. This system targets CAFs using anti-FAP-α mAb, successfully downregulating CXCL12 expression, remodeling the TME, and inhibiting tumor metastasis.[46]

In summary, while the accumulation of CAFs in the oncogenic process contributes to increased solid stress within the TME, both active and passive targeting strategies directed at CAFs can mitigate this stress and promote normalization of the TME. Consequently, targeting CAFs represents a potent approach to enhancing the therapeutic efficacy of nanomaterials in tumor treatment.

### 3.3 Normalization of tumor microenvironment mechanics through inhibition of key signaling pathways

**3.3.1 Modulation of the sonic hedgehog (Shh) signaling pathway.** The hedgehog (Hh) signaling pathway, an evolutionarily conserved signaling cascade, can be subdivided into Indian hedgehog (Ihh), Desert hedgehog (Dhh), and Sonic hedgehog (Shh) based on tissue location. These pathways play pivotal roles in tissue development and homeostasis, with Shh being the most extensively studied.[47] Disruption of the Shh signaling pathway can precipitate or accelerate the onset of cancers, and dysfunction of this pathway is observed in various malignant tumors, including pancreatic cancer and hepatocellular carcinoma.[48–50] The Shh signaling pathway exerts a crucial regulatory influence on CAFs activation and

matrix deposition.[51] The Shh pathway is highly active in paracrine signaling within the ECM of certain pancreatic tumors. Here, Shh binds to the Patched1 protein (PTCH1) on target cells, leading to the activation of the Smoothened (SMO) receptor. Subsequently, this activates the expression of downstream GLI transcription factors and downstream targets GLI1, PTCH, BCL2, MYC, and IGF2 to foster cell proliferation.[52] The SMO receptor is highly expressed in pancreatic cancer-associated fibroblasts but is absent in pancreatic cancer cells.[52] Activation of the Shh pathway results in increased proliferation of pancreatic cancer-related fibroblasts. Therefore, Shh inhibitors can suppress CAFs proliferation, thereby mitigating tumor fibrous tissue proliferation and reducing tumor matrix collagen content.[52] This process effectively regulates the mechanical properties of TME.

While Shh inhibitors present a promising strategy for CAFs depletion, their efficacy in extending median survival in pancreatic ductal adenocarcinoma (PDAC) has been disappointing.[53] Although collagen in the ECM poses a significant barrier to drug penetration, it is crucial to maintain a certain collagen level while degrading the ECM. Collagen loss can induce epithelial–mesenchymal transition (EMT) in tumor cells, leading to a more aggressive and metastatic tumor phenotype.[54] Therefore, preserving the tumor-suppressive function of the collagen matrix during treatment is of paramount importance. High doses of Shh inhibitors may also induce severe systemic toxicity and potential off-target effects. Hence, PDAC can be addressed by developing nanodrug delivery systems. For instance, Jun Zhao *et al.* developed a nanoparticle based on polymer micelles (M-CPA/PTX), which co-encapsulated the classic Shh inhibitor cyclopamine (CPA) with the cytotoxic chemotherapy drug paclitaxel (PTX).[55] This approach reduced the tumor elastic modulus by 55%, and diminished CAFs, HA, and collagen crosslinking enzyme content without eroding the collagen matrix.[55] Consequently, this enhanced cancer cells' sensitivity to treatment and controlled metastasis risk. To achieve better targeted response and improve drug delivery efficiency, Pei-Hsuan Hsieh *et al.* constructed a dual-responsive polypeptide nanoparticle. This nanoparticle was loaded with Dox through self-assembly of two amphipathic polymers in an aqueous phase and simultaneously encapsulated with Shh inhibitor Vismodegib.[56] Under the combined influence of an acidic TME and overexpressed glutathione in cancer cell lysosomes, nanoparticles disintegrated and released Vismodegib. This inhibited the expression of type I collagen, type IV collagen, and fibronectin. Concurrently, due to the abnormal upregulation of cathepsin B (Cat-B) and matrix metalloproteinases (MMPs) in the tumor region, Dox was released from the cleaved polymer substrate to achieve efficient drug delivery.[56]

In recent years, studies have confirmed the role of the CXCL12–CXCR4 signaling axis in the Shh pathway and its pathobiological role in pancreatic cancer.[57] Sheema Khan *et al.* developed superparamagnetic iron oxide nanoparticles (SPION) loaded with curcumin. Curcumin inhibited tumor stromal proliferation by suppressing the CXCL12/CXCR4 signaling axis and Shh signaling pathway, while significantly increasing pancreatic cancer cells' elastic modulus. This approach enhanced chemotherapy drug gemcitabine's sensitivity and inhibited cell migration.[58]

**3.3.2 Modulation of the focal adhesion kinase (FAK) signaling pathway.** The interaction between cells and ECM is not only affected by the chemical composition and structural organization of ECM, but also by its mechanical properties. Therefore, cells can sense and regulate ECM to regulate mechanical homeostasis.[59] The forces generated by the cytoskeleton of tumor cells and tumor stromal cells can be applied to the ECM through mechanical signaling to increase its stiffness.[59,60] These "inside-out" tension transfers are mainly mediated by integrins of attached cells, a process associated with the activation of Focal adhesion kinase (FAK).[61] Therefore, targeting FAK in tumor tissues to regulate the mechanical properties of tumor cells and ECM provides a new perspective for improving the efficiency of tumor therapy. Di Zhang *et al.* delivered small interfering RNA of FAK (siFAK), mRNA of Cas9 and sgRNA (siFAK + CRISPR-LNPs) through lipid nanoparticles (LNP) to achieve tumor targeted delivery and enhance gene editing effect.[62] Experiments have shown that the siRNA of FAK silences the expression of FAK and increases the cellular uptake of LNP by promoting the grid protein and vesicular dependent endocytosis pathway.[62] In addition, compared with the control group, the stress fibers and myosin networks in siFAK + CRISPR-LNPs treated cells were reduced, and the contractile force of cells was decreased. In addition, myosin network accumulated in a large amount in the peripheral region of cells, and the arrangement of stress fibers and F-actin was significantly reduced, which may induce membrane invagination and thus reduce membrane tension, which is conducive to LNP endocytosis.[62] Therefore, inhibition of FAK can reduce the contractile force, membrane tension and ECM stiffness of tumor cells, increase the endocytosis and tumor penetration of LNP, enhance the effect of CRISPR gene editing *in vitro* and *in vivo*, inhibit tumor metastasis and growth, and provide a new idea for using CRISPR gene editing to treat cancer.[62]

**3.3.3 Modulation of the transforming growth factor-β (TGF-β) signaling pathway.** Transforming growth factor-β (TGF-β) is a quintessential ECM regulator that stimulates CAFs to produce proteases, enhancing ECM protein synthesis and inducing excessive ECM deposition.[63] Jitang Chen *et al.* devised a strategy that combines self-assembled nanoparticles (HES-CE6) composed of hydrophilic hydroxyethyl starch (HES) and chlorin e6 (Ce6) with a TGF-β inhibitor (LY2157299). This approach modulates the tumor ECM by blocking TGF-β and enhancing photodynamic therapy (PDT).[64] Pretreatment with the TGF-β inhibitor effectively down-regulates collagen expression, significantly reduces solid stress within tumor tissues, and improves HES-Ce6 delivery.[64]

Furthermore, the application of nanodrug delivery systems to administer antifibrotic drugs, which inhibit the TGF-β signaling pathway and deplete ECM components, represents an alternative strategy for normalizing the mechanics of the TME.

 

Pirfenidone (PFD) is an antifibrotic drug used to treat idiopathic pulmonary fibrosis. It normalizes the TME by inhibiting the TGF-β signaling pathway and reducing collagen and hyaluronic acid content.[65,66] Shi-Bo Wang *et al.* loaded PFD into covalent organic frameworks (COF) to prepare a nanodrug delivery system (PFD@$COF_{TTA-DHTA}$@PLGA-PEG, PCPP).[67] Through the enhanced permeability and retention (EPR) effect of nanoparticles, PCPP accumulates at the tumor site and releases PFD. This down-regulates type I collagen and hyaluronic acid levels, reduces solid stress in tumor tissue, alleviates pressure on tumor blood vessels, restores vascular function, enhances homing of subsequently injected nanomicelles formed by protoporphyrin IX-coupled peptides (NM-PPIX), and enhances the PDT effect.[67] Tranilast, another antifibrotic and antihistamine drug, can also reduce ECM mechanical stress and interstitial fluid pressure by inhibiting TGF-β signaling and expression.[68] To mitigate liver and kidney damage caused by Tranilast, Myrofora Panagi *et al.* developed polymer nanomicelles loaded with Tranilast. Compared with free drugs, micelles loaded with lower drug doses demonstrated more effective TME normalization and improved tumor immunotherapy efficacy.[69]

The angiotensin II receptor inhibitor losartan can also be used to inhibit the expression of TGF-β, reduce pro-fibrosis signaling downstream, decrease collagen and hyaluronic acid content, and reduce ECM solid stress. This contributes to combination therapy in cancer.[70–72] As losartan is an antihypertensive drug that can easily cause hypotension, Suchen Bian *et al.* proposed losartan-loaded nanoparticles based on a small-molecule assembly strategy. They constructed Losartan-linolic acid (Los-LA) conjugates which more effectively deplete the dense tumor interstitial barrier and increase blood perfusion compared to free losartan.[73]

### 3.4 Reduction of tumor interstitial fluid pressure increases drug penetration

The lymphatic reflux in tumor tissues is obstructed and the ECM density is high, leading to the retention of interstitial fluid. Consequently, the fluid pressure within the tumor interstitium is elevated compared to normal tissue, severely impeding the targeting and penetration of nanomaterials. Yuchu He *et al.* grew *in situ* thermoelectric material cadmium sulfide (CdS) on ultra-thin $Nb_2C$ nanosheets and modified them with tumor-targeting hyaluronic acid (HA) to prepare "nano-lymph" (M/CDS-HA). This not only ablates ECM through photothermal therapy but also decomposes water in interstitial fluid through pyroelectricity. This resulted in a 52% reduction in tumor interstitial pressure and effectively enhanced drug penetration.[74] Therefore, mitigating tumor interstitial fluid pressure represents an effective approach to enhance nanomaterial delivery efficiency.

### 3.5 Normalization of tumor microenvironment mechanics enhances immunotherapy

During tumor development, cancer cells can acquire phenotypic characteristics that allow them to evade immune cell-mediated destruction, thereby achieving immune escape and promoting tumor progression.[75] Studies have shown that macrophages are sensitive to matrix stiffness,[76] and John W. Hickey *et al.* demonstrated that softer ECM regulates T cell signaling through mechanical cues, leading to the rapid proliferation of cultured $CD8^+$ T cells, which can inhibit tumor growth.[77] Other immune cells are also influenced by mechanical forces and play various roles in tumor immunity.[78] Therefore, the stiffness of the TME plays a critical role in immune escape mechanisms. Modulating the mechanical properties of the TME to enhance immunotherapy represents an effective cancer treatment strategy. Fotios Mpekris *et al.* combined mechanical therapies, such as antihistamines and ultrasound, with nano-immunotherapy, showed that mechanical treatments effectively reduced TME stiffness, increased drug perfusion, and improved immune responses by increasing the numbers of $CD4^+$ and $CD8^+$ T cells while decreasing the number of immunosuppressive regulatory T cells, thereby enhancing anti-tumor efficacy.[79] Currently, research combining the alteration of TME mechanical properties with cancer immunotherapy is in its early stages. This suggests that future studies should further explore the mechanical characteristics of the TME in different tumor types and their impact on immunotherapy, providing more detailed scientific evidence for precision medicine.

## 4 Influence of nanomaterial mechanical properties on cancer treatment efficacy

To enhance the efficacy of drug delivery and achieve superior targeting effects, the study of nanomaterials' physicochemical properties has garnered significant attention in recent years. The mechanical properties of nanomaterials, which influence their biological distribution, cellular uptake, metabolic clearance, and therapeutic impact, are among their crucial characteristics. When nanomaterials approach cells, the interaction forces between the nanomaterials and the cell membrane mediate the endocytosis of the nanomaterials.[80] Consequently, comprehending the mechanical properties of nanomaterials is a prerequisite for the rational design of efficient nanomaterials.

### 4.1 The effect of nanomaterial stiffness and deformability on cancer therapy

**4.1.1 Therapeutic applications of soft nanomaterials in oncology.** Xin Yi *et al.* developed a theoretical model of nanomaterial endocytosis. Their energetic analysis revealed that the endocytosis process is highly sensitive to the relative stiffness between nanomaterials and the cell membrane.[81] Rigid nanomaterials are more readily enveloped by the cell membrane and subsequently internalized by the cell compared to their softer counterparts.[81] *In vitro* studies have demonstrated that cells exhibit greater phagocytic activity and speed towards hard nanoparticles compared to soft nanoparticles, a feature that is particularly pronounced in macrophages.[82] As cells become

"softer", their capacity to sense the stiffness of nanomaterials tends to decrease. Consequently, although cancer cells ingest more hard nanoparticles than soft ones, the difference is not as pronounced as in macrophages.[83] Soft nanoparticles, due to their deformability during cellular endocytosis and the higher energy required for membrane encapsulation, exhibit greater resistance to phagocytosis and a longer *in vivo* circulation time.[82,84] Furthermore, a decrease in stiffness can reduce the clearance rate of nanoparticles by the spleen,[85] and soft nanoparticles can persist in blood circulation through biological barriers, thereby enhancing their tumor targeting.[83] Prolonging blood circulation and reducing macrophage capture can enhance the EPR effect of nanoparticles. Additionally, the cell adhesion effect of soft nanoparticles aids in their accumulation within tumor tissues, thereby enhancing their targeted accumulation effect.[86] Yue Hui *et al.* co-cultured nanocapsules of varying stiffness with tumor spheroids and found that despite higher intake of hard nanocapsules, their uptake within tumor spheroids sharply declined. In contrast, soft nanocapsules exhibited stronger penetration (Fig. 4a).[83] Hard nanocapsules' poor deformability may prevent them from traversing narrow cellular spaces. Their high cell uptake tendency leads to greater accumulation at the periphery of tumor spheroids. However, soft nanocapsules can deform through intercellular spaces and penetrate deeply into tumor spheroids. In summary, soft nanomaterials demonstrate superior therapeutic effects within tumors.

**4.1.2 Therapeutic applications of hard nanomaterials in oncology.** Despite the numerous advantages of soft nanoparticles, it is not feasible to continuously soften these particles to enhance their penetration. Nanoparticles must traverse biohydrogel barriers, such as mucus and tumor stromal matrices, to reach cancer cells. This represents a significant obstacle for nanomaterial delivery. Miaorong Yu *et al.* demonstrated that nanoparticles of moderate stiffness exhibited superior diffusion efficiency in both fresh undiluted rat intestinal mucus bio-hydrogel and polyethylene oxide (PEO) hydrogel.[87] These moderately stiff spherical nanoparticles deformed into an ellipsoid shape within the complex hydrogel network structure, facilitating rapid diffusion. Conversely, soft nanoparticles underwent excessive and irregular shape changes, became interspersed with and confined by gel polymers, and exhibited lower permeability.[87] Given that tumors are enveloped by biohydrogels, nanoparticles of moderate stiffness demonstrate higher permeability within tumor spheroids (Fig. 4b).[87]

Numerous studies have suggested that hard nanoparticles are more readily phagocytosed by cancer cells. For instance, Jiashu Sun *et al.* demonstrated that hard nanoparticles loaded with doxorubicin and Combustatin A4 exhibited greater cytotoxicity than their soft, drug-loaded counterparts.[88] Hamzah Al-Madani *et al.* have also substantiated that $Zn_xFe_{3-x}O_4$ nanoparticles with higher hardness exhibit increased cellular uptake efficiency and reduced cellular activity.[89] Due to the diverse properties of nanomaterials, cancer cells exhibit different forms of phagocytosis towards these nanomaterials. Peng Guo *et al.* discovered that the uptake of soft liposome nanoparticles by MDA-MB-231 and MCF-7 cancer cells occurs *via* endocytosis and membrane fusion, while rigid hydrogel liposome nanoparticles can only enter cells through endocytosis.[90] Given that membrane fusion requires less energy than endocytosis, the uptake rate of cancer cells for soft liposomes is significantly higher than for hard liposomes when membrane fusion is the primary mode of cellular entry. Therefore, nanomaterials should not be indiscriminately hardened to address the issue of cancer cell uptake. Yuan Liu *et al.* assembled calcium carbonate nanorods (NRs) with a length-to-diameter ratio of approximately 2.4 and a hyaluronic acid (HA) hydrogel layer to prepare nanorods with adjustable stiffness ($CaCO_3$@HA NRs). In the acidic TME, $CaCO_3$ degraded, facilitating a transformation from a rod-like to spherical shape. The stiffness of these spherical nanocapsules was adjusted by HA.[91] An increasing number of HA layers led to a progressive hardening of the nanocapsules' membrane. Experiments demonstrated that HA4 NCs exhibited higher cellular uptake and cytotoxicity than HA2, HA6, and HA8 NCs.[91] Therefore, when utilizing nanomaterials for tumor treatment, it is essen-

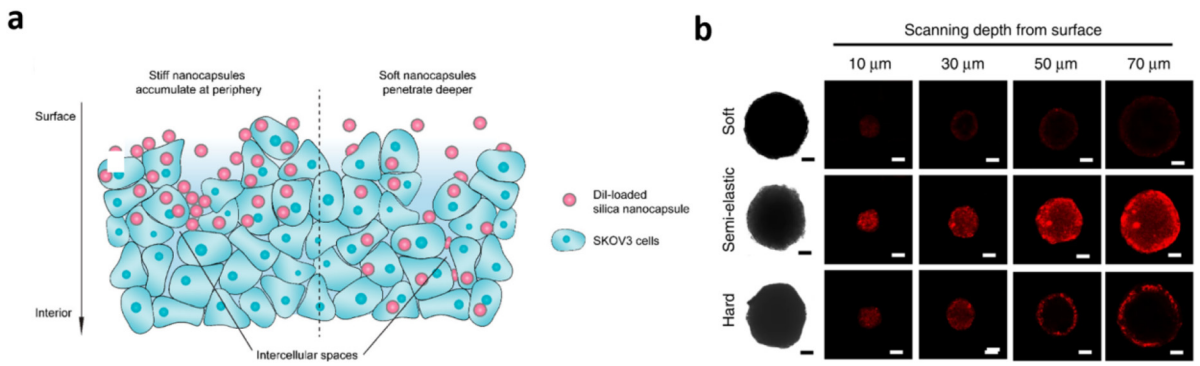


Fig. 4 (a) Schematic illustration showing the penetration of stiff and soft nanocapsules in the tumor spheroids. Reproduced from ref. 83 with permission from American Chemical Society, copyright 2018. (b) NP penetration into the BxPC-3 and HPSC multicellular spheroids. *Z*-stack images were obtained starting from the top and into the core of the spheroid at intervals of 20 μm. Reproduced from ref. 87 with permission from Springer Nature, copyright 2018.

 

tial to fully consider the biological characteristics of tumors, such as biological clearance, cell uptake, tissue penetration, *etc*., and to select nanomaterials with appropriate stiffness to achieve optimal therapeutic effects.

**4.1.3 Utilization of rigid-to-flexible transforming nanomaterials in cancer therapy.** The mononuclear macrophage system, acting as an internal biological barrier, plays a crucial role in isolating and impeding drug delivery. Therefore, to achieve higher drug delivery efficiency, nanomaterials should avoid macrophage uptake as much as possible. However, in cancer treatment, to optimize therapeutic outcomes, it is desirable for cancer cells to internalize more nanoparticles. Current methods for preparing nanoparticles with adjustable stiffness include hydrogel nanoparticles, polymer-lipid nanoparticles, and silica nanocapsules.[92]

Expanding upon the role of nanoparticle stiffness in tumor therapy, Jun Tao *et al.* constructed a manganese oxide hybrid mesoporous organosilica nanoparticle platform (MMON), which transformed into a bowl-shaped soft nanoparticle through Mn–O bond fracture in simulated TME.[93] This transformation resulted in a decrease in Young's modulus from 165.7 MPa to 84.5 MPa.[93] Owing to their unique stiffness transformation characteristics, MMONs reduced macrophage internalization, improved tumor cell uptake, and enhanced penetration of multicellular spheroids. *In vivo* experiments demonstrated that compared with soft and hard MMONs, the non-specific liver distribution of rigidly-converted MMONs decreased by 3.79 and 2.90 times respectively while tumor accumulation increased by 2.87 and 1.83 times respectively. This significantly improved the therapeutic effect on tumors.[93] In conclusion, rigidly-convertible nanomaterials demonstrate significant potential and advantages for tumor therapy and provide a promising direction for future research.

### 4.2 The effect of nanomaterial morphology on cancer therapy

At the nanoscale, the interaction between nanomaterials and cancer cells is influenced not only by size and stiffness, but also by nanomaterial morphology. Udesh Dhawan *et al.* fabricated core–shell cobalt-gold nanoparticles with spherical (Co@Au NPs) and elliptical (Co@Au NEs) morphology, observing that the cytotoxicity of Co@Au NPs towards L929 fibroblasts was fourfold higher compared to Co@Au NEs at equivalent concentrations.[94] These findings underscore the impact of nanomaterial shape on cytotoxicity.[94] Hence, during nanomaterial synthesis, it is imperative to consider the effects of various morphologies on normal cell to ensure biosafety. Additionally, Xuyang Sun *et al.* investigated the photothermal properties of gallium nanospheres and nanorods, revealing that gallium nanorods exhibit superior photothermal conversion efficiency, implicating the influence of nanomaterial morphology on tumor therapy efficacy.[95] In summary, nanomaterial morphology significantly influences cancer treatment, with alterations potentially modifying toxicity towards normal cells. Furthermore, morphology should be factored into assessments of nanomaterial efficacy in tumor treatment to optimize cancer cell killing.

## 5 Conclusion and prospect

The application of nanomaterials in clinical settings is diverse and holds great promise. Significant progress has been made in the use of nanomaterials as drug carriers and imaging agents, while nanosensors have shown tremendous potential in disease diagnosis and monitoring. Leveraging the EPR effect of nanomaterials, numerous active and passive drug targeting strategies have been developed. These strategies aim to reduce systemic toxicity and precisely increase drug accumulation at tumor sites, thereby achieving efficient tumor eradication with higher biocompatibility. These are important prerequisites for nanomaterials to enter clinical application. With the in-depth study of the mechanical properties of tumors, it is found that the mechanical properties of tumors are different from those of normal tissues. Altering these mechanical properties can enhance drug delivery efficiency, increase cancer cell sensitivity, and improve tumor perfusion. Similarly, modifying the mechanical properties of nanomaterials can enhance cellular uptake, prolong circulation time, and improve biocompatibility. Therefore, nanomaterials regulated by mechanical properties hold vast potential for clinical applications.

Cancer, a global threat to human health, has garnered extensive attention in terms of its various physical and chemical properties over the past decades. Researchers are already exploring effective ways to overcome cancer in multiple dimensions. In addition to combination drug therapy,[96] expanding research perspectives on tumors is beneficial for developing novel therapeutic approaches targeting these characteristics. Thanks to advancements in nanomedicine, new therapies such as photodynamic therapy, photothermal therapy, and sonodynamic therapy based on nanomaterials have gained widespread attention in recent years. These therapies are non-invasive, can control the spatiotemporal release of drugs, and minimize systemic side effects. Thus, with further research into tumor mechanics, combining mechanical therapy with other treatment modalities could enhance therapeutic efficacy and potentially eradicate tumors, presenting a new strategy for cancer treatment.

## Author contributions

Xiaolei Wang contributed to the conceptualization and writing of the original draft. Hongxi Yu contributed to the writing of the original draft and review. Dan Liu, Boxian Hu, Ruihang Zhang, Lihua Hu contributed to the writing of the original draft. Cheng Li and Guiping Hu contributed to supervision, funding acquisition, review and editing.

## Data availability

Data availability is not applicable to this article as no new data was created or analyzed in this study.

## Conflicts of interest

There are no conflicts to declare.

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