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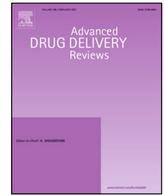

# Mechanotherapy in oncology: Targeting nuclear mechanics and mechanotransduction

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ABSTRACT

Mechanotherapy is proposed as a new option for cancer treatment. Increasing evidence suggests that characteristic differences are present in the nuclear mechanics and mechanotransduction of cancer cells compared with those of normal cells. Recent advances in understanding nuclear mechanics and mechanotransduction provide not only further insights into the process of malignant transformation but also useful references for developing new therapeutic approaches. Herein, we present an overview of the alterations of nuclear mechanics and mechanotransduction in cancer cells and highlight their implications in cancer mechanotherapy.

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## 1. Introduction

In addition to conventional cancer therapeutic approaches (*e.g.*, chemotherapy, radiotherapy, immunotherapy, and surgery), mechanotherapy or mechanomedicine is proposed as a new potential approach in oncology in future, which makes use of the mismatched mechanophenotyping (*e.g.*, mechanical stiffness or mechanotransduction) between cancer and normal cells [1,2]. As the hallmark of eukaryotic cells, the nucleus is typically the largest and stiffest organelle (approximately 5 to 20 μm in diameter [3], approximately 2–10 times stiffer than the cytoplasm [4–7], and twice as viscous as the cytoplasm [5]) that houses genetic information directing the activity of the entire cell. The structural organization and mechanical properties of the cell nucleus are critical for cellular functions (*e.g.*, gene expression [8], cell division [9], differentiation [10,11] and apoptosis [12]) and disease progression (*e.g.*, cancer metastasis [13,14]). Hence, nuclear structural changes have become the 'gold standard' for the clinical diagnosis of cancer (*e.g.*, pharyngeal cancer since the 1860 s [15] and cervical cancer since the 1930 s [16]). These hallmarks include changes in nuclear shape and size, sizes and the numbers of nucleoli, and chromatin texture, which are so characteristic of the given stage and type of tumor that they can be used in cancer diagnosis [17]. The mechanical properties of a material are ubiquitous and not only determine its usage but also imply its internal structure. Thus, nuclear mechanical properties can be an effective indicator of nuclear structure [18]. Furthermore, as the largest and stiffest organelle inside the cell, the nucleus is one of the major contributors to cell mechanical properties [4,19]. Therefore, understanding nuclear mechanics can be of benefit to cancer diagnosis and therapy (Fig. 1).

Due to the limitations of testing technology, little has been known about the mechanical properties of the nucleus for a long time. The mechanical properties of isolated nuclei of articular chondrocytes were first quantified in 2000 by micropipette aspiration [5]. The nucleus is stiffer than the cytoplasm [4–7], which largely depends on A-type lamin [20]. Conversely, the viscosity of the nucleus mainly depends on B-type lamin [20] and exhibits power-law rheology [21]. Furthermore, the nuclei in naive stem cells have been proven to be physically plastic in irreversible deformations without rupture and more pliable than nuclei in differentiated cells [10,11]. The bulk stiffness of the cell nucleus ranges from 0.2 to 2.5 kPa, as quantified by atomic force microscopy (AFM) and extended fitting models [22]. More recently, the nature of nuclear mechanics has been demonstrated to be better described by poroelasticity rather than viscoelasticity [23]. Although cancer cells have been revealed to have reduced stiffness [24–28] and increased traction forces [29], the role of nuclear mechanics in cancer progression has received little attention. With the rapid advancement of measuring and testing techniques [30], interest in exploring the role of nuclear mechanics in diseases, particularly in cancers, has increased [3,30–35].

Cells are constantly subjected to mechanical stimuli from the extracellular environment and hence have developed a timely machinery responding to these stimuli [36]. Cell-extracellular matrix (ECM)-interacting proteins and the cytoskeleton propagate mechanical stimuli from the cell surroundings into the cell; then, the nucleus senses the stimuli transmitted by the LINC complex

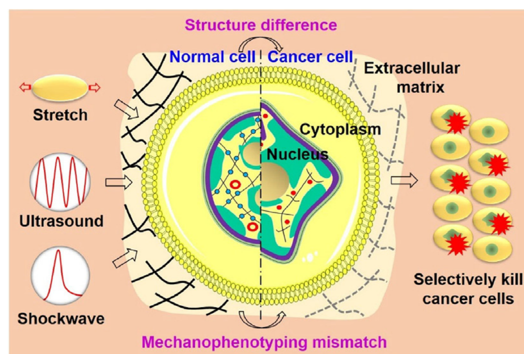


**Fig. 1. Cancer mechanotherapy (*e.g.*, mechanical stretch therapy, ultrasound therapy and shockwave therapy) depends on the mismatched mechanophenotyping (*i.e.*, nuclear mechanics and mechanotransduction) between cancer cells and normal cells, through which the cancer cells can be selectively killed at no risk to normal cells.** The mismatched mechanophenotyping originates from the alteration in the structural organization of the nucleus. In the nucleus, the lamina (purple) is connected to the double-membrane nuclear envelope (light green), which binds to the heterochromatin (green) for most types of cells. The nuclear matrix consists of an internal network (black line) and nuclear matrix proteins (small blue circles). The promyelocytic leukemia (PML) body (red circle) is a type of doughnut-shaped multiprotein complex that controls various apoptotic pathways. In cancer cells, nuclei become irregular and foldable. Nucleoli (deep yellow) can be enlarged. Coarse heterochromatin aggregates. PML bodies mislocalize in microspeckles (red dot). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and eventually responds to these stimuli by altering the gene expression, protein conformation and activation or strengthening of signaling pathways. Because cells convert mechanical signals and stimuli into biochemical responses or behaviors via this mechanism, the entire process is named mechanotransduction. In this process, the mechanosensing and mechanobiological responses of the nucleus are the key steps of signal transduction. In normal cells, the proper operation of nuclear mechanosensing and mechanobiological responses secure the regular homeostasis and functionality of cells. Their dysregulation is highly correlated with the initiation and progression of diseases, including cancer. Structural, mechanical, and conformational aberrations are commonly observed in cancer nuclear architecture, including abnormal nuclear lamina, transcription regulator localization, and chromatin arrangements. Correspondingly, the nuclear mechanosensing and mechanobiological responses of cancer cells diverge from those of healthy cells. For example, the proliferation of normal cells increases on stiffer substrates, whereas cancer cells are insensitive to substrate rigidity [37]. In addition, the nuclear mechanobiological responses of cancer cells depend on cancer types. For example, ovarian cancer cells favor softer substrates for proliferation, whereas glioblastoma cells prefer stiffer substrates [38].

To date, the nuclear mechanophenotypes of cancer cells have been shown to differ from those of normal cells (*e.g.*, Young's modulus, viscosity, mechanotransduction), and such difference has been explored for providing useful references in developing new cancer therapeutic approaches. In the current review, we first introduce the alteration of nuclear composition, structure, and mechanics of cancer cells. We then present an overview of nuclear mechanotransduction in cancer cells from the aspects of mechan-

ical transmission, mechanosensitivity, and the mechanobiological response of the nucleus. Then, we discuss the implications and advances of cancer mechanotherapy potentially benefit by targeting nuclear mechanics and mechanotransduction. Finally, we conclude with some open challenges and future perspectives.

## 2. Nuclear mechanics of cancer cells

### 2.1. Mechanical composition and structure of nucleus

The nucleus is a rather complex organelle inside a cell and includes major structural components, such as the nuclear membrane, nuclear lamina, chromatin, and nucleoplasm. Among these structures, the nuclear lamina and chromatin are the main components contributing to nuclear mechanics.

The nuclear lamina is an elastic meshwork underneath the inner nuclear membrane. It primarily consists of two separated but interacting networks formed by A-type and B-type lamin, which are both type V intermediate filaments, characterized by good strength and elasticity [39]. The lamina is well-known to provide mechanical support to the nucleus during various cellular activities, such as cell migration [40] and cell spreading [41]. The A-type lamin network is a main contributor to the stiffness of the nucleus [10,42,43]. The nucleus, which contains a high level of A-type lamin, is typically stiffer than the cytoplasm and hence is harder to deform. Interestingly, a recent study indicates that the A-type lamin network also contributes to the viscosity of the nucleus, implying the complex role of A-type lamin in nuclear mechanics [44]. The expression of A-type lamin is downregulated in the majority of cancer types, including lung [45], breast [46,47], ovarian [48], prostate [49], and gastrointestinal cancer [50]; as a result, both the cancer cell and nucleus are typically more compliant than the normal cell and nucleus in healthy tissue [26,51,52]. However, A-type lamin is alternatively upregulated in several other cancer types, such as colon [53], rectum [53], and skin cancer [54]. Interestingly, the dysregulation of A-type lamin expression exhibits a pattern of spatial or temporal heterogenicity. For example, the spatial reduction of A-type lamin is not homogeneous in the nuclear lamina, thus leading to a "patchy" nuclear lamina [47,55]. In ovarian [56] and prostate cancers [57], the expression of A-type lamin is initially low but escalates rapidly along with cancer progression, which prevents the nucleus from the structural damage induced by invasion or extravasation of metastasis.

In contrast to the findings of some early studies [43], the B-type lamin network is now generally considered to contribute to nuclear stiffness [58–60]. Similar to A-type lamin, changes in the expression of B-type lamin are also heterogeneous in cancer cells. B-type lamin is typically upregulated in many cancer types, such as prostate [49], ovarian [61], liver [62] and pancreatic cancers [63], but downregulated in a few other cancer types, such as breast [47] and gastrointestinal cancers [50]. The aberrant regulation of B-type lamin has been shown to give rise to abnormal shapes [43] and membrane rupture of the nucleus [60,64]. The expression of B-type lamin has been proposed as an indicator of cancer progression and patient prognosis [62,63,65,66]. In addition, given the interaction with chromatin via linker proteins, such as emerin and the lamin B receptor (LBR), the reduction of B-type lamin causes chromatin instability and results in DNA damage [67,68].

Chromatin is a nucleoprotein complex that not only mediates cellular activities involving genomic DNA, such as gene transcription, DNA repair, and replication but also contributes to the stiffness of the nucleus [69,70]. As a basic structural unit of chromatin, the nucleosome includes DNA and histone proteins and is connected by linker DNA to form chromatin, which can be further compacted by protein histone 1 [71]. Depending on the status of transcriptional activity, chromatin is classified as loose, active euchromatin or compact, repressive heterochromatin, which are generally located in the interior and periphery of the nucleus, respectively [72]. Several studies have shown that chromatin is a stiff mechanical element [70,73–75], and stiffness positively correlated with the status of compaction [74,75]. Hence, loose euchromatin is less stiff than compact heterochromatin. Distinct from the mainly elastic nuclear lamina, the chromatin behaves like a viscoelastic material when subjected to forces, which also corresponds to variations in chromatin compaction [10,21,76,77]. Although the nuclear lamina responds to broad levels of nuclear deformation, chromatin typically dominates in resisting the small deformation of the nucleus (<3 μm), in contrast to the large extensions regulated by A-type lamin-related nuclear strain stiffening [75]. The epigenetic alteration of chromatin is highly involved in oncogenesis and progression [78]. These chromatin modifications typically interact with each other and are highly context specific, and hence their influence on nuclear mechanics is complex. Irrespective of the modulation types, the nucleus softens once the chromatin decompacts, and vice versa. For example, the stiffness of cancer cell nuclei decreases from 35 % to 60 % once chromatin is decondensed after modulation, such as the disruption of histone linker protein H1 [73,79], broad histone acetylation/demethylation [69], or treatment with a decondensing reagent [80].

As the two main intranuclear components related to nuclear mechanics, the lamina and chromatin both appear dysregulated in the cancer nucleus, resulting in abnormal nuclear mechanics. Interestingly, the lamina and chromatin contribute to nuclear mechanics in an interdependent manner; thus this complexity of cancer nuclear mechanics needs to be fully considered.

### 2.2. Mechanical properties of nucleus

Over the years, a variety of measuring technologies have been proposed to test the mechanical properties of nuclei. These approaches include cell stretching [4,43,81], micropipette aspiration [5,21,42,82–84], AFM [85–87], optical stretching [88], magnetic tweezers [89] and microfluidic constriction [90,91]. The nucleus exhibits both elastic behavior due to the nuclear lamina and viscoelastic behavior due to the nuclear interior. Typically, the stiffness of the nucleus is 2 to 10 times higher than that of its surrounding cytoplasm [4–7]. In fact, the cell nucleus is inhomogeneous. For instance, the nucleolus is stiffer than other nuclear domains [92]. In the xenopus oocyte nucleus, the mass density markedly differs between the nucleolus and nucleoplasm [93].

Compared to healthy cells, cancer cells exhibit altered mechanical properties. Regarding whole cells containing a nucleus and cytoplasm, cancer cells generate increased contractile forces [29,94] and show reduce stiffness [24–26] compared to precancerous cells. By measuring metastatic cancer cells (*e.g.*, lung, breast and pancreatic cells) in the pleural fluid of patients, the stiffness of metastatic cancer cells was found to be more than 70 % softer than that of the counterpart normal cells (*i.e.*, benign cells) [28]. Similarly, for invasive and migratory human ovarian cancer cells, the stiffness is up to 5 times softer than that of healthy cells [89]. Human cervical squamous carcinoma cells (CaSki) exhibited a lower whole-cell stiffness (~0.44 kPa *vs* ~ 1.18 kPa in Young's modulus [95]) than their normal counterpart cells (CRL2614). For the nucleus in cancer cells, certain alterations in mechanical properties compared to normal nuclei also occur (Table 1). For example, the density of the nucleus in healthy glial cells is 1.4 g/cm$^3$ [96], while it is only 0.015 g/cm$^3$ (see the chart in ref. [97]) in cancerous glial cells. In breast cancer cells, the Young's modulus of the nucleus in healthy cells was 594.66 ± 540.46 Pa (MCF-10A) [80], while it is reduced to 157.70 ± 78.55 Pa (MDA-MB-231) and 399.

**Table 1**
Mechanical properties of the nucleus in normal and cancer cells.

| Mechanical properties of nucleus | Cell types | Normal cell | Cancer cell | Approaches |
|---|---|---|---|---|
| Diameter | Breast cell | 12.5 μm (MCF-10A) [233] † | 11.3 μm (MCF-7 cells) [234] †<br>15.6 μm (MCF-7 cells) [233] †<br>20.3 μm (MDA-MB-231) [80] † | |
| | Glial cell | 4.0 μm [200] | 5.7 μm (U251) [235] †<br>10.7 μm (U87) [236] †<br>11.1 μm (U373-MG) [237] † | |
| | Liver cell | 10.0 μm (L-02) [238] † | 16.7 μm (MHCC97H) [239] †<br>11.7 μm (HepG2) [240] †<br>20.0 μm (Huh7) [241] † | |
| | Lung | 6.0 μm (bronchial cell) [17] † | 12.5 μm (CL1-5) [242] †17.5 μm (A549) [242] †9.0 μm (small-cell lung carcinoma) [17] †13.0 μm (large-cell lung carcinoma) [17] † | |
| | Embryonic stem cell | 5.0–10.0 μm [200] | | |
| | Hematopoietic stem cell | 3.0–6.0 μm [200]† | | |
| | Cervical cell | | 23.1 μm (HeLa cells) [100] † | |
| | Metastatic adenocarcinoma cell | 8.3 μm [28] † | 13.3 μm [28] † | |
| Mass density | Breast cell | | 0.33 g/cm$^3$ (MCF-7, mass 2.4×10$^{-11}$g) [243] # | Digital holographic microscopy (DHM) |
| | Glial cell | 1.4 g/cm$^3$ [96] | 0.015 g/cm$^3$ [97] * | Third harmonic generation (THG) microscopy |
| | Leukemia cell | | 1.43 g/cm$^3$ (OCI-AML-5) [244] | Calculation based on the wave velocity in the nucleus |
| Young's modulus | Bladder cell | | 5.67 ± 0.48 kPa (T24, in situ) [245]8.4 ± 1.02 kPa (RT4) [245] | AFM |
| | Embryonic kidney cell | 265 Pa (HEK-293) [23] * | | AFM |
| | Mouse fibroblast | 265 Pa (L929) [23] * | | AFM |
| | Endothelial | 3.2 kPa [246] | | Microtensile test system |
| | Chondrocyte | 1.0–5.0 kPa [5] | | Micropipette aspiration |
| | Breast cell | 594.66±540.46 Pa (MCF-10A) [80] | 157.70±78.55 Pa (MDA-MB-231) [80]<br>399.01± 117.16 Pa (MCF-7) [80]0.45 kPa (MCF-7) [247 80] | AFM |
| | Umbilical vein endothelial cell | 22.06 ± 7.29 kPa [248] | | AFM |
| Young's modulus of cytoplasm surrounding nucleus | Breast epithelial cell | 1.13 kPa [233] * | 0.61 kPa [233] * | AFM |
| | Breast cell | 690.85±432.85 (MCF-10A) Pa [80]<br>720 Pa (Hs578Bst) [247] | 394.89 ± 295.97 Pa (MCF-7)cells<br>103.42±89.45 Pa (MDA-MB-231) [80] | AFM<br>Micropipette aspiration |
| | Breast ductal adenocarcinoma | 1.93±0.50 kPa [28] | 0.50±0.08 kPa [28] | AFM |
| | Non-small cell carcinoma of the lung | 2.05±0.87 kPa (Female, 60) [28]<br>2.10±0.79 kPa (Female, 52) [28] | 0.52±0.12 kPa (Female, 60) [28]<br>0.56±0.09 kPa (Female, 52) [28] | AFM |
| | Thyroid cell | 1.2, 1.6, 2.6 kPa [249] | 1.3 kPa [249] | AFM |
| | Cervical cells | 1.20–1.32 kPa (CRL2614) [95] | 0.35–0.47 kPa (CaSki) [95] | AFM |
| | Hepatocyte | 0.75–1 kPa [250] | | AFM |
| | Pancreatic cell | 0.54±0.08 kPa [28] | 0.54±0.12 kPa [28] | AFM |
| | Cervical epithelial cell | 2.05 ±0.48 kPa [251] | 2.80±1.7 kPa [251] | AFM |
| | Bladder cell | 9.7 ±3.6 kPa (Hu609)7.5±3.6 kPa (HCV29) [252] | 0.8 ± 0.4 kPa (T24)0.3 ± 0.2 kPa (Hu456)1.0 ± 0.6 kPa (BC3726) [252] | AFM |
| | Liver cell | 87.5±12.1 Pa (Hepatocyte) [84] | 103.6±12.6 Pa (SMMC 7721) [84] | Micropipette aspiration |
| | Skin cell | 0.62 kPa (HaCaT) [247] | 0.42 kPa (A2058) [247] | Micropipette aspiration |
| | Fetal lung cell | 0.70 kPa (MRC-5) [247] | 0.42 kPa (MSTO-211H) [247] | Micropipette aspiration |
| | Liver cell | 0.79 kPa (L-02) [247] | 0.48 kPa (Hep G2) [247] | Micropipette aspiration |
| | liver metastases cell | 0.79 kPa (L-02) [247] | 1.492 kPa [102] | AFM |
| | Primary Colorectal Cancer cell | | 0.336 kPa [102] | AFM |
| Viscosity coefficient | Chondrocyte | 5 kPa·s[5] # | | Micropipette aspiration |
| | Skin fibroblast | 1.148 mPa·s [253] * | | Micropipette devices |
| | Mouse embryonic fibroblast | 80 Pa·s (lamina A/C) [254] * | | Ballistic intracellular nanorheology |

 

**Table 1** (*continued*)

| Mechanical properties of nucleus | Cell types | Normal cell | Cancer cell | Approaches |
|---|---|---|---|---|
| Viscosity coefficient of cytoplasm surrounding nucleus | Thyroid cell | 230, 515, 470 Pa·s (S747) [249] | 300 Pa·s (S277) [249] | AFM |
| | Kidney cell | 69.6 Pa·s (RC-124) [255] | 28.1 Pa·s (A-498)<br>24.9 Pa·s (ACHN) [255] | AFM |
| | Breast cell | 1.89±0.21 kPa·s (MCF-10A) [256] | 2.56 ±0.38 kPa·s (MDA-MB-231) [256]<br>1.64 ±0.18 kPa·s (MCF-7) [256] | AFM |
| | Liver cell | 5.9±3.0 Pa·s [84] | 4.5±1.9 Pa·s (SMMC 7721) [84] | Micropipette aspiration |
| | Skin cell | 2.9 kPa·s (HaCaT) [247] | 1.2 kPa·s (A2058) [247] | Micropipette aspiration |
| | Fetal lung cell | 3.2 kPa·s (MRC-5) [247] | 1.2 kPa·s (MSTO-211H) [247] | Micropipette aspiration |
| | Breast cell | 3.3 kPa·s (Hs578Bst) [247] | 1.2 kPa·s (MCF-7) [247] | Micropipette aspiration |
| | Liver cell | 3.65 kPa·s (L-02) [247] | 1.3 kPa·s (Hep G2) [247] | Micropipette aspiration |
| Diffusion coefficient | Mouse liver cell | 9±1 $\mu m^2/s$ [98] | 0.37 $\mu m^2/s$ (MDA-MB-231, with indentation depth 1.3 μm) [99] | Fluorescence recovery after photobleaching |
| | Embryonic kidney cell | 4 $\mu m^2/s$ (HEK-293) [23] * | | AFM |
| | Mouse fibroblast | 6 $\mu m^2/s$ (L929) [23] * | | AFM |
| | Embryonic fibroblast | 0.5 $\mu m^2/s$ [257] | | |
| Diffusion coefficient of cytoplasm surrounding nucleus | Liver cell | | 25.6 $\mu m^2/s$ (SMMC 7721) [258] | AFM |
| | Cervical cell | | 41±11 $\mu m^2/s$ (HeLa cell) [100] | AFM |
| | Fibroblast cell | | 40±10 $\mu m^2/s$ (HT1080) [100] | AFM |
| | Dog kidney cell | 61±10 $\mu m^2/s$ (MDCK cell) [100] | | AFM |
| | Breast cancer cell | | 0.14–0.37 $\mu m^2/s$ (MDA-MB-231) [99] | AFM |
| Natural Frequency | Liver cell | 43 kHz [101] | 80 kHz (hepatocellular carcinoma cell) [101] | Simulation |

[#] Estimated value based on the mass and volume of the nucleus.
[*] Data are taken from charts in the references.
[†] Measured value from the figures in references.

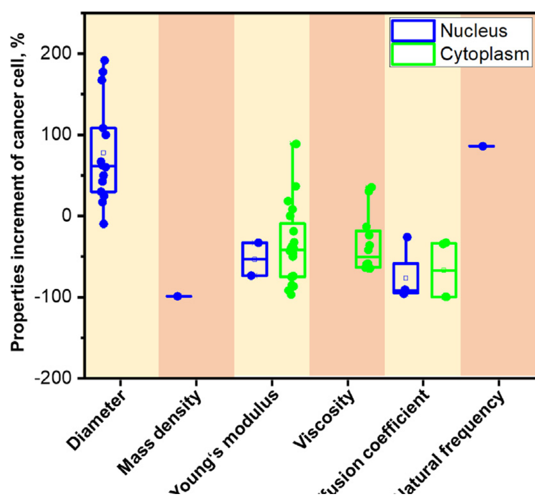


**Fig. 2. Alteration of nuclear mechanics in cancer cells compared to normal cells.** The cancer nuclei are ~ 77.8 % larger in average diameter, 98.9 % smaller in mass density, ~60.3 % smaller in Young's modulus, ~76.6 % smaller in diffusion coefficient, and ~ 86.0 % larger in natural frequency. The cancer cytoplasm is ~ 45.8 % smaller in Young's modulus and ~ 66.6 % smaller in diffusion coefficient. The original date and sources are listed in Table 1.

01 ± 117.16 Pa (MCF-7) [80], in cancer cells. In non-small cell carcinoma of the lung, the Young's modulus of the cytoplasm surrounding the nucleus in healthy cells is 2.05 ± 0.87 kPa (female, 60) and 2.10 ± 0.79 kPa (female, 52) [28], while it is considerably softer in cancer cells, *e.g.*, 0.52 ± 0.12 kPa (female, 60) and 0.56 ± 0 .09 kPa (female, 52) [28]. However, inevitable exceptions exist. In liver cells, the Young's modulus of the cytoplasm surrounding the nucleus in healthy cells in 87.5 ± 12.1 Pa (hepatocytes) [84], while it is increased to 103.6 ± 12.6 Pa (SMMC 7721) [84] in cancer cells. In mouse liver cells, the diffusion coefficient of the nucleus in healthy cells is 9 ± 1 $\mu m^2/s$ [98], while it is 0.37 $\mu m^2/s$ (MDA-MB-231, with an indentation depth of 1.3 μm) [99] in cancer cells. The diffusion coefficient of the cytoplasm surrounding the nucleus in healthy cells is 61 ± 10 $\mu m^2/s$ (MDCK cells) [100], while it is 40 ± 10 $\mu m^2/s$ (HT1080) [100] in cancer cells. Owing to the aberrations in the mechanical properties of the cytoplasm and nucleus, the eigenfrequencies at which resonance occurs should markedly differ between cancer and normal cells. Numerical calculations suggest that the natural frequencies of hepatocellular carcinoma (HCCs) are higher than those of healthy cells, with a typical gap of approximately 37 kHz [101]. The fundamental frequency is calculated to be on the order of 80 kHz for HCCs and 43 kHz for healthy cells. In summary, as shown in Fig. 2, the nucleus of cancer cells is ~ 98.9 % smaller in mass density and ~ 60.3 % smaller in Young's modulus than those of normal cells. The Young's modulus of the cytoplasm surrounding the nucleus in cancerous cells is ~ 43.6 % smaller than that in healthy cells. The nucleus of cancer cells is ~ 76.6 % smaller in diffusion coefficient. The cytoplasm surrounding the nucleus is ~ 66.6 % smaller in diffusion coefficient.

It is worth mentioning that even cancer cells are now divided into different types, such as tumor tissue cells, more aggressive metastatic cells and cancer stem cells. Until now, the mechanical properties of aggressive metastatic cells were mostly measured using the mature cell lines *in vitro*. Therefore, the data is relatively abundant for the mechanical properties of aggressive metastatic cells (Table 1), while it is relatively scarce for the mechanical properties of tumor tissue cells and cancer stem cells. In one study, the mechanical properties of cancer cells were acquired from primary and metastatic colorectal cancer slides with an AFM [102,103]. The Young's modulus of cytoplasm surrounding nucleus of liver metastases cell and primary colorectal cancer cell are 1.492 kPa and 0.336 kPa, respectively, which has been listed in Table 1.

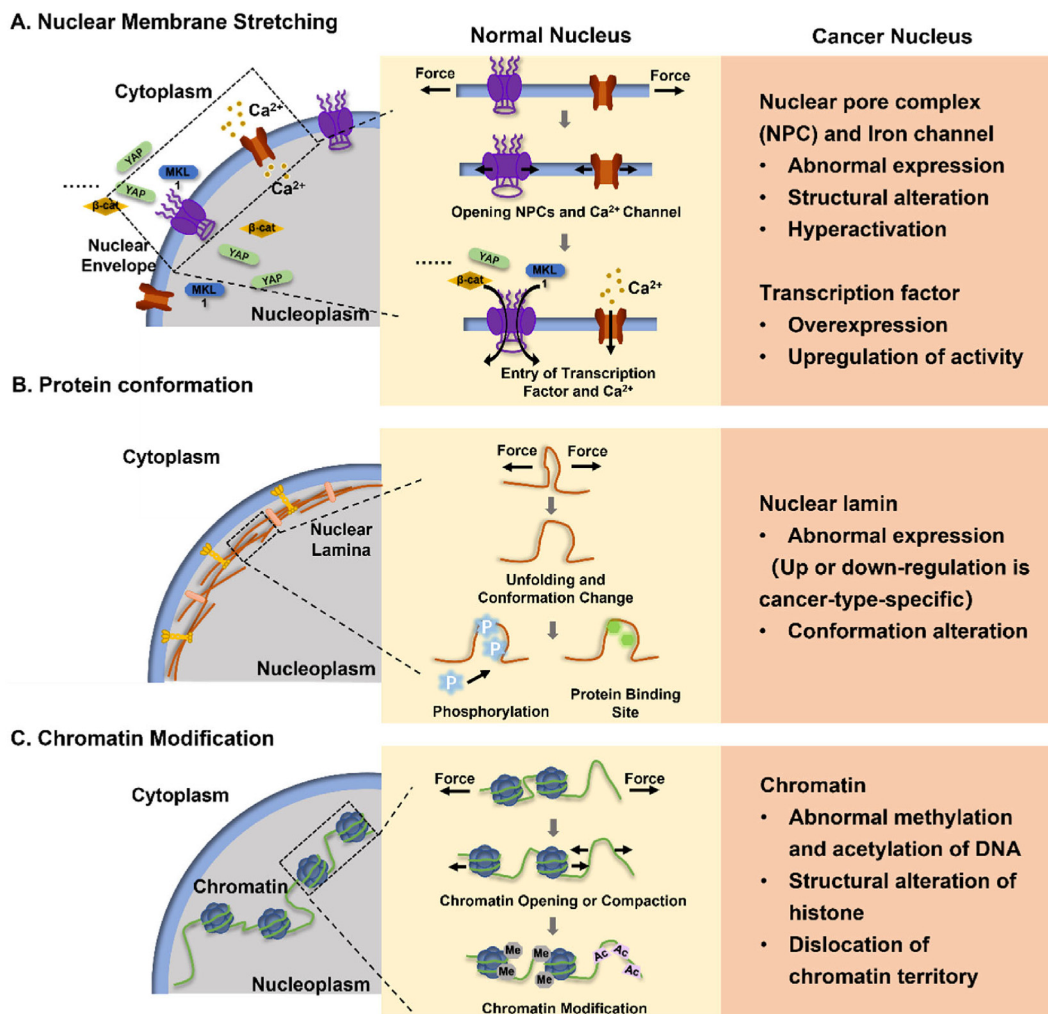


**Fig. 3. Comparison of three main nuclear mechanotransduction approaches**. (A) The stretching of the nuclear membrane enables the intranuclear translocation of transcription factors. (B) Protein conformation change, which includes abnormal expression and structure alteration. (C) Chromatin modification, which consists of molecular structure, condensation and location alteration, between normal and cancer nuclei.

## 3. Nuclear mechanotransduction in cancer cells

Mechanotransduction is the process by which mechanical signals, either from the ECM or cytoskeleton, are converted into intracellular biochemical signals to initiate cellular responses. The participants of mechanotransduction include the ECM surrounding the cell, cytoskeleton, LINC complex (linker between nucleoskeleton and cytoskeleton) and nucleus. Mechanotransduction enables a cell to rapidly adapt to a changed physical environment, playing critical roles in cell and tissue differentiation, function maintenance, and disease development.

Currently, an increasing number of *in-vitro* studies unveil that the nucleus can sense and respond to mechanical stimuli, rather than just mediate force propagation inside cell, as was previously thought [104]. The direct application of force to the nucleus induces alterations in shape of nuclear membrane, lamina composition and chromatin structure, which induces gene expression and consequential cellular responses. The mechano-sensing and mechano-biological response of the nucleus, together with the force transmission of the nucleus, composes the complete picture of nuclear mechanotransduction (Fig. 3).

### 3.1. Mechanical transmission of the nucleus

Similar to the cell surrounded by the ECM, the nucleus is also surrounded by subcellular components, such as the cytosol, cytoskeleton, and LINC (linker of nucleoskeleton and cytoskeleton) complex. Both extracellular (ECM) and intracellular (cytoskeleton) mechanical stimuli are mainly transmitted by the cytoskeleton to the nucleus via the mechanical linker LINC complex [105]. This propagation of mechanical stimuli onto the nucleus initiates nuclear mechanotransduction. However, these subcellular components, especially the cytoskeleton and LINC complex, are dysregulated in cancer cells, resulting in the abnormal mechanotransduction of the nucleus.

The cytoskeleton is a cellular complex that includes three types of filament networks: microfilaments (actin filaments, diameter 5–9 nm) [106], intermediate filaments (diameter 10 nm) [107], and microtubules (diameter 25 nm) [108]. It not only mechanically supports cells to maintain shape but also generates intracellular forces by the polymerization of filament components [109] and motor proteins integrated with these filaments [110]. Microfilaments interact with myosin motor protein [111] and various

crosslink proteins [112–114] to constitute the actomyosin cytoskeleton, which can respond to the generation of intracellular forces [115]. The essential role of actomyosin contraction has been well established in nuclear shaping [116] and positioning [117]. Microtubules are another contributor to intracellular force, and their hollow tubular structure enables dynein [118] and kinesin [119] to "walk" along themselves to transport intracellular cargo [120–122]. For the cytoskeleton, intermediate filaments are rod-like filaments consisting of keratin [123] and vimentin [124,125] in a coiled-coil pattern [126]. Unlike the other two cytoskeleton networks, intermediate filaments typically help the cell and nucleus resist deformation due to their good elasticity and extensibility [39,127].

The LINC complex is a large transmembrane protein structure that mechanically connects the nucleus and cell. It includes outer nuclear membrane nesprin protein, which interacts with the cytoskeleton [128–131], and inner nuclear membrane SUN protein, which interacts with the nuclear lamina [132–134]. These two proteins interact with each other via a conserved KASH domain and then constitute the linkage between the nucleus and cell for force transmission [135,136]. The LINC complex is an indispensable player in cell mechanotransduction, which enables it to regulate nuclear mechanics. The expression of the LINC complex appears dysregulated in cancer. For example, both SUN1/2 and nesprin2 are downregulated in breast cancer tissue and in cell lines [137]. In addition, nesprin1/2 is reported to have a higher mutation frequency in breast [138], colorectal [138], and gastrointestinal cancers [139]. Several *in-vitro* studies imply the potential role of LINC in regulating cancer nuclear mechanics, although the mechanism is unclear. For example, RAC1-mediated nuclear shape alterations require the integrity of the LINC complex to maintain the invasiveness of melanoma cells [140].

In cancer tissue, the increased stiffness is commonly observed and leads to elevated contractility of the actomyosin cytoskeleton in cancer cells given the correlation between actomyosin contraction and ECM stiffness [141]. In consideration that *in-vitro* studies showed that actomyosin contraction can deform cancer nucleus [142] and dysregulated actomyosin contraction causes dysmorphia and genome instability of normal nuclei [143], it is possible that the increase of nuclear fragmentation and instable genome may result from the elevated actomyosin contractility of cancer cells, even with presence of greater magnitude of force such as osmotic pressure. In addition, when actomyosin contractility or network expansion compresses a nucleus, the increase in intracellular pressure deforms the nucleus [144] and even promotes nuclear membrane rupture and chromatin hernia at lamina lesion sites [145]. As a vital participator of cell mitosis, MTOC (MicroTubule Organizing Center) appears aberrations in quantity and structure [146–148], which is positively linear with chromosomal instability [149]. Similar to the microfilament network, microtubule-originated force is relevant to aberrant nuclei in cancer cells. In leukemic cells, for example, microtubules are known to drive nuclear lobulation and micronucleus formation [150]. In addition, in a study of 16 pancreatic cancer cell lines, centrosome abnormalities were positively correlated with abnormal nuclear morphology [151]. Before epithelial cancer cells initiate metastasis, the upregulation of keratin and downregulation of vimentin coincide with the progress of epithelial-mesenchymal transition (EMT) [152,153], thus protecting the nucleus from damage because vimentin stiffens and absorbs more energy than keratin [154].

### 3.2. Mechanosensing of nucleus

The nuclear sensing of mechanical stimuli initiates once stimuli are transmitted to the nucleus. Currently, several mechanisms have been proposed to explain how the nucleus senses mechanical stimuli, including the extensive deformation of the nuclear membrane and pore complex, conformational changes in related proteins, and chromatin modification. These approaches of mechanosensing work together to ensure successful perception of mechanical stimuli by the nucleus.

The stretching of the nuclear membrane and pore complex is a straightforward outcome after force application to the nucleus (Fig. 3**A**). The nuclear pore complex regulates the trafficking of iron or transcription factors between the cytoplasm and nucleoplasm. The extended nuclear pores escalate the influx and outflux of biochemical molecules and ultimately affect gene expression. For example, the contractile force transmitted by the LINC complex on the nucleus can stretch the nuclear pore complex to enhance the entry of YAP/TAZ into the nucleus [155]. In cancer cells, it is highly possible that the upregulated cellular contractility amplifies this type of nuclear mechanosensing. When cancer cells squeeze through a physical constraint, the local unfolding of the nuclear membrane triggers the influx of calcium ions and thereafter the increase of cell contractility, which indicates how the nucleus senses the stress from the limited space for migration [156]. In response to changes in the osmotic environment in damaged tissue, the nucleus can swell and hence offers extra space for cytosolic phospholipase A2 (cPLA2) to become insert in the nuclear membrane and become activated to initiate proinflammatory eicosanoid signaling [12].

Another approach is the conformational change of intracellular or intranuclear proteins via the regulation of their phosphorylation level (Fig. 3**B**). With the force-induced extension of nuclear proteins, initially inaccessible binding sites become available to nuclear kinases or interacting proteins. For example, force exerted on the nucleus can enhance emerin phosphorylation, resulting in the recruitment of more A-type lamin to the nuclear boundary and a stronger interaction between A-type lamin and SUN protein [157]. However, occasionally, the increase in protein phosphorylation favors less tension. For example, *in-vitro* studies show that several phosphorylation sites in A-type lamin become more active when cultured on a soft substrate with low tension, which allows A-type lamin to degrade easier [11,158]. Although cells can sense mechanical stimuli by nuclear protein phosphorylation and conformation, further exploration is needed to explain why they respond to stimuli differently.

In addition, mechanical stimuli can be sensed by the nucleus via changes in chromatin conformation, compactness, and modification (Fig. 3C). For instance, force-induced changes in nuclear shape alter the intranuclear position of chromatin [159,160], also known as chromosome territory. The chromatin toward the nuclear exterior binds with nuclear lamina via enriched GAGA motifs of LADs (lamina associated domains), and these repeated motifs also bond with transcriptional repressors cKrox, which silence genes in chromatin [161]. Once force induces chromatin position change, related genes likely change status for expression due to the loss of bonds with LAD or extension of chromatin in certain region. This speculation is supported to some extent by alteration of gene expression induced by direct force application on chromatin. For example, the transient stretching of chromatin by magnetic beads induces rapid transcription of the GFP-tagged DHFR transgene within the stretching region, and the level of transcription depends on the frequency and magnitude of the applied force [162]. However, it is hard to exclude the possible contribution of integrin and other cytoplasmic molecules, since they can interact with Poly-L-Lysine (PLL), the protein coated on the beads, and trigger the upregulation of gene transcription.

As a key component of force transmission, the LINC complex is also important for nuclear mechanosensing. When osmotic pressure swells the nucleus [163] or cytoskeletal contraction stretches the nucleus [155], the intact LINC complex is necessary for exten-

sion of the nuclear pore complex to enhance the transport of transcription factors, such as YAP/TAZ in *in-vitro* studies. Similarly, the change in protein phosphorylation status relies on the integrity of the LINC complex. For example, the LINC complex enables phosphorylation of emerin in response to nuclear tension [157]. The disruption of the LINC complex, commonly observed in cancer cells, attenuates the response of the nucleus to ECM stiffening [164].

In cancer, nearly all mechano-sensing approaches appear altered considering the complex alteration of involved elements and molecules. Changes in structure, expression or even both are commonly observed in related proteins, such as NPC protein [165], lamin [166], and LINC complex protein [167]. Some changes amplify nuclear mechano-sensing, such as reduced lamin expression [47,65] and the increased phosphorylation of emerin [157], whereas others abolish mechano-sensing, such as the altered structure of NPCs [168] and the disruption of LINC [157]. In addition, due to increased cancer ECM stiffness or upregulated intracellular force, the stretching of the nuclear membrane and nuclear lamina becomes more intense and frequent [158], which may enable more ions and transcription regulators to enter the nucleus. Moreover, the altered modification of chromatin is widely reported in the cancer nucleus, affecting not only nuclear mechanics but also nuclear sensitivity to mechanical stimuli [8,69,169]. Hence, changes in cancer nuclear mechanosensing are quite heterogeneous, and in specific circumstances, the final effect is the converging result of all changes.

In summary, the mechanisms discussed above do not exclude each other when the nucleus senses mechanical stimuli. The dominance of each mechanism depends on cell types, the forms of mechanical stimuli, and the timescale of stimuli application. Moreover, the defect or disruption of the LINC complex attenuates mechanosensing of the nucleus.

### 3.3. Mechanobiological response of nucleus

Following the transmission and detection of extranuclear mechanical stimuli, the nucleus can quickly respond by converting mechanical stimuli to biochemical signals, which is essential in the entire process of mechanotransduction. The biochemical signals trigger wide-spectrum activities in and out of the nucleus in response to mechanical stimuli, mainly including the nuclear lamina, chromatin, and epigenetic modulation. Moreover, the time scale of the response can be either transient or constant, depending on whether the mechanical stimuli switch on the mechanoresponsive feedback loop.

The nuclear lamina not only facilitates nuclear mechanosensing but also participates in nuclear mechanoresponse via self-modulation of phosphorylation status. High tension on the nucleus induced by stiff substrates can be reflected by low phosphorylation and the turnover of A-type lamin, and the nucleus responds to stiff substrates with increasing expression levels of A-type lamin via a feedback loop between the retinoic acid (RA) pathway and A-type lamin-regulated RA receptor translocation in the nucleus [11]. On soft substrates, the nucleus softens with the faster degradation of A-type lamin promoted by increased phosphorylation [158]. In addition to the phosphorylation binding site, mechanical stimuli also interact with other proteins. For example, the unfolding of the C-terminal immunoglobulin (Ig) of A-type lamin of fibroblasts is shown to expose regularly inaccessible residues, such as $Cys^{522}$, to interact with emerin, DNA, and histones [170]. When cervical cancer cell migrates through constraint space, the stretching of the nucleus enables the localization of cytosolic phospholipase A2 (cPLA2) onto the nuclear envelope, followed by the activation of cPLA2 and production of arachidonic acid (ARA), which stimulates actomyosin contractility [156]. Given the vital role of lamins in maintenance of nucleus and genome integrity [171], the manipulation of lamin expression is a delicate work to handle for potential clinical applications.

Force-induced changes alter chromatin in several ways. First, chromatin territories are dislocated upon the nuclear mechanosensing of mechanical stimuli. For example, the spatial arrangements and displacement of chromatin can be reflected and affected by the geometrical constraints of the nucleus [172], thus indicating the close relationship between mechanical stimuli and chromosome arrangements. Alternatively, structure changes open the binding sites and make them accessible to transcription factors. For example, increased binding sites for reporter genes are observed when chromatin is stretched by magnetic beads *in vitro* [162], although this stretching of chromatin is currently unable to precisely target genes of interest. Similarly, gene expression is suppressed if the opened binding sites become inaccessible after structural changes, such as condensation [74]. In response to high intracellular tension, for example, lymphocytes cultured on stiff ECM show upregulated chromatin condensation via increased levels of H3K9me2/3 and nuclear stiffness [173].

The epigenetic regulation of gene expression is the pivotal mechanobiological response of the nucleus to mechanical stimuli. The translocation of transcription factors into the nucleus mainly contributes to the nuclear response to mechanical stimuli. For example, in response to mechanical stimuli, such as ECM stiffness [174], cytoskeletal tension [163], and nuclear shape deformation [155], in *in-vitro* studies. Upon entering the nucleus, YAP-TAZ becomes transcriptionally active and regulates cell functionality and behavior in response to mechanical stimuli [175]. Interestingly, the activation of YAP-TAZ inside the nucleus initiates the nuclear localization of β-catenin, which activates transcriptional activities to help quiescent epithelial cells reenter the cell cycle in response to mechanical strain [176]. Even though the huge number of YAP/TAZ downstream pathways harasses the selection of effective targets, attempts have been made to develop preclinical chemicals to interfere their interaction, such as YAP/TAZ-TEAD complex [177]. When actin polymerization is triggered by mechanical stimuli, the transcriptional regulator MKL1 (megakaryoblastic leukemia 1) becomes available to the NLS (nuclear localization sequence) for nuclear import and accumulation of MKL1, resulting in the coactivation of MKL1 and SRF (serum response factor) for the expression of genes that regulate cellular motility and contractility [178]. Moreover, long-term force application to the nucleus leads to epigenetic alterations rather than chromatin structural changes. For example, the switch of chromatin methylation sites from H3K9me3 to H3K27me3 is observed after constant force application on human primary epidermal keratinocytes, which can permanently suppress gene transcription in these regions of chromatin [179].

Regarding heterogenicity, the cancer nucleus often responds differently to the same mechanical stimuli, not to mention different stimuli. Typically, the final response of the nucleus to certain mechanical circumstances is the collective effect of all mechanoresponsive machineries that become active in that circumstance. These machineries can work individually, interact with each other, or oppose each other.

The abnormal mechanotransduction of cancer nucleus could become potential strategy for cancer treatment, yet challenge remains. First, the identification of main player as target of treatment is arduous task, given the convergent feature of nuclear mechanotransduction alteration in cancer. With the continuously detailed exploration on cancer mechanotransduction and the assistance of AI on data process, it is possible to overcome this challenge. The other one is the inhibitor toxicity to normal cell, resulting from the improvement-required specificity of inhibitors or the unfavorable inhibition of "good" downstream pathway reg-

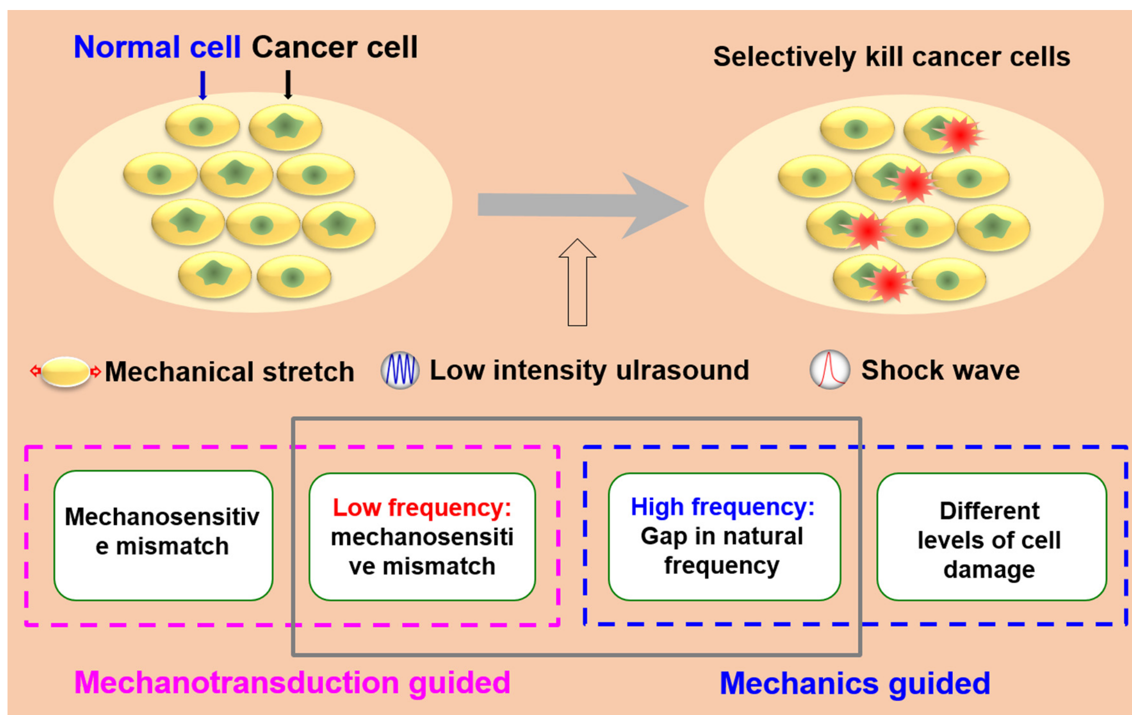


**Fig. 4. Mechanotherapy in oncology.** Cancer cells can be selectively killed by mechanical stimulation methods, such as mechanical stretching, low-intensity pulsated ultrasound, and shock waves, which are mostly related to nuclear mechanics and mechanotransduction. Mechanical stretch and low-frequency LIPU selectively eradicate cancerous cells through mismatched mechanosensitivity compared to healthy cells. High-frequency LIPU and shock waves can selectively lyse cancer cells through mismatched mechanical properties compared to healthy cells.

ulated by the same axis of nuclear mechanotransduction. Currently, the most inhibitors studied in field are not initially designed to manipulate nuclear mechanotransduction, although they are shown to affect nuclear mechanotransduction experimentally. To avoid this inherent lack of targeting specificity, the nuclear mechanical features need to be devoted to the highest priority for inhibitor design, even the pure mechanical approaches can be applied for interference without pathway alterations. It is expected that the nuclear mechanotransduction can be a potential candidate for cancer treatment, although huge efforts are demanded to make it successful.

## 4. Cancer mechanotherapy by targeting the nucleus

Mechanodiagnosis has been proposed in oncology for a long time [28,36,180,181], however, mechanotherapy has been only recently proposed and attracted close attention due to its potential advantages such as noninvasiveness, selectivity for cancer cells and minor side effects. In recent years, guided by nuclear mechanics and mechanotransduction (Fig. 4), cancer mechanotherapy were explored through mechanical stretching, ultrasound irradiation and shock waves, both in *in-vitro* and animal studies (Table 2).

### *4.1. Cancer mechanotherapy guided by nuclear mechanics*

#### *4.1.1. High-frequency LIPU therapy*

Ultrasound waves are mechanical waves that have too high frequency for humans to hear. Since the 1940 s, ultrasound has been studied as a tool in cancer therapy [182,183]. Conventionally, ultrasound is noninvasive and able to penetrate deep tissues to facilitate cancer therapies, such as sonodynamic therapy, ultrasound-mediated gene/drug delivery, anti-vascular ultrasound therapy, and ultrasound-mediated chemotherapy [184]. The present studies were performed in *in-vitro* cancer cell cultures and *in-vivo* small animals with implant tumors. In addition, ultrasound-induced immunotherapy was investigated *in vivo* in the species of human/mouse [185]. Low-intensity pulsed ultrasound (LIPU) has been tested individually to treat *in-vitro* cancer cells [186,187] and *in-vivo* tumors of animal [188,189]. High-intensity pulsed ultrasound (HIPU) [190] and High-intensity focused ultrasound (HIFU) [191] have been tested individually to treat *in-vitro* cancer cells and *in-vivo* tumors of human, respectively. Through local heating or nanobubbles, therapeutic ultrasound with high intensity (spatial-peak temporal-average intensity $I_{SPTA}$ greater than 100 W/cm $^{2}$) has been used to target tumors, but this ultrasound damages both cancer and healthy cells alike in the target area [192]. Low intensity pulsed ultrasound ($I_{SPTA}$ is less than several W/cm$^{2}$), which causes very small strains ($10^{-5}$) [194,195], produces mechanical or mechanobiological effects without hyperthermia, resulting in much higher (~3–5 times) death rate in cancerous cells than in normal cells *in vitro* [187,190]. The frequency of therapeutic ultrasound usually ranges from tens to hundreds of kHz estimated through a theoretical model of vibration of cell nucleus [193]. Here, we only provide an overview of LIPU with either high frequency (hundreds of kHz) or low frequency (tens of kHz), which targets cancer cell through mismatched cell mechanophenotyping and may be guided by nuclear mechanics.

When tuned to correct frequencies, ultrasound can selectively destroy cancer cells guided by their unique mechanical properties while sparing healthy cells, thus providing a potential option for cancer therapies. Recently, an alternative LIPU ($I_{SPTA}$ < 5 W/cm$^{2}$) was employed to inherently select for cancer cells *in vitro* [186]. The proposed approach scales down the intensity and fine-tunes the frequency of ultrasound to match target cells, enabling the shattering of several types of cancer cells while leaving healthy blood cells unscathed. Indeed, LIPU at a frequency of 0.5–0.67 MHz selectively disrupted the leukemia, colon, and breast

**Table 2**
Mechanotherapy in oncology.

| Cancer type | Approaches of mechanotherapy | Loading device | Loading/US parameter | Effect |
|---|---|---|---|---|
| p53PTEN−/− mice breast cancer model [210] | Stretch | Stretched by lifing the base of the tail until reaching ~ 45° angle to horizontal | Treatment time 10 min once/day, for four weeks | Compared to the no-stretch group, tumor volume was 52 % smaller in the stretch group |
| Breast cancer cell (MDA-MB-231) [189] | Cyclic stretch | PDMS plate (60–70 µm thickness) | Frequency 0.1 Hz 0.5 Hz 1 Hz<br>Cyclic strain 5 %<br>Treatment time 24 h | Death rate of cancer cell is 35 % while 5 % for normal cells |
| Eukemia cell (K562 and U937), control *T*-cell [186] | High-frequency low-intensity pulsed ultrasound | Ultrasound transducer & 24-well plate | Frequency 0.3, 0.5, 0.67 MHz<br>Mechanical Index 1.3Pressure (PNP) < 1.2 MPa<br>Spatial-peak temporal-average intensity $I_{SPTA}$ < 5 W/cm$^2$<br>Duty cycle 10 %,<br>Treatment time 60 s | Death rate of cancer cell is 60 % while 20 % for normal cells |
| Mice cervical cancer (HeLa cell) [188] | High-frequency low-intensity pulsed ultrasound | High-frequency linear-array probe (17L8 transducer on the Sequoia system) | Frequency 7 MHz<br>Pressure 1000 kPa<br>Mechanical Index 0.18<br>Duty cycle 20%<br>Treatment time 3 min | Survival rate of tumor-bearing mice increase from 16% in controls to 52% in treated mice (ultrasound trigger intracellular nanobubbles explosion) |
| Breast carcinoma and a malignant melanoma [187] | High-frequency low-intensity pulsed ultrasound | Ultrasonic bath (Sonicor, Sonicor Instrument Corporation, Copiague, NY, USA) | Frequency 2 MHz<br>Spatial-peak temporal-average intensity $I_{SPTA}$=0.33 W/cm$^2$<br>Treatment time 2 or 4 min | Death rate is cancer cell 75–80% while that of normal cells is 20% |
| Breast cancer cell (MDA-MB-231) [189] | Low-frequency low-intensity pulsed ultrasound | Ultrasound transducer (diameters 16 mm and 25 mm) & 96-well plate | Frequency 33 kHz<br>Power 7.5 W<br>Duty cycle 50%<br>Treatment time 24–48 h | Death rate is cancer cell 45% while that of normal cells is 9% |
| Chick embryo grafted tumors (MDA-MB-231) [189] | Low-frequency low-intensity pulsed ultrasound | Ultrasound transducer (diameters 16 mm and 25 mm) | Frequency 33 kHz<br>Power 7.5 W<br>Duty cycle 50%<br>Treatment time 24–48 h | Up to 40% of chick embryos die, while untreated ones continue to grow |
| Murine mammary sarcoma (NRA cell) [224] | Low-frequency low-intensity pulsed ultrasound | Ultrasound transducer (diameters 16 cm) & 6-well plate | Frequency 20 kHz<br>Spatial-peak temporal-average intensity $I_{SPTA}$= 5.09 W/cm$^2$<br>Duty cycle 50%<br>Treatment time 1 min | Death rate of cancer cell is 89% while that of normal cells is 21% |
| *In-vivo* mice implanted KHJJ murine mammary sarcoma [224] | Low-frequency low-intensity pulsed ultrasound | Ultrasound transducer | Frequency 20 kHz<br>Spatial-peak-temporal-average intensity $I_{SPTA}$=7.7 W/cm$^2$, 8.5 W/cm$^2$<br>Duty cycle 50%<br>Treatment time 30 s | The average change of tumor size is only half of the control group for $I_{SPTA}$=8.5 W/cm$^2$ |
| Human foreskin fibroblast, malignant cell [223] | Low-frequency low-intensity pulsed ultrasound | Ultrasound transducer & US tank | Frequency 20 kHz<br>Spatial-peak temporal-average intensity $I_{SPTA}$=0.33 W/cm$^2$<br>Treatment time 4 min | Death rate of cancer cell is 90% while that of normal cells is 12–20% |
| Breast cancer cell (MDA-MB-231), malignant melanoma (A375p), breast epithelial cell (ATCC) [221] | Low-frequency low-intensity pulsed ultrasound | US tank & 96-well plates | Frequency 33 kHz<br>Spatial-peak temporal-average intensity $I_{SPTA}$=7.7 mW/cm$^2$<br>Duty cycle 50%<br>Treatment time 2 h | Death rate of cancer cell reaches 52%, while that of normal cells is 18% |
| Hacat and Cal33 [222] | Low-frequency low-intensity pulsed ultrasound | Ultrasound plate horn & 12-well plate | Frequency 20 kHz<br>Spatial-peak temporal-average intensity $I_{SPTA}$=0.164 W/cm$^2$<br>Duty cycle 50%<br>Treatment time 20 or 40 s | Death rate of cancer cell reaches 73% while that of normal cells is 5% |
| *In-vivo* mice injected with Cal33 HNSCC cell line [222] | Low-frequency low-intensity pulsed ultrasound | Ultrasound transducer & US tank | Frequency 20 kHz<br>Spatial-peak temporal-average intensity $I_{SPTA}$=12.3 W/cm$^2$<br>Duty cycle 50%<br>Treatment time 1 min | The area of the tumor is reduced (15% ± 7%) compared with untreated control group |
| Bladder cancer cell (RT112) and prostatecancer cell (PCA) [202] | Shock-wave | Lithotripter (Siemens Company, Erlangen, Germany) | Frequency 1 Hz<br>Number of pulses 200 or 800<br>Energy density 600 J/m$^2$<br>Treatment time 1h or 24h | Death rate of cancer cell reaches 30%-50% while that of normal cells is 10% |

**Table 2** (*continued*)

| Cancer type | Approaches of mechanotherapy | Loading device | Loading/US parameter | Effect |
| --- | --- | --- | --- | --- |
| Human renal epithelial, cancer cell (CAKI-2), and virus-transformed (HK-2) cell [206] | Shock-wave | Clinical shockwave source (Minilith SL1-0G; STORZ, Tuttlingen, Germany) | Pressure 4.59 MPaDuration: ~1.5 μs (compressive phase) and ~2.1 μs (tensile phase) . | Cancer cells suffered smaller deformation (greater than 5%) and more damage than other cell types |
| Hamster melanomas [204] | Shock-wave | Dornier lithotriptor model XL1 (Dornier Medizintechnik, Germering, Germany) | Frequency 2.3 Hz Voltage 15 kV Condenser capacity 80 nf Treatment time 21 h | Complete remission of local tumor was achieved in more than 90%, while untreated tumors continued to grow. |

cancer cells without significantly damaging normal red blood or immune cells *in vitro* [186]. These results first verified the validity of the "oncotripsy" theory proposed by Ortiz *et al.*: onco from the Greek "Oncos" for tumor and "tripsy" for breaking [101]. As a wine glass can be shattered by a trained singer by singing a specific musical note, oncotripsy is based on the idea that cancer cells are vulnerable to frequency-tuned ultrasound.

In "oncotripsy" theory [101], computational studies suggest that resonance frequencies have a spectral gap between cancer and normal cells, which is be determined by their mismatched cellular/nuclear mechanical properties. Specifically, the spectral gap between HCCs and healthy cells reaches ~ 37 kHz. Further, a first modal analysis reveals a spectral gap in natural frequencies between cancer and normal cells and, most importantly, the difference in resonant growth rates. Thus, the harmonic excitation with tuned frequencies can be exploited to lyse cancer cells without damage the normal cells.

Compared to the cytoplasm, the nucleus has greater stiffness [4] and mass density [194], potentially allowing it to act as a harmonic oscillator [193,195]. The response of a cell to ultrasound is reduced to the simple harmonic vibration of the resonator of nucleus. For the reduced model of a spherical inclusion within a concentric coating, its eigenfrequencies $\omega_i$ follow from the characteristic equation, given by [101,196]:

$$\det\mathbf{A} = 0 \tag{1}$$

where **A** is the coefficient matrix and is determined by the mechanical properties of the inclusion and coating.

The spectral analysis for a tissue consisting of periodically arranged cells embedded in the ECM can be performed by employing the standard Bloch wave theory. The displacement field in the tissue is assumed to be of the form [197]:

$$\mathrm{u}(x) = \hat{\mathrm{u}}(x)e^{ikx} \tag{2}$$

where $\hat{\mathrm{u}}(x)$ is the unknown displacement field in a periodic cell and $k$ is the wavevector of harmonic excitation. The values of wave vector $k$ depend on the Brillouin zone of the periodic lattice. Combining the motion equations, the dispersion relations of the tissue with periodic cells can be defined by the $k$-dependent eigenfrequencies, $\omega_i(k)$.

To understand mechanism by which oncotripsy induces necrosis, a dynamical fatigue model of oncotripsy was proposed on the basis of 'birth–death' kinetics, statistical mechanical theory and cell dynamics to describe the processes of repair and damage in the cytoskeleton [195]. The dynamical model describes the fatigue damage of the cytoskeleton under the relative motion between a rigid nucleus and cell membrane. Based on the Lagrange–D'Alembert principle, the dynamics with damage give the following coupled equations [195]

$$m\ddot{u}(t) + c\dot{u}(t) + (1 - q(t))ku(t) = -m\dot{v}(t) \tag{3}$$

and

$$n\dot{q}(t) + dq(t) = (1 - q(t))ku^2(t) \tag{4}$$

where $m$, $k$ and $c$ are the total mass, stiffness and damping coefficient, respectively; $n$ is a constant related to energy release and $d$ is related to energy cost; $u(t)$ is the displacement of the nucleus, $v(t)$ is the velocity of the cell membrane, and $q$ is the damage parameter. Equation (3) represents the dynamics of a forced and damped nucleus in which the stiffness depends on the degree of damage. Equation (4) governs the kinetics of damage generation and healing. The calibrated model helps in understanding the oncotripsy effect and interpreting experimental observations and thus can be used as a tool for improving the therapeutic effect. Furthermore, the nucleus in eukaryotic cells connects to the cell membrane and ECM through the cytoskeleton, providing additional initial stress and stiffness [198,199]. To identify the cellular responses (*i.e.*, translational and torsional vibrations of the nucleus), a three-dimensional (3D) analytical model accounting for the contractility and anisotropy of the skeleton was proposed [200]. The natural frequency of torsional vibration was predicted to scale as follows:

$$f_{tors} = f_0\sqrt{20\pi(1-\eta+\eta\beta) + \frac{5N}{3}\pi\alpha^2\frac{1-\eta}{\eta^2}\bar{F}_o} \tag{5}$$

where $f_0 = \frac{1}{2\pi}\sqrt{\frac{G_{cp}r_n}{m}}$ is the characteristic frequency, $\eta = r_n/r_c$ is the ratio of the radius of the nucleus to that of the cell, $N$ is the number of cytoskeletal filaments, $\alpha = \frac{d}{l}$ is the slenderness ratio of cytoskeletal filaments, $\beta = \frac{G_{ECM}}{G_{cp}}$ is the normalized shear modulus of the ECM, and $\bar{F}_o = \frac{F_o}{G_{cp}\pi d^2}$ is the dimensionless contractility in cytoskeletal filaments. The natural frequency of translational vibration of the nucleus was given by:

$$f_{tran} = f_0\sqrt{6\pi(1-\eta+\eta\beta) + \frac{N\bar{k}_f}{12}\pi\alpha^2\frac{1-\eta}{\eta}} \tag{6}$$

where $\bar{k}_f = \frac{\xi E_f}{G_{cp}}$ is the dimensionless stiffness of cytoskeletal filaments, in which $\xi = \left(1 + \alpha(1 - \upsilon_{ECM}^2)\frac{E_f}{E_{ECM}}\right)^{-1}$ represents the influence of the ECM on the stiffness of cytoskeletal filaments. The proposed model predicts that the natural frequency of torsional vibration (on the order of ~ 0.1 MHz) depends on cytoskeletal contractility. The natural frequency of the translational vibration of the nucleus depends on cytoskeletal stiffness.

In addition, a much higher frequency of LIPU has been used to selectively target and kill cancer cells in *in-vitro* and animal studies. When applying ultrasound (2 MHz, $I_{SPTA}$ = 0.33 W/cm$^2$) to breast carcinoma and a malignant melanoma *in vitro*, the death rate of cancer cells is 75–80 %, while that of normal cells is 20 % [187]. By triggering intracellular nanobubble explosion with a high-frequency transducer (7 MHz), the survival rate of tumor-bearing mice reached 52 % in treated mice *in vivo* compared to 16 % in control groups [188].

### 4.2. Shock-wave therapy

As a noninvasive approach, the shock wave technique was used as a potential tool in mechanotherapy studies. Cancer cells have been demonstrated to be particularly vulnerable to shock waves [201,202], and the mechanical characteristics of shock waves that affect the viability of metastatic breast epithelial cells (MDA-MB-231) have been investigated *in vitro* [203]. Specifically, the shock wave impulse, but not the peak pressure, was demonstrated to damage MDA-MB-231 breast cancer cells *in vitro*. Experimental results also showed that shock waves selectively killed malignant cells and suppressed tumor growth *in vivo* [204,205]. Moreover, the remission rate of local tumors reached 90 % in shock wave-treated hamsters [204].

To understand the interactions between shock waves and cancer cells, ultrahigh-speed imaging was used to capture the deformation of individual cells *in vitro* under shock wave exposure [206]. Compared to normal counterpart cells, cancer cells showed a faster response but smaller deformation to the shock-wave tensile phase. Cancer cells suffered more damage than healthy cells. Furthermore, a model shows that a shock wave increases the permeability of the cell membrane for cancer cells but not normal cells. In fact, as the largest and stiffest organelle, the nucleus with lamins bears a much larger acoustic radiation force due to its relatively high impedance [207]. Therefore, alterations in the mechanical properties (*e.g.*, Young's modulus) of the nucleus will provide clues to target cancer cells.

### 4.3. Cancer mechanotherapy guided by nuclear mechanotransduction

#### 4.3.1. Mechanical stretch therapy

Recent *in-vitro* and animal studies indicate that tumor cell growth inhibition or the apoptosis of cancer cells can be explained by mechanosensitivity. For instance, *in-vitro* adherent cancer cells and circulating tumor cells are killed by fluid shear stress due to increased susceptibility to mechanical stresses [208,209]. In mouse models, tumor volume was 52 % smaller in response to mechanical stretch compared to the control group, which did not experience stretch treatment [210]. Similarly, exercised mice significantly reduced the tumor growth with a 1.4-fold increase in apoptosis of breast cancer cells [211]. Furthermore, the muscle-associated tumors may reduce their risk due to the mechanical stimulation, which are even not ranked the most common 36 tumors listed in Ref. [212].

Cancer cells differ from normal cells in several features, such as anchorage, mechanosensing and the Warburg effect. For instance, cancer cells present increased calpain activity and altered calcium channel expression [213,214]. Stretch-mediated apoptosis of cancer cells may be due to the activity of the mechanosensitive Piezo1 channel. Mechanical activation enables calcium entry, resulting in calpain-dependent apoptosis [189]. By reducing the rigidity of sensor protein components, *in-vitro* normal cells transform into tumor cells [215,216]. After cyclic stretching (0.1–1 Hz) *in vitro*, the transformed cells become mechanosensitive and then undergo apoptosis [189]. The mechanosensitivity could be specific for tumor cells or transformed cells [217]. Thus, mechanical perturbations may selectively kill tumor cells while stimulating the growth of normal cells. In cancer cells, the persistent activation of ERK results in cell overgrowth [218]. A375p melanoma cells that express proliferating cell nuclear antigen (PCNA) and the ERK Translocation Reporter (ERKTR) were cyclically stretched *in-vitro* to understand ERK activity in cancer cells [219]. When ERK activity increased, ERKTR was phosphorylated and translocated from the nucleus to the cytoplasm. In stretched cells, ERK was active and promoted cell proliferation. As a molecular marker of proliferation [220], PCNA was observed in the cytoplasm of stretched cells but in the nucleus of nonstretched cells *in vitro*. Hence, cyclic stretching inhibited the growth of transformed cells but promoted the growth of normal cells.

### 4.4. Low-frequency LIPU therapy

Low-frequency (tens of kHz) LIPU can selectively kill cancer cells but spare normal cells. *In vitro,* when applying ultrasound (33 kHz, $I_{SPTA}$ = 7.7 mW/cm$^2$) to breast cancer cells (MDA-MB-231), malignant melanoma (A375p), and breast epithelial cells (ATCC), the death rate of cancer cells reached 52 %, while that of normal cells (ATCC) was 18 % [221]. When applying ultrasound (20 kHz, $I_{SPTA}$ = 0.164 W/cm$^2$) to HaCaT and Cal33, the death rate of cancer cells (Cal33) reached 73 %, whereas that of normal cells (Hacat) was 5 % [222]. What's more, cancer cells are highly sensitive to low-frequency LIPU both in *in-vitro* and *in-vivo* animals [223,224]. Upon irradiating human foreskin fibroblasts and malignant cells *in vivo* with an ultrasound transducer (20 kHz, $I_{SPTA}$ = 0.33 W/cm$^2$), the death rate of cancer cells was 90 %, whereas that of normal cells was 12–20 % [223]. When irradiating murine mammary sarcoma (NRA cells) with an ultrasound transducer (20 kHz, $I_{SPTA}$ = 5.09 W/cm$^2$), the death rate of cancer cells was ~ 89 %, whereas that of normal cells was 21 % [224]. *In-vivo* findings reveal a significant difference in viability between cancer and normal cells. In the skin of mice, ultrasound irradiation inhibits tumor growth without affecting healthy tissue. When applying ultrasound (20 kHz) to mice implanted with KHJJ murine mammary sarcoma, the average change in tumor size was only half that of the control group at $I_{SPTA}$ = 8.5 W/cm$^2$ [224]. When applying ultrasound (20 kHz, $I_{SPTA}$ = 12.3 W/cm$^2$) to mice injected with the Cal33 HNSCC cell line, the area of the tumor was reduced by 15 % ± 7 % compared to the control group [222].

Ultrasound produces nonthermal mechanical effects [225,226], inducing stretch/compression and shear stress [227,228] through cavitation and acoustic streaming [225]. *In vitro*, breast cancer cells (MDA-MB-231) in a 96-well plate were irradiated with low-frequency LIPU (33 kHz, 7.5 W), resulting in a 45 % death rate of cancer cells and 9 % death rate of normal cells. *In vivo*, the same ultrasound irradiation causes up to 40 % of chick embryo grafted tumors (MDA-MB-231) to die, whereas untreated tumors continue to grow. Upon ultrasound radiation, the apoptosis of tumor cells was triggered by activating calpain protease and enabling calcium entry through the mechanosensitive Piezo1 channels that disrupt microtubules [189].

### 4.5. Non-mechanically loaded mechanotherapy

In addition to cancer mechanotherapy by directly applying the mechanical loading (*e.g.*, stretch, low-frequency LIPU) mentioned above, it should be noted that it is suggested to intervene signaling pathways related to cell nuclear mechanosensing or mechanotransduction for potential cancer treatment that inhibitors of these pathways are under exploration in clinical trials from preclinical to phase III stages. (See review [229] for more detail). Currently there are several drugs used in clinical cancer treatment by intervening the elements of cancer cells possibly related with nuclear mechanotransduction. For example, anticancer drugs paclitaxel and colchicine [230] can effectively prevent cancer cell mitosis and division in clinical trials by suppressing the dynamic of microtubule cytoskeleton. Given the tight connection between microtubule cytoskeleton and mechanotransduction, it is an open question that whether mechanotransduction interference induced by these drugs contributes to the death of cancer cells. In addition, the inhibition of histone deacetylation and DNA methylation, the two major nuclear mechanoresponses, successfully prevents cancer progression by targeting and "normalizing" chromatin of

rapidly divided cancer cells in clinical trials [231]. It is inspiring to see that more and more efforts are recently devoted to develop novel drugs targeting nuclear mechanotransduction. As the iconic nuclear mechano-responder, YAP/TAZ becomes an attractive option for cancer treatment given its hyper-activity in many types of cancers. Many inhibitors are developed to suppress the hyper-activity of YAP/TAZ [177] by targeting the upstream stimulators of YAP/TAZ, formation of the YAP/TAZ-TEAD complex for transcription or the oncogenic proteins transcriptionally upregulated by YAP/TAZ. Cytochalasin, a drug targeting actin polymerization, is shown to synergistically work with conventional anticancer drugs to kill cancer cells in *in-vitro* and *in-vivo* studies [232].

## 5. Concluding remarks

In addition to conventional therapeutic approaches (*i.e.*, chemotherapy, radiation, immunotherapy, and surgery), mechanotherapy is proposed as a new option for cancer treatment. The development of mechanotherapy was partly attributed to the understanding of nuclear mechanics and mechanotransduction. Taking advantage of the mismatched mechanophenotyping between cancer cells and normal cells, some cancer mechanotherapy strategies that target nuclear mechanics (*e.g.*, high-frequency LIPU therapy, shock-wave therapy) or mechanotransduction (*e.g.*, mechanical stretch therapy, low-frequency LIPU therapy) have been proposed. Among these approaches, the inherent selectivity of low-frequency and high-frequency LIPU, when applied for cancer therapy in future, may offer a broadly applicable and potentially safer alternative to the nonselective ablation of high-intensity ultrasound.

In recent years, with the deepening of cancer research, great progress has been made in the understanding and treatment of cancer. Nevertheless, many treatments for cancer remain challenging for humans and need to further improve the efficacy. Although some translational barriers exist to mechanotherapy in oncology, current *in-vitro* and animal studies preliminarily suggested its feasibility in treating cancers. In situ high-precision measurement technology (*e.g.*, high resolution ultrasonic microscope) is required to distinguish the mechanical properties (*e.g.*, Young's modulus, viscosity or natural frequencies) of the nucleus/cytoplasm/whole-cell between malignant and benign cells. A calibrated mechanical model may facilitate the proceedings of cancer treatment. We believe that mechanotherapy-based therapeutic system will be developed to be used in clinics alongside conventional cancer treatments.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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