Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2024 25(4):280-292*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2300497

Emerging role of lncRNAs as mechanical signaling molecules in mechanotransduction and their association with Hippo-YAP signaling: a review

Siyi LIN[1], Xinyu HE[2,3,4], Ying WANG[2,3,4], Yu CHEN[2,3,4], Aifu LIN[2,3,4,5,6,7]✉

[1]*College of Medicine, Zhejiang University, Hangzhou 310058, China*
[2]*College of Life Sciences, Zhejiang University, Hangzhou 310058, China*
[3]*Cancer Center, Zhejiang University, Hangzhou 310058, China*
[4]*Key Laboratory for Cell and Gene Engineering of Zhejiang Province, Hangzhou 310058, China*
[5]*International School of Medicine, International Institutes of Medicine, the Fourth Affiliated Hospital of Zhejiang University School of Medicine, Yiwu 322000, China*
[6]*Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education, Hangzhou 310058, China*
[7]*Future Health Laboratory, Innovation Center of Yangtze River Delta, Zhejiang University, Jiaxing 314100, China*

Abstract: Cells within tissues are subject to various mechanical forces, including hydrostatic pressure, shear stress, compression, and tension. These mechanical stimuli can be converted into biochemical signals through mechanoreceptors or cytoskeleton-dependent response processes, shaping the microenvironment and maintaining cellular physiological balance. Several studies have demonstrated the roles of Yes-associated protein (YAP) and its homolog transcriptional coactivator with PDZ-binding motif (TAZ) as mechanotransducers, exerting dynamic influence on cellular phenotypes including differentiation and disease pathogenesis. This regulatory function entails the involvement of the cytoskeleton, nucleoskeleton, integrin, focal adhesions (FAs), and the integration of multiple signaling pathways, including extracellular signal-regulated kinase (ERK), wingless/integrated (WNT), and Hippo signaling. Furthermore, emerging evidence substantiates the implication of long non-coding RNAs (lncRNAs) as mechanosensitive molecules in cellular mechanotransduction. In this review, we discuss the mechanisms through which YAP/TAZ and lncRNAs serve as effectors in responding to mechanical stimuli. Additionally, we summarize and elaborate on the crucial signal molecules involved in mechanotransduction.

Key words: YAP/TAZ; Long non-coding RNA (lncRNA); Mechanotransduction; F-actin

1 Introduction

Organisms respond to their environment for survival, adaptation, and subsequent evolution. Mechanical forces play a crucial role in individual development and formation, and any imbalance in these forces can lead to tissue dysregulation and pathologies. At the cellular level, stimuli are perceived and response is given via the extracellular matrix (ECM), including chemical messages like hormones, and mechanical signals such as shear stress, pressure, tissue stiffness, and elastic modulus. This process of transducing mechanical signals to intracellular biochemical messages, known as mechanotransduction, influences cell morphology, proliferation, and differentiation (Maurer and Lammerding, 2019; Uray and Uray, 2021). The understanding of mechanosensitive molecules has evolved over time, with several significant breakthroughs. In the 1980s, the first mechanosensitive ion channel was identified, referred to as the "stretch-activated ion channel" (Corey and Hudspeth, 1979). This channel is responsible for sensing mechanical forces and converting them into electrical signals. Additionally, the potential role of integrin in mechanotransduction was discussed (Ingber, 1997). In the early 2000s, the discovery of Piezo1/2 furthered our understanding of mechanotransduction in mammalian cells (Coste et al., 2010). Moreover,

✉ Aifu LIN, linaifu@zju.edu.cn
Aifu LIN, https://orcid.org/0000-0002-3968-3617

Received July 10, 2023; Revision accepted Dec. 11, 2023;
Crosschecked Mar. 5, 2024

several studies have identified and confirmed numerous other mechanotransduction-dependent proteins, including focal adhesions (FAs), G protein-coupled receptors (GPCRs), and stretch-sensitive ion channels (e.g., two-pore domain K^+ (K2p) channels and transmembrane channels) (Tschumperlin, 2011; Driscoll et al., 2015; Jin et al., 2020). These proteins are capable of perceiving physical stimuli and facilitating the conversion of mechanical messages to biochemical signals through physical unfolding or conformational changes (Goldmann, 2014; Kefauver et al., 2020; Jojoa-Cruz et al., 2022). In addition to these molecular components, the Hippo pathway, a well-known tumor suppressor signaling pathway, has been implicated in various physiological processes, including organ size control, stem cell development, and tumor progression. Zhao et al. (2007) discovered the involvement of the Hippo signaling pathway in regulating organ size and cell density through contact inhibition of proliferation (CIP) in mammalian cells, similar to its role in *Drosophila*. Further studies demonstrated that the Yes-associated protein (YAP) can sense factors like cell density and adhesion space to regulate its activity, highlighting YAP and its homolog transcriptional coactivator with PDZ-binding motif (TAZ) as key mechanosensitive molecules (Zhao et al., 2007). There has been a growing emphasis on comprehending the role of YAP/TAZ as crucial mechanosensitive transcription activators and elucidating their specific mechanisms in mechanotransduction.

The YAP and TAZ proteins serve as the effectors of the Hippo signaling pathway. They regulate target gene expression by translocating to the nucleus and binding to YAP-transcriptional enhanced associate domain (TEAD) family proteins (Dupont et al., 2011). Research has shown that the activity of YAP/TAZ can be influenced by substrate stiffness. That is, on a stiff matrix, YAP becomes activated and translocates to the nucleus, while on a soft substrate, it is phosphorylated and remains in the cytoplasm. This process has been found to be associated with various signaling pathways, including extracellular signal-regulated kinase (ERK), wingless/integrated (WNT), and Hippo signaling (Morgan et al., 2013; Driscoll et al., 2015; Wang et al., 2015; Aharonov et al., 2020; Owens et al., 2020). In addition, the cytoskeleton and nucleoskeleton have been identified as mediators of YAP mechanotransduction, both dependent on and independent of large tumor suppressor kinase 1/2 (LATS1/2) (Driscoll et al., 2015; Elosegui-Artola et al., 2017; Owens et al., 2020). This YAP/TAZ-dependent mechanotransduction is involved in many physiological processes such as stem cell differentiation (Dupont, 2016; Chu et al., 2021; Virdi and Pethe, 2021), bone homeostasis, tissue repair (Yui et al., 2018), and tissue reprogramming (Kurotsu et al., 2020). Besides, YAP/TAZ-mediated mechanotransduction can impact tumorigenesis and other diseases. Therefore, we summarize the mechanisms and molecules involved in the YAP/TAZ-mediated response in mechanotransduction, and thus expand the regulatory network of YAP/TAZ upstream and downstream.

Non-coding RNAs (ncRNAs) represent nearly 98% of all genome outputs in humans, playing a critical role in the downstream regulation of signal transduction (Gao et al., 2022; Hu et al., 2022). Among them, long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides that lack protein-coding ability, although they may encode small peptides (Choi et al., 2019; Wu et al., 2020). Recent evidence underscores the significance of lncRNAs in epigenetic regulation, cell cycle regulation, and cell differentiation regulation. Given the close relationship between cell differentiation and extracellular mechanical forces, lncRNAs have garnered significant attention in the process of mechanotransduction. Herein, we enumerate several lncRNAs that respond to mechanical signals and discuss the potential of lncRNAs to mechanistically respond to these signals by interacting with YAP/TAZ, enhancing our comprehension of mechanotransduction.

2 Responses of YAP/TAZ network to mechanical messages

The mechanism of YAP/TAZ mechanotransduction is complex and involves multiple components. In this study, we present the most widely accepted effectors and summarize their regulatory pathways to streamline and facilitate the comprehension of this process (Fig. 1).

2.1 Cytoskeleton

The cytoskeleton, composed of actin, microtubules, and intermediate fibers, is a dynamic network

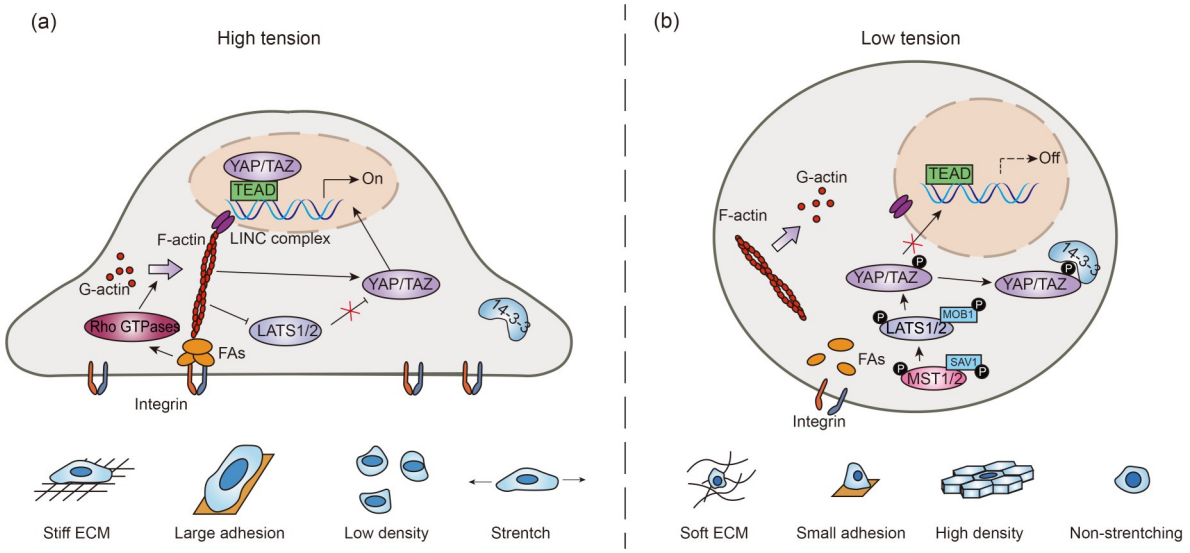

Fig. 1 Proposed mechanisms linking YAP/TAZ activity to mechanical cues from the ECM. (a) Activation of YAP/TAZ in response to high mechanical tension. Increased extracellular tension leads to the interaction between integrins and FAs, triggering Rho GTPase activation, G-actin polymerization, and the formation of F-actin. This complex stretches the LINC complex, leading to the inactivation of LATS1/2 and facilitating the nuclear translocation of YAP/TAZ for gene expression. (b) Inactivation of YAP/TAZ under low mechanical tension conditions. When cells experience low extracellular tension, the connection between integrins and FAs becomes unstable, causing F-actin depolymerization into G-actin. This process triggers the activation of the Hippo pathway, resulting in the cytoplasmic retention of YAP/TAZ and subsequent degradation induced by 14-3-3. YAP: Yes-associated protein; TAZ: transcriptional coactivator with PDZ-binding motif; ECM: extracellular matrix; FAs: focal adhesions; Rho: Ras homology; GTPase: guanosine triphosphatase; G-actin: globular actin; F-actin: filamentous actin; LINC: linker of nucleoskeleton and cytoskeleton; LATS: large tumor suppressor kinase; TEAD: transcriptional enhanced associate domain; MOB1: Mps one binder kinase activator-like 1; MST1/2: macrophage stimulating 1/2; SAV: Salvador family WW-domain-containing protein; P: phosphorylated.

that can sense and transmit mechanical forces through the modulation of regulatory factors such as capping proteins, depolymerizing factors, and severing proteins (Fletcher and Mullins, 2010). Studies have indicated that cytoskeleton dynamics are involved in regulating cell contact and spreading (Aguirre Ghiso et al., 1997; Tanoue and Takeichi, 2004). Zhao et al. (2007) discovered that YAP localization and activation were influenced by cell contact, suggesting a potential connection between YAP and cytoskeleton-mediated mechanotransduction. GPCR signaling, a famous signaling that modulates rearrangements of the cytoskeleton, has also been found to regulate the Hippo pathway, with different effects depending on the coupled G protein (Yu et al., 2012). These findings underscore a regulatory network between YAP and cytoskeleton-related mechanotransduction, implying that YAP may modulate mechanotransduction in a cytoskeleton-dependent manner.

In order to investigate the role of YAP in mechanotransduction, Aragona et al. (2013) discovered that filamentous actin (F-actin)-capping and -severing proteins, such as Cofilin, CapZ, and Gelsolin, suppress YAP nuclear translocation by inhibiting F-actin polymerization. Additionally, inhibitors of globular actin (G-actin), such as Latrunculin B and myosin II inhibitor Blebbistatin, also sequester YAP in the cytoplasm (Bruyère et al., 2019; Liu et al., 2019). Research has shown that F-actin bundles, rather than branches or other forms of cytoskeleton, are essential for modulating YAP activation in mechanotransduction, and this route is mainly LATS-independent (Aragona et al., 2013; Hoffman et al., 2020; Owens et al., 2020).

Further studies have also shown that of all the cytoskeleton components, stress fibers, consisting of F-actin and myosin, have been particularly implicated in the regulation of YAP-mediated mechanotransduction (Driscoll et al., 2015). Impaired stress fiber formation on a soft matrix leads to YAP phosphorylation and cytoplasmic retention (Solon et al., 2007; Tee et al., 2011), whereas a stiff ECM promotes stress fiber formation and translocation of YAP to the nucleus in

a LATS1-independent manner (Engler et al., 2004; Elosegui-Artola et al., 2017).

According to further studies, LATS1/2 kinases and Ras homology (Rho) guanosine triphosphatases (GTPases) have been shown to participate in YAP mechanotransduction related to F-actin. Cytoskeleton polymerization inhibits LATS1/2 and promotes YAP nuclear localization during cell attachment, while cytoskeleton reorganization upon cell detachment activates LATS1/2, leading to YAP phosphorylation and inhibition (Zhao et al., 2012). The Rho/Rho-associated coiled-coil containing protein kinase (ROCK) signaling pathway, which mediates actin cytoskeleton reorganization, acts downstream of cellular tension to promote YAP/TAZ nuclear translocation by inhibiting LATS1/2 activity (Zhang et al., 2018).

However, LATS1/2 knockdown is insufficient to reverse the decrease in YAP/TAZ activity caused by mechanical cues, indicating the involvement of LATS1-independent mechanisms (Dupont et al., 2011). Caveolin-1 (CAV-1), for example, facilitates actin organization and actomyosin contraction, thereby activating YAP independently of LATS (Moreno-Vicente et al., 2018; Chu et al., 2021; Wu et al., 2022). Moreover, the PDZ and LIM domain protein 5/7 (PDLIM5/7, Enigma homolog) has been discovered to directly promote YAP nuclear translocation without affecting the kinase activity of the LATS family (Elbediwy et al., 2018; Liu et al., 2021). In addition, Merlin, a tumor suppressor protein, is involved in YAP/TAZ nuclear localization through the modulation of circumferential actin β tension (Furukawa et al., 2017). Mechanically, the tension in the circumferential actin β at high-density epithelial cells diminished the association between E-cadherin and Merlin, leading to the nucleo-cytoplasmic shutting of Merlin and the formation of YAP/TAZ nuclear export complex, thereby inhibiting the YAP and cell proliferation (Furukawa et al., 2017).

In summary, the polymerization state of F-actin regulates YAP activity through both LATS-dependent and -independent mechanisms in mechanotransduction processes.

2.2 Nucleoskeleton

The dynamic network of the cytoskeleton actively senses and transmits mechanical forces within cells. Apart from the cytoskeleton, the F-actin-mediated nuclear skeleton also plays a significant role in the mechanotransduction process of YAP/TAZ (Driscoll et al., 2015; Elosegui-Artola et al., 2017). The linker of nucleoskeleton and cytoskeleton (LINC) complex, serving as a bridge between cytoskeleton and nucleoskeleton, plays an essential role in mediating the sense and response of the nucleus to mechanical stresses.

The LINC complex consists of an SUN (SAD1/UNC84 homology) domain protein at the inner nuclear membrane and a KASH (Klarsicht, ANC-1 and Syne/Nesprin homology) domain protein at the outer nuclear membrane (Tschumperlin, 2011; Driscoll et al., 2015; Maurer and Lammerding, 2019; Janota et al., 2020; Uray and Uray, 2021). Through their primary components, the SUN protein interacts with the nucleoskeleton and the KASH protein binds to the cytoskeleton, enabling force transmission across the nuclear envelope. It has been observed that disruption of the LINC complex, for instance by the knockout of nuclear envelope spectrin repeat protein 1 (Nesprin-1), results in decreased cell contractility and inhibits YAP nuclear accumulation, highlighting the significant role of a functional LINC complex in facilitating the mechano-responsive behavior of YAP (Driscoll et al., 2015). Conversely, enhancing the LINC complex under certain mechanical conditions increases the sensitivity of YAP to mechanical signals. For example, uniaxial mechanical stimulation reinforces actin assembly and promotes the formation of linear SUN2 (SUN domain protein 2) lines, subsequently activating the nuclear accumulation of mechanically-sensitive transcription factors, including YAP/TAZ (Hoffman et al., 2020). Furthermore, the effect of changes in the LINC complex on the nuclear translocation of YAP has been investigated. It has been found that on a stiff substrate, the integrin/FAs–stress fibers–LINC complex axis transmits stretch force to the nucleus, causing nuclear flattening and loss of nuclear lamina, ultimately promoting YAP nuclear accumulation (Driscoll et al., 2015; Bruyère et al., 2019; Hoffman et al., 2020). Further studies demonstrated that applying mechanical force to Nesprin-1 in isolated nuclei triggers nuclear stiffening, dependent on the nuclear lamina and emerin, emphasizing the irreplaceable role of the LINC complex (Guilluy et al., 2014).

The nuclear lamina also plays a critical role in the LINC complex-mediated regulation of YAP mechanotransduction. As a fibrous meshwork in the inner

nuclear membrane, it consists of A- and B-type lamins and lamin-associated proteins, which determine the morphology and stiffness of the nucleus. Normally, the nuclear lamina acts as a backbone for multiple chromatin anchoring sites, and any structural changes result in chromosome architectural alterations, thereby affecting DNA transcription activity (Shevelyov and Ulianov, 2019). Studies have demonstrated that on a soft matrix, cells and nuclei maintain a rounded shape, with YAP remaining in the cytoplasm for degradation. However, with increasing matrix stiffness, cells become more dispersed, the nucleus flattens, and YAP translocates to the nucleus (Elosegui-Artola et al., 2017). This nucleus deformation induces changes in chromatin stretching and decompensation by losing highly compact A-type lamin, stimulating DNA transcription and the activation of mechanosensitive transcription regulators like YAP/TAZ (Donnaloja et al., 2020). Furthermore, the nuclear lamina interacts with intima proteins, nuclear pore complexes, and other nuclear factors in eukaryotic cells, regulating the size and shape of nuclear pores, and in turn altering transmembrane substance transport. When cells are cultured on a stiff substrate, the stretch forces transmitted from the ECM cause the disintegration of proteins in the nuclear lamina, opening nuclear pores to the cytoplasm and increasing the import rate of YAP through both active and passive transports (Driscoll et al., 2015; Bruyère et al., 2019; Hoffman et al., 2020). Impaired matrix stiffness sensing and the ability to withstand mechanical stretching of the ECM have been observed in muscle stem cells from patients carrying A-type lamin mutations, resulting in the aberrant regulation of YAP and compromising its function (Bertrand et al., 2014; Schwartz et al., 2017; Owens et al., 2020). Furthermore, transcription factors bound to the nucleoskeleton can also impact YAP mechanotransduction. Chang et al. (2018) reported that some nuclear co-factors like AT-rich interaction domain-containing protein 1A (ARID1A, a switch/sucrose non-fermentable (SWI/SNF) subunit) can bind to YAP/TAZ and inhibit its activity. They found that under high mechanical stress, nuclear F-actin can directly bind to the ARID1A-containing SWI/SNF complex (ARID1A-SWI/SNF), limiting the formation of the ARID1A-SWI/SNF-YAP/TAZ complex. This promotes the YAP/TAZ complex formation and the downstream expression of target genes. These findings highlight the significance of the nuclear lamina in connecting cytoplasmic cytoskeletal tension with the nuclear activation of YAP, ultimately expanding our understanding of YAP mechanotransduction.

In conclusion, the LINC complex and the nucleoskeleton, particularly the nuclear lamina, are crucial components in regulating YAP/TAZ mechanotransduction.

2.3 Integrin and focal adhesions

The initial and crucial step in cell mechanotransduction involves the perception of external mechanical signals by mechanosensitive molecules located in the cell membrane. Mechanosensors have been studied extensively and can be categorized into stretch-activated ion channels, GPCR, integrins, and FAs (including focal adhesion kinase (FAK), steroid receptor coactivator (Src), vinculin, and talin). Herein, the focus is mainly on the roles of integrins and FAs in regulating the mechanotransduction of YAP/TAZ.

Integrins are a major class of ECM receptors composed of unique α and β subunits. They respond to various extracellular molecules, such as collagen, laminin, and fibronectin (Humphries et al., 2006), and induce a specific intracellular response (Seetharaman and Etienne-Manneville, 2018). Upon encountering a stiff substrate or high mechanical stress, integrins become activated and clustered, leading to conformational changes in FA components. This in turn recruits downstream signaling molecules and triggers the assembly of the actin-myosin cytoskeleton (Tamada et al., 2004; Goldmann, 2012). For instance, the application of mechanical force can induce an allosteric effect in the extracellular domain of integrin αVβ3, leading to increased expression levels of integrin αVβ3 and fibronectin. Subsequently, FAs aggregate and regulate the actin cytoskeleton function through downstream signals such as RhoA GTPases, thus promoting F-actin assembly (Puklin-Faucher and Sheetz, 2009). Besides, tension applied on cells can cause a conformational change in vinculin, disrupting its binding to vinexin family proteins and promoting high-affinity binding between vinculin and F-actin. These processes result in F-actin polymerization and YAP activation (Kuroda et al., 2018).

Integrins and FAs can interconnect with intracellular signaling pathways, including mitogen-activated protein kinase (MAPK), ERK, and Hippo pathways, to respond to mechanical forces. On stiff matrices, FAs

mature and activate the ERK/MAPK pathway, enhancing YAP/TAZ nuclear translocation (Owens et al., 2020). Conversely, FAs appear immature and vague in cells on soft substrates or small patterns, inhibiting the activity of ERK1/2 and downstream YAP/TAZ (Driscoll et al., 2015; Virdi and Pethe, 2021). Additionally, FAs enhanced by mechanical stress can activate the RhoA/ROCK pathway and promote actin polymerization, which in turn inhibits the LATS1/2 activity and ultimately activates YAP (Zhang et al., 2018). In MCF-10A cells, the stimulation of fibronectin adhesion activates FAK–Src–phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K)–3-phosphoinositide-dependent protein kinase 1 (PDK1) signaling, inhibits LATS, and stimulates YAP (Kim and Gumbiner, 2015). Moreover, ECM collagen type I can modulate FAK/Src to promote the nuclear accumulation of YAP through the canonical WNT pathway, stimulating epithelial repair (Yui et al., 2018). Interestingly, YAP can also regulate the assembly of FAs through a feedback mechanism. YAP activation promotes FA assembly and increases cellular stiffness by upregulating genes encoding integrins and FA docking proteins, thereby forming a positive feedback loop that facilitates YAP signaling.

Although previous studies have emphasized the key role of FAs in mediating YAP mechanotransduction, Nardone et al. (2017) found that the overexpression of FAs (vinculin and zyxin) in adipose tissue-derived mesenchymal stem cells (MSCs) does not impact cell size or YAP localization. They suggested that YAP nuclear accumulation is solely dependent on cell size and not on FA assembly in mechanotransduction. Moreover, their work highlights the significance of integrin αVβ3 in YAP-mediated mechanical transduction by compensatory experiments (Nardone et al., 2017). Overall, as the first responders to mechanical signals, integrins play a role in the regulation of YAP mechanotransduction through FAs and downstream signaling pathways, with FAs serving as intermediaries and solely transmitting the signal.

In summary, integrins and FAs are critical components of the mechanotransduction machinery. They play a crucial role in sensing and transmitting mechanical signals, modulating actin cytoskeletal dynamics, and participating in various signaling pathways to regulate YAP/TAZ activity in response to mechanical forces.

3 Involvement of lncRNAs in mechanotransduction

LncRNAs are a class of single-strand transcripts longer than 200 nucleotides with limited or no protein-coding ability. Numerous studies have demonstrated their involvement in various processes, including epigenetic regulation, cell cycle regulation, and tumorigenesis (Niu et al., 2020; Qu et al., 2022). Recently, attention has been increasingly drawn to the potential role of lncRNAs in mechano-response, leading to the identification of mechano-sensitive lncRNAs (Fig. 2). For example, Mantella et al. (2017) conducted a screening study in human aortic smooth muscle cells exposed to circulatory mechanical stretching intervention and identified 580 differentially expressed lncRNAs out of 30 586, which are implicated in cell differentiation and stress response.

Stem cell differentiation is closely linked to the regulation of external mechanical forces, particularly substrate stiffness (Discher et al., 2005). It has been reported that a soft matrix below 10 kPa promotes the

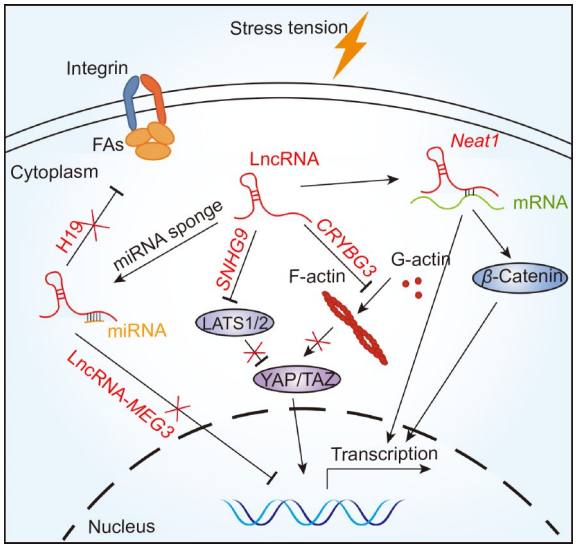

Fig. 2 Involvement of lncRNAs in mechanotransduction. Under stress tension, mechanosensitive lncRNAs function by acting as miRNA sponges or modulating mRNA and proteins related to cell proliferation and differentiation. LncRNA: long non-coding RNA; miRNA: microRNA; mRNA: messenger RNA; FAs: focal adhesions; *Neat1*: nuclear paraspeckle assembly transcript 1; *SNHG9*: small nucleolar RNA host gene 9; *CRYBG3*: crystallin β-γ domain-containing 3; F-actin: filamentous actin; G-actin: globular actin; LATS1/2: large tumor suppressor kinase 1/2; YAP: Yes-associated protein; TAZ: transcriptional coactivator with PDZ-binding motif; *MEG3*: maternally expressed gene 3.

adipogenic differentiation of MSCs, while a stiff matrix above 30 kPa induces osteogenic differentiation. Additionally, MSCs cultured on a 48–53 kPa matrix differentiate into muscle cells (Engler et al., 2006; Guvendiren and Burdick, 2012; Xu et al., 2017). Extensive research has suggested that lncRNAs participate in the regulation of MSC differentiation (Ju et al., 2019). Wu et al. (2018) demonstrated that the lncRNA *H19* acts as a positive regulator for the tension-induced osteogenesis of human bone marrow MSCs (hBMMSCs). *H19* functions as a microRNA-138 (miR-138) sponge, activating FAK and subsequent mechanoresponse (Leucht et al., 2007; Hu et al., 2016). Furthermore, tensile strain upregulates lncRNA maternally expressed gene 3 (*MEG3*) in a time-dependent manner, leading to the enhanced osteogenic differentiation of BMMSCs through the inhibition of miR-140-5p (Zhu GZ et al., 2021). In addition, *MEG3* has been found to induce the endothelial differentiation of mouse-derived adipose-derived stem cells (ADSCs) by reducing miR-145-5p expression (Zhang et al., 2022). Recently, Liu et al. (2022) identified the mechanosensitive lncRNA nuclear paraspeckle assembly transcript 1 (*Neat1*) under simulated microgravity, which forms the backbone of subnuclear "paraspeckle" bodies and plays a crucial role in bone remodeling. *Neat1*-knockout mice exhibited disrupted bone formation and reduced response of osteoblasts to mechanical stimulation. Mechanistically, *Neat1* enhances the paraspeckle-dependent translation of small mothers against decapentaplegic homolog (Smad) ubiquitination regulatory factor 1 (*Smurf1*) messenger RNA (mRNA) to the nucleus and inhibits the ubiquitination-mediated degradation of Runt-related transcription factor 2 (Runx2), an osteoblast-related protein.

Apart from regulating stem cell differentiation, lncRNAs are also involved in other processes related to mechanical transduction. For instance, lncRNA related to mechanical stress (lncRNA-*MSR*, a thymosin *β*-4 (TMSB4) pseudogene), upregulated under cyclic tensile strain (CTS), regulates the expression of TMSB4 and promotes cartilage degradation in chondrocytes by competing with miR-152 (Liu et al., 2016). Besides, studies have found that the expression of lncRNA *Neat1* is enhanced at higher matrix stiffness, promoting the proliferation and epithelial–mesenchymal transition (EMT) of HepG2 cells through the activation of the WNT/*β*-catenin pathway (Xu et al., 2021). Paraspeckles induced by *Neat1* in cancer cells exhibit an inverse relationship to substrate stiffness and show signs of mechanomemory on stiff substrates (Todorovski et al., 2020), suggesting the potential role of *Neat1* as a mechanosensor in cancer mechanobiology. Moreover, certain lncRNAs are involved in converting mechanical signals into biological signals. For example, lncRNA *LINC01569*, by directly binding to the glucocorticoid receptor-mediated mRNA decay (GMD) factor Y-box-binding protein 1 (*YBX1*), guides this complex to mechanosensory mRNA, triggering active GMD and arresting cellular mechanotransduction (Zhu HY et al., 2021).

Given the prominent role of YAP in mechanotransduction, the connection between lncRNAs and YAP in mechanical response is gaining increasing attention. Li et al. (2021) identified differentially expressed lncRNAs in triple-negative breast cancer (TNBC) cells and found that lncRNA small nucleolar RNA host gene 9 (*SNHG9*) significantly responded to three-dimensional (3D) culture among 11 candidates. Subsequent studies revealed that *SNHG9* promotes the liquid-liquid phase separation of LATS, reducing its kinase activity and promoting downstream YAP expression. This suggests the involvement of lncRNA in YAP-mediated mechanotransduction. Furthermore, Zheng et al. (2022) identified an ionizing radiation-induced lncRNA, crystallin β-γ domain containing 3 (*CRYBG3*), which decreases the level of F-actin by preventing its formation and promoting depolymerization, ultimately blocking YAP/TAZ mechanotransduction. This result further supports the idea that lncRNAs can regulate signaling pathways to mediate YAP mechanical response, although the underlying mechanism remains to be elucidated.

4 Discussion

In the process of mechanotransduction, YAP has emerged as a pivotal player in a cytoskeleton-related role. It mediates cellular responses to various mechanical signals, including substrate stiffness, shear stress, pressure, and tissue elasticity. Multiple mechanisms have been identified to involve YAP, with integrin, FAs, cytoskeletal tension, nucleoskeletal tension, and actin dynamics acting as important upstream regulators of YAP via both LATS1-dependent and -independent mechanisms.

On stiff substrates or under stretched conditions, FAs sense tension and transmit signals to increase cytoskeletal tension, ultimately resulting in YAP/TAZ nuclear translocation and activation. This process is known to be regulated by LATS1/2 kinase activity inhibition through various signaling pathways, such as the Rho/ROCK pathway (Zhao et al., 2012; Feng et al., 2014; Zhang et al., 2018). However, LATS1/2 knockdown is insufficient to restore YAP/TAZ function when mechanosignaling is inhibited (Dupont et al., 2011; Panciera et al., 2020), indicating the existence of LATS1/2-independent mechanisms in YAP mechanotransduction. Regarding the nuclear import process, the opening of nuclear pores is a key step, which can be modulated by the F-actin–LINC complex–nucleoskeleton axis independently of LATS1. The involvement of CAV-1 (Moreno-Vicente et al., 2018; Chu et al., 2021) and Enigma homolog (ENH) (Liu et al., 2021) in YAP mechanotransduction without affecting LATS1 kinase activity has also been reported. In contrast, when cells are grown on soft substrates or restricted to small areas, the Hippo pathway is predominantly activated and acts as a major mediator in retaining YAP/TAZ in the cytoplasm. This modulation is closely linked to F-actin (Sun et al., 2014; López-Gay et al., 2020), as the low-level F-actin releases LATS1 to inactivate and phosphorylate YAP (Jia et al., 2016). Through various studies, a YAP mechanical response mechanism independent of F-actin has been revealed, indicating that low ECM stiffness can activate Ras-related protein 2 (RAP2), subsequently triggering MAPK4/6/7 and Rho GTPase activating protein 29 (ARHGAP29), and ultimately activating LATS to inhibit YAP/TAZ (Meng et al., 2018). Furthermore, F-actin depolymerization has been found to impede the nuclear translocation of YAP/TAZ independently of LATS1 (Chen et al., 2016). Nevertheless, the role of LATS1 in YAP mechanotransduction remains elusive and requires further investigation. It has been proposed that LATS1/2 represents a tonic checkpoint that is dispensable for the F-actin–YAP/TAZ axis but is related to axis inhibition. Our understanding of YAP/TAZ-mediated mechanotransduction, both reliant on and independent of Hippo kinases, remains incomplete; an intricate regulatory network exists between Hippo kinases and F-actin-mediated mechanotransduction. Rho and F-actin serve as primary determinants of the regulation of Hippo kinases and their effects on YAP and TAZ. Simultaneously, it is evident that LATS can also affect the cytoskeleton. More in-depth research is needed to understand the delicate equilibrium between these two pillars and whether LATS1/2 directly participates in YAP/TAZ-related mechanotransduction.

Mechanotransduction via YAP participates in various physiological activities of cells. For instance, it plays a crucial role in the differentiation of MSCs, where tension-activated YAP is necessary for maintaining stemness and promoting osteogenic differentiation on stiff substrates. The depletion of YAP/TAZ inhibits osteoblast differentiation on stiff substrates and promotes adipogenic differentiation under low mechanical force conditions (Kuroda et al., 2018; Liu et al., 2019). YAP/TAZ mechanotransduction is also connected to the contact inhibition of proliferation in high-density conditions, where cell−cell contact leads to the activation of junction-related proteins, inhibiting YAP through the Hippo pathway mediated by LATS1/2 (Liu et al., 2018; Ahmad et al., 2022). Moreover, YAP/TAZ mechanotransduction is implicated in cell senescence and aging in vivo by suppressing cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling with the involvement of Lamin B1 and actin-related protein 2 (ACTR2) (Sladitschek-Martens et al., 2022). Apart from these known physiological activities, the role of YAP-associated mechanotransduction in other cellular processes will merit further investigation.

Aberrant YAP mechanotransduction emerges as a pivotal determinant of the pathogenesis of diverse diseases, including cardiovascular diseases (Wang L et al., 2016), inflammation (Meli et al., 2023), and cancer (Zanconato et al., 2016). Studies have elucidated the role of YAP mechanotransduction in mediating the hemodynamic influences on vascular endothelial cells (ECs), thereby contributing to vascular remodeling (Kim et al., 2017; Yamashiro et al., 2020) and atherosclerotic processes (Wang KC et al., 2016; Wang L et al., 2016). Mechanical inputs originating from the aberrant tumor microenvironment induce YAP/TAZ over-activity within cancer cells, establishing a consequential feed-forward loop to regulate ECM remodeling and sustain malignant properties (Calvo et al., 2013; Patwardhan et al., 2021). A fascinating issue to address is whether targeting YAP and TAZ mechanotransduction can be leveraged for therapeutic interventions in these diseases.

Recent research has shed light on the crucial role of lncRNAs in mechanotransduction. These lncRNAs were identified to interact with signaling pathways or microRNAs to perform various functions. However, research in this area is still fragmented and lacks a systematic understanding. It is worth investigating whether these discovered mechanosensitive lncRNAs have common features. Moreover, the relationship between lncRNAs and YAP in mechanotransduction has gained attention, with studies that have identified lncRNAs such as *SNHG9* (Li et al., 2021) and *CRYBG3* (Zheng et al., 2022) to participate in YAP mechanotransduction. However, data on this area are scarce and need to be expanded.

In conclusion, YAP is a key player in cytoskeleton-related mechanotransduction. The relevant regulatory mechanisms involve various upstream mediators and demonstrate both LATS1-dependent and -independent pathways. Additionally, further research is necessary on the involvement of lncRNAs in mechanotransduction and their interplay with YAP.

Acknowledgments

This work was supported by the National Natural Science Foundation for Distinguished Young Scholars of China (No. 32225014), the "Lingyan" R&D Research and Development Project (No. 2023C03023), the National Key R&D Program of China (No. 2021YFC2700903), the National Natural Science Foundation of China (Nos. 81672791 and 81872300), and the Zhejiang Provincial Natural Science Foundation for Distinguished Young Scholars of China (No. LR18C060002).

Author contributions

Aifu LIN determined the topic of the article and proposed this program. Siyi LIN, Xinyu HE, Ying WANG, and Yu CHEN collected the literature. Siyi LIN summarized and drew diagrams of the mechanism. Siyi LIN, Xinyu HE, Ying WANG, Yu CHEN, and Aifu LIN wrote the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Aifu LIN is an Editorial Board Member for *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)* and was not involved in the editorial review or the decision to publish this article. Siyi LIN, Xinyu HE, Ying WANG, Yu CHEN, and Aifu LIN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Aguirre Ghiso JA, Farías EF, Alonso DF, et al., 1997. A phospholipase D and protein kinase C inhibitor blocks the spreading of murine mammary adenocarcinoma cells altering f-actin and β1-integrin point contact distribution. *Int J Cancer*, 71(5):881-890. https://doi.org/10.1002/(sici)1097-0215(19970529)71: 5< 881::aid-ijc29>3.0.co;2-9

Aharonov A, Shakked A, Umansky KB, et al., 2020. ERBB2 drives YAP activation and EMT-like processes during cardiac regeneration. *Nat Cell Biol*, 22(11):1346-1356. https://doi.org/10.1038/s41556-020-00588-4

Ahmad US, Uttagomol J, Wan H, 2022. The regulation of the Hippo pathway by intercellular junction proteins. *Life*, 12(11):1792. https://doi.org/10.3390/life12111792

Aragona M, Panciera T, Manfrin A, et al., 2013. A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors. *Cell*, 154(5): 1047-1059. https://doi.org/10.1016/j.cell.2013.07.042

Bertrand AT, Ziaei S, Ehret C, et al., 2014. Cellular microenvironments reveal defective mechanosensing responses and elevated YAP signaling in *LMNA*-mutated muscle precursors. *J Cell Sci*, 127(13):2873-2884. https://doi.org/10.1242/jcs.144907

Bruyère C, Versaevel M, Mohammed D, et al., 2019. Actomyosin contractility scales with myoblast elongation and enhances differentiation through YAP nuclear export. *Sci Rep*, 9:15565. https://doi.org/10.1038/s41598-019-52129-1

Calvo F, Ege N, Grande-Garcia A, et al., 2013. Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts. *Nat Cell Biol*, 15(6):637-646. https://doi.org/10.1038/ncb2756

Chang L, Azzolin L, di Biagio D, et al., 2018. The SWI/SNF complex is a mechanoregulated inhibitor of YAP and TAZ. *Nature*, 563(7730):265-269. https://doi.org/10.1038/s41586-018-0658-1

Chen Z, Luo Q, Lin CC, et al., 2016. Simulated microgravity inhibits osteogenic differentiation of mesenchymal stem cells via depolymerizing F-actin to impede TAZ nuclear translocation. *Sci Rep*, 6:30322. https://doi.org/10.1038/srep30322

Choi SW, Kim HW, Nam JW, 2019. The small peptide world in long noncoding RNAs. *Brief Bioinform*, 20(5):1853-1864. https://doi.org/10.1093/bib/bby055

Chu GL, Zhang WD, Zhou PH, et al., 2021. Substrate topography regulates differentiation of annulus fibrosus-derived stem cells via CAV1-YAP-mediated mechanotransduction. *ACS Biomater Sci Eng*, 7(3):862-871. https://doi.org/10.1021/acsbiomaterials.9b01823

Corey DP, Hudspeth AJ, 1979. Ionic basis of the receptor

potential in a vertebrate hair cell. *Nature*, 281(5733):675-677. https://doi.org/10.1038/281675a0

Coste B, Mathur J, Schmidt M, et al., 2010. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science*, 330(6000):55-60. https://doi.org/10.1126/science.1193270

Discher DE, Janmey P, Wang YL, 2005. Tissue cells feel and respond to the stiffness of their substrate. *Science*, 310(5751):1139-1143. https://doi.org/10.1126/science.1116995

Donnaloja F, Carnevali F, Jacchetti E, et al., 2020. Lamin A/C mechanotransduction in laminopathies. *Cells*, 9(5):1306. https://doi.org/10.3390/cells9051306

Driscoll TP, Cosgrove BD, Heo SJ, et al., 2015. Cytoskeletal to nuclear strain transfer regulates YAP signaling in mesenchymal stem cells. *Biophys J*, 108(12):2783-2793. https://doi.org/10.1016/j.bpj.2015.05.010

Dupont S, 2016. Role of YAP/TAZ in cell-matrix adhesion-mediated signalling and mechanotransduction. *Exp Cell Res*, 343(1):42-53. https://doi.org/10.1016/j.yexcr.2015.10.034

Dupont S, Morsut L, Aragona M, et al., 2011. Role of YAP/TAZ in mechanotransduction. *Nature*, 474(7350):179-183. https://doi.org/10.1038/nature10137

Elbediwy A, Vanyai H, Diaz-de-la-Loza MDC, et al., 2018. Enigma proteins regulate YAP mechanotransduction. *J Cell Sci*, 131(22):jcs221788. https://doi.org/10.1242/jcs.221788

Elosegui-Artola A, Andreu I, Beedle AEM, et al., 2017. Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell*, 171(6):1397-1410.e14. https://doi.org/10.1016/j.cell.2017.10.008

Engler A, Bacakova L, Newman C, et al., 2004. Substrate compliance versus ligand density in cell on gel responses. *Biophys J*, 86(1 Pt 1):617-628. https://doi.org/10.1016/S0006-3495(04)74140-5

Engler AJ, Sen S, Sweeney HL, et al., 2006. Matrix elasticity directs stem cell lineage specification. *Cell*, 126(4):677-689. https://doi.org/10.1016/j.cell.2006.06.044

Feng XD, Degese MS, Iglesias-Bartolome R, et al., 2014. Hippo-independent activation of YAP by the *GNAQ* uveal melanoma oncogene through a trio-regulated Rho GTPase signaling circuitry. *Cancer Cell*, 25(6):831-845. https://doi.org/10.1016/j.ccr.2014.04.016

Fletcher DA, Mullins RD, 2010. Cell mechanics and the cytoskeleton. *Nature*, 463(7280):485-492. https://doi.org/10.1038/nature08908

Furukawa KT, Yamashita K, Sakurai N, et al., 2017. The epithelial circumferential actin belt regulates YAP/TAZ through nucleocytoplasmic shuttling of Merlin. *Cell Rep*, 20(6):1435-1447. https://doi.org/10.1016/j.celrep.2017.07.032

Gao ZR, Ling XY, Shi CY, et al., 2022. Tumor immune checkpoints and their associated inhibitors. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 23(10):823-843. https://doi.org/10.1631/jzus.B2200195

Goldmann WH, 2012. Mechanotransduction in cells. *Cell Biol Int*, 36(6):567-570. https://doi.org/10.1042/CBI20120071

Goldmann WH, 2014. Vinculin-p130Cas interaction is critical for focal adhesion dynamics and mechano-transduction. *Cell Biol Int*, 38(3):283-286. https://doi.org/10.1002/cbin.10204

Guilluy C, Osborne LD, van Landeghem L, et al., 2014. Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus. *Nat Cell Biol*, 16(4):376-381. https://doi.org/10.1038/ncb2927

Guvendiren M, Burdick JA, 2012. Stiffening hydrogels to probe short- and long-term cellular responses to dynamic mechanics. *Nat Commun*, 3:792. https://doi.org/10.1038/ncomms1792

Hoffman LM, Smith MA, Jensen CC, et al., 2020. Mechanical stress triggers nuclear remodeling and the formation of transmembrane actin nuclear lines with associated nuclear pore complexes. *Mol Biol Cell*, 31(16):1774-1787. https://doi.org/10.1091/mbc.E19-01-0027

Hu J, Liao HJ, Ma ZB, et al., 2016. Focal adhesion kinase signaling mediated the enhancement of osteogenesis of human mesenchymal stem cells induced by extracorporeal shockwave. *Sci Rep*, 6:20875. https://doi.org/10.1038/srep20875

Hu LH, Wu W, Zou J, 2022. Circular RNAs: typical biomarkers for bone-related diseases. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 23(12):975-988. https://doi.org/10.1631/jzus.B2200211

Humphries JD, Byron A, Humphries MJ, 2006. Integrin ligands at a glance. *J Cell Sci*, 119(Pt 19):3901-3903. https://doi.org/10.1242/jcs.03098

Ingber DE, 1997. Tensegrity: the architectural basis of cellular mechanotransduction. *Annu Rev Physiol*, 59:575-599. https://doi.org/10.1146/annurev.physiol.59.1.575

Janota CS, Calero-Cuenca FJ, Gomes ER, 2020. The role of the cell nucleus in mechanotransduction. *Curr Opin Cell Biol*, 63:204-211. https://doi.org/10.1016/j.ceb.2020.03.001

Jia Q, Zhou W, Yao W, et al., 2016. Downregulation of YAP-dependent Nupr1 promotes tumor-repopulating cell growth in soft matrices. *Oncogenesis*, 5(4):e220. https://doi.org/10.1038/oncsis.2016.29

Jin P, Jan LY, Jan YN, 2020. Mechanosensitive ion channels: structural features relevant to mechanotransduction mechanisms. *Annu Rev Neurosci*, 43:207-229. https://doi.org/10.1146/annurev-neuro-070918-050509

Jojoa-Cruz S, Saotome K, Tsui CCA, et al., 2022. Structural insights into the Venus flytrap mechanosensitive ion channel Flycatcher1. *Nat Commun*, 13:850. https://doi.org/10.1038/s41467-022-28511-5

Ju C, Liu RF, Zhang YW, et al., 2019. Mesenchymal stem cell-associated lncRNA in osteogenic differentiation. *Biomed Pharmacother*, 115:108912.

https://doi.org/10.1016/j.biopha.2019.108912

Kefauver JM, Ward AB, Patapoutian A, 2020. Discoveries in structure and physiology of mechanically activated ion channels. *Nature*, 587(7835):567-576. https://doi.org/10.1038/s41586-020-2933-1

Kim J, Kim YH, Kim J, et al., 2017. YAP/TAZ regulates sprouting angiogenesis and vascular barrier maturation. *J Clin Invest*, 127(9):3441-3461. https://doi.org/10.1172/JCI93825

Kim NG, Gumbiner BM, 2015. Adhesion to fibronectin regulates Hippo signaling via the FAK-Src-PI3K pathway. *J Cell Biol*, 210(3):503-515. https://doi.org/10.1083/jcb.201501025

Kuroda M, Ueda K, Kioka N, 2018. Vinexin family (SORBS) proteins regulate mechanotransduction in mesenchymal stem cells. *Sci Rep*, 8:11581. https://doi.org/10.1038/s41598-018-29700-3

Kurotsu S, Sadahiro T, Fujita R, et al., 2020. Soft matrix promotes cardiac reprogramming via inhibition of YAP/TAZ and suppression of fibroblast signatures. *Stem Cell Rep*, 15(3):612-628. https://doi.org/10.1016/j.stemcr.2020.07.022

Leucht P, Kim JB, Currey JA, et al., 2007. FAK-mediated mechanotransduction in skeletal regeneration. *PLoS ONE*, 2(4):e390. https://doi.org/10.1371/journal.pone.0000390

Li RH, Tian T, Ge QW, et al., 2021. A phosphatidic acid-binding lncRNA *SNHG9* facilitates LATS1 liquid-liquid phase separation to promote oncogenic YAP signaling. *Cell Res*, 31(10):1088-1105. https://doi.org/10.1038/s41422-021-00530-9

Liu CZ, Gao XC, Li YH, et al., 2022. The mechanosensitive lncRNA *Neat1* promotes osteoblast function through paraspeckle-dependent *Smurf1* mRNA retention. *Bone Res*, 10:18. https://doi.org/10.1038/s41413-022-00191-3

Liu L, Liu MC, Xie DF, et al., 2021. Role of the extracellular matrix and YAP/TAZ in cell reprogramming. *Differentiation*, 122:1-6. https://doi.org/10.1016/j.diff.2021.11.001

Liu OX, Lin LB, Chew T, et al., 2018. ZO-2 induces cytoplasmic retention of YAP by promoting a LATS1-ZO-2-YAP complex at tight junctions. bioRxiv, preprint. https://doi.org/10.1101/355081

Liu Q, Hu XQ, Zhang X, et al., 2016. The TMSB4 pseudogene lncRNA functions as a competing endogenous RNA to promote cartilage degradation in human osteoarthritis. *Mol Ther*, 24(10):1726-1733. https://doi.org/10.1038/mt.2016.151

Liu X, Hou WQ, He L, et al., 2019. AMOT130/YAP pathway in topography-induced BMSC osteoblastic differentiation. *Colloids Surf B Biointerfaces*, 182:110332. https://doi.org/10.1016/j.colsurfb.2019.06.061

López-Gay JM, Nunley H, Spencer M, et al., 2020. Apical stress fibers enable a scaling between cell mechanical response and area in epithelial tissue. *Science*, 370(6514): eabb2169. https://doi.org/10.1126/science.abb2169

Mantella LE, Singh KK, Sandhu P, et al., 2017. Fingerprint of long non-coding RNA regulated by cyclic mechanical stretch in human aortic smooth muscle cells: implications for hypertension. *Mol Cell Biochem*, 435(1-2):163-173. https://doi.org/10.1007/s11010-017-3065-2

Maurer M, Lammerding J, 2019. The driving force: nuclear mechanotransduction in cellular function, fate, and disease. *Annu Rev Biomed Eng*, 21:443-468. https://doi.org/10.1146/annurev-bioeng-060418-052139

Meli VS, Veerasubramanian PK, Downing TL, et al., 2023. Mechanosensation to inflammation: roles for YAP/TAZ in innate immune cells. *Sci Signal*, 16(783):eadc9656. https://doi.org/10.1126/scisignal.adc9656

Meng ZP, Qiu YJ, Lin KC, et al., 2018. RAP2 mediates mechanoresponses of the Hippo pathway. *Nature*, 560(7720): 655-660. https://doi.org/10.1038/s41586-018-0444-0

Moreno-Vicente R, Pavón DM, Martín-Padura I, et al., 2018. Caveolin-1 modulates mechanotransduction responses to substrate stiffness through actin-dependent control of YAP. *Cell Rep*, 25(6):1622-1635.e6. https://doi.org/10.1016/j.celrep.2018.10.024

Morgan JT, Murphy CJ, Russell P, 2013. What do mechanotransduction, Hippo, Wnt, and TGFβ have in common? YAP and TAZ as key orchestrating molecules in ocular health and disease. *Exp Eye Res*, 115:1-12. https://doi.org/10.1016/j.exer.2013.06.012

Nardone G, Oliver-de la Cruz J, Vrbsky J, et al., 2017. YAP regulates cell mechanics by controlling focal adhesion assembly. *Nat Commun*, 8:15321. https://doi.org/10.1038/ncomms15321

Niu LM, Lou FZ, Sun Y, et al., 2020. A micropeptide encoded by lncRNA MIR155HG suppresses autoimmune inflammation via modulating antigen presentation. *Sci Adv*, 6(21):eaaz2059. https://doi.org/10.1126/sciadv.aaz2059

Owens DJ, Fischer M, Jabre S, et al., 2020. Lamin mutations cause increased YAP nuclear entry in muscle stem cells. *Cells*, 9(4):816. https://doi.org/10.3390/cells9040816

Panciera T, Citron A, di Biagio D, et al., 2020. Reprogramming normal cells into tumour precursors requires ECM stiffness and oncogene-mediated changes of cell mechanical properties. *Nat Mater*, 19(7):797-806. https://doi.org/10.1038/s41563-020-0615-x

Patwardhan S, Mahadik P, Shetty O, et al., 2021. ECM stiffness-tuned exosomes drive breast cancer motility through thrombospondin-1. *Biomaterials*, 279:121185. https://doi.org/10.1016/j.biomaterials.2021.121185

Puklin-Faucher E, Sheetz MP, 2009. The mechanical integrin cycle. *J Cell Sci*, 122(2):179-186. https://doi.org/10.1242/jcs.042127

Qu L, He XY, Tang Q, et al., 2022. Iron metabolism, ferroptosis, and lncRNA in cancer: knowns and unknowns. *J Zhejiang*

Univ-Sci B (Biomed & Biotechnol), 23(10):844-862. https://doi.org/10.1631/jzus.B2200194

Schwartz C, Fischer M, Mamchaoui K, et al., 2017. Lamins and nesprin-1 mediate inside-out mechanical coupling in muscle cell precursors through FHOD1. *Sci Rep*, 7:1253. https://doi.org/10.1038/s41598-017-01324-z

Seetharaman S, Etienne-Manneville S, 2018. Integrin diversity brings specificity in mechanotransduction. *Biol Cell*, 110(3): 49-64. https://doi.org/10.1111/boc.201700060

Shevelyov YY, Ulianov SV, 2019. The nuclear lamina as an organizer of chromosome architecture. *Cells*, 8(2):136. https://doi.org/10.3390/cells8020136

Sladitschek-Martens HL, Guarnieri A, Brumana G, et al., 2022. YAP/TAZ activity in stromal cells prevents ageing by controlling cGAS-STING. *Nature*, 607(7920):790-798. https://doi.org/10.1038/s41586-022-04924-6

Solon J, Levental I, Sengupta K, et al., 2007. Fibroblast adaptation and stiffness matching to soft elastic substrates. *Biophys J*, 93(12):4453-4461. https://doi.org/10.1529/biophysj.106.101386

Sun YB, Yong KMA, Villa-Diaz LG, et al., 2014. Hippo/YAP-mediated rigidity-dependent motor neuron differentiation of human pluripotent stem cells. *Nat Mater*, 13(6):599-604. https://doi.org/10.1038/nmat3945

Tamada M, Sheetz MP, Sawada Y, 2004. Activation of a signaling cascade by cytoskeleton stretch. *Dev Cell*, 7(5): 709-718. https://doi.org/10.1016/j.devcel.2004.08.021

Tanoue T, Takeichi M, 2004. Mammalian Fat1 cadherin regulates actin dynamics and cell–cell contact. *J Cell Biol*, 165(4):517-528. https://doi.org/10.1083/jcb.200403006

Tee SY, Fu JP, Chen CS, et al., 2011. Cell shape and substrate rigidity both regulate cell stiffness. *Biophys J*, 100(5): L25-L27. https://doi.org/10.1016/j.bpj.2010.12.3744

Todorovski V, Fox AH, Choi YS, 2020. Matrix stiffness-sensitive long noncoding RNA NEAT1 seeded paraspeckles in cancer cells. *Mol Biol Cell*, 31(16):1654-1662. https://doi.org/10.1091/mbc.E20-02-0097

Tschumperlin DJ, 2011. Mechanotransduction. *Compr Physiol*, 1(2):1057-1073. https://doi.org/10.1002/cphy.c100016

Uray IP, Uray K, 2021. Mechanotransduction at the plasma membrane-cytoskeleton interface. *Int J Mol Sci*, 22(21): 11566. https://doi.org/10.3390/ijms222111566

Virdi JK, Pethe P, 2021. Biomaterials regulate mechanosensors YAP/TAZ in stem cell growth and differentiation. *Tissue Eng Regen Med*, 18(2):199-215. https://doi.org/10.1007/s13770-020-00301-4

Wang J, Zhang YF, Zhang N, et al., 2015. An updated review of mechanotransduction in skin disorders: transcriptional regulators, ion channels, and microRNAs. *Cell Mol Life Sci*, 72(11):2091-2106. https://doi.org/10.1007/s00018-015-1853-y

Wang KC, Yeh YT, Nguyen P, et al., 2016. Flow-dependent YAP/TAZ activities regulate endothelial phenotypes and atherosclerosis. *Proc Natl Acad Sci USA*, 113(41):11525-11530. https://doi.org/10.1073/pnas.1613121113

Wang L, Luo JY, Li BC, et al., 2016. Integrin-YAP/TAZ-JNK cascade mediates atheroprotective effect of unidirectional shear flow. *Nature*, 540(7634):579-582. https://doi.org/10.1038/nature20602

Wu JJ, Zhao J, Sun L, et al., 2018. Long non-coding RNA H19 mediates mechanical tension-induced osteogenesis of bone marrow mesenchymal stem cells via FAK by sponging miR-138. *Bone*, 108:62-70. https://doi.org/10.1016/j.bone.2017.12.013

Wu LY, Han CL, Lin HH, et al., 2022. Ha-Ras^{V12}-induced multilayer cellular aggregates is mediated by Rac1 activation rather than YAP activation. *Biomedicines*, 10(5):977. https://doi.org/10.3390/biomedicines10050977

Wu P, Mo YZ, Peng M, et al., 2020. Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. *Mol Cancer*, 19:22. https://doi.org/10.1186/s12943-020-1147-3

Xu JJ, Sun MY, Tan Y, et al., 2017. Effect of matrix stiffness on the proliferation and differentiation of umbilical cord mesenchymal stem cells. *Differentiation*, 96:30-39. https://doi.org/10.1016/j.diff.2017.07.001

Xu XC, Zhang Y, Wang X, et al., 2021. Substrate stiffness drives epithelial to mesenchymal transition and proliferation through the *NEAT1*-Wnt/β-catenin pathway in liver cancer. *Int J Mol Sci*, 22(21):12066. https://doi.org/10.3390/ijms222112066

Yamashiro Y, Thang BQ, Ramirez K, et al., 2020. Matrix mechanotransduction mediated by thrombospondin-1/integrin/YAP in the vascular remodeling. *Proc Natl Acad Sci USA*, 117(18):9896-9905. https://doi.org/10.1073/pnas.1919702117

Yu FX, Zhao B, Panupinthu N, et al., 2012. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell*, 150(4):780-791. https://doi.org/10.1016/j.cell.2012.06.037

Yui S, Azzolin L, Maimets M, et al., 2018. YAP/TAZ-dependent reprogramming of colonic epithelium links ECM remodeling to tissue regeneration. *Cell Stem Cell*, 22(1):35-49.e7. https://doi.org/10.1016/j.stem.2017.11.001

Zanconato F, Cordenonsi M, Piccolo S, 2016. YAP/TAZ at the roots of cancer. *Cancer Cell*, 29(6):783-803. https://doi.org/10.1016/j.ccell.2016.05.005

Zhang HL, Liu G, Mao X, et al., 2022. LncRNA MEG3 induces endothelial differentiation of mouse derived adipose-derived stem cells by targeting miR-145-5p/KLF4. *Mol Biol Rep*, 49(9):8495-8505. https://doi.org/10.1007/s11033-022-07671-z

Zhang Q, Lin SY, Liao JF, et al., 2018. Physical cues drive chondrogenic differentiation. *Curr Stem Cell Res Ther*, 13(7):576-582.

https://doi.org/10.2174/1574888X13666180102121455

Zhao B, Wei XM, Li WQ, et al., 2007. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev*, 21(21):2747-2761. https://doi.org/10.1101/gad.1602907

Zhao B, Li L, Wang L, et al., 2012. Cell detachment activates the Hippo pathway via cytoskeleton reorganization to induce anoikis. *Genes Dev*, 26(1):54-68. https://doi.org/10.1101/gad.173435.111

Zheng LJ, Luo CY, Yang N, et al., 2022. Ionizing radiation-induced long noncoding RNA CRYBG3 regulates YAP/TAZ through mechanotransduction. *Cell Death Dis*, 13(3):209. https://doi.org/10.1038/s41419-022-04650-x

Zhu GZ, Zeng CJ, Qian YP, et al., 2021. Tensile strain promotes osteogenic differentiation of bone marrow mesenchymal stem cells through upregulating lncRNA-MEG3. *Histol Histopathol*, 36(9):939-946. https://doi.org/10.14670/HH-18-365

Zhu HY, Li J, Li YZ, et al., 2021. Glucocorticoid counteracts cellular mechanoresponses by LINC01569-dependent glucocorticoid receptor-mediated mRNA decay. *Sci Adv*, 7(9):eabd9923. https://doi.org/10.1126/sciadv.abd9923