

## Mechanotransduction in Cellular Physiology: From Cytoskeleton Dynamics to Gene Expression

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### Abstract

Mechanotransduction is the process through which cells convert mechanical cues from their microenvironment into biochemical signals that regulate gene expression and cellular behavior. This review aims to critically integrate current evidence on how mechanical forces are transmitted from the extracellular matrix through adhesion complexes and cytoskeletal structures to the nucleus, thereby shaping transcriptional regulation. The discussion focuses on the coordinated roles of cytoskeletal dynamics and mechanosensitive signaling pathways, including YAP/TAZ, MRTF-A,

and RhoA/ROCK, in controlling cellular proliferation, differentiation, and tissue adaptation. The physiological relevance of these mechanisms is examined in key biological contexts such as stem cell lineage specification, skeletal muscle adaptation to mechanical loading, and endothelial regulation under hemodynamic forces. In parallel, the review addresses how disruptions in mechanotransduction contribute to disease pathogenesis, particularly in cancer, fibrosis, and atherosclerosis, where altered mechanical environments lead to aberrant gene regulatory responses. Finally, this article highlights emerging methodological advances, including three-dimensional culture systems, organ-on-chip platforms, and integrated multi-omics approaches, as essential tools for improving mechanobiological modeling and identifying novel therapeutic targets related to mechanically driven cellular dysfunction.

**Keywords:** Mechanotransduction, Cytoskeleton, Disease, Integrins, Gene expression, Mechanical signaling

## Introduction

Mechanical forces are key factors that significantly determine cellular function and behavior [1]. Every living cell operates in an environment that constantly exerts mechanical influences through tension, pressure, strain, and shear forces originating from the extracellular matrix (ECM), intercellular interactions, and tissue fluid movement [2]. Variations in these forces not only influence cell morphology and architecture but also regulate important biological processes such as migration, proliferation, differentiation, and apoptosis [3]. In the context of tissue physiology, mechanical forces serve as primary signals that enable cells to adapt to microenvironmental dynamics, maintain functional balance, and preserve structural integrity and organ homeostasis [4].

Mechanotransduction is a fundamental mechanism by which cells convert mechanical stimuli into biochemical responses that play a role in regulating cellular function [5]. This process involves coordinated interactions between cytoskeletal elements, adhesion complexes, mechanosensory proteins, and various intracellular signaling components [6]. Through mechanotransduction, physical changes in the cell's environment are translated into changes in protein conformation, activation of signaling cascades, and regulation of gene expression [7]. The cytoskeleton—composed of actin filaments, microtubules, and intermediate filaments—acts as a dynamic structural network that transmits mechanical forces from the plasma membrane to the nucleus and organelles, thus linking mechanical responses to genetic regulatory mechanisms within the cell [8].

The physiological significance of mechanotransduction is evident in a wide range of biological processes. In stem cell differentiation, the

mechanical properties of the extracellular matrix play a role in determining the direction of cell specialization: A matrix with high stiffness promotes osteogenic differentiation, while a softer matrix favors differentiation toward neurogenic or adipogenic lineages [9]. In the cardiovascular system, shear forces generated by blood flow influence the activation of mechanosensitive transcription factors such as krüppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS), which play a role in maintaining vasodilation and blood pressure stability [10]. In skeletal muscle tissue, repetitive strain during contraction stimulates the phosphoinositide 3-kinase–protein kinase B–mechanistic target of rapamycin (PI3K–Akt–mTOR) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways, thereby increasing protein synthesis, muscle hypertrophy, and mitochondrial biogenesis in response to increased mechanical load [11]. Furthermore, mechanotransduction plays a crucial role in wound healing, tissue remodeling, and embryonic development, where the integration of mechanical and chemical signals ensures the spatial and temporal coordination of cell growth, migration, and differentiation [12].

Dysregulation of mechanotransduction has important implications for various pathological processes. Increased tissue stiffness in fibrosis can trigger overactivation of mechanosensitive pathways such as Yes-associated protein/Transcriptional coactivator with PDZ-binding motif (YAP/TAZ), which promotes fibroblast differentiation into myofibroblasts and accelerates extracellular matrix deposition [13]. In the context of cancer, changes in the mechanical characteristics of the tumor microenvironment increase cytoskeletal tension,

contributing to uncontrolled cell proliferation, epithelial–mesenchymal transition (EMT), and increased metastatic potential [14]. Meanwhile, in atherosclerosis, nonlaminar blood flow inhibits endothelial anti-inflammatory gene expression and favors vascular plaque formation [15]. Overall, these phenomena emphasize that the balance of mechanotransduction plays a crucial role in determining whether cellular responses will be adaptive or pathological [5].

The aim of this review is to provide a comprehensive understanding of mechanotransduction in cellular physiology, with an emphasis on the interplay between cytoskeleton dynamics, mechanosensors, and gene expression regulation. This article will discuss the key signaling pathways that translate mechanical forces into transcriptional activity, highlighting the physiological role of mechanotransduction in cell differentiation, tissue adaptation, and maintenance of homeostasis. Furthermore, this review will evaluate the impact of mechanotransduction dysregulation on various pathological conditions and highlight advances in experimental technology that enable quantitative analysis of mechanotransduction, providing a basis for further research and developing mechanobiology-based therapeutic strategies.

### Data collection method

This scoping review was conducted in accordance with the PRISMA-ScR guidelines. A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, and Web of Science to identify English-language studies published between January 1, 2008, and November 3, 2025. Controlled vocabulary terms and relevant keywords were used to capture studies related to mechanotransduction and mechanosensing; integrins, cadherins, and PIEZO channels; focal adhesion and cytoskeletal signaling pathways, including FAK/Src, RhoA/ROCK, MAPK/ERK, and PI3K/AKT; nucleo-cytoskeletal coupling mechanisms such as the LINC complex and lamins; and nuclear and chromatin-associated regulators, including YAP/TAZ and MRTF-A, in relation to gene expression.

Eligible studies included *in vitro* and *in vivo* primary research as well as mechanistic reviews that

explicitly linked mechanical stimuli to biochemical signaling and gene regulatory outcomes. Non-peer-reviewed publications, non-English articles, and studies lacking defined mechanical perturbation or measurable mechanobiological readouts were excluded. Data extraction was independently performed by two reviewers using a standardized framework encompassing experimental system, mechanical stimuli, signaling routes, nuclear or chromatin effects, functional readouts, and biological context, with discrepancies resolved through consensus. Study design features and potential sources of bias were assessed qualitatively, and the findings were synthesized narratively along a force-to-gene continuum without conducting a meta-analysis.

### Basic mechanisms of mechanotransduction

Mechanotransduction plays an essential role in maintaining the physiological balance of cells by transforming mechanical stimuli from the environment into biochemical signals that regulate function and gene expression. This process involves a network of structural and molecular components that interact synergistically to detect, transmit, and integrate mechanical forces into appropriate biological responses at the cellular level.

### Main components of mechanotransduction

Mechanotransduction is increasingly understood not as a linear signaling cascade, but as an integrated, multiscale system in which mechanical cues are sensed, transmitted, and interpreted through coordinated interactions between the plasma membrane, the extracellular matrix (ECM), and the cytoskeleton [16,17]. While early models emphasized single mechanosensors, more recent frameworks highlight the cooperative and context-dependent nature of these components, where mechanical information is distributed across multiple structural elements rather than processed by a single dominant pathway [18].

At the cell surface, the plasma membrane functions as the primary interface for mechanical input; however, its mechanosensory capacity largely depends on associated adhesion complexes rather than the lipid bilayer itself [19]. Integrins and cadherins represent two mechanistically distinct but complementary adhesion systems. Integrin-based adhesions primarily

mediate cell–ECM interactions and are optimized for sensing substrate stiffness and tensile forces, whereas cadherin-based junctions specialize in transducing intercellular tension within tissues [20]. This functional divergence explains why integrin signaling dominates in studies of matrix stiffness, while cadherin-mediated pathways are more prominent in morphogenesis and collective cell behavior.

Integrin-mediated mechanotransduction has been extensively characterized through focal adhesion complexes involving talin, vinculin, paxillin, and focal adhesion kinase (FAK) [21]. In stiffness-driven models, force-induced unfolding of talin exposes vinculin-binding sites, reinforcing integrin–actin coupling and activating downstream signaling cascades such as RhoA/ROCK, PI3K/AKT, and MAPK [22]. However, the relative contribution of these pathways varies across experimental systems. For example, RhoA/ROCK signaling dominates force transmission in mesenchymal cells, whereas PI3K/AKT signaling appears more relevant in epithelial or endothelial contexts. These differences underscore the limitation of extrapolating mechanotransduction mechanisms from single cell types or two-dimensional substrates.

In contrast, cadherin-based adhesions transmit mechanical forces between neighboring cells and regulate tissue-scale mechanics [23]. Tension across cadherins modulates  $\beta$ -catenin availability and transcriptional activity, linking mechanical coupling to cell fate decisions during development and tissue remodeling [24]. Notably, some studies suggest that cadherin-mediated mechanotransduction can attenuate YAP/TAZ activity under high cell density, highlighting a mechanistic counterbalance to integrin-driven signaling. This apparent contradiction illustrates how mechanical inputs can produce divergent transcriptional outcomes depending on adhesion context and tissue architecture.

The ECM acts not merely as a passive scaffold but as an active regulator of mechanotransduction by defining the magnitude, direction, and persistence of mechanical forces [25]. Variations in ECM stiffness, elasticity, and topology modulate cellular contractility and focal adhesion maturation, thereby influencing intracellular tension [26]. While increased ECM stiffness is frequently associated with YAP/TAZ activation and pro-proliferative gene expression, this

relationship is not universal. In highly confined three-dimensional environments, for example, nuclear deformation rather than matrix stiffness may dominate mechanosensitive signaling, suggesting that stiffness-centric models have limited applicability outside simplified culture systems [27].

The cytoskeleton integrates signals from adhesion complexes and distributes mechanical forces throughout the cell, forming a continuous force-transmission network from the plasma membrane to the nucleus [31]. Actin filaments, microtubules, and intermediate filaments contribute distinct mechanical functions: Actin generates contractile tension, microtubules provide compressive resistance and spatial organization, and intermediate filaments enhance mechanical resilience under large deformations [32–34]. Importantly, these components do not act independently. Crosstalk between actin and microtubules fine-tunes intracellular tension, while intermediate filaments modulate force dissipation, particularly under pathological mechanical stress.

Changes in cytoskeletal tension can directly influence nuclear shape, chromatin organization, and transcriptional accessibility [35]. However, the extent to which cytoskeletal forces alone regulate gene expression remains debated, as biochemical signaling pathways often operate in parallel. Thus, while the cytoskeleton is indispensable for mechanical signal propagation, its regulatory role must be interpreted within a broader mechano-biochemical framework rather than as a standalone determinant of gene regulation [36].

### **Conversion of mechanical forces into biochemical signals**

The defining feature of mechanotransduction lies in the conversion of physical forces—such as tension, compression, and shear stress—into biochemical signals that regulate cellular behavior [37]. Rather than relying on a single mechanosensor, cells employ multiple force-sensitive proteins that respond through conformational changes, altered binding affinities, and activation of downstream signaling pathways [38]. This redundancy enhances robustness but also introduces complexity and variability across experimental models.

Focal adhesion proteins such as talin, vinculin, and paxillin serve as prototypical mechanosensitive

elements [39,40]. Talin unfolding under tensile load exposes cryptic vinculin-binding sites, reinforcing integrin–actin coupling and stabilizing focal adhesions [41]. While this mechanism is well supported *in vitro*, its quantitative contribution *in vivo* remains difficult to resolve, as force magnitudes and loading rates differ substantially across tissues. Moreover, not all integrin-dependent signaling requires talin unfolding, suggesting alternative force-sensing modes within adhesion complexes [42].

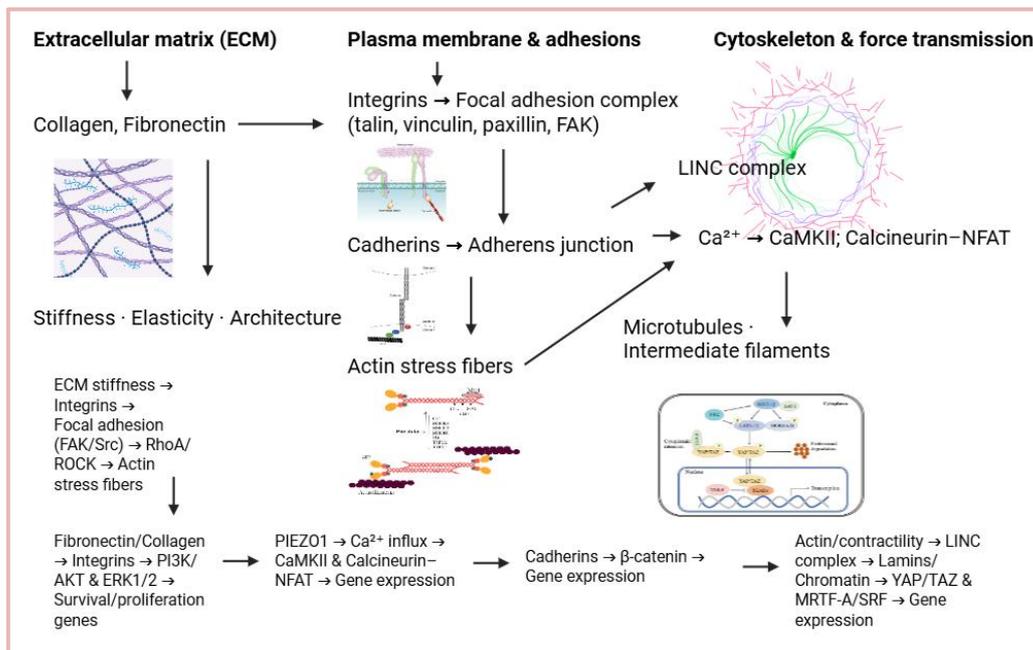
Mechanosensitive ion channels, particularly Piezo1, represent a distinct class of mechanotransducers that directly couple membrane deformation to intracellular signaling [43]. Piezo1-mediated  $\text{Ca}^{2+}$  influx activates downstream pathways such as CaMKII and calcineurin–NFAT, influencing transcriptional programs related to calcium homeostasis and inflammation [44]. Compared to adhesion-based mechanotransduction, ion channel-mediated signaling operates on faster timescales but may lack the spatial specificity provided by focal adhesions. This functional distinction highlights how different mechanotransduction pathways are preferentially engaged depending on the nature and duration of mechanical stimuli.

At the nuclear level, YAP and TAZ function as central integrators of mechanical signals derived from both cytoskeletal tension and adhesion-mediated signaling [45]. In rigid or highly contractile environments, YAP/TAZ translocate to the nucleus and activate transcriptional programs that promote proliferation and differentiation [46]. However, emerging evidence indicates that YAP/TAZ activity can also be modulated independently of substrate stiffness, for example through nuclear deformation or changes in cell geometry. These findings challenge stiffness-centric models and suggest that multiple mechanical parameters converge on YAP/TAZ regulation [47].

A unifying principle across mechanosensitive proteins is their capacity for force-induced conformational change, which exposes hidden binding sites and alters signaling networks [48,49]. Talin stretching and lamin A/C deformation exemplify how mechanical forces directly modify protein structure and function [50,51]. Nonetheless, detecting these conformational changes in living tissues remains technically challenging, limiting direct validation of many proposed mechanisms [52].

Downstream of mechanosensors, signaling pathways such as RhoA/ROCK, MAPK/ERK, and PI3K/AKT coordinate cytoskeletal remodeling, survival, and transcriptional responses [21,53–56]. While these pathways are often presented as parallel outputs of mechanotransduction, evidence suggests substantial cross-regulation and context dependence. For instance, RhoA/ROCK-driven contractility can enhance YAP/TAZ activity, whereas PI3K/AKT signaling may modulate mechanosensitivity indirectly through metabolic regulation. This interdependence complicates efforts to isolate linear cause–effect relationships.

Overall, mechanotransduction emerges as a distributed signaling network in which mechanical inputs are decoded through multiple, partially overlapping biochemical pathways [57]. The conversion of mechanical forces into biochemical signals is therefore not a singular event but a dynamic and context-dependent process shaped by cell type, dimensionality, and mechanical history. Recognizing these limitations is essential for interpreting experimental findings and translating mechanotransduction principles into physiological and pathological contexts [38]. Bottom of Form As shown in **Figure 1**, ECM stiffness is sensed by integrins/cadherins and PIEZO1, transmitted through focal adhesions and the cytoskeleton, and culminates in YAP/TAZ and MRTF-A/SRF-driven gene expression.



**Figure 1** Mechanotransduction across the ECM–adhesion–cytoskeleton–nucleus axis.

**Cytoskeleton dynamics in mechanotransduction**

The cytoskeleton functions as a dynamic structural network, transmitting mechanical forces from the external environment into the cell while coordinating the resulting biochemical responses. Changes in cytoskeletal organization and tension are

key elements of mechanotransduction, allowing cells to adjust their shape, adhesion, and genetic activity according to mechanical stimuli. **Table 1** summarizes the major roles of cytoskeleton components, including actin and microtubules, their interactions, and focal adhesion complexes, in cellular mechanotransduction.

**Table 1** The role of cytoskeleton dynamics and adhesion complexes in cellular mechanotransduction.

Component	Role in mechanotransduction	Signaling pathway/Mediator	Functional impact/Cellular response
Actin filaments	Generates and transmits contractile force through interaction with myosin II and forms stress fibers	RhoA/ROCK, MLC phosphorylation, YAP/TAZ, and MRTF-A	Cytoskeleton reorganization, translocation of mechanosensitive transcription factors to the nucleus, regulation of gene expression, cell differentiation, and structural adaptation
Microtubules	Balancing actin contractile forces, distributing intracellular tension, and transporting vesicles and organelles	Dynein, Kinesin, and RhoA regulation	Maintaining mechanical homeostasis, cellular plasticity, spatiotemporal tension regulation, and coordination of cell migration and shape
Actin–Microtubule interactions	Coordination of contractile and compressive forces and regulation of membrane protrusions (lamellipodia/filopodia)	Formins, CLASP, IQGAP1, and the LINC complex	Transmission of force to the nucleus, directed cell migration, and physiological adaptation to mechanical stress
Focal	The interface of internal and	Integrin, FAK, Src, talin, and paxillin	Adhesion stability, cytoskeleton

Component	Role in mechanotransduction	Signaling pathway/Mediator	Functional impact/Cellular response
adhesion complex	external forces and converting mechanical stimulation into molecular responses		reorganization, force orientation, activation of MAPK/ERK, PI3K/AKT, and Rho GTPases pathways
Integrin	Force sensors and transducers and bonding with the ECM	Talin and vinculin	Force reinforcement, stable cell adhesion, and adaptive responses to external mechanical stress
Actomyosin contraction	Major source of internal contractile force; transmits tension to adhesion complexes and ECM	Actin–myosin II, MLC phosphorylation, and RhoA/ROCK	Regulates cytoskeletal tension, intracellular force orientation, and mediates force transmission to the nucleus via LINC

### The role of actin and microtubules in force transmission

Actin and microtubules are the main components of the cytoskeleton, playing a central role in the transmission of mechanical forces within cells [58]. These two structures not only provide support for cellular architecture but also function as dynamic mediators that transmit forces from the plasma membrane to the nucleus and intracellular organelles [31]. Through coordinated interactions, the actin-microtubule network enables cells to detect, transmit, and adapt in response to changes in forces from both the external and internal environments [59].

Actin filaments form a dynamic network that functions in generating and transmitting contractile force through interactions with the motor protein myosin II [60]. The formation of stress fibers around focal adhesion points allows the tensile force generated by actomyosin contraction to be transmitted to the adhesion complex and the ECM [61].

This activity is mediated by the RhoA/ROCK pathway, which regulates the phosphorylation of myosin light chains (MLCs) to enhance cytoskeleton contractility [62]. Furthermore, actin filament reorganization directly influences the cell's mechanosensitive response [63]. Increased actin tension can stimulate the translocation of mechanosensitive transcription factors such as YAP/TAZ and Myocardin-Related Transcription Factor A (MRTF-A) into the nucleus, thereby modulating the expression of genes that regulate cell

growth and differentiation [64]. Thus, actin functions not only to maintain the mechanical integrity of the cell but also as a functional bridge connecting physical forces to the regulation of genetic expression [65].

Microtubules act as a counterbalance to the contractions generated by actin filaments [66]. Composed of  $\alpha$ - and  $\beta$ -tubulin heterodimers, microtubules form a semi-rigid tubular network that can dynamically polymerize and depolymerize [67]. This structure serves to distribute forces throughout the cell and maintain mechanical balance between focal adhesion sites and the nucleus [68].

Furthermore, microtubules play a crucial role in the transport of vesicles and organelles through the motor proteins dynein and kinesin, which also help distribute tension within the cell [69]. Microtubule instability, for example, due to depolymerizing agents like nocodazole, can increase actin contractility and modify cell shape and stiffness [70].

The reciprocal interaction between microtubules and actin allows for spatiotemporal force regulation, where microtubule depolymerization can trigger RhoA activation, while microtubule stabilization tends to suppress contractile signals [71]. This cross-linking makes microtubules key regulators in maintaining mechanical balance and cell plasticity [72].

Actin and microtubules function in an integrated manner through linker proteins such as formins, Cytoplasmic Linker-Associated Protein (CLASP), and IQ Motif Containing GTPase Activating Protein 1 (IQGAP1), which help coordinate the dynamics of both

components [66]. This collaboration is crucial for regulating cell migration, the formation of membrane protrusions such as lamellipodia and filopodia, and the transmission of force to the nucleus via the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex [73].

By combining the contractile forces generated by actin filaments and the compressive forces of microtubules, cells are able to precisely adjust their mechanical response to environmental changes [74]. This synergy maintains a balance between structural strength, elasticity, and the physiological adaptation capacity of cells to various mechanical stresses [33].

### Adhesion complex and contractile forces

The cell adhesion complex acts as a central hub for transmitting mechanical forces while also regulating biochemical signals that influence cell behavior [20]. This structure enables integration between external forces from the ECM and internal forces generated by the actomyosin system [75]. Through precise coordination between adhesion proteins, cytoskeletal elements, and signaling enzymes, the adhesion complex serves as a dynamic interface that translates mechanical stimuli into molecular responses that regulate cell morphology, motility, and gene expression [76].

Actomyosin contraction is the primary source of contractile force in cells and plays a key role in regulating cytoskeletal tension [77]. This process relies on the interaction between actin filaments (F-actin) and myosin II, which is controlled through phosphorylation [78]. Activation of RhoA by Rho-associated kinase (ROCK) increases myosin light chain (MLC) phosphorylation, thereby activating myosin II ATPase activity and enhancing actin filament contractility [79].

The force generated by actomyosin contraction is transmitted to the focal adhesion complex and the extracellular matrix via integrins, forming a mechanical feedback loop that regulates adhesion stability and force direction within the cell [80]. The dynamics of

this contraction are spatiotemporal, with the magnitude and direction of the force determining the cell's response to microenvironmental conditions [81]. For example, increased internal tensile forces can trigger focal adhesion reorganization, increasing cell stiffness, and enhancing force transmission to the nucleus through the LINC complex [82].

FAK is a non-receptor tyrosine kinase that plays a key role in mechanotransduction in focal adhesion complexes [83]. FAK activation begins when integrins bind to ECM ligands, such as fibronectin or collagen, triggering integrin oligomerization and FAK recruitment to the adhesion site [84]. Next, FAK undergoes autophosphorylation at tyrosine residue 397, forming a binding site for Src kinase and other adaptor proteins, including paxillin and talin [85].

Activation of the focal adhesion kinase–steroid receptor coactivator (FAK–Src) complex triggers a series of downstream signaling cascades, including the MAPK/ERK, PI3K/AKT, and rho guanine triphosphate hydrolases (Rho GTPases) pathways, which play a role in regulating cytoskeleton reorganization, proliferation, and cell survival [86]. Furthermore, integrin- and FAK-mediated signals can also modulate gene expression through the activation of mechanosensitive transcription factors such as YAP/TAZ and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) [87].

Integrins function as both sensors and conductors of mechanical force [88]. Upon tensile stress, integrins undergo conformational changes that increase their affinity for ECM ligands and strengthen their association with actin filaments via talin and vinculin [89]. This mechanism forms a force reinforcement mechanism, allowing cells to maintain stable adhesion while adaptively responding to changes in external mechanical stress [90]. As shown in **Figure 2**, external mechanical cues are relayed from the ECM through integrins and focal adhesions to actin and microtubules, then to the nucleus via the gene expression complex.

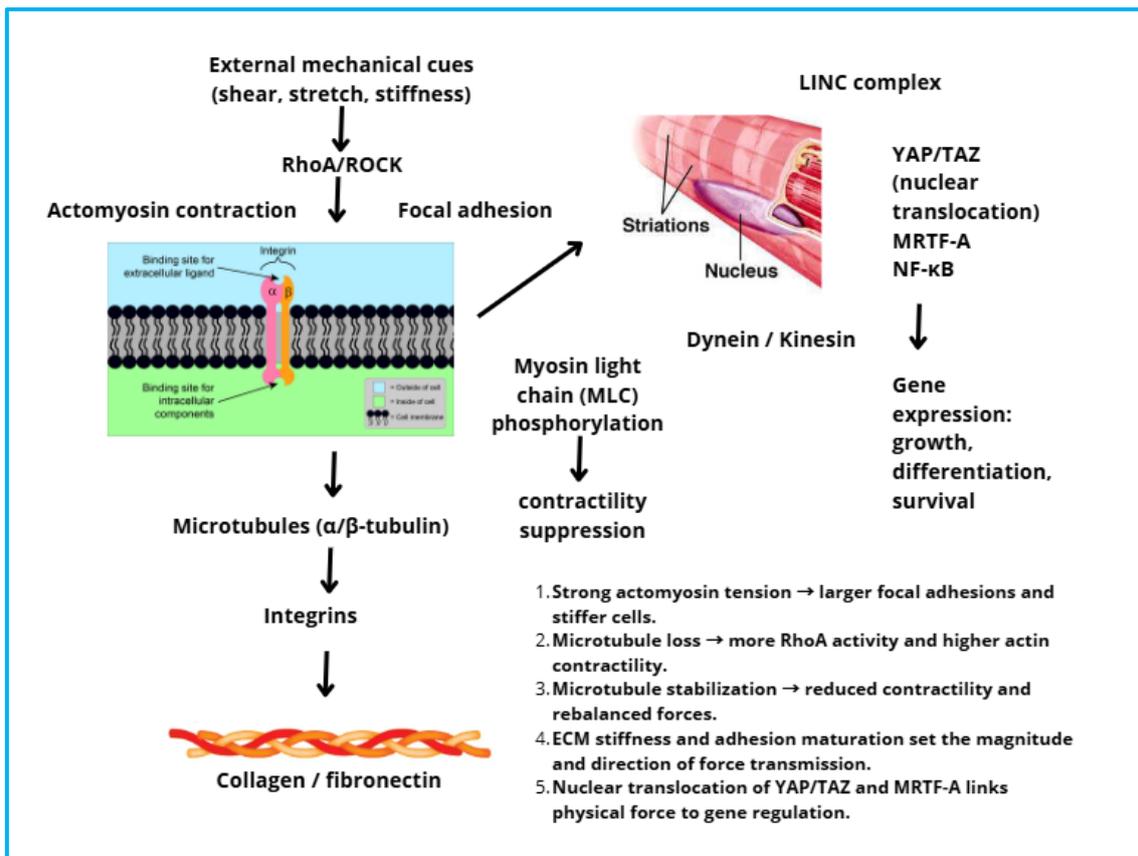


Figure 2 Cytoskeletal force transmission in mechanotransduction.

**Signaling pathways and regulation of gene expression**

Mechanical signals received by cells are not confined to the cytoskeleton but are transmitted to the nucleus to regulate gene transcription and expression. This process involves complex interactions between

cellular structures, adaptor proteins, and transcription factors that collectively determine the cell's response to mechanical forces. **Table 2** presents a summary of the major signaling pathways and transcription factors that link mechanical forces to the regulation of gene expression in mechanotransduction.

Table 2 Mechanotransduction signaling pathways and regulation of cellular gene expression.

Components/Factors	Activation mechanism	Target/Downstream path	Functional impact/Cellular response
LINC Complex (Nesprin-SUN)	Connects the cytoskeleton to the nuclear lamina and transmits mechanical stress to the nucleus	Lamin A/C and chromatin remodeling	Regulates nuclear rigidity, chromatin accessibility, and expression of genes related to proliferation and differentiation
YAP / TAZ	Dephosphorylation due to stiff substrate or high tension and translocation to the nucleus	TEAD → CTGF, CYR61, and ANKRD1	Activation of proliferative genes and tissue remodeling and supports cell differentiation and growth
MRTF-A	Detach from G-actin as actin polymerizes and enters the nucleus	SRF → ACTA2, VCL, and MYH9	Regulates cytoskeletal gene expression, contractility, and cell morphology
NF-κB	Membrane deformation or	ICAM1, VCAM1, and IL6	Triggers pro-inflammatory gene

Components/Factors	Activation mechanism	Target/Downstream path	Functional impact/Cellular response
	cytoskeletal tension		expression and vascular and immune responses
$\beta$ -catenin	Activation by mechanical stretching	Wnt target genes	Supports cell proliferation and tissue repair
KLF2	Response to shear stress (shear flow)	Anti-inflammatory and antithrombogenic genes	Suppresses pro-inflammatory gene expression and maintains vascular homeostasis
Epigenetics	Nuclear deformation and cytoskeletal stress	Histone acetyltransferase (p300/CBP) and DNMT1	Chromatin modification, regulation of mechanosensitive gene expression, and long-term regulation of cell responses
Mechanical force responsive gene	Activation by YAP/TAZ, MRTF-A, NF- $\kappa$ B, and $\beta$ -catenin	CTGF, CYR61, EGR1, FOS, JUN, and TGF $\beta$ 1	Structural adaptation of cells, autocrine/paracrine signals, tissue remodeling, and proliferation or pathological responses

### Signal transmission from the cytoskeleton to the nucleus

Signal transmission from the cytoskeleton to the nucleus represents a critical physical phase of mechanotransduction, in which externally applied or internally generated mechanical forces are propagated across cellular structures to directly deform the nucleus and its chromatin architecture [16,91]. Rather than acting solely through biochemical signaling cascades, this process relies on a continuous mechanical linkage that enables force transfer from the plasma membrane to the nuclear interior, thereby influencing nuclear mechanics and chromatin accessibility in response to changes in the mechanical microenvironment [92].

Central to this force transmission is the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex, a multiprotein assembly that mechanically couples cytoskeletal filaments to the nuclear lamina [93]. The LINC complex is composed of nesprin proteins located at the outer nuclear membrane, which bind actin filaments, microtubules, or intermediate filaments, and SUN domain proteins embedded in the inner nuclear membrane that connect to lamin A/C [94]. Together, these components form a load-bearing molecular bridge that allows mechanical forces generated at adhesion sites or within the cytoskeleton to be transmitted directly to the nucleus and chromatin [95].

When cells experience mechanical cues such as substrate stiffness, tensile strain, or shear stress, cytoskeletal remodeling alters the magnitude and direction of forces conveyed through the LINC complex [96]. These forces induce nuclear deformation, manifested as changes in nuclear shape, volume, and stiffness, which are largely determined by the composition and organization of the nuclear lamina [97]. Lamin A/C, in particular, functions as a key mechanical determinant of nuclear rigidity, with increased mechanical loading promoting lamin A/C expression and nuclear stiffening, thereby enhancing resistance to deformation and preserving genomic stability [98-100].

Conversely, disruption of LINC complex components or alterations in lamin organization weaken nuclear mechanical integrity, resulting in increased nuclear deformability and aberrant force dissipation [101]. Such mechanical imbalance affects the spatial organization of chromatin and can lead to altered accessibility of genomic regions, especially those located near the nuclear periphery [99]. These observations indicate that nuclear mechanics act as a mechanical filter, modulating how external forces are translated into structural changes within the genome.

Mechanical deformation of the nucleus also influences chromatin accessibility through mechano-epigenetic mechanisms [102]. Physical strain on the

nucleus can reorganize chromatin compaction states, affecting histone modifications such as H3K9 acetylation and H3K27 trimethylation, which are associated with permissive or repressive chromatin configurations, respectively [103]. Importantly, these changes can occur independently of classical signaling intermediates, highlighting that direct mechanical coupling between the cytoskeleton and chromatin constitutes a distinct regulatory layer in mechanotransduction.

Collectively, the cytoskeleton–LINC–nucleus axis establishes a bidirectional mechanical continuum, in which forces transmitted from the extracellular matrix reshape nuclear architecture, while nuclear stiffness feeds back to influence cytoskeletal tension distribution [94,110]. This mechanically integrated system enables cells to adapt structurally to physical stress and maintain tissue integrity. Failure of this force transmission pathway, due to defects in LINC components or nuclear lamins, is associated with a range of mechanopathologies, including cancer, laminopathies, and connective tissue disorders characterized by impaired nuclear mechanoadaptation [111].

### Transcription factors and genes responsive to stress

Transcription factors constitute the regulatory layer of mechanotransduction, translating mechanically induced structural cues into specific gene expression programs that govern cell fate, function, and tissue homeostasis [112,113]. Once mechanical forces have been transmitted to the nucleus, cells respond by selectively activating or suppressing mechanosensitive transcription factors, enabling adaptive transcriptional outputs in response to variations in cytoskeletal tension, substrate stiffness, or fluid shear stress [114].

Among these factors, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) act as central transcriptional effectors of mechanical signaling [115]. Under conditions of high mechanical load or rigid substrates, inhibition of the Hippo kinase cascade (LATS1/2) permits YAP/TAZ dephosphorylation and nuclear accumulation, where they associate with TEAD transcription factors to drive the expression of genes such as *CTGF*, *CYR61*, and *ANKRD1* [116,117]. These target genes promote cell proliferation, migration, and

extracellular matrix remodeling, supporting tissue growth and mechanical adaptation. In contrast, low mechanical stress or compliant matrices maintain YAP/TAZ in an inactive cytoplasmic state, thereby limiting mechanosensitive gene expression and restraining excessive growth responses [118].

Myocardin-related transcription factor A (MRTF-A) represents another key mechanosensitive regulator whose activity is tightly coupled to actin dynamics [119]. Mechanical stimuli that promote actin polymerization reduce the pool of cytoplasmic G-actin, releasing MRTF-A and enabling its translocation to the nucleus [109]. There, MRTF-A cooperates with Serum Response Factor (SRF) to induce the transcription of cytoskeletal and contractile genes, including *ACTA2*, *VCL*, and *MYH9*, reinforcing actomyosin tension and cellular structural integrity [120,121]. This feed-forward mechanism links mechanical force sensing directly to transcriptional programs that stabilize cellular mechanics.

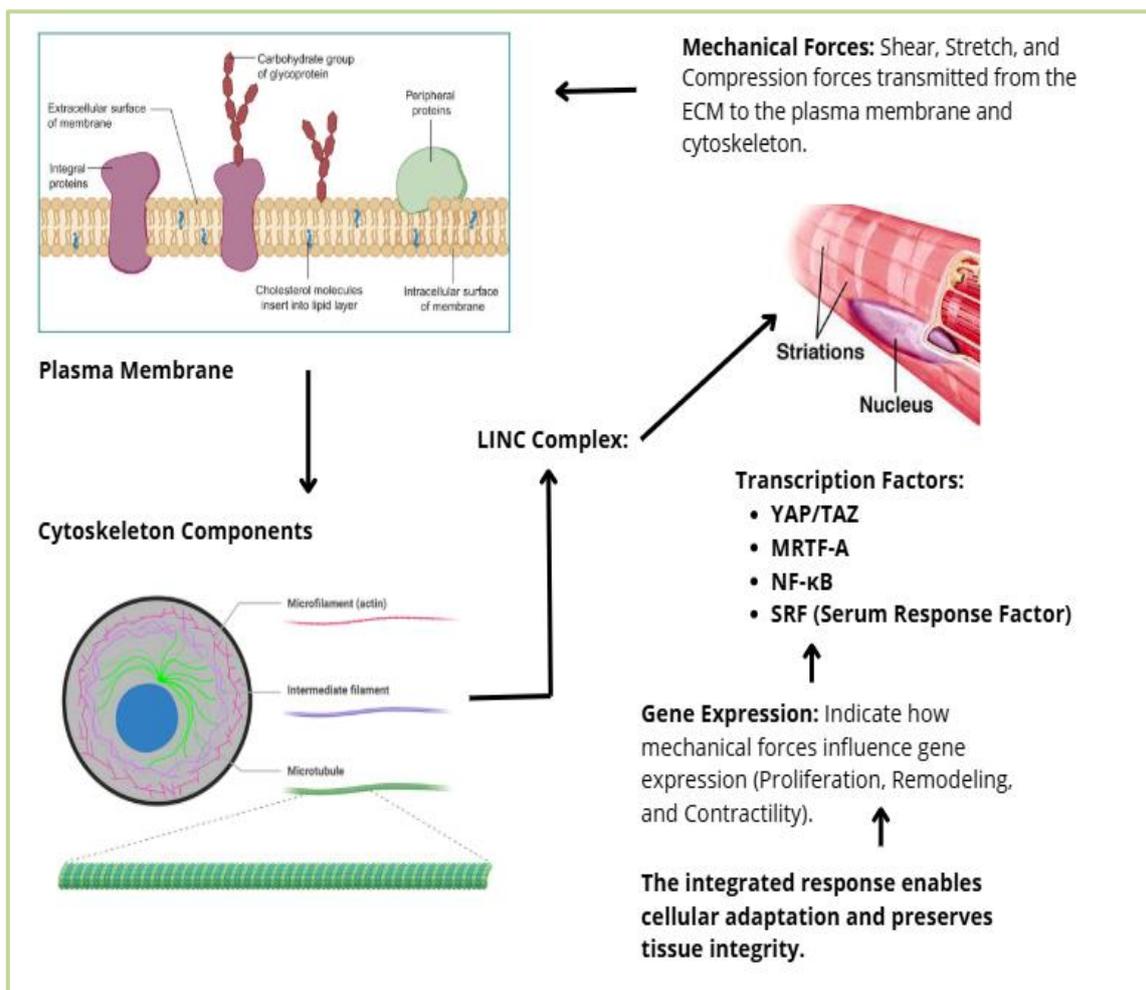
In addition to YAP/TAZ and MRTF-A, other transcription factors contribute to context-dependent mechanotranscriptional responses. Nuclear factor kappa B (NF- $\kappa$ B) is activated by mechanical deformation and shear stress, particularly in vascular cells, driving the expression of pro-inflammatory genes such as *ICAM1*, *VCAM1*, and *IL6* [122,123].  $\beta$ -catenin, traditionally associated with Wnt signaling, can also be mechanically activated to promote genes involved in proliferation and tissue repair [124]. Conversely, Kruppel-like factor 2 (KLF2) functions as a protective mechanosensitive transcription factor in endothelial cells, where shear stress–induced activation suppresses inflammatory and thrombogenic gene expression, thereby preserving vascular homeostasis [125].

The transcriptional outcomes of mechanotransduction reflect the integrated activity of these mechanosensitive regulators. Mechanical stimulation commonly induces immediate-early and remodeling-associated genes, including *CTGF*, *CYR61*, *EGRI*, *FOS*, *JUN*, and *TGF $\beta$ 1*, which coordinate cytoskeletal adaptation, extracellular matrix remodeling, and paracrine signaling within tissues [126,127]. In parallel, mechanical cues can modulate the expression of epigenetic regulators such as histone acetyltransferases (*p300/CBP*) and DNA methyltransferases (*DNMT1*), suggesting that sustained

mechanical environments can imprint longer-term transcriptional memory through chromatin regulation [128].

Importantly, the balance among mechanosensitive transcription factors determines physiological versus pathological outcomes. Coordinated activation of YAP/TAZ, MRTF-A, and NF-κB favors proliferative, fibrotic, or inflammatory gene programs, as observed in cancer progression and tissue fibrosis [130]. In contrast, dominance of protective pathways, such as KLF2 signaling

accompanied by restrained YAP/TAZ activity, supports anti-inflammatory responses and tissue homeostasis [131,132]. Thus, transcriptional mechanotransduction functions as a decision-making layer that integrates mechanical inputs to drive either adaptive remodeling or disease-associated gene expression programs. As shown in **Figure 3**, mechanical cues from the ECM travel through the cytoskeleton and the LINC complex to remodel chromatin and reprogram gene expression.



**Figure 3** Mechanotransduction from the cytoskeleton to the nucleus via the LINC complex.

**Mechanotransduction in physiology and pathophysiology**

Mechanotransduction plays a crucial role in maintaining the balance between cellular structure and function under physiological conditions, while also contributing to disease when mechanosensitive pathways are disrupted. Understanding

mechanotransduction in the context of physiology and pathophysiology provides insight into how mechanical forces influence cellular adaptation or dysfunction. **Table 3** summarizes the role of mechanotransduction under normal and pathological conditions in various tissues.

**Table 3** The role of mechanotransduction in cellular physiology and pathophysiology.

Condition	System/Network	Mechanotransduction mechanism	Signaling pathways/ Transcription factors	Mobile impact/response
Normal physiology	Stem cells	Mechanotransduction mediates differentiation based on matrix stiffness	YAP/TAZ, RhoA/ROCK, and integrin-FAK	Osteogenic, neurogenic, or adipogenic differentiation and specialization of cells according to the mechanical environment
	Skeletal muscle	Contraction and stretching strains trigger activation of mechanoreceptors	PI3K-Akt-mTOR and MAPK/ERK	Muscle hypertrophy, mitochondrial biogenesis, and increased protein synthesis and metabolic capacity
	Vascular system (endothelium)	Hemodynamic force sensor (shear stress)	KLF2 and eNOS	NO production, vasodilation, blood pressure homeostasis, and vascular integrity
Pathological physiology	Tumor/cancer microenvironment	Increased matrix stiffness and interstitial pressure	YAP/TAZ, $\beta$ -catenin, RhoA/ROCK, and integrin-FAK	Abnormal proliferation, cell migration and invasion, epithelial-mesenchymal transition (EMT), and metastasis
	Fibrosis	Increased tissue stiffness and fibroblast activation	TGF- $\beta$ /SMAD, YAP/TAZ, and $\alpha$ -SMA	Transformation of fibroblasts into myofibroblasts, excessive collagen production, fibrosis progression, and inhibition of tissue resolution
	Cardiovascular system (endothelium + smooth muscle)	Turbulent blood flow and stiff arterial walls	KLF2, eNOS, and NF- $\kappa$ B	Decreased NO, increased oxidative stress, proinflammatory gene expression (VCAM1 and ICAM1), smooth muscle proliferation, vascular remodeling, hypertension, and atherosclerosis

**Normal physiology**

Mechanotransduction plays an essential role in a variety of normal physiological processes by enabling cells to detect and respond to changes in mechanical forces in their environment [5]. By integrating mechanical and biochemical signals, mechanotransduction dynamically regulates cell differentiation, tissue function, and organ homeostasis [133]. This process underpins physiological

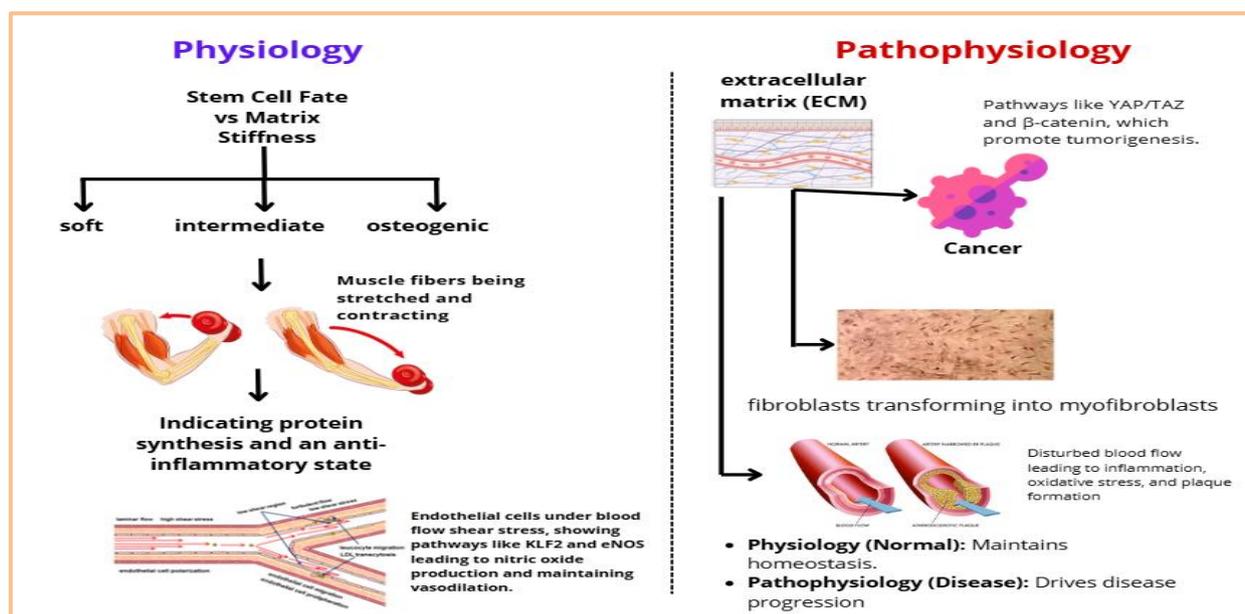
adaptations in the musculoskeletal, cardiovascular, and nervous systems, while maintaining a balance between cellular structure and function [134].

Stem cell differentiation is strongly influenced by the mechanical characteristics of the extracellular environment, including matrix stiffness and the stress experienced by the cells [135]. Stiff matrices tend to direct cells toward osteogenic differentiation, while softer matrices promote neurogenic or adipogenic

differentiation [136]. Mechanosensitive pathways such as YAP/TAZ, RhoA/ROCK, and integrin–FAK play key roles in determining cell fate by regulating tissue-specific gene expression [137]. Thus, mechanotransduction provides a link between physical stimuli and transcriptional regulation that determines cell specialization [138].

In skeletal muscle tissue, mechanical forces generated during repeated contraction and stretching activate mechanoreceptors and signaling pathways such as PI3K–Akt–mTOR and MAPK/ERK, which

control hypertrophy and mitochondrial biogenesis [139]. Activation of these pathways increases protein synthesis and metabolic capacity, allowing muscles to adapt to increased workload [140]. Furthermore, shear and tension forces on the plasma membrane influence the expression of contractile genes and cytoskeletal proteins, strengthening muscle structure to maintain optimal function [141]. Thus, mechanotransduction is the molecular basis of muscle functional adaptation to physical activity [19].



**Figure 4** Mechanotransduction across physiology and pathophysiology.

In the vascular system, endothelial cells serve as primary sensors for hemodynamic forces, such as shear stress from blood flow [142]. Endothelial mechanotransduction regulates the activation of the krüppel-like factor 2–endothelial nitric oxide synthase (KLF2–eNOS) pathway, which triggers nitric oxide (NO) production to maintain vasodilation and lower blood pressure [143]. Conversely, endothelial mechanotransduction dysfunction can lead to increased expression of pro-inflammatory and procoagulant genes, thereby increasing the risk of vascular disorders [144]. Thus, mechanotransduction plays a crucial role in maintaining blood pressure homeostasis and vascular integrity through adaptive responses to mechanical forces [145].

### Pathological physiology

Dysregulation of mechanotransduction plays a crucial role in the development of various diseases, including cancer, fibrosis, and cardiovascular disorders [5]. An imbalance between mechanical forces, tissue stiffness, and cellular responses induces profound alterations in cell behavior, gene expression, and cell–matrix interactions, ultimately driving chronic pathological remodeling [146]. Beyond its pathogenic significance, growing evidence indicates that mechanotransduction represents a promising therapeutic entry point, enabling the development of mechanobiology-driven interventions that target force-sensitive signaling pathways and cellular mechanosensors [147].

In the tumor microenvironment, increased extracellular matrix stiffness and elevated interstitial pressure actively promote malignant transformation rather than merely reflecting tumor progression [148]. Aberrant activation of mechanosensitive pathways such as YAP/TAZ,  $\beta$ -catenin, and RhoA/ROCK enhances cancer cell proliferation, invasion, and metastatic dissemination [149]. Importantly, this mechanistic insight has led to the emergence of YAP/TAZ-targeted therapeutic strategies, including small-molecule inhibitors, transcriptional disruptors, and upstream Hippo pathway modulators, which have shown potential in suppressing tumor growth and overcoming therapy resistance in preclinical cancer models [150,151]. Furthermore, targeting integrin–FAK signaling and cytoskeletal tension has been proposed as a complementary strategy to disrupt mechano-driven epithelial–mesenchymal transition (EMT) and tumor invasiveness.

Fibrosis is another pathological condition in which aberrant mechanotransduction plays a central role. Excessive extracellular matrix deposition increases tissue stiffness, which in turn activates fibroblasts and sustains their differentiation into  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA)-positive myofibroblasts [152,153]. Persistent activation of mechanosensitive pathways, particularly TGF- $\beta$ /SMAD and YAP/TAZ signaling, reinforces a feed-forward loop between mechanical stiffening and fibroblast activation, accelerating fibrotic progression [154]. These findings have stimulated the development of anti-fibrotic mechanotherapies, including YAP/TAZ inhibitors, integrin antagonists, and mechanoresponsive biomaterials designed to soften the cellular microenvironment and promote fibrosis resolution [155]. Such approaches highlight the therapeutic potential of modulating mechanical cues rather than targeting biochemical pathways alone.

In the cardiovascular system, endothelial mechanotransduction is critically influenced by hemodynamic forces, particularly shear stress generated by blood flow [156]. Disturbed or turbulent flow suppresses protective mechanosensitive pathways such as KLF2–eNOS signaling, leading to reduced nitric oxide (NO) bioavailability, increased oxidative stress, and activation of pro-inflammatory transcription factors including NF- $\kappa$ B [157,158]. These molecular

events promote leukocyte adhesion, vascular inflammation, and atherosclerotic plaque formation. Translationally, organ-on-chip and vessel-on-chip platforms have emerged as powerful tools to model pathological flow patterns and screen drugs that restore endothelial mechanosensitivity, enabling more physiologically relevant evaluation of cardiovascular therapeutics [159].

Collectively, these insights underscore the growing relevance of mechanopharmacology, an emerging field that integrates mechanical cues into drug discovery and therapeutic design. Mechanosensitive scaffolds in regenerative medicine, force-responsive drug delivery systems, and microengineered organ-on-chip platforms are increasingly being used to modulate cell fate, enhance tissue regeneration, and improve predictive accuracy in drug screening. Future research integrating mechanotransduction with multi-omics profiling, advanced biomaterials, and microphysiological systems will be essential for translating mechanobiological principles into effective clinical interventions across cancer, fibrosis, and cardiovascular disease.

### Experimental technologies and approaches

Advances in experimental technology now allow for a more detailed understanding of mechanotransduction mechanisms at the molecular, cellular, and tissue levels [160]. Multidisciplinary approaches combining cell biology, biophysics, and microengineering enable quantitative analysis of mechanical forces and cellular responses to them [161]. A variety of experimental techniques are used to visualize, manipulate, and quantify the forces that influence cell behavior and regulate gene expression [162].

Atomic force microscopy (AFM) is one of the most sensitive methods for assessing plasma membrane stiffness, adhesion forces, and the elastic response of cells to external forces [163]. Using force spectroscopy, AFM can map the topography and force distribution at the nanometer scale, providing valuable information about the local stiffness and dynamics of the cytoskeleton [164].

Additionally, micropatterning techniques are used to regulate adhesion geometry and cell orientation on specific substrates, allowing for a more focused

analysis of how cell shape and internal tension influence the activation of mechanosensitive pathways such as YAP/TAZ and RhoA/ROCK [165].

On the other hand, traction force microscopy (TFM) allows the measurement of traction forces generated by cells on fluorescent elastic substrates [166]. This approach provides in-depth insights into the internal force distribution and stress transmission through focal adhesion complexes, making it an important method for studying cell–matrix interactions in real time [167].

Three-dimensional (3D) culture models have transformed the approach to mechanotransduction studies by providing an environment that more closely mimics physiological conditions than traditional two-dimensional culture [168]. In these systems, cells interact spatially with the extracellular matrix and receive forces from multiple directions, allowing for more accurate analysis of mechanical responses and cell differentiation [169].

Additionally, organ-on-chip technology based on microfluidic platforms enables the simulation of physiological forces, including shear stress, cyclic strain, and hydrostatic pressure [170]. These systems support mechanotransduction studies in complex tissues such as vascular endothelium, alveolar epithelium, or myocardium, while also enabling pharmacological evaluation to assess the response to therapeutic interventions that utilize mechanics [171].

RNA sequencing (RNA-seq) approaches have become a key technique for identifying genes and molecular pathways involved in mechanosensitive responses [172]. Through comprehensive transcriptomic analysis, RNA-seq can detect changes in gene expression resulting from variations in mechanical force, substrate stiffness, or cell deformation [173]. Integrating RNA-seq data with epigenomics and proteomics allows mapping complex regulatory networks between mechanosensitive transcription factors, such as YAP/TAZ, MRTF-A, and KLF2, and target genes that regulate cell adaptation to the mechanical environment [174]. This approach provides systemic insights into gene expression dynamics and helps identify mechanogenomic signatures characteristic of both physiological and pathological conditions [175].

### Challenges and future research directions

Although understanding of the fundamental mechanisms of mechanotransduction has advanced significantly, several unresolved scientific questions remain that limit the translation of this knowledge into broader biological and clinical applications [176]. The inherent complexity of mechanotransduction—arising from the intertwined nature of mechanical forces, biochemical signaling, and gene regulation—necessitates a systemic, quantitative, and interdisciplinary research framework [177].

One major open question concerns how mechanical signals can be reliably disentangled from biochemical cues within complex cellular systems [147]. While multi-omics approaches integrating transcriptomics, epigenomics, and proteomics have enabled large-scale mapping of force-responsive gene networks, it remains unclear how mechanical inputs independently shape gene regulatory programs across different cell types and tissue contexts [178]. Moreover, the lack of standardized experimental pipelines for mechanogenomic data acquisition and integration hampers cross-study comparability and reproducibility, particularly in pathological models [179].

Another unresolved challenge lies in predicting cellular fate decisions under dynamic and heterogeneous mechanical environments. Computational modeling and biomechanical simulations have shown promise in linking matrix stiffness, cytoskeletal tension, and molecular signaling to outcomes such as differentiation or apoptosis [180]. However, current models often oversimplify biological variability, raising the question of how accurately *in silico* predictions can reflect *in vivo* mechanotransduction dynamics [134]. The integration of machine learning and Artificial Intelligence (AI) into mechanobiology offers new opportunities to address this limitation, yet the interpretability and biological generalizability of AI-driven models remain significant concerns [181].

From a translational perspective, a critical open question is how mechanotransduction principles can be effectively harnessed for therapeutic intervention [147]. Although mechanosensitive biomaterials and stiffness-tunable scaffolds have demonstrated potential in tissue engineering and regenerative medicine, their

long-term biological stability and clinical scalability require further validation [182]. Similarly, while anti-fibrotic strategies targeting YAP/TAZ or integrin–FAK signaling pathways show therapeutic promise, the risk of disrupting physiological mechanoadaptive functions remains insufficiently understood [183].

Finally, the emergence of organ-on-chip platforms raises important questions regarding the extent to which these systems can faithfully recapitulate multiscale mechanical cues present in native tissues. While organ-on-chip and mechanopharmacology approaches provide powerful tools for drug screening and disease modeling, their standardization, validation, and integration with omics-based readouts remain ongoing challenges [184]. Addressing these open questions will be essential for advancing mechanotransduction research from descriptive frameworks toward predictive, translational, and clinically actionable paradigms.

## Conclusions

Mechanotransduction constitutes a fundamental regulatory axis through which mechanical cues are integrated with biochemical signaling to control gene expression and cellular fate. Rather than functioning solely as a passive force-transmission system, the cytoskeleton–adhesion–nucleus continuum actively shapes transcriptional programs via mechanosensitive regulators such as YAP/TAZ and MRTF-A, thereby determining whether mechanical stimuli elicit adaptive or pathological responses. Emerging evidence highlights that context-dependent factors—including matrix dimensionality, cell type, and force magnitude—critically influence mechanotransduction outcomes, underscoring the need for integrative and comparative mechanobiological models. Future advances will depend on combining three-dimensional culture systems, organ-on-chip platforms, and multi-omics approaches to disentangle mechanical and biochemical signaling with higher precision. Such efforts are expected to accelerate the translation of mechanotransduction principles into mechanotherapy, mechanoresponsive biomaterials, and targeted interventions for fibrosis, cancer, and cardiovascular diseases.

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## Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

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**Hamidatul Aliyah:** Project administration, Supervision, Writing – review and editing, and Validation. **Wita Yulianti:** Writing – review and editing, Visualization, and Validation.

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