



Review

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Mechano-epigenetic regulatory axis: mechanical signal- driven gene-expression reprogramming

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Abstract: Beyond the traditional concept of genes as the core regulators of cellular phenotypes, epigenetic modifications—which are largely influenced by the external environment and do not alter DNA sequence—also have a significant impact on gene expression. Mechanical signals serve as key mediators through which cells perceive the physical properties of their microenvironment. By means of structures such as integrins, Piezo channels, and the cytoskeleton-LINC (Linker of nucleoskeleton and cytoskeleton) complex, physical stimuli like ECM (Extracellular matrix) stiffness and mechanical strain are transmitted to the cell nucleus. By interacting with epigenetic modifications, these signals play a pivotal role in regulating cell fate and disease progression. At the chromatin level, mechanical forces dynamically alter DNA methylation and histone modification states by regulating the enzyme activity of DNMTs, TETs, HDACs, KDM5B, and more, via the cytoskeletal system and mechanosensitive molecules. For instance, during atherosclerosis, mechanical forces from matrix stiffening transmit intracellularly through the DDR1-DNMT1 axis to silence vascular protective genes, accelerating collagen deposition. At the RNA level, mechanical signals regulate m⁶A (N6-methyladenosine) modification-related factors (such as METTL3/14, FTO, ALKBH5, and YTHDFs) via the cytoskeleton, calcium ions, and YAP signaling pathways, influencing mRNA stability and translation. This contributes to osteogenic differentiation, inflammation, and tumor adaptation. Dysregulation of the mechanical-epigenetic axis forms a vicious "mechanical signaling—epigenetic reprogramming—disease-progression" cycle, contributing extensively to pathological processes such as atherosclerosis, tumors, fibrosis, and osteoarthritis. This review aims to systematically present the regulation of epigenetic modifications—including DNA methylation, histone acetylation, and RNA methylation—by mechanical signals under physiological and pathological conditions, thereby providing insights for identifying disease molecular targets and developing mechanoresponsive materials.

Key words: Mechanical signals; Epigenetic modifications; DNA methylation; Histone acetylation; N6-methyladenosine (m⁶A) modification

1 Introduction

In traditional cell biology, biochemical signals such as growth factors, hormones, and cytokines have long been regarded as the core messengers regulating cell fate and tissue homeostasis. However, accumulating evidence indicates that physical and mechanical signals—forces sensed and responded to by cells from the microenvironment—represent another fundamental class of signals that profoundly influence cell proliferation, differentiation, migration, and overall cellular activity (Humphrey et al., 2014; de Belly et al., 2021). From morphogenesis during embryonic development to tissue regeneration and repair in adults, from blood flow in

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the cardiovascular system to bone loading, living organisms constantly exist within a dynamic mechanical environment. Cells perceive these mechanical signals through structures such as integrins, mechanosensitive ion channels (e.g., Piezo channels), and the cytoskeletal network, translating them into intracellular biochemical responses (Jin et al., 2020; Tian et al., 2025). Abnormal mechanical transmission can easily lead to various diseases related to mechanical forces. For example, the hardening of the extracellular matrix (ECM), associated with excessive collagen-fiber deposition, is a phenotypic manifestation of rapidly progressing atherosclerosis, liver cirrhosis, and tumors. Abnormal hemodynamics resulting from intravascular plaque formation can exacerbate the progression of atherosclerotic disease.

Concurrently, epigenetic mechanisms, which serve to regulate gene expression without altering DNA sequence, grant cells the flexibility to dynamically adjust their transcriptional states in response to environmental stimuli (Xiong and Zhu, 2025). Classic epigenetic modifications, such as DNA methylation and histone modifications, regulate gene expression and silencing by modulating chromatin states. DNA methylation involves the addition of methyl groups to cytosine bases by DNA methyltransferases (DNMTs) and is generally associated with gene silencing. Histone modifications, such as acetylation and methylation, alter chromatin structure through chemical changes, thereby regulating gene expression. Acetylation typically loosens chromatin and promotes gene expression (Langstein et al., 2018; Wilkinson et al., 2023). In recent years, the research perspective has expanded to the RNA level, where N6-methyladenosine (m⁶A) modification on mRNA—a dynamic and reversible mode of epitranscriptomic regulation—has been shown to rapidly respond to external stimuli and finely regulate mRNA metabolism and translation, emerging as an important mediator in helping cells adapt quickly to environmental change (Cheung et al., 2025).

Mechanical signals, one type of external stimulus, have been found to regulate cellular behavior and fate by influencing epigenetic modifications (Song et al., 2020). When cells are subjected to external mechanical forces—such as matrix stiffness, fluid shear stress, tension, or compression—these forces are transmitted to the cell nucleus through cell-surface adhesion molecules (e.g., integrins) and the cytoskeleton. This process directly induces physical deformation of nuclear morphology and chromatin structure. The compaction level of chromatin is critical in regulating gene expression (Sun et al., 2023; Tajik et al., 2016). Nuclear cytoskeletal proteins (e.g., Lamin A/C) and chromatin-binding proteins sense changes in nuclear-membrane tension, leading to alterations in chromatin spatial conformation (Stephens et al., 2017). Compact heterochromatin may loosen under tension, exposing previously concealed gene-promoter regions. On the other hand, mechanical forces can activate signaling pathways such as Hippo/YAP, ROCK, and MRTF-SRF, which regulate enzymes, including histone acetyltransferases (HATs) and histone demethylases (KDMs), to directly modify histones (Iyer, 2025; Liu et al., 2025). Beyond chromosomal modifications, under rigid-substrate or high-tension conditions, YAP/TAZ becomes activated and translocates to the nucleus. Studies reveal that activated YAP/TAZ binds to the promoter of METTL3 (a core m⁶A "writer") and directly upregulates its transcriptional expression, leading to elevated global m⁶A modification levels within cells (Jin et al., 2023; Lin et al., 2025). Dysregulation of this "mechano-epigenetic axis" has been widely implicated in various pathologies associated with matrix stiffening (e.g., atherosclerosis, tumor progression, fibrotic diseases), hemodynamic abnormalities (e.g., atherosclerosis), and biomechanical overload or imbalance (e.g., arthritis and muscular atrophy).

Understanding the impact of mechanical forces on epigenetic modifications offers a novel perspective on how cells respond to environmental changes and regulate their functions. Understanding how mechanical forces influence epigenetic modifications provides a novel perspective on how cells perceive and adapt to environmental changes while regulating their own functions. In-depth investigation of this mechanism will help elucidate disease pathogenesis and offer a theoretical foundation for developing new therapeutic strategies (Fig. 1). This article reviews how mechanical signals regulate epigenetic modifications at both the chromatin and RNA level, and the roles of the mechano-epigenetic axis in physiological and pathological processes.

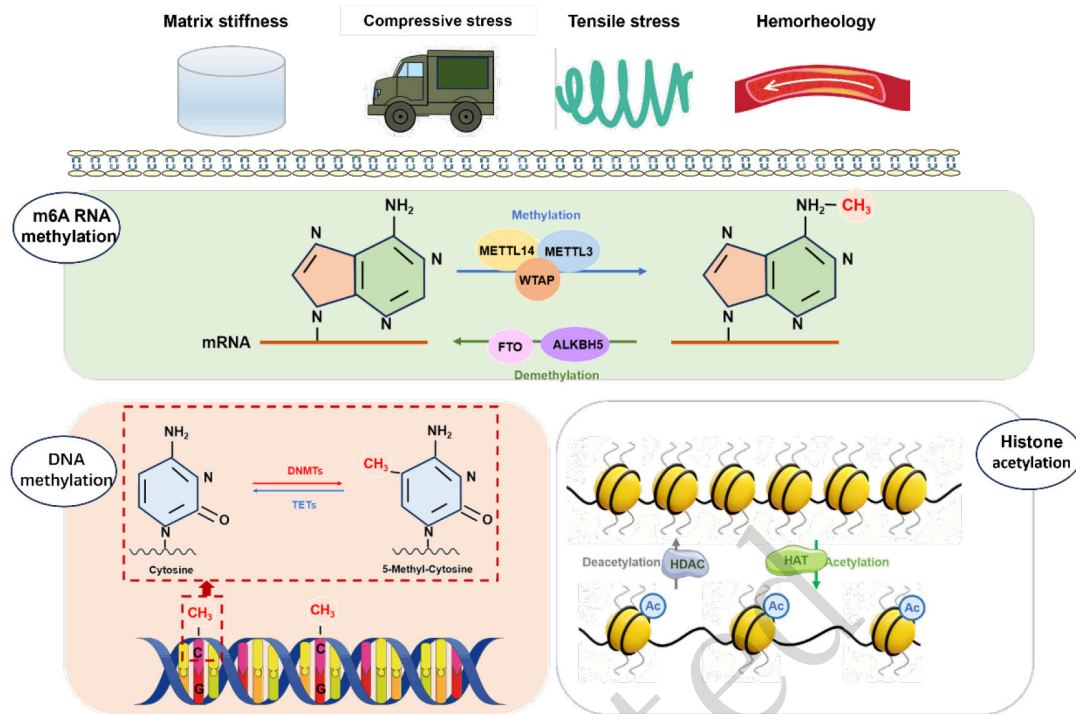


Fig. 1 Mechanical signals derived from matrix stiffness, compressive forces, tensile forces, hemodynamic forces, etc., can influence RNA epigenetic modifications (e.g. N^6 -methyladenosine [m^6A] modification) and chromatin epigenetic modifications (e.g. DNA methylation, histone acetylation).

2. Effects of Mechanical Signals on Epigenetic Modification at the Chromatin Level

Chromatin is composed of nucleosomes, the fundamental structural units in which DNA wraps around histone proteins, and the associated epigenetic modifications include alterations to both DNA and histones. These changes are heritable and do not involve changes in the DNA sequence (Schellenberg et al., 2014; Xie et al., 2018). Histone modifications encompass a diverse array of chemical marks, including acetylation, methylation, phosphorylation, ubiquitination, and others. Among these, histone acetylation is the most extensively characterized histone mark in the context of mechanotransduction. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are among the best-studied mechanosensitive epigenetic regulators, with well-established links to RhoA/ROCK, YAP, and calcium signaling pathways. Furthermore, the rapid reversibility of acetylation makes it particularly suited for mediating both acute and chronic cellular responses to changing mechanical environments (Wu et al., 2024). Therefore, we will primarily discuss histone acetylation, alongside DNA methylation. Histone acetylation generally promotes chromatin relaxation, whereas DNA methylation tends to induce chromatin compaction. Such changes in chromatin structure can affect gene transcription and expression. Notably, gene silencing mediated by DNA methylation has been shown to be more persistent and less readily reversible compared to other epigenetic alterations, such as histone modification (Bintu et al., 2016; Flavahan et al., 2017). These epigenetic modifications of the genome play crucial roles in both physiological and pathological processes.

Research indicates that the loose or compact states of chromatin can be influenced by mechanical forces, thereby affecting epigenetic modifications on chromatin (Fig. 2). For instance, stretching osteoblasts cultured on polycaprolactone fiber scaffolds has been shown to significantly upregulate global levels of DNA methylation (5-methylcytosine, 5mC), hydroxymethylation (5-hydroxymethylcytosine, 5hmC), and N^6 -methyladenosine (m^6A), ultimately enhancing osteogenic differentiation (Han et al., 2021). Conversely, developmental disorders

such as Sjögren's syndrome, atherosclerosis, arthritis, osteoporosis, cardiomyopathy, Hutchinson-Gilford progeria, and Duchenne muscular dystrophy trigger abnormal mechanical signaling and chromatin remodeling through tissue fibrosis. This leads to ECM stiffening, disruption of the tissue mechanical environment, and impairment of cell-morphology and adhesion functions (González et al., 2011; Maurer and Lammerding, 2019). Changes in tissue stiffness, cytoskeletal reorganization, and the cellular physical environment induce mechanical tension within intracellular protein networks. This tension is recognized, amplified, and transmitted by mechanosensitive proteins. Signals are directly conveyed to the nucleus via connections between the cytoskeleton and nucleoskeleton, a process faster than biochemical signal cascades (Mishra et al., 2024). Changes in cell shape, integrity, or adhesion-element positioning, along with cell movement, generate tensile and compressive forces which are transmitted to the nucleus. Within the nucleus, these forces induce chromatin remodeling, leading to activation or suppression of gene expression (Lelièvre, 2009).

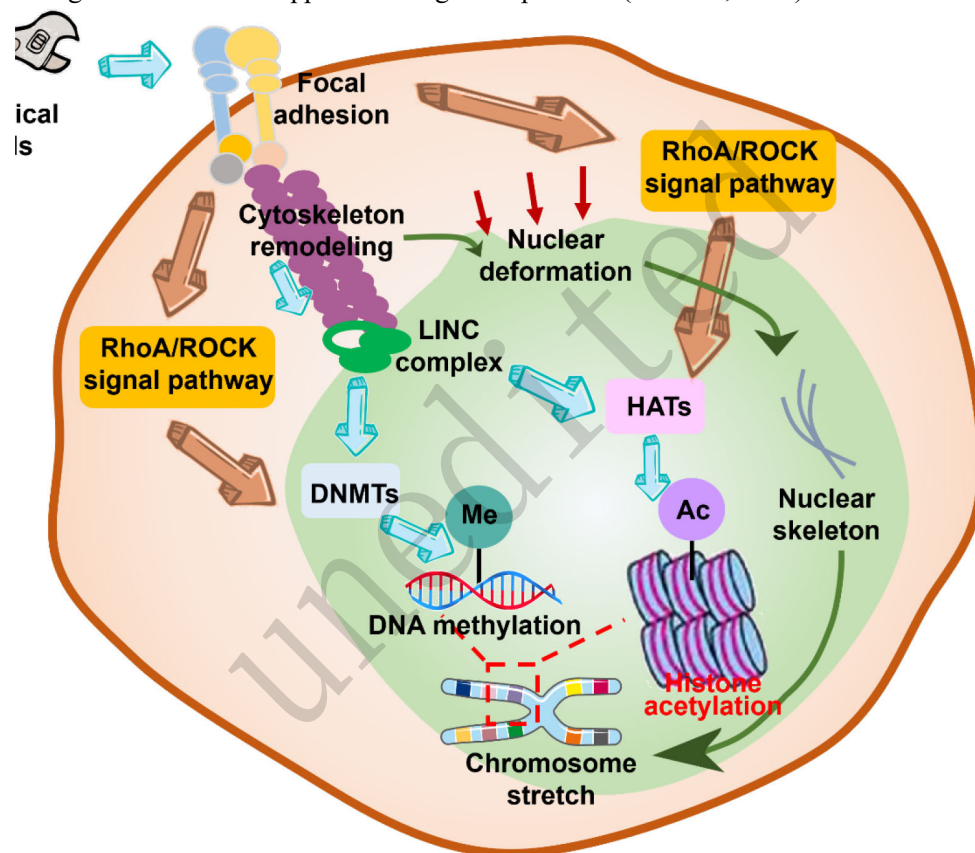


Fig. 2 Schematic diagram of how mechanical signals induce changes in DNA methylation and histone acetylation. Yellow arrow: Mechanical signals are converted into chemical signals via focal adhesions and RhoA/ROCK pathways, modulating DNA methylation and histone acetylation enzymes to increase or decrease both modifications. Blue arrow: Mechanical signals are transmitted from focal adhesions to the cytoskeleton and then to the LINC complex, directly regulating the nuclear import of DNMT and HAT proteins. Green arrow: Mechanical signals pass from focal adhesions to the cytoskeleton, stretching the nuclear envelope and causing deformation of the nucleus, nuclear lamina, and chromatin, thereby influencing epigenetic modifications of DNA and histones.

2.1 Extracellular matrix stiffness

ECM stiffness, a crucial physical property within the tissue microenvironment, undergoes dynamic alterations during processes such as disease, aging, or fibrosis. This change serves as a key mechanical signal that directly triggers chromatin spatial reorganization and epigenetic reprogramming by activating intracellular mechanotransduction pathways, thereby influencing cellular fate (Yu et al., 2025).

2.1.1 ECM Sclerosis Resulting from Vascular Hardening

The onset and progression of vascular sclerosis constitute a vicious cycle driven by chronic inflammation and intertwined with extracellular matrix (ECM) stiffening and nuclear epigenetic reprogramming. Following endothelial injury, vascular smooth muscle cells (VSMCs) are activated to secrete abundant collagen and deposit proteoglycans. Meanwhile, matrix metalloproteinases (MMPs) selectively degrade elastic components, and hypoxia triggers calcium-salt deposition, jointly constructing a highly cross-linked, mineralized sclerotic plaque microenvironment (Di Nubila et al., 2024; Xu et al., 2025).

Elevated matrix stiffness is transduced into nuclei via mechanoreceptors including integrins, discoidin domain receptor 1 (DDR1), and Piezo to reshape the epigenetic landscape. In VSMCs, increased stiffness activates the DDR1-Src-RhoA-ROCK axis and upregulates DNMT1. In endothelium, disturbed turbulent flow elevates KDM5B through Piezo1 (Wang et al., 2022; Xie et al., 2018; Wu et al., 2024). This force-enzyme expression coupling is universally present across organs. For example, in liver fibrosis, enhanced stiffness mediates mechanotransduction in liver sinusoidal endothelial cells, modifying nuclear pores, NF- κ B translocation, and chromatin spatial organization (Greuter et al., 2022).

At the DNA methylation level, hypermethylation-driven silencing of protective genes coexists with hypomethylation-triggered activation of pro-inflammatory genes. Upregulated DNMT1 induces promoter hypermethylation of contractile genes (ACTA2, MYH11) and KLF2, facilitating VSMC dedifferentiation and endothelial inflammation. Hypermethylation also inactivates protective genes such as ER- α . Reduced TET2 activity impedes inflammation resolution and fosters necrotic-core formation (Kumar et al., 2013; Zhang et al., 2023; Grimaldi et al., 2015; Khyzha et al., 2017). Genome-wide hypomethylation and site-specific hypomethylation of pro-inflammatory genes such as IL-6 lead to their aberrant activation. This imbalance arises from disrupted homeostasis between DNMTs and TETs, and TET1 deletion aggravates atherosclerosis (Dai et al., 2022; Zhang et al., 2023).

Histone modifications also undergo profound changes. Pro-inflammatory stimuli recruit HDAC1/3 and enhancer of zeste homolog 2 (EZH2) to silence anti-proliferative and cholesterol efflux-related genes. p300/CBP-dependent histone H3 lysine 27 acetylation (H3K27ac) enrichment amplifies the NF- κ B/IL-6 cascade. Piezo1-induced KDM5B suppresses antioxidant and anti-inflammatory genes including nuclear factor erythroid 2-related factor 2 (Nrf2), Krüppel-like factor 2/4 (KLF2/4), and endothelial nitric oxide synthase (eNOS), whereas it activates the NF- κ B-VCAM-1/ICAM-1 pathway to promote monocyte infiltration (Khyzha et al., 2017; Wu et al., 2024). Matrix stiffness directly modulates HDACs; long-term rigid matrix stimulation causes irreversible epigenetic alteration, which explains why short-term anti-inflammatory treatment cannot reverse established pathological phenotypes (Killaars et al., 2019).

These epigenetic changes lock pathological phenotypes and further aggravate ECM stiffening, forming a positive-feedback loop. Animal experiments demonstrate that endothelial-specific Dnmt1 knockout alleviates endothelial-to-mesenchymal transition and neointimal hyperplasia, while bone-marrow-derived HDAC3 deletion reduces plaque burden in ApoE^{-/-} mice, confirming the essential role of epigenetic regulation in cellular homeostasis (Li et al., 2019; Jiang et al., 2022) (Fig. 3).

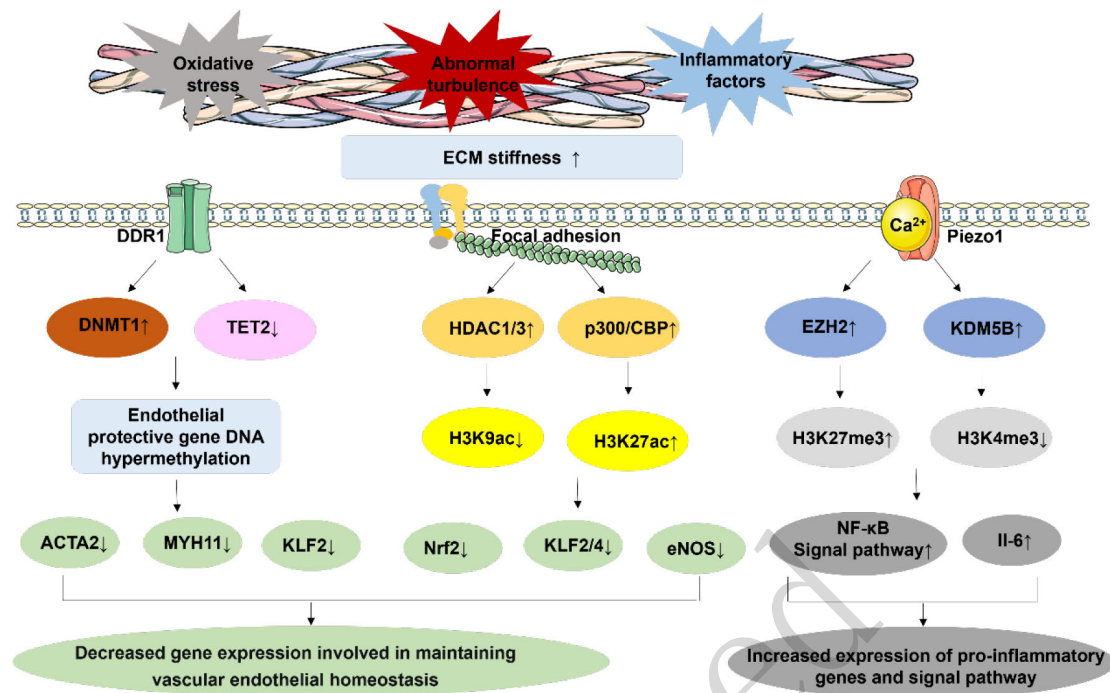


Fig. 3 Increased extracellular matrix stiffness transmits mechanical signals into cells via ion channels and focal adhesion systems, and exacerbates atherosclerosis by interfering with a series of epigenetic molecular networks on chromatin.

2.1.2 ECM stiffening induced by malignant tumors

Malignant tumor tissue often exhibits stiffer ECM than healthy tissue, which not only promotes cancer-cell migration and invasion but also induces normal cell transformation, which involves increased ECM deposition and fibrous network remodeling (Huang et al., 2021). Cells perceive ECM stiffness through mechanotransduction processes including integrin-mediated adhesion, actin contraction, and cytoskeletal reorganization, activating transcription factors such as YAP (Piersma et al., 2020). YAP is a key downstream effector of mechanical signals, and its localization and activity are regulated by stiffness, which not only induces nuclear deformation via cytoskeletal contraction but also directly triggers epigenetic alterations in YAP (Lee et al., 2019; Shiu et al., 2018).

ECM stiffness reversibly modulates DNA methylation at the YAP promoter: YAP interacts with GRHL2, TET2, and KMT2A, leading to promoter hypomethylation and activation of oncogenic pathways, while matrix softening reverses this process (Jang et al., 2020). Stiff matrices also induce nuclear deformation, increase lamin-associated chromatin and chromatin accessibility, and cause Sp1 to cooperate with HDAC3/8 to regulate stiffness-mediated tumor invasion (Stowers et al., 2019). Stiffness is also closely linked to cancer-associated fibroblast (CAF) phenotype regulation: cancer cells release LIF to activate JAK1/STAT3, and p300 acetylates STAT3 and upregulates DNMT3b, which induces CpG methylation at the SHP-1 promoter, silencing SHP-1 and relieving JAK1 inhibition; DNMT1 maintains this methylation state, driving sustained CAF pro-tumor behavior (Albregues et al., 2015).

Tumor dormancy is critical for a tumor's long-term survival, as well as evasion of immune surveillance and cytotoxic drugs (Sosa et al., 2014). Stem-cell—like tumor-repopulating cells (TRCs) sense mechanical signals: they proliferate rapidly in soft matrices (90 Pa), whereas stiff matrices ($\approx 1,000$ Pa) induce Cdc42 nuclear translocation, upregulate Tet2, activate p21/p27, and downregulate Integrin $\beta 3$, inducing TRC dormancy (Liu et al., 2018).

2.2 Mechanical Strain

Mechanical strain can induce epigenetic remodeling of chromatin. The cytoplasmic actin cytoskeleton connects with peripheral chromatin via lamins and the LINC complex. Mechanical strain can be transmitted through this cytoskeletal network into the nucleus, and such structural continuity links the extracellular environment to chromatin (Lin, 2024). Lamin serves as a hub for transducing mechanical signals in this process. Meanwhile, chromatin and DNA-related factors are also regulated by globular actin (G-actin) and filamentous actin (F-actin) within the nuclear skeleton (Dupont and Wickström, 2022). The mechanical stress generated by cell-ECM adhesion can promote acetylation of H3 and H4 histones, thereby facilitating the formation of transcriptionally active chromatin structures (Gieni and Hendzel, 2008; Herrmann et al., 2007). Mechanical forces transmitted through the nuclear envelope can induce chromatin stretching within seconds, and sustained application for one hour activates the expression of mechanoresponsive genes (Sun et al., 2020; Tajik et al., 2016). Short-term stretching may reduce H3K9 methylation, relaxing chromatin structure; whereas prolonged action may induce compensatory modifications, such as increased H3K27 methylation to maintain gene silencing (Le et al., 2016).

Different types of mechanical strain exert distinct effects on nuclear epigenetic modification (Hu et al., 2022). Laminar shear stress of 20 dynes/cm² reduces histone methyltransferase EZH2 expression via the mechanosensitive microRNA miR101 in endothelial cells (ECs), concurrently decreasing H3K27 methylation. This limits endothelial inflammatory factor expression, exerting anti-atherosclerotic effects (Xu et al., 2018). Using the Flexcell compression loading system, Wang et al. applied a static compressive force of 1.5 g/cm² to cells to simulate the mechanical environment on the pressure side during orthodontic treatment. They found that sustained compressive force can promote the acetylation of histone H3 (H3K9/14ac) by activating histone acetyltransferases (HATs), thereby driving the polarization of macrophages toward the M2 anti-inflammatory phenotype (Wang et al., 2023).

Furthermore, mechanically mediated gene activation correlates with nuclear spatial localization; for instance, genes within the epidermal differentiation complex (EDC) cluster, situated near the nuclear center, exhibit heightened activation potential (Mardaryev et al., 2014).

2.3 Cell Deformation

Morphological changes in cells and nuclei serve as crucial physical regulation factors for chromatin organization and epigenetic states. External constraints directly induce a series of chromatin modifications by altering intracellular tension distribution.

First, alterations in cell morphology directly regulate histone modifications and gene expression. When cells are forced to spread or flatten, histone deacetylation and chromatin condensation are often triggered. For instance, mammary epithelial cells compressed into circular shapes by micro-patterning exhibit global histone deacetylation, chromatin condensation, and overall reduced gene expression (Lebeyec et al., 2007). Similarly, human mesenchymal stem cells compressed into spindle shapes demonstrate increased histone deacetylase activity and decreased global histone acetylation levels (Li et al., 2011). Conversely, increasing the spreading area of fibroblasts leads to opposite outcomes by affecting actin contractility—increased histone acetylation levels and altered expression of cytoskeletal genes (Jain et al., 2013).

Second, changes in cell morphology transmit to the nucleus, triggering nuclear morphologic alterations and localized chromatin reorganization. Tensile changes induced by morphologic alterations activate calcium channels, and the resulting intracellular Ca²⁺ elevation drives the formation of a perinuclear actin network. This mechanism links cytoplasmic mechanical stress to transcriptional regulation within the nucleus (Shao et al., 2015). Furthermore, tension in the perinuclear cytoskeleton can cause localized deformation of the nuclear envelope, leading to lobulated nuclei (Nastaly et al., 2020). Crucially, such lobular nuclear morphologies directly correlate with altered local epigenetic landscapes. Recent studies have shown that during early differentiation of human hematopoietic stem cells, microtubule-generated compressive forces can trigger nuclear lob-

ulation, accompanied by localized loss of heterochromatin which is marked by H3K9me3 in nuclear-membrane invagination regions (Biedzinski et al., 2020).

3. Effects of mechanical signals on RNA epitranslational modification

m⁶A is the most prevalent epitranslational modification in mRNA, involving the addition of a methyl group to the sixth carbon of adenosine. Unlike the relatively stable DNA methylation, m⁶A modification on mRNA is a highly dynamic, reversible epitranscriptional modification that is susceptible to external environments and various internal factors, such as cell type, developmental stage, nutrient availability, circadian rhythms, and environmental stressors (Mitsuhashi and Nagy, 2023; Zhang and Wang, 2023). It plays a crucial role in cellular stress responses to external stimuli (Zhao et al., 2022). M⁶A modification constitutes a rapid response mechanism to external stimuli. Upon stimulation, m⁶A-marked transcripts that encode key regulatory factors are promoted for transport and metabolism, thereby altering the transcriptome and influencing protein translation (Liu et al., 2022).

3.1 How mechanical signals regulate m⁶A modification

3.1.1. Regulation of m⁶A modification by the force-cytoskeleton-nucleus transmission pathway

Cells perceive mechanical signals from the matrix or neighboring cells and translate them into biochemical responses, with the core mechanism being the transduction of force signals through the cytoskeleton to the nucleus (Handorf et al., 2015; Zhu et al., 2021). Cellular deformation directly triggers actin cytoskeletal assembly and remodeling (Soto et al., 2023), transmitting tension from the cytoplasmic cytoskeleton to the nuclear cytoskeleton via the LINC complex (as a mechanical relay hub) (Sankaran et al., 2019). Sustained force transmission alters nuclear morphology and positioning, inducing nuclear deformation and internal chromatin structural rearrangement (Sankaran et al., 2019; Song et al., 2022).

Structural changes in nuclear chromatin serve as a critical bridge regulating m⁶A modification. Nuclear deformation and cytoskeletal traction directly alter DNA methylation states, influencing gene transcription and providing the transcript basis for subsequent m⁶A RNA modification (Song et al., 2022). In addition, mechanical strain (e.g., via the YAP-TEAD pathway) and actin assembly significantly enhance chromatin accessibility, promoting a more open chromatin structure (Handorf et al., 2015; Soto et al., 2023; Zhu et al., 2021). This dynamic alteration in chromatin structure has been shown to regulate the recruitment and activity of m⁶A "writers," "readers," and "erasers" at specific gene loci. Consequently, it precisely influences the m⁶A modification levels of corresponding mRNAs, ultimately driving functional cellular differentiation.

The significance of this regulatory pathway is further supported by omics data: KEGG analysis of differential m⁶A peaks following alkaloid treatment of colon cancer cells revealed enrichment in pathways including those for the actin cytoskeleton, tight junctions, and adherens junctions, indicating that cytoskeletal rearrangement plays a crucial role in m⁶A modification (Wu et al., 2022).

3.1.2. Regulation of m⁶A by calcium signaling

Intracellular calcium signaling is also significantly correlated with m⁶A modification. For instance, cyclophosphamide induces cardiotoxicity by blocking calcium signaling pathways while simultaneously upregulating the methyltransferase METTL3. This leads to increased m⁶A modification and reduced expression of the key gene JPH2 mRNA, ultimately causing prolonged electrophysiological duration in cardiomyocytes (Zhu et al., 2021). This regulatory process involves ion channels such as Piezo1 and TMEM, as well as calcium-dependent proteins like YAP.

The Piezo1 channel serves as a critical mechanical force sensor. For instance, within a left-handed hydrogel microenvironment, cellular Piezo1 channels activate, increasing calcium influx and inducing cytoskeletal rearrangement. Concurrently, m⁶A modification levels mediated by WTAP are significantly reduced, driving macrophage polarization toward an M2 reparative phenotype (Jiang et al., 2022; Yang et al., 2024). TMEM38B, a channel gene which regulates endoplasmic reticulum calcium release, exhibits BACE2-regulated

expression. Inhibition of the BACE2/TMEM38B axis depletes intracellular calcium stores and suppresses tumor progression; conversely, channel activation enhances m⁶A modification levels on BACE2 mRNA itself (He et al., 2021).

Furthermore, the calcium-responsive protein YAP directly interacts with m⁶A regulatory factors. For instance, during magnesium-alloy degradation, changes in mechanical properties and ion release promote YAP overexpression and nuclear localization. Activated YAP interacts with core m⁶A regulators such as METTL3, METTL14, WTAP, and FTO, modulating their mRNA expression and altering RNA methylation patterns of inflammation-related genes, potentially exacerbating inflammatory responses in atherosclerotic vessels (Yu et al., 2022).

3.2 Linkage Between Mechanosignaling-Related Diseases and m⁶A Regulation

3.2.1 Effects of Extracellular Matrix Stiffness on m⁶A Modification

Changes in extracellular matrix stiffness are key hallmarks of various pathological states including inflammation, fibrosis, and tumors.

In immune regulation, studies using gradient-stiffness hydrogels to mimic the extracellular matrix revealed that increased rigidity activates Jak-STAT and NF- κ B signaling pathways while lowering expression of the demethylase FTO. FTO deficiency enhances m⁶A levels on suppressor of cytokine signaling 1 (Socs1) mRNA, strengthening its binding to the “Reader” YTHDF1. This stabilizes Socs1 mRNA and promotes its translation, ultimately exerting an anti-inflammatory effect (Hu et al., 2022).

In oncology, the association between matrix stiffness and m⁶A modification is particularly pronounced. Studies on pituitary adenomas reveal significantly downregulated expression of m⁶A regulators FTO and RBM15 in stiffer tumors, indicating lower overall m⁶A levels. Correlation analyses further demonstrate that m⁶A methylation predominantly negatively regulates target-gene expression (Wang et al., 2022). Deeper mechanistic studies indicate that cells perceive environmental stiffness through the integrin-GSK3 β -FTO-mTOR signaling axis: substrate stiffening reduces mRNA m⁶A modification via this pathway, thereby activating mTORC1 signaling to promote anabolic metabolism. This helps tumor cells adapt to a rigid microenvironment and resist death (Zhang et al., 2024).

m⁶A modification itself actively contributes to extracellular-matrix (ECM) remodeling. The methyltransferase METTL3 promotes epithelial-mesenchymal transition and downstream fibrotic gene Snail expression, directly exacerbating ECM deposition and stabilization by increasing m⁶A levels on collagen transcripts. Conversely, the demethylases FTO and ALKBH5 exert opposing effects, mitigating the fibrotic process (Ye et al., 2023).

3.2.2 Relationship between abnormal forces and m⁶A modification in cardiovascular disease

In the cardiovascular system, abnormal mechanical stress serves as a key driver of disease progression. In atherosclerosis, for example, oscillatory stresses generated by blood flow at arterial bends and bifurcations constitute the primary pathogenic mechanical signal. Studies indicate that oscillatory stresses significantly upregulate expression of the methyltransferase METTL3, triggering global m⁶A hypermethylation. This subsequently enhances phosphorylation of NF- κ B p65, promoting inflammatory response and monocyte adhesion. Mechanistically, YTHDF1 and YTHDF2 recognize m⁶A modifications on key target mRNAs like NLR family pyrin domain containing 1 (NLRP1) and Krüppel-like factor 4 (KLF4) to regulate their fate, ultimately accelerating atherosclerosis progression. In vivo experiments confirm that reducing METTL3 expression effectively delays disease development (Chien et al., 2021).

In low fluid shear stress models, m⁶A modifications exhibit earlier and more sensitive responses than mRNA expression changes. Transcriptome-wide analysis has revealed that low fluid shear stress causes m⁶A enrichment in coding regions while reducing it in 3' UTRs, a process primarily regulated by factors like RBM15 and EIF3A. Functional analysis further revealed that these differentially enriched m⁶A peaks significantly

cluster in pathways including mTOR, PI3K-AKT, and oxidative stress-related transcription factors such as HIF1A and NFE2L2—all closely associated with the pathophysiology of cardiovascular disease (Xu et al., 2023).

3.2.3 Relationship Between Bone and Cartilage Injury and m⁶A Regulation

Dynamic remodeling of bone tissue is also regulated by m⁶A. Bone-marrow mesenchymal stem cells (BMSCs) are key cells in bone repair, and their osteogenic differentiation is precisely regulated by mechanical forces. Studies indicate that fluid shear stress and tensile forces promote F-actin remodeling, transmitting signals through the cytoskeletal-Lamin A pathway to the nucleus. This upregulates expression of the methyltransferase METTL3, thereby enhancing m⁶A modification levels and promoting osteogenic differentiation in BMSCs (Guo et al., 2022). However, the regulation of mechanical signals is quite complex: another study found that under cyclic tensile stress, expression of the demethylase FTO is also significantly upregulated in BMSCs and correlates with enhanced osteogenic differentiation; knocking down FTO inhibits this process, suggesting that different mechanical patterns may influence osteogenesis through distinct m⁶A regulatory factors (Sun et al., 2022).

BMSCs are also present in intervertebral-disc nucleus pulposus tissue, where they attenuate senescence of nucleus pulposus cells (Li et al., 2019). In co-culture systems with BMSCs, compressive force induces a reduction in the overall m⁶A level of nucleus pulposus cells (NPCs). This process is mediated by the demethylase ALKBH5, which decreases m⁶A levels in the coding region of the autophagy-critical gene FIP200 mRNA, thereby reducing YTHDF2-dependent mRNA degradation, enhancing autophagy, and delaying apoptosis (Li et al., 2020).

While METTL3 plays a positive role in force-induced bone repair, mechanical stress in cartilage induces chondrocyte senescence via METTL3-mediated m⁶A modification. In temporomandibular joint osteoarthritis (TMJOA) models, mechanical overload triggers chondrocyte senescence accompanied by diminished YAP signaling and increased METTL3-mediated m⁶A modification. Inhibiting m⁶A modification halts cellular senescence and delays disease progression both in vivo and in vitro (Yang et al., 2023). Similarly, in degenerated endplate cartilage, both METTL3 expression and m⁶A levels are significantly elevated. METTL3 suppresses type-II collagen expression by mediating SOX9 mRNA methylation and reducing its stability, thereby weakening chondrocyte resistance to tension and accelerating disc degeneration (Xiao et al., 2022).

Furthermore, the m⁶A reader protein IGF2BP3 has been demonstrated to undergo mechanically stress-specific regulation in osteoarthritis. In arthritic joints, IGF2BP3 exhibits high expression and colocalization with pro-inflammatory macrophages. In vitro experiments indicate that its upregulation is directly induced by mechanical overload rather than inflammatory stimuli (e.g., LPS), confirming the dominant role of mechanical stress in altering m⁶A modifications within articular cartilage (Lu et al., 2023).

3.2.4. Myofibers and m⁶A Modification

Myofibers, most closely linked to mechanical signaling, are also regulated by m⁶A modification. Following overload-induced stress, increased myofibrillar number within myofibers leads to skeletal-muscle hypertrophy. This process may involve m⁶A epigenetic regulation, as enhanced skeletal muscle hypertrophy correlates with elevated METTL3 expression. Moreover, METTL3 can induce skeletal muscle growth even in the absence of exogenous mechanical signals. Conditional knockout of METTL3 leads to spontaneous muscle atrophy over time and eliminates overload-induced hypertrophy; this phenotype is reversed by concurrent administration of muscle-atrophy-factor inhibitors (Petrosino et al., 2022). Thus, METTL3 positively correlates with skeletal muscle growth.

3.2.5 Orthodontic Treatment and m⁶A Modification

Periodontal tissues in the oral cavity continuously remodel in response to mechanical signals. Based on this, orthodontic treatment primarily applies mechanical forces to induce periodontal tissue remodeling, ultimately facilitating tooth movement. Compressive-force treatment of human periodontal ligament stem cells (hPDLSCs)

to mimic orthodontic therapy was found to promote osteogenic differentiation of hPDLSCs and increase m⁶A modification and METTL14 expression levels, while METTL14 knockdown inhibited the osteogenic effect of hPDLSCs under compressive force (Wu, 2023).

However, periodontitis can impair orthodontic outcomes. Research indicates that periodontal-ligament stem cells derived from periodontitis tissue (pPDLSCs) exhibit higher sensitivity to static mechanical strain (SMS) than those from healthy tissue (hPDLSCs). m⁶A microarray analysis of pPDLSCs and hPDLSCs exposed to 12% SMS revealed differentially methylated RNAs as being primarily involved in inflammatory responses. Moreover, pPDLSCs under strain exhibit lower METTL3 expression than hPDLSCs under the same strain, and METTL3 promotes osteogenic differentiation in pPDLSCs (Sun et al., 2022).

Mechanical forces induce m⁶A-modification-related diseases, as summarized in Table 1.

Table 1. Relationship between mechanical forces and m⁶A modification in diseases and certain physiological states

Physiological/Pathological State	Mechanical Effect	m ⁶ A Enzyme	m ⁶ A Modification Change	Final Effect
Pituitary adenoma	ECM stiffening	Significant downregulation of FTO and RBM15	Low overall m ⁶ A level	Exacerbates ECM stiffening and promotes tumor cell metabolism
Atherosclerosis	Increased oscillatory shear stress	METTL3 up-regulation	m ⁶ A hypermethylation	Enhances NF-κB p65 phosphorylation, promoting inflammation and monocyte adhesion
Bone tissue remodeling after fracture	Fluid stress and shear and tensile strain	METTL3 up-regulation	m ⁶ A hypermethylation	Promotes osteogenic differentiation of BMSCs
	Tensile stress	FTO upregulation		Promotes osteogenic differentiation of BMSCs
Prevention of intervertebral disc nucleus pulposus aging	Appropriate compressive force	ALKBH5 up-regulation	Decreased overall m ⁶ A level	Enhances autophagy and delays cell apoptosis
Intervertebral disc aging	Excessive tension	METTL3 up-regulation	Significantly increased m ⁶ A level	Suppresses type II collagen expression and exacerbates disc degeneration
Temporomandibular	Mechanical	METTL3 up-	Significantly	Triggers

joint osteoarthritis	overloading	regulation		increased level	m ⁶ A	chondrocyte senescence, accompanied by weakened YAP signaling
Skeletal muscle hypertrophy induced by excessive muscle fiber stress	Mechanical overloading	METTL3 regulation	up-	Significantly increased level	m ⁶ A	Increased myofibrils lead to skeletal muscle hypertrophy
Orthodontic treatment	Compressive force	METTL14 regulation	up-	Increased modification	m ⁶ A	Promotes osteogenic differentiation of hPDLSCs

4. Conclusions

The interaction between mechanical signals and epigenetic modifications constitutes a core regulatory axis governing cellular response to microenvironmental mechanics. Through integrins, mechanosensitive ion channels (e.g., Piezo1), and cytoskeletal-LINC complexes, physical signals are transmitted to the nucleus, rapidly triggering nuclear deformation and chromatin reorganization, and achieving sustained reprogramming of DNA methylation, histone modifications, and RNA m⁶A modifications. At the chromatin level, mechanical stimuli such as ECM stiffness, mechanical strain, and cell deformation reshape chromatin architecture by regulating the activity of enzymes including DNMTs, HDACs, and KDM5B, thereby determining gene activation or silencing. At the RNA level, m⁶A modification serves as a rapid-response epitranscriptomic mechanism which is finely tuned by mechanical signals to influence mRNA metabolism and cellular functions. The pathological significance of this axis is particularly evident in atherosclerosis, tumor progression, fibrosis, and osteoarthritis, where dysregulated mechano-epigenetic positive-feedback loops—such as the DDR1-DNMT1 axis in vascular stiffening or the integrin-GSK3β-FTO-mTOR axis in tumors—drive disease progression. However, several critical gaps remain to be addressed in this field. For instance, it remains unclear how cells distinguish between different types, durations, and magnitudes of mechanical stimuli to elicit modification-specific responses at distinct genomic loci. Second, most current evidence has been derived from in vitro models with simplified mechanical environments (e.g. two-dimensional culture or uniform stiffness substrates), which inadequately recapitulate the complex, dynamic, and heterogeneous mechanical features of native tissues. The translation of these findings to in vivo physiology and pathology therefore requires further validation. Third, the functional interplay between different epigenetic layers—DNA methylation, histone modification, and RNA m⁶A modification—in response to mechanical cues remains largely unexplored. Whether these modifications act synergistically or hierarchically to coordinate mechanoresponsive gene programs is an open question that demands integrated multi-omics approaches.

Deepening understanding of the mechano-epigenetic axis opens promising avenues for therapeutic and bioengineering applications. Pharmacological targeting of mechanosensitive epigenetic enzymes represents a potential therapeutic strategy for intervening in mechanically driven diseases. For example, lysine-specific demethylase 1 (LSD1) has emerged as a key target linking the mechanical microenvironment to invasiveness in malignancies such as acute lymphoblastic leukemia, and its inhibitors have demonstrated therapeutic potential in multiple preclinical studies (González-Novo et al., 2025). The design of mechanoresponsive biomaterials capable of dynamically modulating epigenetic states in a spatiotemporally controlled manner holds great promise for tissue engineering and regenerative medicine. A recent study reported a cell-programmed adap-

tive-contraction (CPAC) hydrogel that responds to alkaline phosphatase (ALP) secreted by mesenchymal stem cells, to trigger localized contraction and stiffening. This process upregulates mechanosensitive microRNAs (e.g., miR-124-3-1, miR-214, miR-26a), which suppress EZH2 and reduce H3K27me3 levels, thereby epigenetically activating osteogenic gene programs and significantly promoting calvarial bone-defect repair in rats (Ling et al., 2026). Furthermore, biomaterials with tunable stiffness or controlled stress-relaxation properties could be engineered to deliver epigenetic modulators specifically to diseased tissues, reprogramming pathological cell phenotypes while minimizing systemic side effects. Finally, integrating mechano-epigenetic principles into diagnostic strategies—for instance, using epigenetic signatures as early detection biomarkers for mechanically induced pathologies—merits further exploration. In summary, the convergence of mechanobiology, epigenetics, and materials science holds the potential to transform precision medicine.

Data Availability Statement

No additional data are available.

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Author contributions

Xinwei GUO and Yi ZHENG contributed equally to this work. Xinwei GUO conducted the literature search, collected and organized the relevant references, and drafted the manuscript. Yi ZHENG participated in the literature screening, and manuscript preparation. Dan YU conceived and designed the review, supervised the writing process, revised the manuscript.

Compliance with ethics guidelines

Xinwei Guo, Yi Zheng, Dan Yu declare that they have no conflicts of interest

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

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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