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Chromatin plasticity in mechanotransduction

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Abstract

Living organisms can detect and respond to physical forces at the cellular level. The pathways that transmit these forces to the nucleus allow cells to react quickly and consistently to environmental changes. Mechanobiology involves the interaction between physical forces and biological processes and is crucial for driving embryonic development and adapting to environmental cues during adulthood. Molecular studies have shown that cells can sense mechanical signals directly through membrane receptors linked to the cytoskeleton or indirectly through biochemical cascades that can influence gene expression for environmental adaptation. This review will explore the role of epigenetic modifications, emphasizing the 3D genome architecture and nuclear structures as responders to mechanical stimuli, which ensure cellular memory and adaptability. Understanding how mechanical cues are transduced and regulate cell functioning, governing processes such as cell programming and reprogramming, is essential for advancing our knowledge of human diseases.

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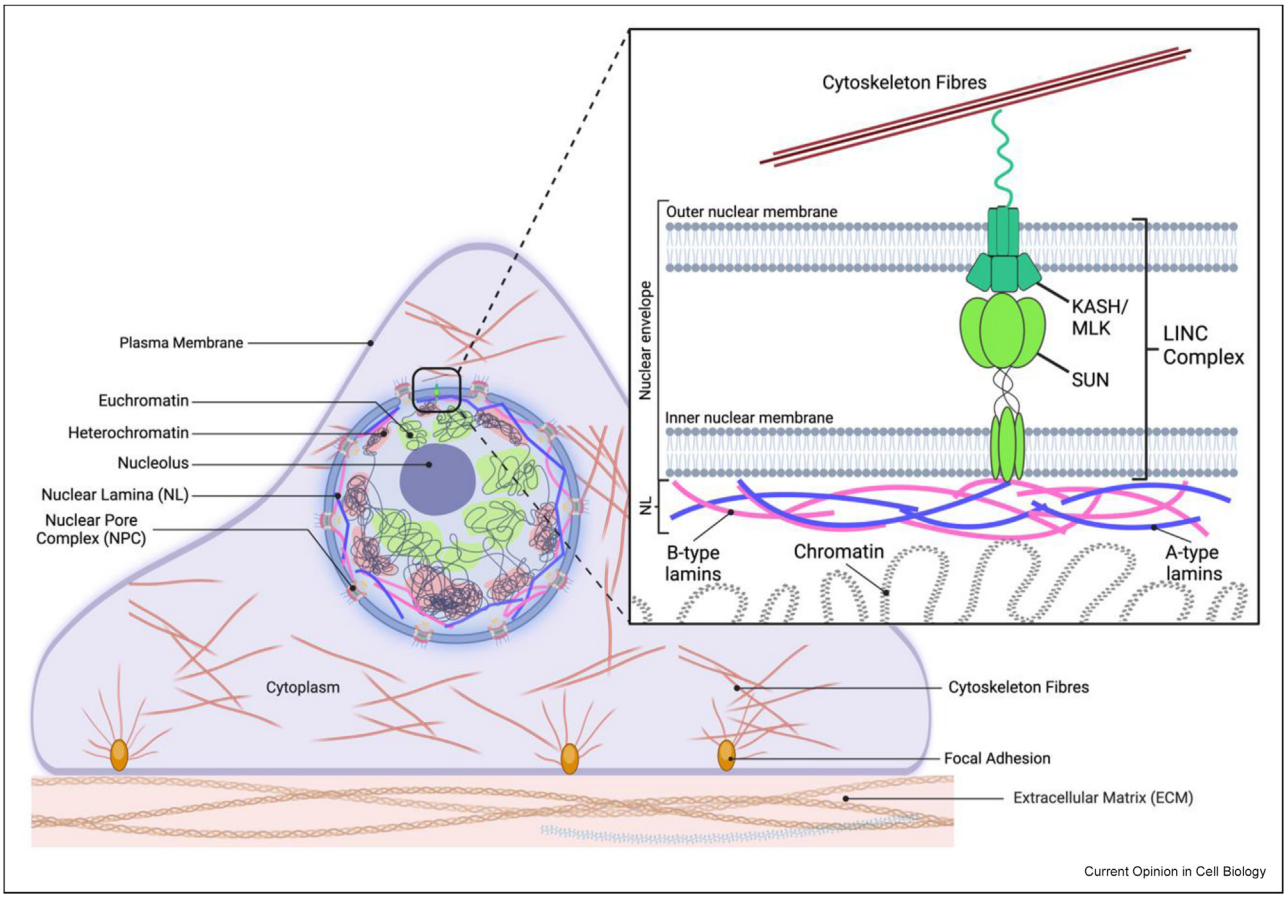
Introduction

Cells of complex organisms continuously respond to external stimuli to adapt to environmental changes. Over time, various cell pathways were developed to transmit mechanical stimuli to the nucleus and to react quickly and consistently [1]. The ensemble of physical and molecular mechanisms that enable the crosstalk between the cells and their microenvironment, known as mechanobiology, governs major developmental processes such as embryogenesis and organogenesis [2]. Early studies on mechanotransduction identified cell focal contacts; segments of the cell membrane that adhere to the substrate and have mechano-responsive properties [3,4] (Figure 1). In these regions, cytoplasmic fibers are highly organized, extending from the focal contact toward the center of the cell. Mainly composed of actomyosin, these contractile structures known as stress fibers play a central role in these processes and are also involved in cell locomotion [5]. Further studies have identified various proteins that play a role in the formation or composition of focal adhesion, including integrins, focal adhesion kinase, vinculin, and others (reviewed in Ref. [6]). These structures are sensitive to mechanical forces and can transmit this stimulus to the nucleus via the LINC (linker of nucleoskeleton and cytoskeleton) complex [7,8], an evolutionarily conserved macromolecular bridge which physically connects the cytoskeleton to the nuclear lamina (NL), a meshwork of intermediate filaments underlying the inner nuclear membrane [9] (Figure 1). The core of the LINC complex is composed of two types of membrane proteins: the Klarischt/ANC-1/SYNE homology (KASH) proteins, embedded in the outer nuclear membrane and Sad1/UNC-84 (SUN) proteins, localized in the inner nuclear membrane [8].

Activation or engagement of mechano-responsive structures in the cytoplasm plays a crucial role in the regulation of the activity of the transcriptional co-activators YAP/TAZ (yes-associated protein/transcriptional co-activator with PDZ-binding motif), in response to various stimuli. These stimuli can be caused by changes in cell density and area, or from tissue stretch, shear forces, and substrate stiffness [10,11]. YAP/TAZ is biochemically regulated by the activity of the Hippo pathway through a cascade of signaling events that modify their phosphorylation status [10]. When dephosphorylated, YAP/TAZ accumulate in the nucleus, where they associate with TEAD (TEA DNA-binding domain) transcription factors, to activate specific transcriptional programs that allow cells to adapt to environmental cues [10–12]. Mechanical stimuli can contribute to the nuclear accumulation of YAP/TAZ. Modifications of filamentous actin (F-actin) levels can

Figure 1



Graphical representation of a cell with its microenvironment and organization of the genome in the nucleus. Cells adhere to the extra-cellular matrix (ECM) through the formation of focal adhesions, specialized subcellular structures where inputs from the environment are transduced to the cell core during the entire cell lifespan. These mechano-responsive structures are enriched in highly organized cytoskeleton fibers, going from the focal contact toward the center of the cell. The dynamics of the cytoskeleton are essential in regulating cell movements, cell polarity, and cell migration. In particular, mechanical stimulation of the cytoskeleton is transmitted to the nucleus through the LINC (linker of nucleoskeleton and cytoskeleton) complex, a highly conserved macromolecular bridge. The LINC complex consists of SUN proteins embedded in the inner nuclear membrane and KASH proteins anchored in the outer nuclear membrane. KASH proteins interact with the cytoskeletal fibers, such as actin, while SUN proteins are linked to the nuclear lamina (NL). This structure mainly comprises nuclear intermediate filaments composed of A-type, labelled in blue (lamin A/C) or B-type, labelled in pink (lamin B1, B2). B-type lamins primarily localize at the nuclear membrane and are present in all tissues, while A-type lamins are expressed in a regulated manner and can be localized both at the nuclear membrane and at the nuclear interior. The NL has both structural and regulative functions, being responsible for nuclear mechanical stability, nuclear positioning, genome organization, and mechano-sensing. In the nucleus, the genome is spatially compartmentalized into heterochromatin, transcriptionally inactive domains located at the nuclear periphery, and euchromatin, transcriptionally active domains located in the nuclear center.

impact YAP/TAZ activity, with an increase in cytoplasmic F-actin levels generally promoting the nuclear localization of YAP/TAZ [13]. In addition, when the nucleus is mechanically challenged, the stretching induces the opening of the nuclear pore complex (NPC), allowing increased protein import. Interestingly, it has been observed that molecules with low mechanical stability and molecular weight, such as YAP, can readily travel through the NPC, and accumulate within the nuclear compartment [13,14]. Once in the nucleus, YAP/TAZ induces the expression of target genes involved in cell proliferation, stemness, and inhibition of cell death [10–12].

Altogether, these mechanisms transmit the mechanical stimuli from the external environment to the internal cell core. However, the nucleus itself can detect and react to extra-cellular matrix (ECM) rigidity and cell shape changes: when subjected to compression, it can unfold and stretch, leading to a calcium-mediated response that results in the contractility of the acto-myosin localized at the cell cortex [15,16]. This response rapidly produces forces that push back against the initial stimuli and assist the cell in escaping its compressive microenvironment. Recent studies suggest that changes in the shape of the nucleus can trigger processes that lead to epigenetic adaptations of the cell

to its surroundings [17]. This indicates that the genome is involved in the mechano-response and shifts the focus of mechano-related studies from cytoplasmic signaling to the nucleus. It is widely accepted that the chromatin, the ensemble of genome and associated proteins, possesses essential non-genetic functions, and recent studies currently support the hypothesis that chromatin structure changes are an essential common feature of cellular mechano-response [1]. This review will focus on epigenetic changes involved in mechanotransduction and is believed to encode the memory and adaptability to these responses.

The multiple layers of the epigenome architecture

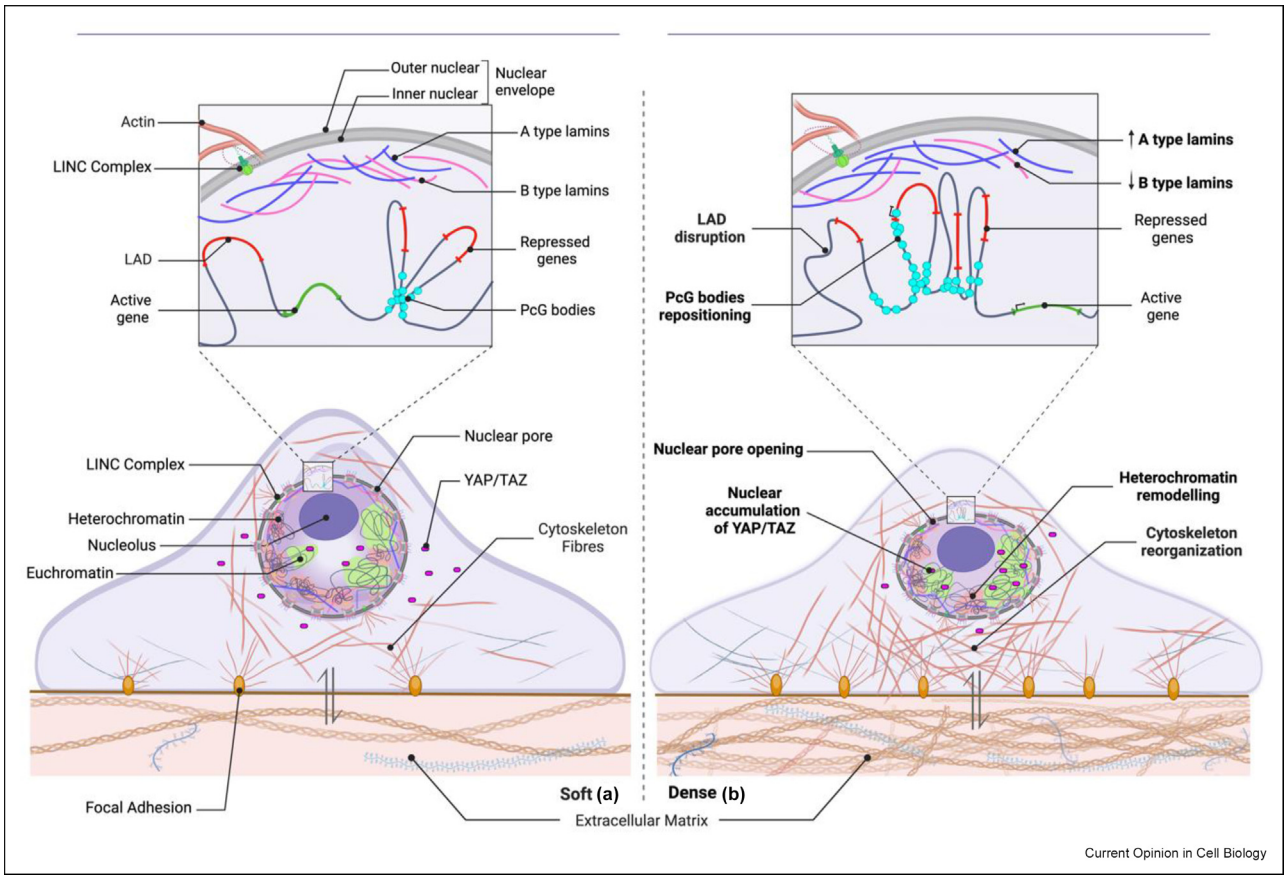
Spatial genome organization is a fundamental characteristic of cellular architecture, revealed by studies that became seminal works [18,19]. Tracing back to the inception of the "chromosome territories" through pioneering light microscopy studies by Boveri in 1909, later confirmed by *in situ* hybridization [20], our understanding of nuclear structure dynamics has expanded dramatically. It is now well known that the genome is physically separated into euchromatin, localized in the central part of the nucleus and heterochromatin, at the nuclear periphery [21] (Figure 1). The euchromatin is the transcriptionally active part of the genome, enriched with histone H3 tail modifications as acetylation of lysine 27 (H3K27ac) or trimethylation of lysine 4 or 36 (H3K4me3, H3K36me3). The heterochromatin is further divided into constitutive, which is more compacted and gene-poor, characterized by dimethylation and trimethylation of lysine 9 of the histone H3 (H3K9me2,3), and facultative which can rapidly switch to an active transcriptional state and is marked by trimethylated lysine 27 of the histone H3 (H3K27me3). Contemporary high-throughput molecular techniques have uncovered that eukaryotic genomes are hierarchically organized and encompass distinct structural levels characterized by specific protein interactions, from nucleosomes to chromatin compartments [19]. These compartments are further segmented into topologically associating domains (TADs) and smaller self-associating regions, demonstrating the genome's intricate higher-order structure alongside its remarkable flexibility [22,23]. The genomic organization exhibits dynamism during several biological processes such as differentiation, activation, DNA repair, and mitosis [24–30]. How different levels of chromatin organization interact to influence gene expression is still an active field of research. Additionally, it is unknown how mechanical signals detected by the nucleus affect the epigenome architecture and the molecular mechanisms involved.

The nuclear membrane is at the edge of the crosstalk between cytoplasmic signals and the nuclear genome. Hence, it is not surprising that its components can display mechanotransduction properties [31,32]. An emblematic example is represented by the nuclear lamina (NL) that, as aforementioned, is linked to cytoplasmic actomyosin fibers while, on the nuclear side, is involved in genome folding and function [33,34]. The NL, mostly constituted by lamin A and lamin B intermediate filaments, directly binds and represses large genomic regions of constitutive heterochromatin enriched with H3K9me2,3, called lamin-associated domains [35]. This binding ensures the maintenance of genome stability, by setting structural constraints necessary for the genome folding. Besides, NL plays a regulatory role in the epigenome, governing several biological processes such as differentiation and reprogramming [36,37]. Interestingly, nuclear lamins can also influence other epigenetic mechanisms, interacting with many transcriptional factors and regulatory complexes which contribute to chromatin structures' dynamics. We previously demonstrated that lamin A/C functionally interacts with the polycomb group of proteins (PcG) [38,39], involved in the formation and maintenance of H3K27me3-enriched facultative heterochromatin (reviewed in Ref. [40]) as others later reported [41–44]. Thus, changes in the cell environment and consequent activation of mechano-signaling pathways acting on the nuclear lamina can potentially trigger the remodeling of genome architecture at distinct layers of epigenetic regulation.

Nuclear mechano-programming and reprogramming

The key role of NL in cell lineage specification has been previously proposed by Swift et al. Using quantitative mass spectrometry on multiple adult solid tissues, they showed that the relative abundance of the nuclear lamina components, mainly the increased lamin A/B ratio, is associated with increased tissue stiffness [45]. Thus, they suggested that the extracellular microenvironment governs the cell fate by altering the biophysical properties of the nucleus. Several other studies have corroborated the link between NL and cell differentiation. In a pioneer work from Wickstrom laboratory in epidermal stem cells, it has been described a mechanotransduction mechanism during cell lineage commitment that involves a sequence of events: the induction of extracellular mechanical strain determines a decrease of lamin A/C interaction with Emerin, a component of the NL [32]; this leads to a decrease in H3K9me2,3-marked constitutive heterochromatin and an accumulation of H3K27me3 on facultative heterochromatin at other lineage-specific genes, promoting transcriptional choice toward the epidermal differentiation [46] (Figure 2). This dynamic was confirmed in a keratinocyte differentiation model, where nuclear tension exerted by the LINC complex preserves the

Figure 2



Graphical representation of the interplay between mechanical stretching forces and chromatin nuclear architecture of cells in contact with soft density (**a**) or high density (**b**) extracellular matrix. An increase in extracellular stiffness initiates a cascade of events that ultimately lead to the expression of mechano-sensing-dependent genes. The increased mechanical cues determine more focal adhesion contacts and F-Actin cytoskeleton reorganization. These mechanical signals are then transmitted to the nucleus via the LINC complexes with the consequent opening of nuclear pores and the nuclear translocation of YAP/TAZ transcription factors. The high contractility state also changes lamin A/lamin B relative levels, causing a reorganization of lamin-associated domains (LADs) and polycomb-dependent higher-order structures. This leads to decreased constitutive heterochromatin and an accumulation of facultative heterochromatin. These events ultimately influence gene expression and cell fate determination.

keratinocyte progenitor pool, while LINC-dependent tension release promotes keratinocyte differentiation [47]. In different tissues, the mechano-remodeling of the NL can have different outcomes: osteogenic differentiation is promoted by a stiff environment accompanied by higher lamin A/C levels that mediate chromatin remodeling at osteogenesis-related genes [48]. These findings suggest that similar mechano-sensing stimuli can modulate the genome function differently and that NL represents the key intermediary along this axis. Corroborating these observations, mechanical stress induced by stretching favors skin expansion in mice, epigenetically promoting stem cell renewal while not affecting the commitment toward epidermal differentiation [49]. In a more complex scenario, the extracellular matrix composition regulates the polyclonal activation and the epigenetic diversification of local fibroblasts contributing to wound healing during regenerative post-injury processes [50]. The profibrotic activity of myofibroblasts, necessary for scarring, is stimulated by the mechanical stress that, inducing nuclear softening and loss of the H3K9me3 mark, enables a permissive state of profibrotic genes [51]. In the latter study, atomic force microscopy, used to measure nuclei stiffness, clarified that activated myofibroblasts induced by mechanical stress display increasing expression levels of both lamin A and lamin B associated with a decrease in nuclear stiffness [51]. On the other hand, mutants of actomyosin signaling that show dysregulation of the mechanical signaling and impairment in myofibroblast activation have stiff nuclei and higher lamin B levels. Together, these findings suggest that increasing levels of lamin A provide elasticity and nuclear softening during cell activation, which is necessary for chromatin remodeling and the initiation of mechano-sensing-dependent genes expression.

Lamin A dynamics are also required during cell reprogramming toward undifferentiated states [52]. Similar to cell activation, this process requires a profound remodeling of the epigenome that leads to the activation of several genes, such as cell cycle-related genes and stemness genes [53]. Accordingly, genome reprogramming passes through a decrease of heterochromatin domains that precedes an increase in genome accessibility [54,55]. Cyclic stretching of fibroblasts enhances cell reprogramming and the production of induced pluripotent stem cells (iPSCs), which is in line with and further corroborates the hypothesis that extracellular stiffness induces nuclear softening [56]. Other studies performed on induced neuronal (iN) reprogramming showed a different scenario. Reduction in actin cytoskeletal tension and cell adhesion in early reprogramming phases are required to accomplish the heterochromatin release and accessibility increase [57]. Apparently, in contrast with findings obtained in differentiation models, this evidence reveals a more complex network of extra-cellular and intracellular interplay. It suggests that epigenome remodeling, and mechanosensing mechanisms are tightly connected and depend on the cell identity to be acquired. More recently, other mechanisms of cell mechano-programming have been elucidated, pointing to the notion that post-translational modifications of lamins may influence several biological processes such as genome stability, cell cycle, and cell identity choice [58]. Studies executed in two different human models, mesenchymal stem cells and epithelial cells, showed that an increased extracellular matrix rigidity leads to dephosphorylation of lamin A/C protein [59,60]. The balance between distinct phosphorylated forms of lamin A/C and how they influence the epigenetic mechanisms is still under investigation.

Nuclear actin in chromatin regulation

Actin, a cytoskeleton component, is a versatile molecule that plays a central role in all mechanotransduction events [11]. It can be found as a single, globular unit (G actin) or as a chain constituting the so-called filamentous actin (F-actin) (detailed in Ref. [61]). A variety of actin-binding proteins orchestrate these transitions and are differently involved in initiating new filaments (such as ARP2/3, Spire, and formins), linking or holding filaments in bundles (such as fimbrin, filamin, villin, and α-actinin), and modulating the formation or breakdown of filaments (such as profilin, ADF/cofilin, gelsolin, and others) [62]. Previously identified and studied in the cytoplasm, the actin nuclear fraction has gained increasing interest for its involvement in chromatin regulation. Monomeric actin pool appears to constantly shuttle between the nucleus and cytoplasm in a regulated fashion, through an importin 9- (complexed with cofilin) and exportin 6- (complexed with profilin) dependent manner [63,64]. This behavior suggests the need to regulate the balance of the protein within the two compartments [65].

Moreover, nuclear actin assembly can be quickly reorganized, with filament formation observed in fibroblast nuclei within 20 s of serum stimulation [66]. Recent studies further support the dynamic nature of the polymerization and depolymerization cycle in the two cytoplasm and nuclear cell compartments [67]. During the first step of embryos' development, increasing actomyosin contractile forces at the apical cortex determines an increase of lamin A and a cascade of events that lead to trophectoderm specification. However, during this process, the rapid internalization of cells and concomitant lamin A decrease shift the actin nucleators from the nucleus to the cytoplasm, promoting the formation of a different lineage constituting the inner cell mass (ICM). These data, linking the actomyosin forces, the nuclear lamina, and lineage specification, strongly suggest that a fine regulation of actin organization in the nucleus and cytoplasm is essential for correct cell identity determination and maintenance.

Nuclear actin, in both monomeric or polymeric form, can display distinct functional roles [65], participating in multiple processes such as transcription [68–70], mRNA processing [71], and chromatin remodeling as part of complexes including SWI/SNF [72], SWR1, and INO80 [73,74]. Direct binding of actin on chromatin have been addressed by chromatin immunoprecipitation–sequencing (ChIP-seq) experiments in mammalian and *Drosophila* genomes [75,76]. These studies suggested that the role of β-actin is to preserve active epigenetic marks on transcriptionally activated genes through the recruitment of DNA remodeling complexes.

Although the complete view and mechanistic implications of these events need further investigation, a common theme so far for the role of nuclear actin seems to be related to the organization of nuclear content, maintenance of genomic integrity, repositioning of nuclear organelles and chromosomes to bring genomic regions to transcription-permissive locations [65]. In line with this hypothesis, various actin filaments of different lengths and distribution patterns within the cell nucleus are also observed upon DNA damage induced by various genotoxic agents [77]. These elongated, nucleoplasmic, clustered, or peri- and intra-nucleolar actin filaments promote the clearance of double-strand DNA breaks (DSB), thanks to the presence of the MRN complex, the nuclear actin organizer Formin 2 (FMN2) and the LINC complex [77]. Further studies on chromatin conformation suggested that actin polymerization per se governs the DSB clustering and facilitates DSB mobility to nuclear regions where DSB can be repaired [78–81].

In the last few years, studies on differentiation and reprogramming have suggested the role of actin in regulating distinct levels of genome architecture [82,83]. One example of such regulation is given by the counteracting actions between BRG1, a key ATPase

component of the mammalian BRG1 associated factor (BAF) complex and the epigenetic repressors polycomb group of proteins (PcG) [40]. The interplay between BAF and PcG offers a mechanism of epigenetic flexibility, which is crucial for the modulation of chromatin states in key developmental genomic loci.

Notably, BRG1 relies on β-actin to enhance its ATPase function [72]. The β-actin knockout and concomitant disruption of BRG1-β-actin complex causes a broad change in genomic accessibility, particularly a decrease in regulatory regions of genes governing cell-fate determination and neuron differentiation and, simultaneously, an increase in the accessibility of enhancers of genes implicated in the development of the skeletal system, vasculature, and blood vessels [84]. These gene-specific alterations may be due to the dysfunction of the interplay between BRG1 and repressive chromatin remodeling complexes as the polycomb group of proteins caused by β-actin's absence [82]. Although increasing evidence describes the involvement of actin in genome regulation, its direct action on chromatin upon mechanical stimuli is still an open question in the field. Interestingly, it has been reported in mouse immortalized fibroblasts that integrin signaling during the process of cell spreading induces, through the LINC complex, nuclear actin polymerization and the activation of the serum response factor (SRF)-mediated transcription program [85]. The induction of the actin network within the nucleus also causes the release of the inhibitory binding of monomeric actin to the SRF co-activator and actin-binding protein MRTF-A, enabling SRF-mediated transcription.

Epigenome mechano-dysfunction in disease

As a direct consequence of the interplay between the nucleus and the extracellular matrix, every pathological state accompanied by cell environment changes, in principle, might determine chromatin dysfunctions. This has been extensively analyzed in cancer research, where the abnormal remodeling of the extracellular matrix is crucial in determining tumor growth, survival, and propagation [86–88], even independently on YAP pathway [89]. However, one of the open questions in the field regards the opposite process: is a stiffness-reprogrammed epigenome capable of changing the extracellular environment? The observation that the polycomb Ezh2 protein can post-transcriptionally induce intranuclear actin bundles formation intertwined with the chromatin fibers provided a proof-of-concept that the epigenetic machinery can indeed exploit the dynamic mechanical forces of the intranuclear actin skeleton to remodel chromatin during differentiation [90]. In another work, Watson and colleagues interestingly reported that the stiffness-induced cell phenotype responsible for metastatization is maintained after cell migration and colonization [91]. This is due to a heritable chromatin reprogramming that preserves chromatin accessibility at specific gene loci. These works will trace the way for further studies to clarify how chromatin mechano-remodeling can influence the extracellular environment.

Another process tightly linked to mechanical stress is aging, in which epigenetic mechanisms are critically affected with drastic consequences in cell regeneration [92]. As recently reported, age-dependent mechano-dependent epigenetic chromatin remodeling affects the murine hair follicle stem cell niche [93]. Here, variation in the extracellular matrix composition leads to an increase in mechanical stress. However, on the opposite trend to normal conditions [46,49,50], an inhibition of cell differentiation with a consequent exhaustion of stem cells has been observed in old mice. Thus, similar stiffness in extracellular conditions leads to diverse output, mirroring the tissue's age. Molecularly, pathological repression of chromatin has been observed, primarily affecting bivalent genes [93]. Similar molecular dysfunction on polycomb-regulated bivalent genes has been described in lamin A mutant background [94,95]. Given its key role in premature senescence [96] and mechanotransduction, these data support the involvement of the nuclear lamina in non-pathological aging. Further studies to clarify these processes are crucial in implementing the use of different biomaterials in tissue engineering to promote the maintenance of stem-like properties and avoid premature senescence of the implanted tissues.

Conclusions and perspectives

How a cell perceives forces due to mechanical changes in its environment is a fascinating topic that has attracted the scientific community's interest in recent years. In particular, understanding how these pathways can influence gene expression in different cell types and situations is of great interest, both during normal cellular homeostasis and pathology. A complex picture emerges in which different elements and different regulatory pathways intertwine. The fine regulation of these events is recapitulated by the first steps of development, where the embryo is subjected to several mechanical stimuli leading to the crucial event of implantation [67]. How physical forces influence the development of functionally distinct cells and the signaling at embryo-maternal crosstalk are mostly unknown phenomena.

Moreover, increasing evidence described distinct cell fates triggered by similar external stimuli [46–48,54,56,57]. Elucidating at the genome-wide levels, the epigenetic mechanisms involved in the adaptation response can complete the picture by describing how the epigenome senses and translates multiple stimuli. The other open question in the field is

how the chromatin stiffness can affect the nuclear mechanics and cells' ability to apply forces to the environment. Stroma-epithelia crosstalk exemplifies how mechanical cues can affect cancer evolution [97]. Epithelial neoplastic cells constantly contact with and alter their surrounding stromal microenvironment. The dynamic process of tumor−stroma interactions plays a role in the mechanical feedback loop between external forces and the nucleus, influencing the tumor progression. Cell reactions to mechanical changes, if dependent on epigenetic mechanisms, could significantly vary from one patient to another. Recent advancements in new technologies, such as bio-fabrication and organoid generation, mimicking the natural environment of cell populations, will improve our knowledge of the mechanisms of crosstalk between the genome and the extracellular environment in different physiological and pathological models.

Authors contributions

Maria Vivo and Chiara Lanzuolo: Conceptualization and Writing − Original Draft; Valentina Rosti and Sara Cervone: Writing - Review & Editing.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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