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Reorganizing chromatin by cellular deformation

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Biologists have the capability to edit a genome at the nanometer scale and then observe whether or not the edit affects the structure of a developing organ or organism at the centimeter scale. Our understanding of the underlying mechanisms driving this emergent phenomenon from a multiscale perspective remains incomplete. This review focuses predominantly on recent experimental developments in uncovering the mechanical interplay between the chromatin and cell scale since mechanics plays a major role in determining nuclear, cellular, and tissue structure. Here, we discuss the generation and transmission of forces through the cytoskeleton, affecting chromatin diffusivity and organization. Decoding such pieces of these multiscale connections lays the groundwork for solving the genotype-to-phenotype puzzle in biology.

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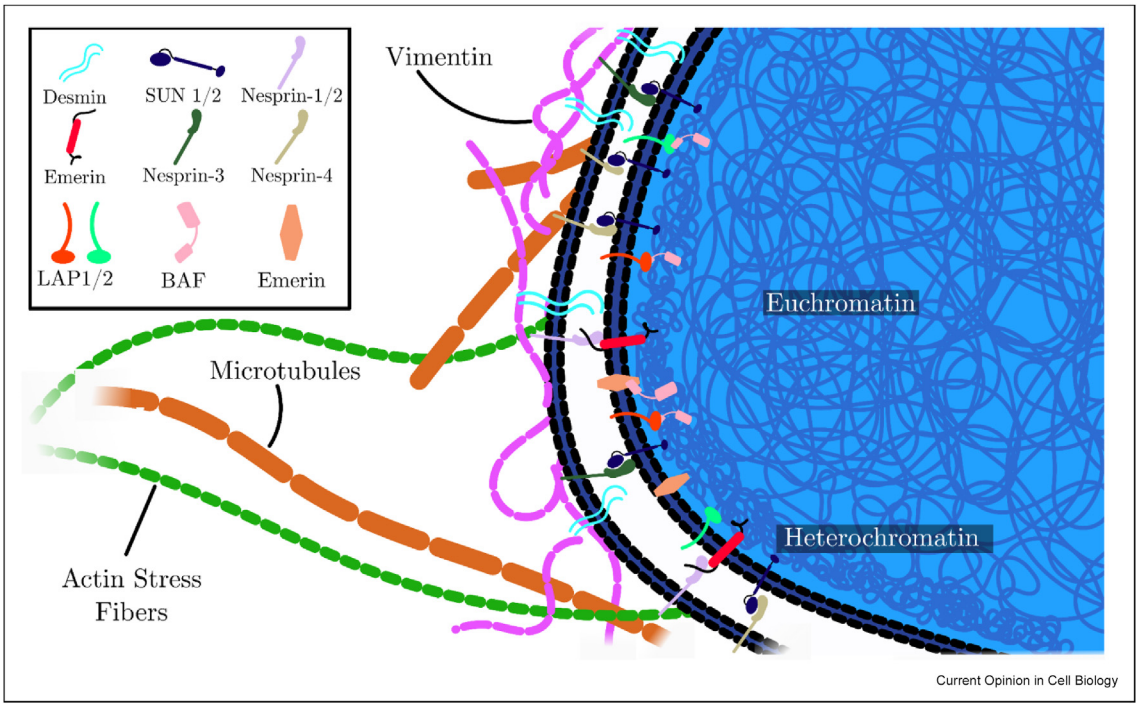
Introduction

Cells are fascinating learning machines, exhibiting remarkable adaptability to external stimuli while performing biological functions to maintain tissue homeostasis. This adaptability is governed by signaling pathways and their numerous feedback loops spanning the system across various spatial and temporal scales [1–3]. While traditionally most work has focused on how cells respond to chemical signals, cells also respond to mechanical signals that can affect their phenotype [1–3]. These mechanical signals can be transduced into biochemical signals by cells and perpetuate through cells acutely in ways that depend on their complex material properties. New work is therefore focusing on understanding questions, such as, how do cells adapt at the chromatin scale to mechanical stresses? Further, how does this adaptation differ between stationary and motile cells? To answer such questions, one must take a multitiered approach as mechanical stresses can be transmitted from the extracellular matrix and cell focal adhesions to the cytoskeleton and the nuclear envelope, ultimately leading to the reorganization of our chromatin.

Chromatin houses a cell's genome and exists in different forms, most notably heterochromatin and euchromatin. Heterochromatin is less transcriptionally active and denser, while euchromatin is more transcriptionally active and less dense. Heterochromatin is typically located near a thin underlying meshwork consisting of nuclear lamins, known as a lamina shell, surrounding the chromatin, while euchromatin is typically located near the core of the nucleus (Figure 1) [4]. Lamin-associated binding domains in DNA tether the chromatin to the lamina shell. Moreover, the nuclear envelope interacts with chromatin via multiple mechanical pathways through proteins, such as emerin, LAP1, and LAP2, and biochemical signaling. Understanding how these signaling pathways influence chromatin's physical and biochemical makeup is crucial to understanding multiple human pathologies, including progeria (HGPS), muscular dystrophy, and cancer [5,6].

The nuclear envelope provides a connection between chromatin and the cytoskeleton. The linker of the nucleo-skeleton and cytoskeleton (LINC) complex, in particular, establishes connections between cytoskeletal filaments and the nuclear envelope (Figure 1). Nesprin components, external to the nuclear envelope, link with the KASH domain in the outer nuclear membrane. Recent studies highlight the role of lamins in regulating cytoplasmic stiffness by tuning the dynamics of LINC complexes, connecting actin and vimentin [7–9]. F-actin and vimentin are connected to lamin A/C via LINC complexes containing nesprin 2g and nesprin 3α, respectively. The loss of lamin A/C increases the mobility of nesprin 2g and nesprin 3α, which impairs the coupling between the nucleus and actin and vimentin, leading to the softening of the cell cytoplasm and cortex. On the other hand, type B lamins (LB1 or LB2) are connected only to nesprin 3g, therefore loss of type B lamins increases the mobility of nesprin-3α, resulting in

Figure 1



LINC connects cytoskeleton and chromatin: Cytoskeleton architecture composed of microtubules, actin, and intermediate filaments, such as vimentin, has mechanical connections to the chromatin via LINC proteins. Nesprin family proteins establish a link between the outer nuclear membrane and cytoskeletal elements. On the inner nuclear membrane, Nesprin connects to emerin and SUN family proteins, which are attached to euchromatin. Furthermore, proteins like desmin relate the cytoskeleton to the outer nuclear membrane, and LAP1/2 forms bonds between the inner nuclear membrane and euchromatin via the BAF protein. Together, LINC proteins assist in transmitting mechanical signals from the cytoskeleton to the chromatin scale.

defective connections between the nucleus and vimentin and, thereby, a softer cytoplasm [7].

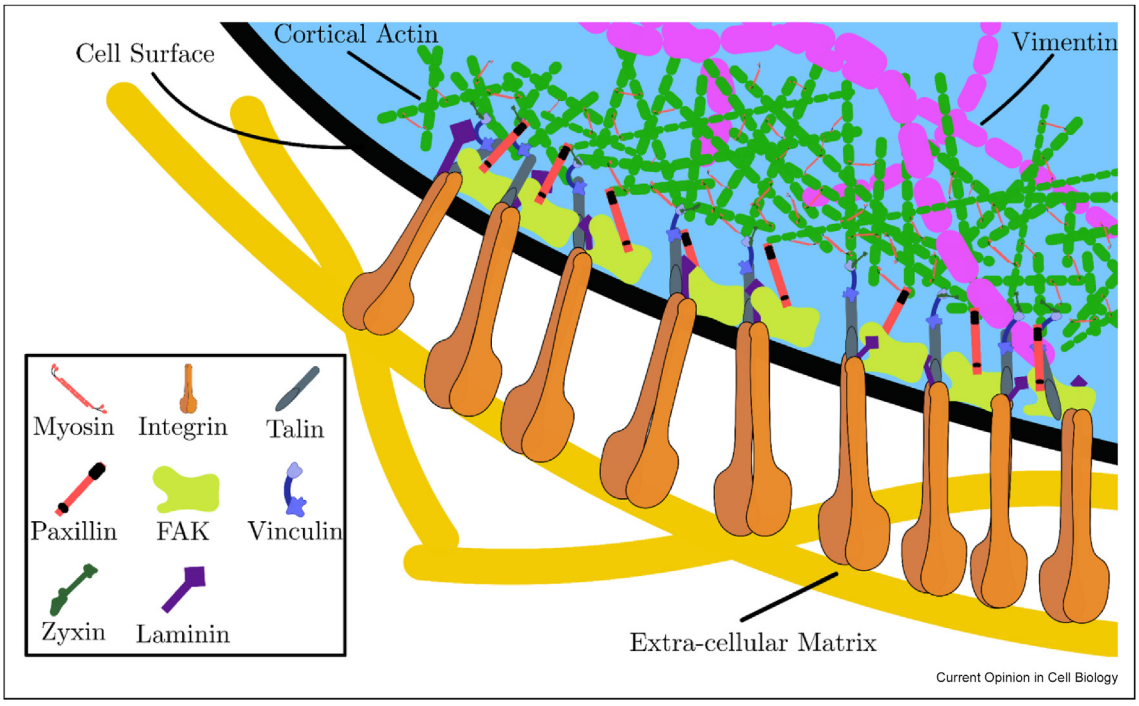
Integrins and cell focal adhesion complexes form the molecular linkages between the cell cytoskeleton and the extracellular environment by binding to extracellular matrix (ECM) ligands, such as collagen, fibronectin, and laminin (Figure 2). Focal adhesions are well known as a central component of cellular mechanosensing, the ability for cells to sense and respond to mechanical cues in their environment [10–12]. Recent studies are also revealing new feedback loops between focal adhesion and cytoskeletal mechanics regulated by mechano-sensitive signaling pathways. For instance, clocking mechanosensitive ion channels in 3T3 fibroblasts results in a loss of focal adhesion maturation and reduced cytoskeletal tensions [13]. Cells expressing truncated mutants of vinculin lose the correlation between applied external force and focal adhesion kinase (FAK), indicating a role for vinculin in mechanosensitive FAK mediation [14]. Furthermore, disruption of the vimentin cytoskeleton leads to an overexpression of β1 integrins, leading to a higher binding rate and higher adhesion strength to collagen-coated surfaces and indicating a role of the vimentin in β1 integrin trafficking [15].

Now that the connections between the players have been introduced, we focus on the latest achievements underlying the transmission of mechanical signals as they travel from the cell surface through the cytoskeleton and toward the nucleus and chromatin levels.

Focal adhesions and nuclear organization

New studies have revealed fresh insights into the connections between focal adhesions and force-dependent cytoskeletal and nuclear changes [12]. For example, a recent study by Rashid *et al.* showed that applying local exogenous forces on integrins via magnetic beads led to downstream changes in chromatin and nucleoplasm protein diffusivity in epithelial cells [16]. More specifically, chromatin and nucleoplasm protein diffusivity increase as the chromatin decondenses for up to 10 min after the applied forces cease. Another recent study by Carley *et al.* showed disrupting β1 integrins resulted in a significant loss of tension in the nucleo-skeleton and cytoskeleton (LINC) complex, indicating faulty force transmission to the nuclei and impacting epidermal differential in an *in vivo* mouse model [12]. During epidermal differentiation, the chromosome region housing the epidermal differentiation complex moves away from the nuclear lamina suggesting that the

Figure 2



Focal adhesions form cell surface-ECM and cell-cell surface connections: Cell's cytoskeleton elements such as cortical actin and vimentin with multiple inter and intra-cellular proteins make focal adhesion complex. Integrin plays a central role in this process, linking the ECM and the internal cell surface through proteins like FAK and talin. Additionally, proteins like paxillin and vinculin serve as anchors, connecting integrins to other structural proteins like zyxin and laminin. Finally, these protein complexes have links with cortical actin and vimentin to create mechanical bridges that allow the cell to respond to external forces and maintain structural integrity.

stretching of lamins may help drive this nuclear reorganization [17].

Integrins and focal adhesion proteins are linked to Yes-associated protein (YAP) transcription factors, mechanosensitive molecules located in the cytoplasm that when activated, translocate to the nucleus to trigger the transcription of different genes [18]. For example, knocking down zyxin, a focal adhesion protein and actin linker, diminishes YAP nuclear translocation in mesenchymal stem cells undergoing stretch. Inhibiting FAK activity impairs actin recovery after periods of anisotropic stretching of cells through zyxin-mediated processes [19]. How diminishing YAP nuclear translocation modifies gene expression is not yet clear, though it has been linked with DNA damage and nuclear envelope rupture [20]. A recent study using MCF10A breast cancer cells found that laminin-specific $\beta 4$ integrins establish linkages with keratin intermediate filaments, which, in turn, shield nuclear deformations and reduce nuclear YAP localization [21]. Another study by Seetharaman *et al.* showed microtubule acetylation tunes the mechanosensitivity of focal adhesion proteins and YAP translocation [22]. A new approach to determine molecular forces for focal adhesion maturation and YAP nucleation has been developed by Chien, Chou, and Lee using RGD-peptide conjugated DNA tension gauge tethers. These sensors allowed the determination of a threshold for YAP nuclear localization of 50–53 pN and a cut-off for focal adhesion maturation of approximately 40 pN [23]. Combining this technique with super-resolution microscopy allows detailed measurements between focal adhesion complex proteins and actin cytoskeletal elements. This has important implications for the generation and transmission of force from the cell surface to the nuclear envelope, which can potentially lead to changes in chromatin organization [24,25].

Taken together, these results highlight the effect that integrin and focal adhesion complex protein expression can have on global cytoskeletal and nuclear mechanical states.

Cytoskeletal influence on nuclear morphology and mechanics

The cellular cytoskeleton serves as a conduit for transmitting mechanical forces from the cell plasma membrane to the nucleus [4,24,26]. As cells spread, their nuclei typically morph from a balled-up, wrinkled raisin

shape to a smoother taut nucleus, which has been pulled and pushed on by cytoskeletal forces [27,28]. Microtubules, the stiffest cytoskeletal filament, can also prod the nucleus and form deep invaginations [29,30]. These invaginations and wrinkles can impact chromatin by reducing chromatin accessibility for transcription by increasing chromatin condensation [31]. Similarly, in oocytes, cytoplasmic forces have been shown to reorganize nuclear condensates [32].

New studies are also highlighting the role of cytoskeletal intermediate filaments, particularly vimentin, in nuclear positioning and deformability [21,33–36], although the precise mechanisms remain unclear. Recent *in vitro* studies show that the mechanical behavior of vimentin is different from networks of F-actin and microtubules under compressive loading, which is physiologically relevant to the dense environment of real tissue. Specifically, vimentin networks stiffen under applied compression, whereas networks of F-actin and microtubules soften, suggesting an increased role of vimentin in supporting forces under compressive loading conditions [35]. Further, AFM studies showed fibroblasts stiffen under large uniaxial compression, but the loss of vimentin significantly diminished the mechanical response that correlated with significant nuclear damage and blebbing [35]. A recent study by Wang *et al*. showed that strong confinement in HeLa cells led to downregulation in nuclear lamin A/C and a decrease in vimentin, suggesting lamins and vimentin work together to regulate nuclear deformability [36]. In the context of cell migration, recent studies show loss of vimentin alters cell persistence, leading to abnormally persistent motion [33,37,38]. Computational modeling from our group predicts this abnormal, persistent motion arises from a decoupling of nuclear positioning and deformation from the cell shape and structure [38]. This reveals how cytoskeletal components assists cells in navigating through constrictions while also protecting the nucleus. How nuclear positioning and deformability affect chromatin organization in this setting is under current investigation [39].

Chromatin architecture and cell migration

Researchers have recently focused on how cell migration and chromatin architecture could influence each other [40–43]. During confined cell migration, nuclear deformation leads to "confined migration-induced heterochromatin" (CMiH), with increased heterochromatin marks and decreased chromatin accessibility impacting gene expression and other functions. On the other hand, preventing CMiH formation significantly increases migration time [41]. Another recent study shows a functional connection between chromatin organization and cell motility through the regulation of Golgi organization by the LINC complex. This work highlights that SUV49H1 depletion, a histone H3 lysine 9 methyltransferase, induces Golgi dispersion, leading to decreased directional cell migration. However, interference with SUN2, nesprin-2, or microtubule plus-end-directed kinesin-like protein KIF20A prevents this effect [42]. Another recent investigation shows that confining cells into microfluidic channels induces millisecond deformation of the cell nucleus. This leads to nuclear lamina wrinkling, transient disassembly, local detachment of lamina-associated domains in heterochromatin, and a reduction in histone methylation (specifically, histone H3 lysine 9 trimethylation) and DNA methylation [43]. These studies demonstrate that changes in chromatin architecture could influence a cell's global behavior through multiple pathways.

Chromatin architecture and cell mechanics

Another recent direction of inquiry investigates the role of intracellular stresses on chromatin, such as cytoskeleton-chromatin interactions via the nuclear surface. Recent work indicates that SUN2 reacts to actomyosin contractility by moving bidirectionally between the endoplasmic reticulum (ER) and the nuclear membrane. This mechanotransduction role of SUN2 plays a part in perinuclear gene transcription. By creating three cell lines with distinct modifications—SUN2 knockout, Lamin-A non-binding, and Actin cytoskeleton non-binding—the study reveals that disrupting SUN2 causes H3K9me3 to be uniformly distributed, contrasting with the perinuclear localization seen in the wild-type distribution [8]. Another cytoskeleton-chromatin interaction study showed that maintaining a balance between dynamic microtubules and desmin intermediate filaments is crucial for preserving the nuclear shape and the integrity of the nuclear envelope and lamina. Depletion of desmin or its binding partner nesprin-3 in the LINC complex leads to severe consequences, including nuclear collapse, infoldings of the nuclear membrane, DNA damage, loss of genome organization, and significant transcriptional changes. This collapse in nuclear integrity is associated with compromised contractile function, potentially contributing to the pathophysiological alterations observed in desmin-related myopathies [29]. Nesprin-2 also affects the actin cytoskeleton organization. Studies in nesprin2 knockout keratinocytes showed disrupting nesprin-2 leads to less α-smooth muscle actin, altered microtubule organization, and a non-uniform distribution of H3K9Me3 [9].

Not only intracellular and extracellular stresses but also intranuclear stresses could lead to changes in chromatin and nuclear surface dynamics; for example, abnormal nuclear membrane shape could be induced due to internal nuclear dynamics, including transcription factor activity. Recent work shows that the inhibition of RNA Pol II could lead to a decrease in nuclear bleb formation without altering the usual blebbing factors, including

nuclear rigidity, actin compression, and histone H3 lysine 9 modification state [44]. Nuclear blebs may then impact cytoskeletal reorganization. Such a finding reminds us that there is indeed feedback between chromatin architecture and cell mechanics thereby complexifying the chromatin-cell relationship.

Future perspective on the tissue-to-chromatin organization relationship

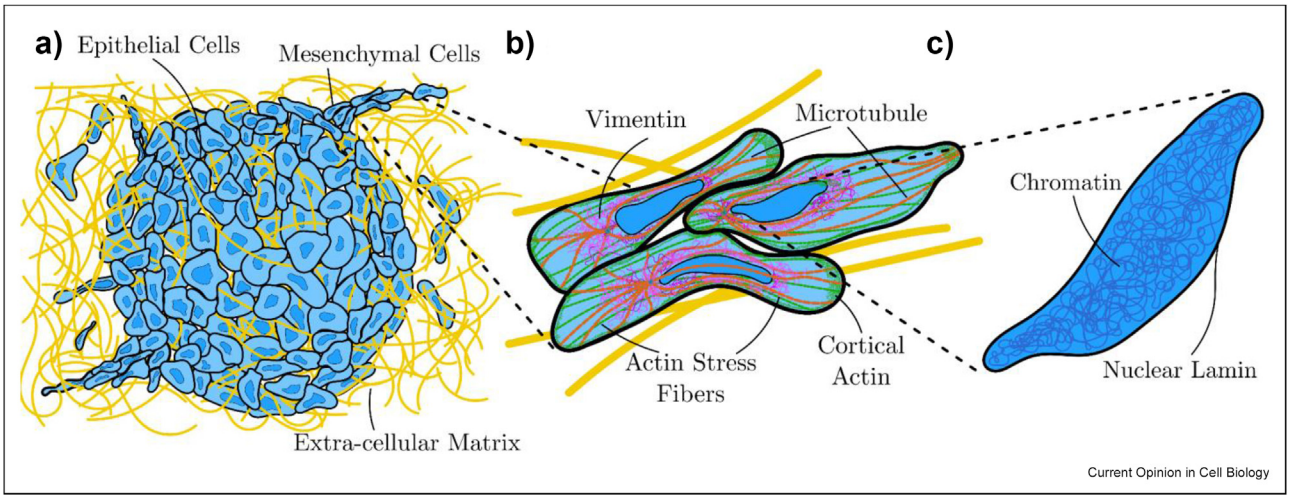
While we have focused on mechanical stresses as applied to individual cells and the potential downstream effects on the chromatin scale (Figure 3), researchers have begun to link stresses applied externally to tissues with the chromatin scale. Recent studies are revealing how these bulk tissue deformations can trigger molecular changes in DNA, such as the accessibility of different chromatin domains [20,45]. Moreover, mechanical tissue stress can be generated during different development stages as bulk tissues grow, fold, wrinkle, and invaginate [46–49]. Understanding how chromatin responds to mechanical cues at the tissue or cellular level and vice-versa can offer key insights into biological phenomena such as organogenesis, cell differentiation, and tissue homeostasis. Moreover, as many diseases, such as cancers and fibrosis, are linked with increased matrix tension [50,51], this understanding could help reveal relevant molecular targets for therapeutic applications.

Understanding of multicellular tissue requires multiscale approaches to help glean how a gene or protein impacts biological forms and functions and vice versa. A number of new studies are emerging to solve this puzzle and bridge scales between genes, nuclei, and cells to multicellular structures [52–54]. One interesting example is in the context of cancerous tissue fluidization, marked by the ability of cancerous cells to move and divide in dense tissue. A study by Grosser *et al.* showed that the degree of fluidity in 3D multicellular tissues correlates with elongated cell shapes in the tissue and that this correlation scales with the cell nucleus, where much stretch and elongation allows cells to move past one another [52]. Frittoli *et al.* further showed how cells adapt to tissue fluidization and its accompanying repeated mechanical deformations of cells and nuclei [53]. In particular, the investigators found that fluidization-induced tissue forces result in increases in nuclear size and rigidity, heterochromatin distribution, and remodeling of the actin network. Increased tissue strains could result in higher DNA damage and nuclear envelope rupture that triggers a long-term cGAS–STING-mediated, transcriptional-dependent phenotype switch in invasive breast carcinoma.

Conclusions

Recent work makes it clear that cellular-level forces and deformation modify chromatin organization. As living tissues are organized in a multi-tiered fashion with cells nested in tissues, nuclei nested in cells, and chromatin nested in nuclei, a link between tissue-level forces and chromatin organization is also beginning to emerge.

Figure 3



Multiscale organization of cells and tissue. **a)** Model multicellular spheroid embedded in the extracellular matrix (ECM). During the epithelial-to-mesenchymal transition, non-polar epithelial cells lose their cell-cell contacts and shift to a polarized motile mesenchymal phenotype, capable of invading surrounding ECM. **b)** At the cell level, mechanics is strongly impacted by the structure and composition of the ECM, the cell nucleus, and the cytoskeleton network, consisting of actin, microtubules, and intermediate filaments, such as vimentin. **c)** Zooming in on the cell nucleus, its structure is dominated by chromatin organization and the nuclear envelope, which is intertwined from the inside with the nuclear lamina - a mesh-like scaffold for the nuclear envelope and links to domains of DNA - and connected on the outside with the cytoskeleton, via the linker of the nucleo-skeleton and cytoskeleton (LINC) complex.

Identifying the key mechanical linkages that connect tissue and cell scales to nuclear and protein scales, and how biochemical signaling pathways regulate those linkages, will require continued efforts from many multidisciplinary teams.

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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