

REVIEW

Emerging roles of mechanical forces in chromatin regulation

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ABSTRACT

Cells are constantly subjected to a spectrum of mechanical cues, such as shear stress, compression, differential tissue rigidity and strain, to which they adapt by engaging mechanisms of mechanotransduction. While the central role of cell adhesion receptors in this process is established, it has only recently been appreciated that mechanical cues reach far beyond the plasma membrane and the cytoskeleton, and are directly transmitted to the nucleus. Furthermore, changes in the mechanical properties of the perinuclear cytoskeleton, nuclear lamina and chromatin are critical for cellular responses and adaptation to external mechanical cues. In that respect, dynamic changes in the nuclear lamina and the surrounding cytoskeleton modify mechanical properties of the nucleus, thereby protecting genetic material from damage. The importance of this mechanism is highlighted by debilitating genetic diseases, termed laminopathies, that result from impaired mechanoresistance of the nuclear lamina. What has been less evident, and represents one of the exciting emerging concepts, is that chromatin itself is an active rheological element of the nucleus, which undergoes dynamic changes upon application of force, thereby facilitating cellular adaptation to differential force environments. This Review aims to highlight these emerging concepts by discussing the latest literature in this area and by proposing an integrative model of cytoskeletal and chromatin-mediated responses to mechanical stress.

KEY WORDS: Mechanotransduction, Nucleus, Nuclear lamina, Nucleoskeleton, Nuclear mechanical response

Introduction

Cells are constantly exposed to dynamic changes in their physical microenvironment; these require biochemical rewiring and physical reshaping of all cellular compartments on both short (seconds to minutes) and long (hours to days) time scales. In that respect, in addition to harboring most of the genetic material of the cells, the nucleus is the largest and stiffest stable intercellular structure (Booth-Gauthier et al., 2012; Dahl et al., 2004; Dunder and Misteli, 2001; Misteli et al., 2007). Owing to its stiffness, the nucleus in particular needs to be able to sense and respond rapidly to changes in mechanical forces, and recent work has begun to unravel the molecular mechanisms and physiological consequences of these responses.

The nucleus is enclosed by a fluid-like nuclear envelope (NE), which is composed of the inner nuclear membrane (INM) and the

outer nuclear membrane (ONM) with embedded nuclear pore complexes. The NE encapsulates an assembly of fibrillary intermediate filaments, the lamins, which lie below the INM and serve as main structural components of the NE (Belaadi et al., 2016; Isermann and Lammerding, 2013). The lamins interact and are functionally supported by other cytoskeletal proteins, such as an array of actin monomers and polymers, myosin and kinesin motors, titin, nuclear mitotic apparatus (NuMA) and others (Simon and Wilson, 2011). This filamentous, insoluble component of the nucleus is collectively termed the nucleoskeleton (Dahl and Kalinowski, 2011) (see the glossary in Box 1). Importantly, the nucleus is mechanically tethered to the extracellular environment through linker of nucleoskeleton and cytoskeleton complex proteins (LINC proteins), most notably the SUN proteins and nesprins (Crisp et al., 2006), which are anchored within the INM and the ONM, respectively, and are able to bind the contractile cytoskeleton interacting with the extracellular matrix or neighboring cells via adhesion complexes (Belaadi et al., 2016; Heo et al., 2016a; Martins et al., 2012). Thereby the NE is directly physically linked to the contractile cytoskeleton. For more detailed information on the structure of the NE, please refer to some recent reviews on this topic (Cho et al., 2017; Ungrecht and Kutay, 2017).

Agreeing with the above, and much like the plasma membrane, the NE not only serves a critical compartmentalization function but is also a highly dynamic force-sensing barrier. This is partially due to it harboring the LINC (Cho et al., 2017) and associated mechanosensing proteins such as the LEM family protein emerlin (Guilluy et al., 2014; Le et al., 2016), but also because of the adaptable mechanical properties of the nuclear lamina proteins themselves (Denais et al., 2016; Thiam et al., 2016). The nuclear lamina is a deformable solid elastic shell (Rowat et al., 2006) and is therefore an ideal structure to exert the mechanoadaptation and mechanoresponsive functions of the nucleus that are capable of buffering mechanical stimuli arising from both inside and outside the nucleus. This buffering is required to coordinate the compressive gel-like properties of the inner nuclear components (Rowat et al., 2006) with the stiff nucleoskeleton (Kumar et al., 2014; Simon and Wilson, 2011).

Deeper within the nucleus, beyond the NE and nuclear lamins, lies the cellular genetic material in a form of chromatin, a complex of DNA and histones. The degree of DNA packing around histones determines the ease of transcriptional availability of DNA. When not actively transcribed, DNA is in a tightly packed heterochromatin state, whereas when it is loosely packed and available to the transcriptional machinery, it is termed euchromatin. Chromatin remodeling by a spectrum of post-translational modifications, such as methylation and acetylation, allows shifts between the two states, and this process is highly implicated in epigenetic regulation of cellular fate (Laugesen and Helin, 2014; Tessarz and Kouzarides, 2014). Interestingly, although seemingly disconnected from the outer structural components of the nucleus and rather embedded within the liquid-like nucleoplasm, chromatin in its heterochromatin state is intimately physically linked to the NE though the

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Box 1. Glossary

Nucleoskeleton: also known as the nuclear matrix, refers to the filamentous, non-soluble component of the nucleus. It is primarily composed of intermediate type V filaments, which consist of lamin proteins, but also contains myosins, actin, spectrins and kinesins. Cytoplasmic cytoskeletal filaments are interconnected and linked to the nucleoskeleton through proteins of the LINC complex.

A fluid: a substance that continually deforms (flows) under an applied shear stress (i.e. parallel with the direction of flow).

Viscosity: a measure of the resistance of a fluid to flow. A fluid with a high viscosity resists motion and strains over time in response to stress.

Stiffness: the rigidity of an object, the extent to which it resists deformation in response to an applied force.

Elasticity: the ability of a material to resist a deforming force and to return to its original size and shape when that force is removed.

Viscoelasticity: is the property of materials that exhibit both viscous and elastic characteristics when undergoing deformation. Biological materials as well as synthetic polymers display significant viscoelastic effects. Owing to their viscosity, viscoelastic materials have a strain rate that is dependent on time. Viscoelastic materials dissipate energy when a load is applied and subsequently removed whereas a purely elastic material does not.

Rheology: describes the deformation and flow of materials and substances that have a complex microstructure (e.g. polymers, body fluids and other biological materials) under force.

Reynolds number: is the ratio of inertial to viscous forces, typically used to describe fluid flow patterns. At low Reynolds numbers, where viscous forces are dominant, laminar (smooth, constant) fluid motion occurs, whereas at high Reynolds numbers where inertial forces dominate, flows are turbulent.

lamin-associated chromatin domains (LADs) (Lemaître and Bickmore, 2015). Furthermore, heterochromatin is quite dynamic and undergoes many topological changes, especially in the replicating and condensing chromosomes, and is therefore itself a major source of internal mechanical stimulation for the nucleus (Kumar et al., 2014). Moreover, in fact, although it globally may behave like a liquid (Belaadi et al., 2016), relaxation and torsional rearrangement of the various heterochromatin elements over smaller lengths can potentially dissipate mechanical energy that could otherwise damage the genetic material (Kumar et al., 2014). Thus, by virtue of being an internal mechanical stimulus, as well as a force-absorbing element, chromatin appears to be an active mechanosensor and mechanoresponder in the nucleus along with the nuclear lamina and nuclear/perinuclear actins. This review will discuss the mechanisms by which force is sensed and dissipated within the nucleus and its components, especially the chromatin, and the functional consequences of these mechanical forces on cell physiology and disease.

Mechanical stress responses at the nuclear lamina – chromatin interface

The thin, filamentous meshwork of nuclear lamins is remarkably different from other cytoskeletal assemblies (Turgay et al., 2017), and this unique structure, together with dynamic changes in the different isoforms and their levels, most likely facilitates the ability of the lamina to bear and adapt to a wide range of mechanical insults. Rheological changes in the A-type lamins, which are encoded by the *LMNA* gene (lamins A/C), accommodate cellular needs for plastic deformation of the nucleus. These include changes in expression, phosphorylation and even mechanical unfolding (Cho et al., 2017). Such rheological changes facilitate the scaling of nuclear mechanics with inherent tissue mechanics to ensure correct tissue-specific function (Swift et al., 2013), promote nuclear

stiffening during mesenchymal stem cell differentiation to induce the differentiation gene expression program (Heo et al., 2016a), or induce nuclear softening during cellular migration through confined environments (Cao et al., 2016; Denais et al., 2016; Skau et al., 2016; Thiam et al., 2016) to ensure successful passage through narrow three-dimensional (3D) spaces while maintaining genetic integrity (Fig. 1). Both the force-bearing function of the lamina as well as its ability to undergo rheological changes are essential for proper cellular function, as depletion of the lamina leads to the inability of a cell to resist mechanical stress imposed by physical constraints and mechanical stimulations, resulting in NE rupture and cell death (Harada et al., 2014). Impressively, in addition to providing an elastic nuclear lamina shell that is able to bear mechanical load by modifying its own rheology (see glossary in Box 1), lamin A/C also dissipates mechanical stress through modifying the molecular dynamics of the genome within the nucleus by differentially interacting with the genetic material under load (Bronstein et al., 2015). This function requires intricate controls, as even incremental modifications to global organization and differential packaging of specific genetic regions are likely to profoundly impact on gene activity and thereby alter the cellular state (Pombo and Dillon, 2015).

Another critical component that is intimately implicated in mechanics-induced reorganization of nuclear and chromatin state is actin. Recent studies have begun to decipher the biophysical role of nuclear actin in maintaining nuclear integrity. Using *Xenopus laevis* oocytes as a model system, in which gravity plays a dominant role due to the large size of the cells (>1 mm) and the nuclei (which are ~400 µm and typically referred to as germinal vesicles), Feric et al. demonstrated that nuclear actin provides a viscoelastic mesh (see glossary in Box 1) that stabilizes and supports the emulsion of liquid-like nuclear bodies and ribonucleoprotein droplets (including nucleoli and histone locus bodies) that would otherwise sediment, aggregate and fuse owing to gravitational creep (Feric and Brangwynne, 2013; Feric et al., 2015). Although gravitational stress can be typically neglected for a majority of eukaryotic cells, which have a size of ~10 µm with low Reynolds numbers (indicative of smooth, constant fluid motion; see glossary in Box 1) and of relatively homogenous density, this work demonstrates the scalability and adaptability of cytoskeletal structures within and around the nucleus. In accordance with this idea, it has been shown that short actin filaments are able to assemble into scaffolds that form a viscoelastic mesh in the nucleoplasm to organize nuclear content (Belin et al., 2013). Again, the ability to guide and organize genetic material within the nucleus, especially in response to extracellular cues, implies that nuclear actin has a strong instructional role in mediating nuclear mechanosensing and mechanotransduction.

Indeed, a number of recent studies have expanded the role of nuclear actin beyond that of the non-polymeric form, which is a critical co-factor for a number of transcription factors (Grosse and Vartiainen, 2013; Treisman, 2013; Virtanen and Vartiainen, 2017). Importantly, we recently found that cell-extrinsic force, acting through nuclear actin is directly implicated in modifying chromatin organization (Le et al., 2016). Specifically, we have shown that mechanical strain is transmitted directly to the chromatin through the formation of a perinuclear actin ring with the aid of non-muscle myosin IIA (NMIIA) and emerin, which accumulate around the nucleus to facilitate F-actin polymerization upon mechanical strain, thereby establishing a nuclear mechanosensing role for the actin–NMIIA–emerin complex (Le et al., 2016). Interestingly, in parallel, emerin decreased its association with lamin A/C, pointing to a force-decoupling of these two structures (Le et al., 2016). These

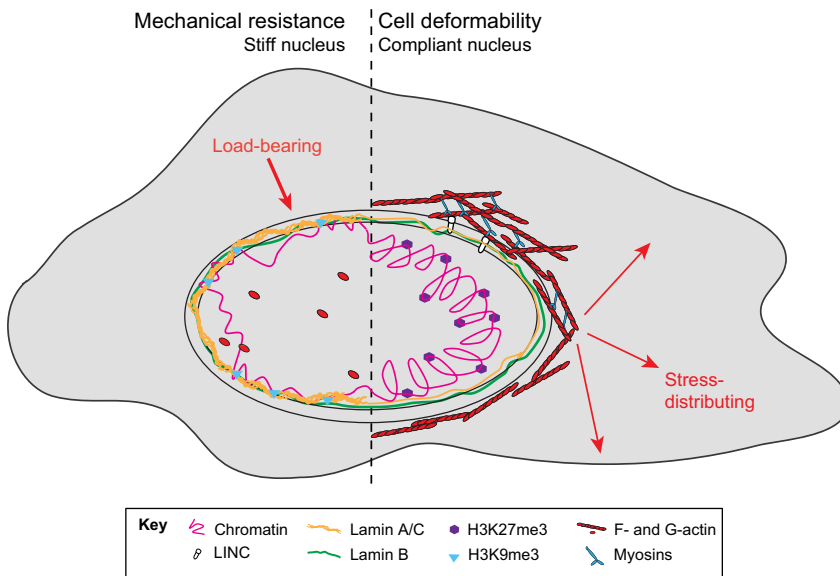


Fig. 1. Rheological adaptation of the nucleus and regulation of perinuclear actin, lamins and chromatin. Illustrated here is a schematic model that places the nucleus as a rheological element of the cell that is able to serve both a load-bearing function to support structural integrity of the genetic material through a stiff, lamin A/C-rich nuclear meshwork (left), as well as, in the case of mechanical deformation of the cell and the nucleus, a stress-dissipating function that is mediated by transducing mechanical stress to the contractile cytoskeleton through the LINC proteins and perinuclear actin ring (right). Recent experimental evidence also indicates that the lamin A/C-rich regions of the nuclear periphery promote the establishment of lamina-associated, constitutive heterochromatin exhibiting the H3K9me3 histone mark, whereas perinuclear actin-rich nuclear domains coincides with a switch of chromatin to a more loosely packed, lamina-disassociated state as indicated but the presence of the permissive H3K27me3 mark.

large-scale changes in perinuclear actin were accompanied by a reduction in the free nuclear G-actin pool, resulting in global transcriptional repression (Le et al., 2016). The precise molecular mechanism(s) by which nuclear actin regulates transcription remain open for further studies, but this work provides initial evidence for direct coupling of cytoskeletal and transcriptional states in response to mechanical strain.

Taken together, these data point to a dynamic structural dialog between nuclear/perinuclear actin and nuclear lamins in mediating the nuclear response to mechanical stress. The nuclear lamina provides reliable mechanical integrity and mechanical defense for the nucleus, yet it also reorganizes or even partially disassembles in response to mechanical challenge, such as when cells migrate through narrow pores or channels. These circumstances might favor actin-dependent mechanical adaptation and stress dissipation mechanisms (i.e. deformation) both in the cytoplasmic cytoskeleton, as well as the nucleus and the nucleoskeleton. Consistently, a number of recent studies have begun to decipher the mechanisms of such nuclear mechanoadaptation and cellular plasticity. It can thereby be envisioned that at the same time as the reorganization and/or disassembly of the stiff nuclear lamina occurs, perinuclear F-actin ring assembly increases nuclear compliance while still facilitating sufficient mechanical protection for genetic material. This is essential in cases of external mechanical stresses that require a high degree of cellular and nuclear deformation, as has been shown for both cancer and immune cells that migrate through complex microenvironments. One of the first indications that the stiff nuclear lamina was a barrier for migration came from studies in the hematopoietic lineage, where nucleated lineages that traffic into blood were shown to have lower lamin levels and higher nuclear compliance than bone marrow-resident cells, facilitating the migration of these cells through narrow pores (Shin et al., 2013). Intriguingly, recent studies have further observed nuclear rupture to be a frequent event during migration through constrained space, resulting in DNA damage at this site (Denais et al., 2016; Harada et al., 2014; Raab et al., 2016; Skau et al., 2016; Thiam et al., 2016). This damage could be further perpetuated by the mechanical exclusion of DNA repair proteins by virtue of their mobility from the site of nuclear constriction (Irianto et al., 2016). Consistent with this, a more elastic nucleus with perinuclear F-actin and reduced lamin A/C at the lamina protected cells from nuclear

rupture (Denais et al., 2016; Skau et al., 2016; Thiam et al., 2016). Interestingly, however, while high levels of lamin A/C clearly increased the frequency of nuclear envelope damage, lamin A/C-depleted cells show reduced survival in long term, highlighting the importance of this protein in facilitating DNA repair (Harada et al., 2014; Raab et al., 2016). On the other hand, the genomic instability caused by migration-induced nuclear deformation and DNA damage has been shown to promote cancer heterogeneity (Irianto et al., 2017a), establishing an interesting interplay between nuclear mechanics, genome integrity and phenotypic transformation. Taken together, although these studies implicate distinct perinuclear actin formation systems across a number of cellular types, they all point out the necessity to disassemble the stiff nuclear lamina in order to prevent nuclear rupture and DNA damage, further highlighting a critical role for the nucleus as an adaptive mechanical element of a cell (Fig. 1).

Chromatin as a rheological element of the cell and the nucleus

Although the nuclear lamina has an indisputably critical role in nuclear mechanics, both at the level of mechanosensing and mechanoresponding to external physical cues, it is important to acknowledge that the nucleus has in fact two components with distinct mechanical properties – the rigid elastic lamina and the more viscous nucleoplasm, which contains the viscoelastic nucleoskeleton and the viscous liquid-like chromatin. The stiffness of the nucleoplasm is of the order of a few tens to a hundreds pascals while that of the nuclear lamina is of the order of a few kilopascals (Martins et al., 2012). It has further become apparent that not only the global mechanical properties of chromatin, but also those that are specific for some components likely play a critical role in the transmission of forces from the mechanosensitive and tensed actomyosin cytoskeleton, which directly links to chromatin through the LINC complexes and the nucleoskeleton (Driscoll et al., 2015; Heo et al., 2016a,b; Martins et al., 2012).

One of the first indications that chromatin is a mechanical element of the nucleus came out of an investigation of the forces underlying kinetochore positioning and spindle-length control during cell division in yeast (Bouck and Bloom, 2007). During metaphase, after sister chromatids are aligned along the metaphase plate, spindle

length remains constant, indicating a balancing of inward and outward spindle forces. Intriguingly, a modification of chromatin packaging increased mitotic spindle length and kinetochore separation. Furthermore, the outward force exerted by the kinesins Cin8p and Kip1p was shown to be balanced by the stretching of pericentric chromatin, with the stretching of chromatin scaling proportionally to the applied force, indicating an elastic spring behavior of the chromatin (Bouck and Bloom, 2007). Therefore, in the context of the mitotic spindle, chromatin behaves as a mechanical spring that resists outward spindle forces. Accordingly, nuclear plasticity and deformation, especially in response to confined migration, has been a subject of much recent experimental and theoretical work, and it turns out that the mechanical properties of chromatin are also relevant in that context. For instance, a chemomechanical model describing the nucleus as an elastic shell (NE and lamins) with a soft poroelastic material (nucleoplasm) predicts that damage-free cell migration (i.e. free of irreversible nuclear deformations) through narrow pores is only possible in the presence of elastic and non-plastic chromatin (Cao et al., 2016). These findings place chromatin deformability at the center of the cellular ability to cope with spatially confined microenvironments.

Intriguingly, the application of mechanical force (fluid shear stress or compressive stress) elicits time- and magnitude-dependent alterations in subnuclear movements, the majority of which largely represent chromatin mobility (Booth-Gauthier et al., 2012). Importantly, the initial force response is independent of the magnitude of applied stress with only a minimal, anisotropic increase in intranuclear movement (stress response regime), while prolonged application of force (more than 30 min) provokes a magnitude-sensitive and directional increase in intranuclear movement, resulting in the repositioning of nuclear bodies and chromatin (Booth-Gauthier et al., 2012). These data provide evidence that cell extrinsic force directly modifies chromatin organization and mobility, and point to an extreme plasticity of chromatin as a rheological element of the nucleus. This is consistent with recent micropipette aspiration studies indicating that chromatin integrity is maintained over a tenfold elongation of the nucleus during alignment and stretching of the nucleus along the narrow dimension of a pore that a cell is migrating through (Irianto et al., 2017b).

It is thus clear that the mobility, deformability and architecture of chromatin, along with a restructuring of the lamin A/C network and modifications in nuclear and/or perinuclear actin, biophysically redistribute stress within the nucleus. Until recently, the question remained whether epigenetically driven spatial rearrangements within the nucleus and changes in its 3D structure itself correlate with the mechanical properties of chromatin. To that end, a recent study demonstrated a differential viscosity of heterochromatin and euchromatin by using the histone deacetylase inhibitor trichostatin A to decondense and sodium azide and 2-deoxyglucose to condense chromatin (Spagnol and Dahl, 2016). Specifically, the nuclear interior becomes more viscous and deformable upon decondensation of the tightly-packed heterochromatin (Chalut et al., 2012; Spagnol and Dahl, 2016). The mechanical changes of chromatin can be explained simply by changes in local chromatin concentration and the accompanying change in the chromatin-free nucleoplasm. As with any polymer, chromatin will stiffen when concentrated, and the local chromatin concentration relates directly to the amount of fluid-phase chromatin-free nucleoplasm at this site (Irianto et al., 2016; Pajeroski et al., 2007). Such alterations in the mechanical properties of chromatin lead us to hypothesize that

chromatin exerts a stress-absorbing function upon mechanical challenge. This is supported by our own observation that mechanical strain induces decondensation of the tightly packed H3K9me3-modified (me3 denotes trimethylation) heterochromatin into a more loosely packed H3K27me3-modified heterochromatin upon mechanical stimulation, which, moreover, is fully reversible (Le et al., 2016).

In the context of stem cells, pluripotent stem cells have little to no lamin A that becomes upregulated only during differentiation (Eckersley-Maslin et al., 2013; Röber et al., 1989). Upon differentiation (independent of the specific cue) the nucleus is transformed from a compliant strain sink capable of absorbing mechanical energy into a rigid stress concentrator owing to the redistribution of lamin A/C from the nucleoplasm to the NE and the increase in stiff heterochromatin (Heo et al., 2016a; Pajeroski et al., 2007). Interestingly, when transitioning from pluripotency to differentiation, nuclei of embryonic stem cells exhibit transient auxetic behavior, a distinct mechanical property characterized by a negative Poisson's ratio (the ratio of transverse strain to axial strain). Here, the nuclei either expand or contract perpendicular to the applied tensile or compressive load, respectively, accompanied by an increase in compression-induced stiffness. This behavior is driven at least in part by a transient chromatin decondensation, further highlighting the intimate but dynamic relationship between chromatin packing and nuclear mechanics (Pagliara et al., 2014).

Functionally, chromatin condensation results in gene silencing, while allowing the selective access of the transcription machinery to some lineage-specific and constitutively expressed genes within euchromatin, which makes sense in the context of differentiation. Yet, such nuclear rearrangements also have direct implications for the cellular response to mechanical cues. In the case of undifferentiated cells, upon mechanical perturbation, nuclear deformation occurs in tandem with cellular deformation, whereas in the differentiated state, the stiff nucleus fails to absorb the exerted mechanical stress and instead transfers it to the cytoskeletal-LINC-nucleoskeletal network, inducing its deformation (Heo et al., 2016a). However, it is interesting to note that some lineage-specific differences exist, and as pointed out earlier, certain cells such as nucleated, circulating blood cells maintain low lamin A levels facilitating their efficient migration (Shin et al., 2013). In this case, the lamin A levels further guide lineage specification, possibly through their ability to regulate gene activity, providing an efficient mechanism to couple nuclear elasticity and fate (Shin et al., 2013). Taking all these data into account, we propose a model where chromatin plays a central role in cell and nuclear mechanics as a viscoelastic rheological element of the nucleus that can dynamically adapt to altered mechanics by changing its own state (Fig. 2).

Force-mediated regulation of chromatin state and transcription

Shifts in gene expression patterns are critical for changes in cell fate or state. In that respect, a large body of work has highlighted the role of soluble factors in modulating cell plasticity. However, more recent findings have begun to dissect the independent role of physical cues on cell adaptation (Engler et al., 2006; Paszek et al., 2005).

Cell-intrinsic and -extrinsic mechanical forces not only induce cellular and nuclear deformation, but also alter gene expression through mechanosensitive transcription factors, most notably the actin-regulated transcription co-regulators MAL-SRF and YAP/TAZ (Dupont et al., 2011; Miralles et al., 2003). Mechanotransduction through both the MAL-SRF and YAP/TAZ

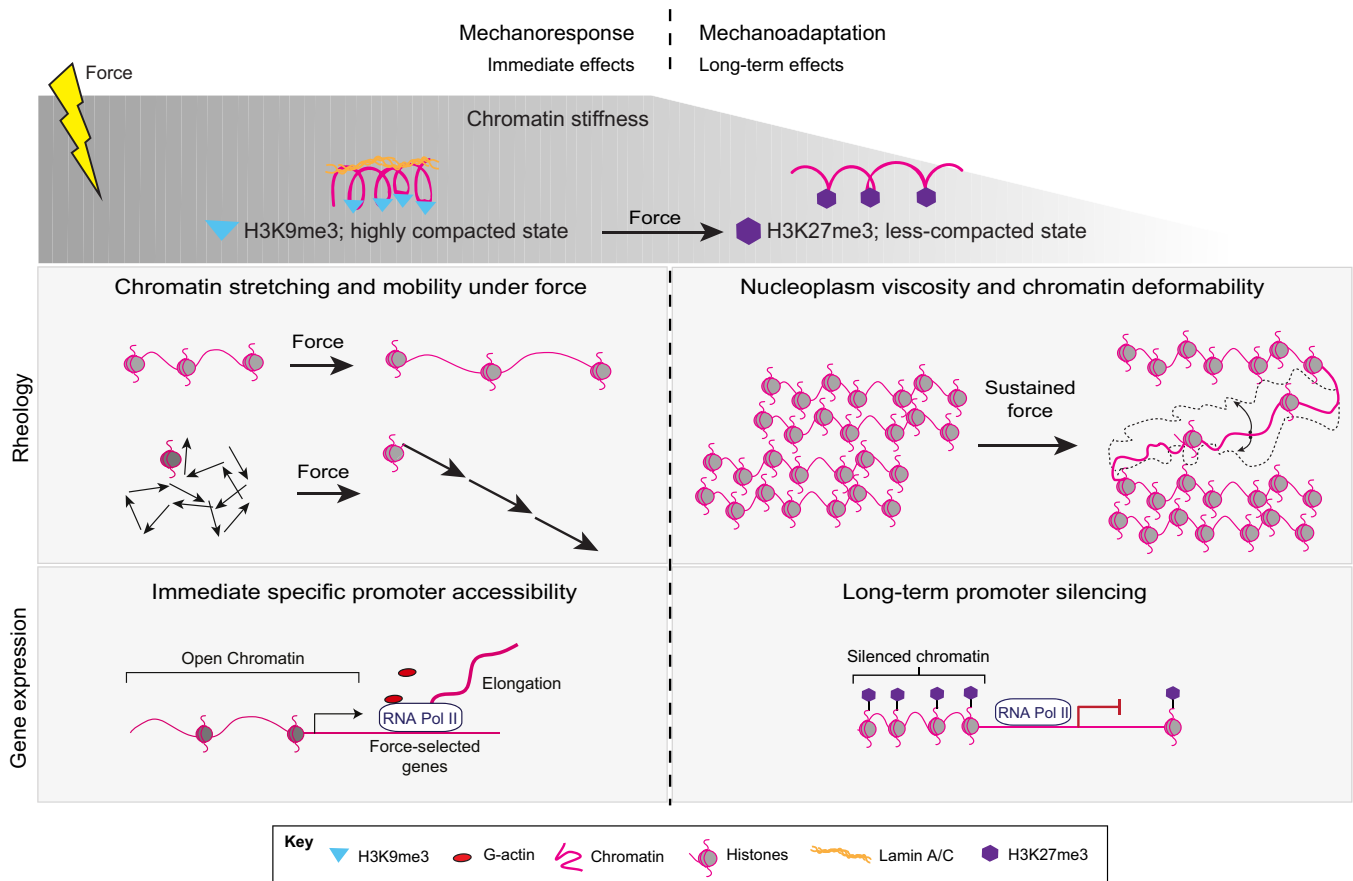


Fig. 2. The effect of cell-extrinsic and cell-intrinsic force on chromatin function and architecture over different time scales. We propose that in a high-force environment, chromatin displays both a short-term mechanoreponse (left) and long-term mechanoadaptation (right). Architecturally, exogenous mechanical force induces chromatin decondensation and softening, potentially as means of dissipating mechanical stress. This is facilitated by the loss of lamin A/C-interacting, H3K9me3-marked heterochromatin and its switch to a H3K27me3-marked heterochromatin that becomes embedded within the more viscous nucleoskeleton (top panel). In addition to altering its compaction state and global architecture, chromatin can also be stretched to absorb mechanical insults or transform mechanical force into altered directional movement and repositioning of specific DNA regions in the short-term (middle left). Long-term adaptation to a persistent high-force environment likely manifests in global changes in the deformability of the chromatin fibers with increased nucleoskeleton viscosity (middle right). At the same time, a high-force environment requires a functional chromatin response at the level of transcription. Indeed, recent data indicate that force initially triggers an open state of the chromatin in the short term (bottom left), likely allowing the cells to cope with mechanical insults on short time scales, but that upon prolonged force application, global promoter silencing occurs (bottom right).

pathways requires active Rho-GTPase signaling and actomyosin-mediated contractility, which results in the translocation of these transcription factors from the cytoplasm to the nucleus where they initiate their respective transcriptional activities. While such transcription factor-mediated changes in gene expression as means of transducing a mechanical signal to the nucleus are well accepted, novel emerging concepts implicate a direct stress-wave-like propagation of mechanical stress to alter nuclear architecture and modify the state of the chromatin and transcription, as discussed below.

Intriguingly, it has been shown that mechanical load induces rapid chromatin stretching within seconds, which subsequently results in increases in transcription that are proportional to the magnitude of chromatin stretching (Tajik et al., 2016). In this study, a multi-copy insertion of a BAC genomic insert containing the *DHFR* gene tagged with a lac operator repeat was engineered and co-expressed with a EGFP-dimer lac repressor, enabling live visualization of the *DHFR* BAC. Subsequently, shear stresses were applied on integrins using a magnetic bead. Application of a 8.8-Pa or a 17.5-Pa stress at 0.3 Hz for 1 h resulted in ~70% or ~100% increases, respectively, in the transcription of the transgene.

The strain-induced chromatin stretching was dependent on the presence of an intact actomyosin cytoskeleton as well as nucleoskeletal proteins such as lamins, emerin and SUN1/2 (Tajik et al., 2016). On longer time scales (10 min) and in presence of a sustained mechanical stimulus, both cell-extrinsic (dynamic tensile loading) and cell-intrinsic (elevation of cellular contractility) mechanical stimulation induces ATP-dependent condensation of chromatin into heterochromatin in mesenchymal stem cells upon their differentiation, leading to a suppression of gene expression in condensed regions (Heo et al., 2016b). Consistently, a long-term, mechanical force-driven increase in H3K27me3, a histone mark indicative of compacted, facultative heterochromatin, has been implicated in restricting lineage commitment in multipotent stem and/or progenitor cells (EPCs) of the human epidermis (Le et al., 2016). As discussed earlier, the application of extrinsic mechanical strain in this case induces the formation of a perinuclear F-actin ring in response to mechanical stimulus, which results in a depletion of free nuclear G-actin. As nuclear actin is an important transcriptional cofactor, this decrease in nuclear actin leads to a downregulation of global transcription. Although this transcriptional repression is global, it specifically facilitates accumulation of the silencing

H3K27me3 mark on promoters of lineage-specific differentiation genes that are under the control of this specific epigenetic mark, thereby attenuating EPC differentiation (Le et al., 2016). Together, these studies put forward a model, whereby cell-extrinsic forces are propagated directly to the nucleus as the force sensed by the mechanically-sensitive cell surface receptors is transduced through the tensed actomyosin cytoskeleton directly to nuclear lamins (via LINC proteins). Lamins are, in turn, physically tethered to chromatin by chromatin-binding proteins on the INM, for example, the barrier to autointegration factor (BAF), which also binds to emerin (Ungricht and Kutay, 2017). In this way, extracellular forces can directly facilitate the deformation and stretching of chromatin and so modify gene expression patterns and cellular fate (Heo et al., 2016a; Irianto et al., 2017b; Le et al., 2016; Seong et al., 2013). In addition to changes in chromatin compaction, mechanical stresses transmitted to the nuclear interior may also impact on chromosome organization more globally. Chromosomes reside in specific “territories” that are further organized into topologically associating domains (TADs) (Dixon et al., 2016). The spatial arrangement of specific DNA loops and segments can vary between cell types and even change position over time. Forces arising from the nuclear-cytoskeletal machinery may affect the topology/organization of specific gene loci resulting in their activation or silencing (Fedorchak et al., 2014; Le et al., 2016; Maharana et al., 2016; Shachar and Misteli, 2017). Interestingly, a potential mechanical code for a topological genome regulation has been recently proposed, which implies that topological arrangements and force-induced displacements can be dictated and imposed by the geometrical constraints of the nucleus (Fedorchak et al., 2014; Maharana et al., 2016), providing an interesting link between mechanics and chromosome topology to be further tested experimentally.

Thus, although high-resolution mapping of chromatin architecture and its effect on global gene expression under both low and high mechanical loading at different time scales still needs to be carried out, the current data suggest to us that initially, within seconds, any applied force leading to nuclear deformation elicits an open chromatin state and so upregulates transcription, perhaps allowing for a rapid rheological response, whereas the long-term effect of persistent mechanical load is a global acquisition of the H3K27me3 mark through a combination of gene silencing and loss and/or detachment of H3K9me3 from the lamina, thus reflecting a sustained mechanoadaptive process (Le et al., 2016; Tajik et al., 2016). It is interesting to note that open chromatin is more accessible to DNA repair factors than the tightly packed heterochromatin (Price and D’Andrea, 2013). Whether this strain-induced chromatin decondensation functions not only to alter nuclear mechanics but also to facilitate more efficient DNA repair as a means for mechanoprotection remains to be addressed.

Perspectives

In summary, nuclear and chromatin mechanics is a highly active area of ongoing research, and accumulating evidence implicate a central role for mechanical signaling to chromatin both in the regulation of gene activity as well as in the modulation of the mechanical properties of the nucleus. Recent studies on compressive forces and strain in particular highlight the impact of mechanics on chromatin conformation and thereby its mechanical properties.

It is, however, important to consider that mechanical forces manifest on various length scales (i.e. molecular, single-cell, monolayer, or even tissue level), and thereby likely elicit specific and distinct responses. Thus, more precise measurements of the

dynamic mechanical properties of the nucleus and subnuclear structures, as well as improved multiscale and multiphysics mechanical models are now needed to understand how and to what extent specific types of loads, such as their magnitude, the particular regime and/or duration, or their region of application, affect nuclear mechanics and alter cellular mechanotransduction. The main challenge in developing such models is the accurate integration of computations from these distinct scales. In particular, the integration of robust and reliable experimental models with available *in silico* chemo-mechanical tools that account for both active cytoskeletal contraction (Reynolds et al., 2014; Vigliotti et al., 2016), as well as the active remodeling of the nuclear lamina will be useful to capture the influence of mechanical load on the nucleus (Szczesny and Mauck, 2017).

Mutations in nuclear lamins (especially in the *LMNA* gene) and LINC complex components cause a diverse spectrum of genetic disorders, collectively termed laminopathies, that include muscular dystrophy, neuropathy, premature aging, dilated cardiomyopathy, and many others (Schreiber and Kennedy, 2013). Peculiarly, despite being ubiquitously expressed, although to a varying degree (Swift et al., 2013), laminopathies are most prevalent in highly mechanically-loaded tissues, such as heart and muscle (Schreiber and Kennedy, 2013). Perhaps this is not surprising given that lamins have multiple functions. In addition to providing structural support to the nucleus and modulating chromatin organization, lamins link the nucleus to the cytoskeleton and are intimately involved in mechanotransduction, as discussed above. Taken together with the recent evidence indicating that the ability to modify nuclear lamins is the rate-limiting step for migration through constricted 3D spaces (Rowat et al., 2013; Skau et al., 2016; Thiam et al., 2016; Zaman et al., 2006), the expression levels and the stoichiometry of the different lamin isoforms likely modulates an array of processes ranging from development and immune cell function to cancer metastasis. Both tissue mechanics (Huang and Ingber, 2005; Ingber, 2006; Laklai et al., 2016; Levental et al., 2009; Miroshnikova et al., 2016) and chromatin status (Denais et al., 2016; Heo et al., 2016a,b; Le et al., 2016; Swift et al., 2013) are dynamically regulated depending on the cellular fate with regard to their stemness or differentiation state, and are often corrupted in disease.

Many key questions remain as to how mechanical cues feed into the nuclear mechanosensing machinery to balance the critical tasks of maintaining genetic integrity, while allowing for cellular plasticity and supporting the dynamic changes required for normal cellular functions. Specifically, the precise contribution of altered nuclear rheology and modified chromatin organization and dynamics in driving the associated diseases remains to be elucidated. In that respect, emerging genomic technologies, such as the chromatin conformation capture assays (Dekker et al., 2002; Dostie et al., 2006; Lieberman-aiden et al., 2009), together with novel tools for targeted mechanical stimulation with high spatiotemporal resolution and live-imaging capabilities (Seo et al., 2016), will undoubtedly aid in answering these important questions.

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Competing interests

The authors declare no competing or financial interests.

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