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Chromatin's physical properties shape the nucleus and its functions

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The cell nucleus encloses, organizes, and protects the genome. Chromatin maintains nuclear mechanical stability and shape in coordination with lamins and the cytoskeleton. Abnormal nuclear shape is a diagnostic marker for human diseases, and it can cause nuclear dysfunction. Chromatin mechanics underlies this link, as alterations to chromatin and its physical properties can disrupt or rescue nuclear shape. The cell can regulate nuclear shape through mechanotransduction pathways that sense and respond to extracellular cues, thus modulating chromatin compaction and rigidity. These findings reveal how chromatin's physical properties can regulate cellular function and drive abnormal nuclear morphology and dysfunction in disease.

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Introduction

The cell nucleus is a mechanically responsive organelle that protects and organizes the genome it encloses. Forces can directly dictate gene transcription through the physical positioning [1,2] and stretching of genes [3•], as well as through force transduction that alters nuclear import and export of transcription factors [4,5]. Moreover, the nucleus must resist forces from within the cell and its microenvironment to prevent catastrophic events, such as nuclear rupture and deformations, which result in mixing nuclear and cytoplasmic contents, DNA damage, and disrupted transcription [6,7,8••]. An essential component of this mechanical response is chromatin, the genome and associated proteins, which behaves like a spring, elastically resisting few-micron-sized deformations [9–13]. With the advent of chromosome capture and various imaging techniques, there have been numerous studies of chromatin's spatial organization [14,15]. However, less is known about how the mechanical properties of chromatin dictate spatial organization and what role forces play in governing it, as well as the shape and stability of the nucleus as a whole. Recent research on nuclear mechanics and morphology has provided insights into the basic biophysical mechanisms underlying nuclear architecture, and consequently, the ways in which chromatin's physical properties affect nuclear function and human diseases.

Physiological impact of defects in nuclear shape and mechanics

Abnormal nuclear shape is a pathognomonic trait that has been used as a diagnostic indicator of human disease for nearly a century, albeit without an understanding of the mechanisms of nucleus deformations and their effects on function. Cancer diagnostic assays examine cell nuclei for unusual sizes and shapes via Pap smear (cervical) [16], nuclear herniations termed 'blebs' that correlate with Gleason score (prostate) [17], and aberrant shapes and orientations via quantitative histomorphometrics (breast) [18,19]. Aberrantly shaped nuclei also occur in mechanically demanding environments, such as muscle cells in heart disease (cardiomyopathy) associated with progeria and aging and muscular dystrophy [20]. The prevalence of abnormal nuclear morphology in cancers and other diseases suggests that nuclear shape is normally regulated by the cell. Furthermore, because shape stability of an object depends on its mechanical properties, these observations suggest that nuclear shape regulation and diseases in which abnormal nuclear shapes occur are linked to the mechanics of the nucleus. Indeed, nuclear mechanics plays a significant role in malignant cancer cells that migrate and invade tissue; nuclear deformation is the rate-limiting step in migration [21–23], and deficient nuclear rigidity leads to ruptures and DNA damage upon migration through confined volumes [8••,24,25].

Abnormal nuclear morphology disrupts nuclear function in several ways. Nuclei that are mechanically perturbed by altered lamins or chromatin are prone to rupture, which induces exchange of nuclear and cytosolic contents (including chromosomes) [6,26–29,30••,31,32]. Loss of nuclear compartmentalization can lead to DNA damage

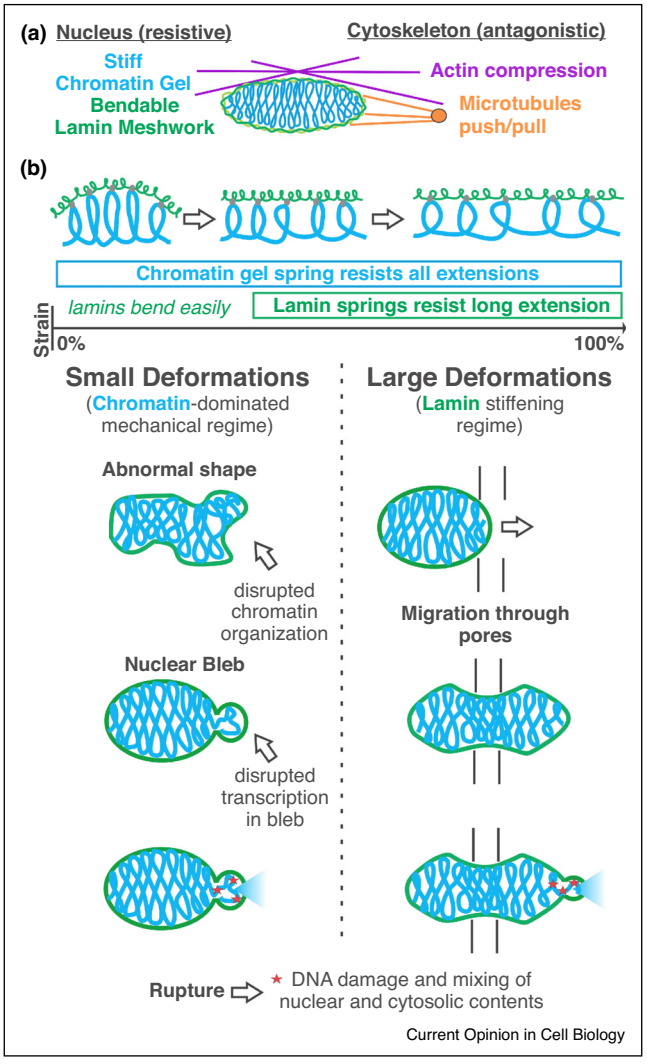
[24,25,33], at least in part due to concurrent mislocalization of chromatin and DNA repair factors [8••,34]. It has furthermore been hypothesized that nuclear rupture could activate the cGAS-STING innate immune response pathway leading to inflammation, senescence, and cancer (reviewed in Ref. [35]). Morphological disruption is also associated with changes in the overall spatial organization of chromatin and gene expression profile [28,36••]. Nuclear blebs arising with ruptures correlate with decreased transcription and mRNA transport for the chromatin held within [7,37]. Abnormal shape and mechanics could also disrupt mechanotransduction, which would result in further perturbations to transcription. Together, these findings demonstrate the cell-biological importance of the *physical* properties of the cell nucleus – perturbations of which can lead to nuclear dysfunction – and highlight the role of altered nuclear mechanics as a factor underlying human disease.

Mechanical components dictating nuclear shape: chromatin, lamins, and the cytoskeleton

The ability of the nucleus to maintain its shape is dictated by a trio of mechanical components: chromatin, lamins, and the cytoskeleton (Figure 1a). Chromatin and lamin A are the two major resistive elements that protect the nucleus, as shown by atomic force microscopy [10,11,38], micropipette aspiration [39,40], substrate stretching [41], and micromanipulation [12,13]. However, experiments with nuclei treated with the chromatin-degrading enzyme MNase [13,42] show that lamins alone cannot maintain nuclear shape. Instead, the lamina buckles under mechanical stress when it is unsupported by chromatin. This is consistent with experiments revealing that lamins comprise a thin (10–30 nm) peripheral meshwork of highly bendable intermediate filaments with a short (few hundred nm) persistence length [43,44,45••]. In turn, lamin networks can unfold during cell and nuclear spreading [46], but resist large stretching deformations [13,42,47]. Chromatin is a variably compacted polymer filling the nucleus [48] that interacts both with both itself (e.g. compartments and topologically associating domains, TADs, seen in Hi-C [14]) and the nuclear periphery (e.g. lamin associated domains, LADs [49]). Variations in compaction may correspond to variations in chromatin stiffness [13,50] and viscoelasticity [40,51–53]. Moreover, a number of mechanical measurements demonstrate that chromatin is a stiff mechanical element [9,10,12,13,54,55]. Altogether, these data suggest a physical model of the nucleus as a semiflexible meshwork of lamins at the nuclear periphery that encloses a stiff polymeric chromatin gel [56] (Figure 1a).

Chromatin and lamins have distinct contributions to nuclear mechanics, as detailed by micromanipulation force measurements [13]. Chromatin acts as an elastic spring that dominates the force response to small

Figure 1



Chromatin is a major contributor to nuclear mechanics and shape along with lamins and the cytoskeleton. **(a)** The major protective mechanical components of the nucleus that aid nuclear shape stability are chromatin (blue), which is a stiff polymer gel, and lamins (green), which are an intermixed meshwork of easily bendable intermediate filaments of lamin A, B1, B2, and C. The cytoskeleton components actin (purple) and microtubules (orange) antagonize nuclear shape stability, although actin and vimentin (not shown) can also aid stability. **(b)** Top: schematic showing differential force response regimes arising due to geometric considerations for lamins (a 2D meshwork) and chromatin (a 3D gel). For short, few-micron deformations (i.e. small strains), the chromatin gel acts as a spring that resists stretching, while lamins contribute little as they bend easily until they are aligned with the tension axis. Longer deformations, for which the lamins are aligned with the force, generate lamin-A-based strain stiffening. Chromatin continues to resist stretching of the nucleus at long deformations as a secondary component. Bottom: abnormal nuclear shape and blebs are small deformations, occurring in the regime dominated by chromatin. During migration through pores, the nucleus extends many microns (>3 μm) into a deformation regime that necessitates and activates lamin A resistance to maintain shape stability. Failure to maintain shape stability in either condition can result in disruption of transcription through chromatin disorganization or blebs that inhibit it. Either shape disruption can result in nuclear ruptures that lead to DNA damage and loss of nuclear compartmentalization.

deformations (few μm), while the lamin A meshwork deforms easily for small extensions and stiffens to resist large deformations (Figure 1b) [13,42]. These two regimes reflect the geometry of the cell nucleus [42]. Differential force response is biologically important because almost all cell nuclei undergo small deformations which are resisted by chromatin, while generally only nuclei in mechanically demanding tissues and microenvironments have high lamin A levels [5]. Overall, the interdependence of chromatin and lamin organization, as well as extranuclear factors, makes understanding nuclear morphology and mechanics a rich and complex physical biology problem.

The cytoskeleton is external to the nucleus, but it is nonetheless an important contributor to nuclear shape maintenance that can both antagonize and promote nuclear stability. In its antagonistic role, actin-based confinement or compression lead to abnormal shape and rupture of perturbed nuclei or models of diseased nuclei [27,28,30••,31,57••]. Similarly, microtubules, along with dynein motors, exert forces that can deform or rupture the nucleus [33,55,58–60]. In contrast, the intermediate filament vimentin has a protective role essential for nuclear positional stability [61] and for perinuclear stiffness, which impedes 3D motility [62]. Additionally, actin cap cables can stabilize nuclear shape [63] in coordination with microtubules [64]. Altogether, the balance of the trio of lamins, chromatin, and the cytoskeleton tightly regulates nuclear morphology, and the perturbation of any one element can lead to global nuclear shape dysfunction.

Lamin perturbations impact nuclear shape via chromatin

Lamin perturbations are well known to induce abnormal nuclear morphology, but the physical basis for this is not well understood. Progerin, a misprocessed, permanently farnesylated lamin A mutant, causes the premature aging disease progeria and disrupts nuclear morphology [65]. Further studies show that depletion of either lamin A or lamin B results in similar abnormal morphologies and blebbing of cell nuclei [27,32,41]. While all of these alterations of lamins perturb nuclear morphology, each has a different effect on lamin-based nuclear mechanics. Lamin A mutant progerin increases nuclear stiffness, while lamin A depletion decreases stiffness, and lamin B depletion leads to either no change or increased rigidity, depending on lamin A content [5,13,41,66]. Moreover, lamins provide little contribution to the mechanical response to deformations on the small length scales of blebs and typical nuclear deformations [13,56]. Instead, lamin A is more important in cells migrating through pores where the nucleus is highly strained and compressed [22,24,25] (Figure 1b). These observations challenge the idea that blebs and other nuclear shape aberrations arise from the biophysical properties of lamins alone.

Lamins are interconnected with chromatin, which can cause downstream effects that impact the biophysical properties of the cell nucleus. Disruption of proteins that tether chromatin to the nuclear envelope results in abnormalities in nuclear fluctuations, overall shape, and chromatin organization [55,67–71]. Depletion of lamin A can disrupt lamin associated domains (LADs) of chromatin and change chromatin's spatial localization [72–74,75•]. Mutant lamin A progerin causes disruption of chromatin connections to the lamina and induces decreased heterochromatin and chromatin softening [7,76–79]. Depletion of lamin B1 also decreases chromatin connections to the periphery [75•] and decreases heterochromatin [30••,80]. It is significant that each of these downstream chromatin perturbations – loss of connections to the periphery, decondensation, and decreased heterochromatin content – can independently induce abnormal nuclear morphology (as discussed below). Moreover, in many of these lamin-perturbed cases, normal nuclear morphologies can be rescued by restoring heterochromatin to normal levels [30••,81]. This suggests that heterochromatin mechanics may dominate the regulation of nuclear shape, and that lamin defects may induce blebs *indirectly* through their downstream effects on chromatin and its anchoring to the nuclear periphery.

Chromatin is a key regulator of nuclear shape

Various chromatin perturbations induce blebbing, ruptures, and other abnormal nuclear morphologies, independent of altering lamins. Histone perturbations and modifications are a major class of such chromatin alterations. Overexpression of HMGN5 disrupts histone linker H1, which results in decreased chromatin compaction, nuclear stability, and rigidity, and consequently, increased nuclear blebbing [54]. HMGN5 overexpression in transgenic mice leads to cardiac defects and premature death, demonstrating the physiological importance of chromatin-based nuclear mechanics and morphology. Alterations in the amount of compact heterochromatin and decompact euchromatin are also commonly found in cancers and other diseases [82]. Chromatin histone modifications that broadly increase euchromatin or decrease heterochromatin result in weakened chromatin-based nuclear rigidity, abnormal nuclear morphology, and nuclear ruptures [30••]. Increases in heterochromatin, in contrast, can rescue nuclear shape and rigidity. Rescue by heterochromatin has been demonstrated for both chromatin and lamin perturbations, including in cells with excess histone acetylation, lamin B1 depletion, or mutant lamin A progerin overexpression, as well as in Hutchinson–Gilford progeria syndrome patient cells [30••,81]. Similarly, chromatin condensation coincides with bleb healing and reabsorption into the nuclear body [29]. Additionally, loss of heterochromatin at the nuclear periphery, a common occurrence in lamin-perturbed nuclei, by depletion or mutation of heterochromatin–lamin tethering protein PRR14 causes abnormal nuclear

morphology [71]. Regulators of histone modifications, such as WDR5, which promotes the euchromatin mark H3K4me^3, can also regulate nuclear deformability, independent of transcription [83•]. Thus, changes to the histone modification state of chromatin through different molecular mechanisms are sufficient to disrupt or restore nuclear morphology without requiring lamin alterations (Table 1).

Aside from cases with altered histones, nuclear rupture has also been reported for RPE-1 cells depleted of well-known cancer-related chromatin proteins Rb and p53, due to enlarged nuclei [84]. Depletion of the SWI/SNF chromatin-remodeling ATPase BRG1 causes abnormal nuclear morphology in breast epithelia MCF10A cells, due to BRG1-related changes in internal nuclear forces [85]. This mimics the abnormal nuclear shape seen in more metastatic breast cancers [18]. Depletion of other cancer-relevant molecules, particularly p63 [86], miR29-b [87], and NOP53 [88], can also induce abnormal nuclear shape, although these perturbations may have effects beyond those on chromatin. Even before nuclear formation, chromatin mechanics regulates shape; barrier-to-autointegration factor (BAF) stiffens chromatin by bridging chromatin sites, which inhibits the formation of micronuclei [89]. It remains to be determined whether the other diverse types of chromatin–chromatin bridging factors, such as loop-forming cohesin [90,91] and phase-separating HP1α [92,93], help stabilize chromatin-based nuclear mechanical response. These studies (summarized in Table 1) reveal that biophysical properties of

Table 1

Summary of comparison of lamin-based and chromatin-based perturbations that change nuclear morphology. Lamin perturbations that disturb nuclear shape can either strengthen, weaken, or not change the mechanics of the nucleus. The commonality is that they disrupt chromatin in some fashion. Increasing stiffness by heterochromatin formation stabilizes nuclear shape in lamin perturbations. Chromatin perturbations that soften the nucleus destabilize nuclear shape without the need to alter lamins.

Lamin perturbations that result in abnormal nuclear morphology

Type	Mechanics	Effect on chromatin	Shape rescue via chromatin
Lamin A depletion	Weaker ~50%	Decreased chromatin–lamina attachments [72–74,75•]	(Not tested)
Progerin, mutant lamin A	Stiffer 100%	Decreased chromatin–lamina attachments and decreased heterochromatin [7,76–79]; softer chromatin by 50% [76]	Increased heterochromatin [30••,81]
Lamin B depletion	No change or stiffer (lamin A amount dependent)	Decreased chromatin–lamina attachments [75•]; decreased heterochromatin [30••,80]	Increased heterochromatin [30••,81]

Chromatin perturbations that result in abnormal nuclear morphology

Type	Mechanics	Chromatin perturbation	Lamins	Citations
HMGN5 overexpression	Weaker ~40%	H1 (linker histone 1) disruption, chromatin decondensation	No change	Furusawa *et al*. [54]
Broad histone acetylation	35% Weaker chromatin; lamin A stiffening unchanged	Increased euchromatin (H3K9ac, H4K5ac)	No change	Stephens *et al*. [30••]
Broad histone demethylation	35% Weaker chromatin; lamin A stiffening unchanged	Decreased heterochromatin (H3K9me^{2,3}, H3K27me^3)	No change	Stephens *et al*. [30••]
WDR5/RbBP5	Correlated to weaker ~60%	Increased euchromatin H3K4me^3, activated in 3D, but not 2D, culture	No change	Wang *et al*. [83•]
PRR14 depletion	(Not tested)	Chromatin/HP1-lamin A tethering protein, loss of heterochromatin at periphery	No change	Poleshko *et al*. [71]
BRG1 depletion	(Not tested)	SWI/SNF ATPase chromatin-remodeler	Lamin grooves	Imbalzano *et al*. [85]
p53 depletion	(Not tested)	Chromatin protein associated with cancer	No change	Yang *et al*. [84]
Rb depletion	(Not tested)	Chromatin protein associated with cancer	No change	Yang *et al*. [84]
p63 depletion	(Not tested)	Transcription factor, decreased heterochromatin and HP1	Decreased lamin expr.	Rapisarda *et al*. [86]
miR-29b blockade	(Not tested)	Cancer-relevant microRNA that modulates DNA methylation	(Not tested)	Kriegel *et al*. [87]
NOP53 depletion	(Not tested)	p53 Interacting protein	(Not tested)	Lee *et al*. [88]
BAF depletion	Weaker, *in vitro*	Depletes chromatin bridging during nuclear formation	No change reported	Samwer *et al*. [89]

chromatin – spatial organization, structure, and rigidity – are paramount in maintaining normal nuclear shape and function throughout the cell cycle.

Native pathways for regulating nuclear morphology through chromatin

Recent experiments have begun to reveal how chromatin is natively regulated to maintain nuclear morphology. While there are several known mechanisms for regulation of the cytoskeleton and the lamina that modulate nuclear shape [46,69,94••,95–97], these alterations are often upstream of chromatin modifications. Recent studies have demonstrated that cells can also directly regulate chromatin compaction through a native pathway. External mechanical stimuli trigger mechanotransduction through mechanosensitive ion channels in the plasma membrane [98–100], leading to chromatin condensation and heterochromatin formation [81,94••,101••,102]. Mechanotransduction via mechanosensitive ion channels can increase heterochromatin levels and chromatin-based nuclear rigidity, while concurrently rescuing nuclear shape in lamin-perturbed, chromatin-pertubed, and disease model cells (e.g. progeria and breast cancer) [81]. This provides a native chromatin regulation pathway for the cell to sense and respond to the extracellular environment in order to protect nuclear shape and organization.

Similarly, chromatin condensation and compaction can be regulated through extracellular osmotic changes [103,104], compression [105], substrate micropatterning [97,106], cell substrate stretching [94••,101••,102,107], changes in charge composition [81], and cell migration [36••,108,109]. Notably, heterochromatin levels increase during cell migration, and migration through pores can be blocked by the concurrent increase in nuclear rigidity [110••]. Similar to nuclear rigidity changes due to lamin A increases [22], this increase in chromatin-based rigidity could protect nuclei from ruptures that occur when cells migrate through narrow pores [24,25] or block migration through pores entirely, thus stopping cancerous invasion [21,83•,110••]. Altogether, cells possess a variety of native mechanisms for regulating nuclear shape through rigidity linked to the underlying chromatin compaction state.

Biophysical modeling of nuclear shape

Despite knowing many of the biological factors involved in nuclear morphology, the biophysical mechanisms by which chromatin, lamins, and the cytoskeleton regulate nuclear morphology remain unclear. Physical modeling may fill the gaps in our mechanistic understanding of how these three components cooperate and compete to maintain or disrupt nuclear morphology. Several existing models for nuclear shape and rupture focus exclusively on the role of lamins [111,112], consider only osmotic pressure associated with the nucleoplasm [113], or treat chromatin as a viscoelastic material that is secondary to the lamina [114]. Other studies incorporate more robust models for chromatin but primarily apply to specific experimental conditions [42,115] or do not extensively explore the physical role of chromatin and its linkages to the lamina [115]. Most of these models omit the cytoskeleton. Each of these models illustrates how the mechanical properties of different cellular components may regulate nuclear morphology, yet altogether, they provide an incomplete mechanistic picture. Figure 1 depicts key concepts that could be elucidated by further modeling efforts. Such efforts are likely to both inform and be informed by continuing experiments in this developing field.

Conclusion

The tight interplay between chromatin's genetic regulation, compaction, spatial organization, and mechanics controls nuclear function. Chromatin is a stiff polymer gel that fills the nucleus, providing the nucleus with a robust mechanical response complementing the strain stiffening of the nuclear lamina. These two nuclear components, along with the cytoskeleton, shape the nucleus and the genome within. An imbalance between these three components can induce abnormal nuclear shape, which can disrupt chromatin organization and transcription, cause nuclear rupture, and increase DNA damage. We have emphasized that chromatin-based mechanics is an underlying mechanism of abnormal nuclear morphology. Furthermore, emerging data reveal that extracellular stimuli sensed by the cell can regulate chromatin mechanics, and thus, shape through modulating histone modification state. Chromatin itself, through its structure and mechanics, is emerging as key factor that determines normal nuclear function, as well as dysfunction in a variety of disease contexts.

Many intriguing questions remain regarding the connections between chromatin organization, nuclear shape, and nuclear function. Are there specific histone modifications and chromatin remodeling factors that are particularly important in governing nuclear shape? Can we develop a detailed understanding of how shape impacts chromatin organization, for example, via Hi-C experiments? There are also many interesting questions about function, such as how do chromatin modifications that control nuclear shape affect transcription? And how do we separate the effects chromatin modifications have on mechanics, organization, biochemistry, and transcription from each other? As we have begun to see for cell migration and DNA damage response, addressing these questions will provide insight into broader questions of how chromatin organization and nuclear shape impact cellular functions, for example, the cell cycle, development, homeostasis, and tissue self-organization. Study of nuclear shape and mechanoregulation may reveal new therapeutic targets across a range of diseases spanning cancers, dystrophies, progerias, aging, and more.

Conflict of interest statement

Nothing declared.

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