Towards an integrated understanding of the structure and mechanics of the cell nucleus

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Summary
Changes in the shape and structural organization of the cell nucleus occur during many fundamental processes including development, differentiation and aging. In many of these processes, the cell responds to physical forces by altering gene expression within the nucleus. How the nucleus itself senses and responds to such mechanical cues is not well understood. In addition to these external forces, epigenetic modifications of chromatin structure inside the nucleus could also alter its physical properties. To achieve a better understanding, we need to elucidate the relationship between nuclear structure and material properties. Recently, new approaches have been developed to systematically investigate nuclear mechanical properties. These experiments provide important new insights into the disease mechanism of a growing class of tissue-specific disorders termed 'nuclear envelopathies'. Here we review our current understanding of what determines the shape and mechanical properties of the cell nucleus. ***BioEssays* 30:226–236, 2008.** **© 2008 Wiley Periodicals, Inc.**

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Abbreviations: LBR, lamin B receptor; EDMD, Emery-Dreifuss muscular dystrophy; FPLD, familial partial lipodystrophy; FRAP, fluorescence recovery after photobleaching; GFP, green fluorescent protein; HGPS, Hutchison-Gilford progeria syndrome.

Introduction

Cells are highly dynamic. They interact with their environment, sensing and responding to chemical signals and mechanical stimuli, throughout development, differentiation and aging.[4,5] The role of biochemical signaling mechanisms in regulating these processes is well studied; however, mechanical forces also penetrate to the cell nucleus and may act as mechanical signals regulating gene expression.[6,7] Each nucleus is embedded within a cell, and thus exists in a mechanical continuum with the surrounding cytoskeleton, neighbor cells and the surrounding extracellular matrix that comprise tissues. Studying how different components of the cell's cytoplasm and nucleus bear mechanical stress is crucial for our knowledge of how mechanical stimuli can act, together with biochemical signals, in fundamental biological processes from differentiation to aging.

Beginning in the late 1970s, studies began to suggest that the cell's physical environment and forces acting on the cell exterior through adhesion are linked to events in the nucleus such as gene regulation.[8,9] Over a decade later, direct observations of force transmission from the plasma membrane to the nucleus were reported.[10] Since these pioneering studies, much work has been dedicated to characterizing the material properties of cells,[11] but the three-dimensional structure and physical properties of the nucleus remain poorly understood, especially in light of evidence that nuclear structure changes during development,[12] differentiation,[13,14] aging[15] and disease.[16,17] Moreover, altered nuclear structure affects cell migration,[18] cytoskeletal organization[19] and the properties of the cell as a whole. For example, mutations in genes encoding nuclear envelope proteins, such as lamins, emerin, LAP2β or lamin B receptor (LBR) lead to over twelve tissue-specific disorders, termed 'nuclear envelopathies', including Emery-Dreifuss muscular dystrophy (EDMD), dilated cardiomyopathy, Pelger Huet anomaly and familial partial lipodystrophy (FPLD).[20–22] The pathological mechanisms of envelopathies are not fully elucidated, but compromised nuclear mechanics is one proposed model.[23] This model suggests that mutations in

nuclear envelope proteins cause changes in nuclear envelope structure and stability, which could affect force transmission from the cytoskeleton to the nucleus,[10] predispose cells to damage and death in mechanically strained tissue and/or alter transcriptional regulation and gene expression. Other models propose changes in gene regulation to explain the disease effects and are not mutually exclusive to the abnormal nuclear fragility model. Depending on the specific mutation, compromised nuclear mechanical properties could contribute to the disease mechanism to varying degrees, ranging from severe skeletal muscular dystrophies and cardiomyopathies to loss of smooth muscle cells in HGPS patients. A deeper understanding of diseases linked to the nuclear envelope further motivates studies of nuclear physical properties and shape stability. Here we describe our current knowledge of the relationship between nuclear structure and mechanical properties.

The nucleus is the site of many fundamental biochemical processes such as replication, transcription, splicing and ribosome biogenesis, and its architecture is essential to many of its biological functions. Containing approximately two meters of DNA, the nucleus is encapsulated by the nuclear envelope, a highly crosslinked, complex meshwork of proteins and membranes (Fig. 1). We focus here on metazoan cells where the nuclear envelope consists of two lipid membranes punctuated by nuclear pore complexes and an underlying protein meshwork, the nuclear lamina. Force transmission from the plasma membrane to the nucleus[10] suggests that the lamina is mechanically linked to the cytoskeletal filament system.[24] A mechanical connection between the cytoskeleton and nucleus may be provided by recently discovered proteins that span across both nuclear membranes and link structural components of the nuclear envelope and cytoskeleton, such as actin,[10,25–27] microtubules[10,28] and intermediate filaments[29–31] (Fig. 1). Many of these proteins are essential for the positioning and mobility of the nucleus within the cell.[32,33]

While the nucleus dynamically interacts with the cytoskeleton, it has its own mechanical stability: isolated nuclei resist shape deformation[34–37] and exhibit similar nuclear envelope elastic properties to those in living cells.[35] Additionally, nuclei have been observed moving and even rotating within living cells while maintaining their internal structure.[38,39] What provides this structural stability to the nucleus? One major contributor is the nuclear lamina, a highly crosslinked protein meshwork that associates both with inner nuclear membrane proteins as well as chromatin. This supramolecular structure is critical for maintaining the shape of the nucleus (Box 1). The lamina consists largely of lamins, nuclear intermediate filament proteins that are found in two major isoforms, A-type (lamins A and C) and B-type (lamins B1 and B2/B3). B-type lamins are critical for viability in different species[40,41] and A-type lamins are exclusive to differentiated cells.[17] Mutations in the *LMNA* gene encoding A-type lamins are implicated in numerous diseases. The post-translational attachment of a farnesyl chain to lamin A and all B-type lamins promotes the association of these proteins with the nuclear envelope, either by direct interactions with lipid membranes or by facilitating protein–protein interactions.[42–44] While the farnesyl-containing amino terminal sequence is cleaved from prelamin A to yield mature lamin A, B-type lamins remain farnesylated. Both types of lamins reside at the nuclear envelope, but lamin A is also found in the nuclear interior, where it forms stable structures.[45] In addition to lamins, chromosomes occupy distinct territories within the nuclear interior during interphase[46] and subnuclear bodies compartmentalize specific nuclear structures and functions. Other structural components such as actin may be involved in forming higher-order structures within the nucleus. Here we discuss how (i) the nuclear envelope and (ii) the nuclear interior contribute to the mechanical stability of the nucleus. More specifically, we focus on how distinct structural components of the nucleus such as lamins and chromatin can influence the material properties of intact isolated nuclei as well as nuclei in living cells.

To study nuclear material properties, several experimental techniques have been developed to mechanically perturb the nucleus (Table 1). These kinds of experiments, together with quantitative analysis of the induced deformations, provide information about the material properties (Box 2) and underlying structural organization of the nucleus. Sources of nuclei used in these experiments range from mammalian fibroblasts to *Xenopus* oocytes. It is important to note the following differences: whereas *Xenopus* oocyte nuclei are up to ~400 μm in diameter, mammalian cell nuclei are much smaller (typically 5–20 μm in diameter) yet they contain approximately the same amount of DNA. Nuclei can be isolated from most cell types in sufficient quantities for biophysical studies. To arrive at a complete understanding of nuclear properties, a variety of complementary approaches to investigate different types of nuclei are required. Ultimately, such studies will provide us with insights into the structure and organization of the cell nucleus that is critical for understanding the disease mechanisms of envelopathies, as well as physiological situations where cells and nuclei undergo large deformations, such as in muscle tissue or during trans-endothelial migration. In this review, we summarize our current understanding of the material properties of the cell nucleus, the components that determine these properties and the physiological implications of altered nuclear mechanical properties.

Elucidating nuclear mechanical properties from studies of nuclear shape

Throughout the cell cycle, nuclei undergo massive transformations in shape, from a stable structure in interphase to

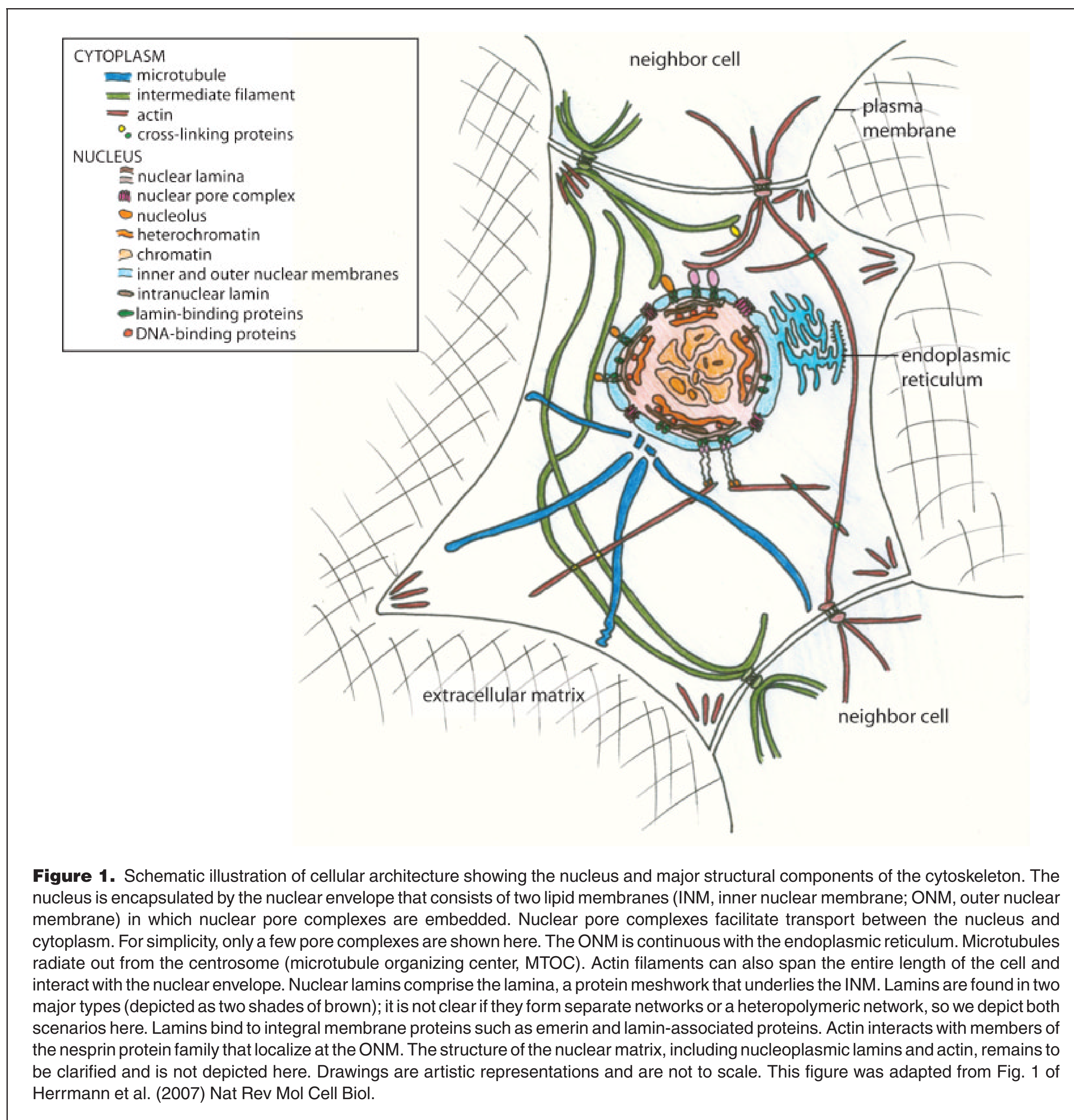


Figure 1. Schematic illustration of cellular architecture showing the nucleus and major structural components of the cytoskeleton. The nucleus is encapsulated by the nuclear envelope that consists of two lipid membranes (INM, inner nuclear membrane; ONM, outer nuclear membrane) in which nuclear pore complexes are embedded. Nuclear pore complexes facilitate transport between the nucleus and cytoplasm. For simplicity, only a few pore complexes are shown here. The ONM is continuous with the endoplasmic reticulum. Microtubules radiate out from the centrosome (microtubule organizing center, MTOC). Actin filaments can also span the entire length of the cell and interact with the nuclear envelope. Nuclear lamins comprise the lamina, a protein meshwork that underlies the INM. Lamins are found in two major types (depicted as two shades of brown); it is not clear if they form separate networks or a heteropolymeric network, so we depict both scenarios here. Lamins bind to integral membrane proteins such as emerin and lamin-associated proteins. Actin interacts with members of the nesprin protein family that localize at the ONM. The structure of the nuclear matrix, including nucleoplasmic lamins and actin, remains to be clarified and is not depicted here. Drawings are artistic representations and are not to scale. This figure was adapted from Fig. 1 of Herrmann et al. (2007) Nat Rev Mol Cell Biol.

complete dissolution at mitosis. Here we focus on nuclei in interphase. During this stage of the cell cycle, nuclear structure is well defined but the nucleus is nonetheless a dynamic organelle that continuously undergoes changes in shape. The extent of nuclear shape changes depends on nuclear envelope composition: mouse embryo fibroblasts lacking lamin A/C and emerin show greater changes in nuclear shape compared to wild-type controls.[47,48] Changes in lamina composition also induce nuclear shape changes essential to spermatogenesis. For example, expression of the spermatocyte-specific lamin B variant induces changes in nuclear shape in somatic cells causing them to resemble meiotic cells.[49] Moreover, overexpression of other farnesylated nuclear envelope-associated proteins (such as Kugelkern, Kurzkern, Charleston) also alters nuclear shape,[13,50] possibly by affecting nuclear envelope structure and material properties. Greater changes in nuclear shape would result if less energy is required to deform the nuclear envelope.

Box 1. Lateral organization of the lamina? Information about the lateral organization of the lamina is essential for developing a mechanistic model of network behavior and properties. Typical of intermediate filament proteins, lamins contain N-and C-terminal domains flanking a central rod domain that leads to coiled-coil dimer formation. Our understanding of lamina structure is based largely on observations of the nucleoplasmic face of a detergent extracted, metal-shadowed *Xenopus* oocyte nuclear envelope imaged by electron microscopy[1] (Fig. 3a). That study revealed a protein meshwork localized at the inner nuclear membrane exhibiting patches of regular lattice network, leading to a model describing the nuclear lamina as a regular network structure. However, other studies in somatic cells provide evidence of a lamina structure that is a heterogeneous, electron-dense meshwork[2,3] (Fig. 3b).

To learn more about the structures that determine nuclear shape stability, changes in nuclear shape can be actively induced, and the resulting nuclear and subnuclear deformations monitored. For example, micropipette aspiration has been used to induce extensive changes in nuclear shape and volume.[34] Despite these marked changes, nuclei demonstrated remarkable shape invariance, maintaining an ellipsoid form even under large local deformations several times larger than the original width of the nucleus. Major volume changes in the nucleus can also be osmotically induced in living cells[51] and isolated nuclei.[52] For example, when nuclei isolated from *Xenopus* oocytes are exposed to varying dextran concentrations, the nucleus is osmotically swelled or compressed.[52] That study revealed a compressibility limit of nuclei with higher dextran concentrations that was attributed to the nuclear lamina. However, the nuclear interior could also contribute to such resistance to compression as nuclei become more resistant to deformation as they are compressed.[34]

The nuclear interior is a largely aqueous, porous material

Analysis of changes in nuclear volume under micropipette aspiration revealed that the nuclear volume can be decreased by 60–70% before attaining a state that is highly resistant to further deformation.[34] These findings indicate that the aqueous fraction of the nucleus is 60–70%. This behavior was observed both in isolated nuclei and in living cells, suggesting that this inner nuclear structure was not an artefact of the isolation procedure. The large volume loss under aspiration implies that the nuclear interior is a primarily aqueous material that behaves as a soft gel.[34] These results are consistent with the water content of biological matter as well as with observations of the rapid diffusion of small molecules in the nucleus.[53] Studies of nuclear structure upon an *increase* in nuclear volume revealed the disassembly of subnuclear compartments, indicating that macromolecular crowding may induce the formation of subnuclear structures,[54] such as nucleoli and Cajal bodies. The size and composition of these subnuclear bodies are dynamically regulated for biological function. While crowding may play a role in their formation, the physical mechanisms that determine their organization and structure remain largely elusive. When cells are exposed to shear flow,[55] or when their nucleus or plasma membrane[10] is deformed,[34] nucleoli undergo relatively confined displacement. Recent studies of Cajal bodies in *Xenopus* oocyte nuclei revealed that Cajal bodies have a sponge-like structure with a network of channels penetrating the interior of these inner nuclear bodies.[56] Collectively, these experimental results are in agreement with a proposed model of the nuclear interior as a highly compartmentalized structure consisting of chromatin domains and interchromatin compartments forming a three-dimensional network of lacunae and channels.[57] With a structure much like a sponge, the nucleus is a porous material that becomes stiffer the more it is compressed.

What structural components contribute to the material properties of the nuclear interior? *Chromatin* is proposed to occupy distinct domains within the nucleus[46] that are mechanically linked together.[10] Since chromatin is also attached to the nuclear envelope, it has been proposed to cause nuclear surface buckling under micropipette aspiration as the DNA pulls on the nuclear envelope and causes it to crumple.[37] However, any two-dimensional surface that resists shear forces can also exhibit buckling in response to in-plane stress.[34] In addition to chromatin, the non-aqueous structure of the inner nucleus consists of a protein scaffold ('nuclear matrix') consisting of a ribonucleoprotein network[58–61] and possibly other proteins. *Nuclear actin* has long been speculated to have physiological roles in the nucleus,[62,63] but there has been much controversy about nuclear actin being a cytoplasmic artefact. Recent experiments, however, provide compelling evidence for the presence of actin in the nucleus although its form and function are not completely understood. Actin is involved in transcription[64–66] and may also have a structural role. Blocking nuclear export of actin stabilizes giant nuclei in *Xenopus* oocytes,[67] substantiating that actin may form a cortical network at the nuclear periphery.[68] Indeed, this hypothesis is supported by in vitro evidence showing interactions between actin and emerin,[68] as well as between actin and the carboxyl-terminal domain of lamin A.[69] While these observations suggest a structural role for actin in the nucleus, ultrastructural evidence is lacking. *Lamins* are localized at the nuclear periphery, but also form a nucleoplasmic veil and foci.[70,71] These inner nuclear structures are prominently observed after expression of GFP-labeled lamins. Note that while GFP is a useful tool to

Table 1. Experimental methods to probe the mechanical properties of the cell nucleus. Such techniques often involve analysis of how the nucleus responds to a physical perturbation.

Technique	Mode of deformation	Applied force	Strengths and shortcomings
Atomic force spectroscopy	A cantilever with tip (~nm – μm) is used to induce local deformations in isolated nuclei or nuclei in living cells, quantifying deformation in response to a given force yields energy of deformation.	$\sim 10^{-7}$–10^{-9}N, local deformation	+ Single cell technique; nm scale spatial resolution. – Results must be interpreted with aid of theory/simulation; caution must be taken when interpreting contact area.[37] Stiffness can exhibit spatial variations, and also depends on the substrate and geometry.
Micropipette aspiration	Cell/nucleus is aspirated into a pipette (radius ~1–4 μm) (Fig. 2), response to deformation is monitored by microscopy.	$\sim 10^{-7}$–10^{-9}N, local deformation	+ Image over time for viscoelastic response.[37] – Single cell technique. Typically with isolated nuclei, take caution as buffer conditions affect nuclear properties.
Confocal imaged microdeformation	Micropipette aspiration of isolated nuclei or nuclei in living cells, imaging by confocal microscopy.	$\sim 10^{-7}$–10^{-9} N, local deformation	+ Monitor how specific nuclear components respond to deformation in 3D. Well suited for studies of living cells and the nuclear envelope,[34,35] both adherent and suspension cells. – Single cell technique.
Cell compression	Compression of cell between two plates (Fig. 2), nuclear shape deformations are imaged.	$\sim 10^{-7}$N, global deformation	+ Global deformation can be applied to entire cell.[19,75,104] – Single cell technique.
Cell strain	Stretching of cells grown on an elastic silica membrane (Fig. 2), deformations imaged by microscopy.	Up to 140% strain, repeated at a defined frequency, global deformation	+ Can be applied to a large number of cells, allowing for extraction and quantification of mRNA and protein levels in response to mechanical strain.[47,48,105] – Not applicable for suspension cells.
Magnetic bead microrheology	Magnetic bead is attached to cell surface or embedded in the nucleus, external magnetic field is used to apply a stress to the bead and its position is tracked.	$\sim 10^{-7}$–10^{-9} N, local deformation	+ Local deformation is precisely controlled.[48,73] – Variation in contact area between bead and cell surface can challenge interpretation.[48]
Particle tracking	Nanosized beads are injected into the nucleus of living cells, their trajectories are tracked over time by video or laser tracking techniques.	No applied force - thermal motion of beads in local microenvironment	+ Involves no external perturbation; can probe the dimensions of spatial domains inside the nucleus.[55,106] – Probing interchromatin voids, not the load-bearing elements of the nucleus, does not provide meaningful information about material properties.
Cellular micromanipulation	Attach functionalized bead to plasma membrane, manipulate bead and visualize nuclear deformations.	Forces not determined.	+ Cell is intact.[10] – Difficult to interpret molecular details, and to quantify applied forces.

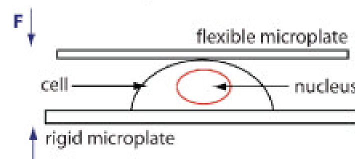
By labeling specific nuclear components with fluorescent probes, the response of specific nuclear components, including chromatin, lamins, and pore complexes, can be independently studied. Forces exerted by the experimental techniques presented here range from 10^{-7} to 10^{-9} N; forces on the nucleus in living cells are estimated to be on the order of $\sim 10^{-9}$–10^{-12} N (e.g. forces generated by microtubules,[107] fluid shear, and adhesion stress [108]). While the nature of these physical perturbations is not necessarily physiological, such studies provide essential information about the underlying structure and material properties of the nucleus. Note that it is challenging to obtain statistically significant results with single cell techniques.

Box 2. A primer to understanding nuclear mechanics. The degree to which a material can sustain stress is dictated by its mechanical properties and is described in terms of elasticity and viscosity. *Elasticity* describes how a solid material reversibly deforms in response to external stress; in other words, the ability of a material to resist deformation and to return to its original shape [units = Pa = kg $m^{-1} \cdot s^{-2}$]. Larger elasticity values indicate that the material will deform less under a given mechanical stress. The stiffness of a cell is similar to Jello (~100 Pa). *Viscosity* is a measure of the resistance of a fluid to deformation under shear stress [units = Pa · s = kg $m^{-1} \cdot s^{-1}$]. A *viscoelastic* material thus exhibits behavior that is both viscous (liquid-like) and elastic (solid-like).

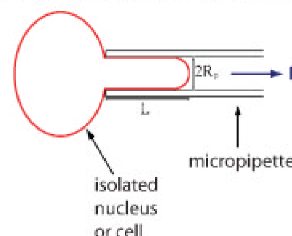
In three-dimensions, elastic properties are often described in terms of a *bulk modulus* that describes the degree of deformation in reponse to an external force [units = Pa]. Structures such as a membrane or the nuclear envelope can be described as two-dimensional materials whose material properties are characterized in terms of three moduli that correspond to the three unique ways a two-dimensional material can be deformed: bending (out-of-plane) deformations, stretching (in-plane area dilation) and shearing (in-plane deformation with constant area). Each of these deformations requires energy and is associated with a corresponding elastic constant: the *bending modulus*, κ (units = J), the *area expansion modulus*, K (units = N/m) and the *shear modulus*, μ (units = N/m). Dilation of a membrane under stretching is usually quite small as K for a lipid membrane is large (300–500 mN/m). However, the energy required to bend a membrane is much less, on the order of 10^{-21} J.

A survey of methods used to deform nuclei.

a cell compression



b micropipette aspiration



c cell strain

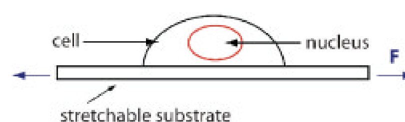


Figure 2. Techniques used to investigate mechanical stability of the nucleus. (**a**) Cell compression (between plates), (**b**) micropipette aspiration, (**c**) cell strain. This figure illustrates only a few common methods; several variations of these techniques exist.

investigate protein dynamics and localization, it is possible that overexpression of GFP-tagged proteins could alter amounts of protein synthesized as well as their behavior. Even though intranuclear lamins are less resistant to detergent and high-salt extraction than peripheral lamins, fluorescence recovery after photobleaching (FRAP) recovery rates are very slow (>180 minutes) in late G_1 and other interphase stages for both intranuclear and peripheral pools of GFP-lamin A, indicating that even intranuclear lamins form stable structures.[45] Intranuclear lamin A/C may thus act as a scaffolding protein for transcription factors, associating with various subnuclear particles, nuclear bodies and structural RNAs. However, the role of lamins within the nuclear interior and contributions of these lamins to the material properties of the nucleus remain unclear. Future studies of the mechanisms that regulate the structure and organization of the nuclear interior will be of key interest, especially since the spatial organization of the genome plays an important role in regulating gene expression.[46,72] It is also of interest to study the extent to which the nuclear interior contributes to properties of the entire nucleus[73] and cell; by determining how components of the nuclear interior respond to deformation, we can gain knowledge about the connectivity between components of the nuclear interior, as well as the mechanisms that regulate its spatial organization.

The nucleus is stiff relative to the cytoplasm

When considering the role of nuclear mechanics in the physiological functions of the cell, it is important to understand the differences in stiffness between the nucleus and the surrounding cytoskeleton, as extracellular forces are transmitted to the nucleus through the cytoskeleton. Experiments that apply mechanical forces to intact cells by micropipette aspiration or compression between plates, together with subsequent analysis of the deformation of whole cell and nucleus, provide a measure of the stiffness of the nucleus relative to the cytoplasm. Using these methods, chondrocyte, neutrophil and endothelial cell nuclei all appeared to be stiffer

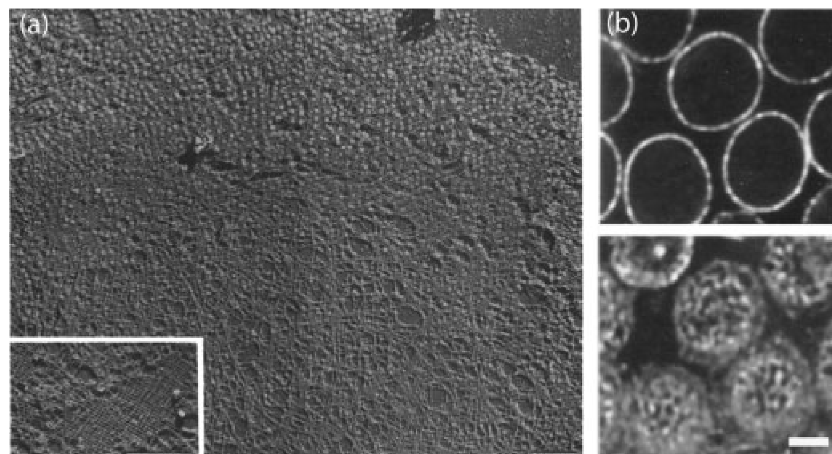


Figure 3. Structural analysis of the nucleus. (**a**) Nuclear lamina of *Xenopus* oocyte imaged by electron microscopy reveals a meshwork with embedded nuclear pore complexes and regions of regular lattice network structure (see inset). The sample was prepared by extracting the nuclear envelope with Triton X-100, then freeze-drying and metal shadowing. Scale, 1 μm. Image reprinted with permission from Aebi U, Cohn J, Buhle L, Gerace L 1986 Nature 323:560–564.[1] (**b**) Anti-lamin staining in interphase *Drosophila* nuclear cycle 14 embryos. These light microscope optical sections show the discontinuous filament network as stained by an anti-lamin monoclonal antibody (T40): (**top**) mid-optical section, (*bottom*) section grazing the surface of the nucleus. Out-of-focus information has been computationally removed. Scale, 2 μm. Image reprinted with permission from Paddy MR, Belmont AS, Saumweber H, Agard DA, Sedat JW 1990 Cell 62:89–106.[2]

than the cytoplasm.[36,74,75] Nuclei were also observed to behave as a viscoelastic solid with bulk moduli measured between 1 and 5 kPa for nuclei in living cells,[36,75] and 8 kPa for nuclei isolated by detergent extraction.[75] It should be noted that these studies did not account for the loss of nuclear volume under deformation, a factor that must be considered when interpreting measurements of nuclear stiffness because volume loss results in nuclear stiffening,[34] much like compressing a gel. It is important to note that, in experiments with isolated nuclei, buffer conditions can affect their viscoelastic properties (ACR, unpublished observations). Moreover, cells adapt their shape and cytoskeleton structure in response to substrate stiffness,[4,76] an environmental factor that could also affect nuclear mechanical properties.

The fact that the nucleus is stiffer than the surrounding cytoskeleton in normal chondrocyte, neutrophil and endothelial cells can have important implications under physiological conditions as the nucleus deforms much less than the rest of the cell. For example, nuclei in mechanically stressed tissue such as muscle may benefit by being more resistant to deformations, while migrating fibroblasts or lymphocytes that squeeze themselves through narrow blood vessels may modify their nuclei[77] to become more deformable and achieve such extreme reductions in nuclear diameter. How can the nucleus regulate its stiffness? Evidence of greater changes in nuclear shape with altered nuclear envelope composition[47] suggests that nuclear envelope material properties play a major role in determining nuclear shape stability.

The nuclear envelope stretches and resists shear forces

To obtain a more detailed understanding of the material properties of nuclear envelopes, specific components of the nuclear envelope can be labeled with distinct fluorescent probes and deformed by micropipette aspiration. The resulting response of specific nuclear envelope components is monitored. Such studies of isolated nuclei reveal buckling and crumpling of the nuclear surface upon aspiration,[34,35,52] a behavior that contrasts that of fluid membranes and indicates that the nuclear envelope resists shear forces. To quantitatively describe nuclear envelope elastic properties, the nuclear envelope of both isolated nuclei and nuclei within living cells transiently expressing green fluorescent protein conjugated to lamin A (GFP–lamin A) was investigated by confocal imaged microdeformation.[35] In these experiments, large nuclear deformations were induced by micropipette aspiration and imaged by confocal microscopy. The observed decrease in the intensity of GFP–lamin A within the aspirated part of the nuclear envelope indicates that the nuclear envelope behaves as a solid-elastic material. Labeling nuclear pore complexes in addition to lamins reveals that both nuclear envelope moieties behave as a continuous two-dimensional elastic solid.[35] This is in agreement with FRAP measurements which document that some nuclear pore complex proteins (for example, nucleoporin 153) as well as the B-type lamins exhibit low mobility on time scales of up to 40 hours.[78] The solid-elastic behavior of the GFP–lamin delineated nuclear envelope is observed in various cell types

from different species: for example, HeLa[35] and mouse embryonic fibroblasts labeled with GFP–lamin A,[34] as well as *Xenopus* oocytes[52] and TC7 epithelial cells (a subline of African green monkey kidney cells[37]), that are labeled with GFP–lamin B. All of these cells exhibit a nuclear envelope that stretches and resists shear, thus suggesting the existence of universal nuclear envelope features in all metazoan cells.

Nuclear membranes exhibit fluid characteristics

Fluorescently labelling individual components of the nuclear envelope and then deforming the nucleus can provide more detailed information about the connectivity and strength of interaction between different nuclear components. In addition to the lamins that peripherally associate with the nuclear envelope, a large number of transmembrane protein complexes and integral membrane proteins[79] are embedded in the nuclear membranes. Indeed, the chemical composition of the nuclear membrane is dominated by proteins: the ratio of phospholipids to proteins by weight ranges from 0.2 to 0.5.[80,81] While lamins and certain nuclear pore complexes exhibited behaviour of a contiguous two-dimensional supramolecular scaffold with material properties of a solid, nuclear membranes of isolated HeLa cell nuclei stained with a lipophilic probe deform and irreversibly vesiculate in response to micropipette aspiration.[34] This shows that nuclear membranes are fluid-like and deform at energies that are typically needed to induce out-of-plane deformations in lipid bilayers (i.e. 10^{-21} J) rather than those required to deform the lamina–nuclear pore complex scaffold. These observations indicate that nuclear membranes themselves do not contribute significantly to nuclear shape stability. Moreover, these observations are consistent with the deformation patterns observed after micromanipulation of cells both before and after Triton X-100 treatment.[10] The continuous vesiculation of nuclear membranes during micropipette aspiration further implies that nuclear membranes are connected to a membrane reservoir that may include intranuclear membrane invaginations.[82] Interestingly, overexpression of proteins such as B-type lamins with the C-terminal motif that targets them to nuclear membranes causes proliferation of intranuclear membranes.[83,84] The structure and function of such intranuclear membranes remains to be determined.

As described above, localization of most lamins to the nuclear envelope is facilitated by the C-terminal farnesyl-group, a lipid-like moiety that is post-translationally attached to lamins. Farnesol itself does not influence membrane shape stability,[85] indicating that farnesylation is a non-perturbing way to localize lamins at the nuclear envelope. The molecular organization of the lamina remains unclear (Box 1), but farnesylation plays a critical role in nuclear envelope structure: in Hutchison-Gilford progeria syndrome (HGPS), farnesylated progerin becomes irreversibly anchored to the nuclear membrane, thereby disrupting lamina structure and function. Recent evidence indicates that the persistent farnesylation of the mutant protein is toxic to cells.[86,87] Inhibiting farnesylation can decrease nuclear shape irregularities in fibroblasts from humans with progeria syndromes[88,89] This suggests great potential for therapeutic treatment of at least some of the envelopathies by regulating farnesylation.[17]

Altered nuclear shape and stability in envelopathies

Studies of nuclear envelope material properties are motivated by evidence that changes in nuclear envelope composition alter nuclear shape and stability: downregulation of lamin in *C. elegans* causes rapid changes in nuclear shape;[40] dominant negative lamin mutants disrupt lamina organization resulting in nuclei that are mechanically fragile and exhibit abnormal shapes;[90,91] and mouse embryonic fibroblasts lacking the *Lmna* gene encoding lamin A and C have irregularly shaped nuclei.[92,93] In these cells, nuclei deform more easily in response to cell strain and compression and are more likely to rupture under mechanical stress.[19,47] Lamin A/C–deficient cells can serve as a model for envelopathies where mutations in *LMNA* can lead to structural changes in the lamina and loss of functional lamins from the nuclear envelope. Indeed, many cells from patients with envelopathies including muscular dystrophies, FPLD and HGPS also have nuclei with either depleted or accumulated lamins and exhibit nuclei with abnormal shape when taken into culture.[94–96] In contrast to lamin mutations resulting in muscular dystrophies, cells from HGPS patients exhibit altered nuclear envelope ultrastructure that is characterized by nuclei with a thicker lamina; these nuclei are more resistant to compression by external forces.[97]

In addition to lamins, mutations in other nuclear envelope proteins can also cause envelopathies. For example, the loss of function of the inner nuclear membrane protein emerin gives rise to EDMD. Emerin binds to structural proteins including lamins and is essential for the proper localization of lamins at the nuclear envelope. To address how emerin affects nuclear shape and mechanics, emerin-deficient mouse embryo fibroblasts have been used as a model system. These cells display greater variations in nuclear shape over time and repetitive mechanical stretching results in increased rates of apoptosis that is linked to impaired induction of mechanosensitive genes.[48] While these cells exhibited apparently normal nuclear deformations in cellular strain experiments and no obvious defects in nuclear fragility when perturbed by the positive pressure of micropipette injection,[48] subsequent confocal imaged microdeformation of these cells revealed a ratio of the area expansion to shear modulus (K/μ) that is less than half that of the wild-type cells. These observations clearly demonstrate altered nuclear envelope properties in

the emerin-deficient mouse embryo fibroblasts.[34] Taken together, these results show that loss of emerin affects nuclear envelope ultrastructure and mechanical properties as well as the response of mechanosensitive genes, possibly by stabilizing an actin-containing supramolecular scaffold at the nuclear envelope.[68]

Towards an integrated understanding

Exactly how nuclear envelope elasticity is altered by mutations in nuclear envelope proteins is far from clear; possible mechanisms include structural changes such as defects (e.g. holes, vacancies) in the lamina meshwork and interference with binding of cytoplasmic proteins such as nesprins or actin to the nuclear envelope.[68,98–100] Loss by mutation of lamins at the nuclear periphery[94,101] may also lead to changes in nuclear envelope mechanical properties: as discussed above, lamin A/C-deficient nuclei are more susceptible to deformation by mechanical stress.[19,47] In contrast, mutations causing HGPS render nuclei *more* resistant to deformation. One possible explanation for this behavior is that structural and mechanical changes of the nuclear envelope alter force transduction to the nucleus. Mutations in nuclear envelope proteins may also affect their binding to transcriptional regulators, thereby altering tissue-specific gene expression patterns and/or other epigenetic mechanisms by affecting higher-order chromatin structure. To gain further insights into the disease mechanism of envelopathies requires multiscale studies ranging from single molecules to whole cells and tissues to elucidate the lateral organization of the lamina network (Box 1) as well as the elastic properties of individual lamina proteins, lamin filaments,[102] and lamin networks. Unraveling the enigma of tissue-specific phenotypes of envelopathies requires studies that address how the mechanical properties of nuclei, cells and, ultimately, tissues change during development, differentiation and aging. A plausible explanation of the tissue-specific effects observed in envelopathies is that prolonged exposure to repeated strain may result in variations in the stiffness of different tissues.

While our understanding of the supramolecular architecture and mechanical properties of nuclei has progressed rapidly within the last decade, many questions have remained elusive. For example, what is the lateral organization of the nuclear lamina and how does it provide mechanical stability to the nucleus? Can the nucleus mechanically sense forces for regulating gene expression? Here we have discussed metazoan nuclei that have lamins, but what are the physical properties of nuclei in cells that lack lamins such as yeast, amoebae and plants? Further insights into nuclear mechanical properties require studies ranging from the molecular to the tissue level. To achieve a fully integrated view must involve a transdisciplinary experimental approach including physics, chemistry, biology and engineering as well as theory, modeling and simulation. Assimilating our knowledge of nuclear mechanics and structural organization together with large-scale studies profiling gene expression will ultimately lead to a more integrated understanding of nuclear structure and function, as well as how the nucleus contributes to the physical properties of the cell and tissues.[11,103] Such studies will ultimately broaden our mechanistic view of how physical forces are transmitted through the cell and, moreover, how cells and tissues respond to mechanical stimuli and their physical environment.

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