Mechanics and functional consequences of nuclear deformations

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Abstract | As the home of cellular genetic information, the nucleus has a critical role in determining cell fate and function in response to various signals and stimuli. In addition to biochemical inputs, the nucleus is constantly exposed to intrinsic and extrinsic mechanical forces that trigger dynamic changes in nuclear structure and morphology. Emerging data suggest that the physical deformation of the nucleus modulates many cellular and nuclear functions. These functions have long been considered to be downstream of cytoplasmic signalling pathways and dictated by gene expression. In this Review, we discuss an emerging perspective on the mechanoregulation of the nucleus that considers the physical connections from chromatin to nuclear lamina and cytoskeletal filaments as a single mechanical unit. We describe key mechanisms of nuclear deformations in time and space and provide a critical review of the structural and functional adaptive responses of the nucleus to deformations. We then consider the contribution of nuclear deformations to the regulation of important cellular functions, including muscle contraction, cell migration and human disease pathogenesis. Collectively, these emerging insights shed new light on the dynamics of nuclear deformations and their roles in cellular mechanobiology.

As the largest and stiffest organelle of eukaryotic cells[1], the nucleus is constantly subjected to intrinsic and extrinsic forces that can lead to small and large nuclear deformations. For example, cytoskeletal forces position the nucleus within polarized cells, and actomyosin forces are required to squeeze the nucleus of migrating cells through small constrictions such as interstitial spaces. Accumulating evidence suggests that the nucleus contributes to cellular perception of mechanical stimuli and the corresponding cellular response through dynamic changes of its structure and morphology[2,3]. Therefore, the nucleus must be considered not only as the primary site of gene replication and transcription but also as a fundamental mechanotransduction component of the cell, capable of mechanosensing and orchestrating key cellular functions in response to mechanical stimulation.

The mechanotransduction properties of the nucleus are now well recognized, including its ability to adapt to the physical microenvironment of the cell with changes in nuclear morphology or the expression of specific genes[4,5]. By contrast, the role of the nucleus as a mechanosensitive organelle — whereby physical deformations induced by forces transmitted to the nuclear envelope directly impact nuclear and cellular functions — has only recently begun to emerge (BOX 1). For example, several lines of evidence indicate that forces acting on the nucleus can induce sufficient nuclear deformations to modulate chromatin structure and trigger important protein conformational changes, thereby activating or repressing mechanoresponsive genes[6,7]. In vivo, the impact of nuclear deformations has been highlighted by the observation that many human diseases are associated with abnormal nuclear shapes[8] and disturbed mechanotransduction processes[9] such as impaired activation of genes in response to mechanical stimulation or mechanically induced DNA damage (BOX 2).

In this Review, we discuss the current understanding of the physical properties of the nucleus, and how the different nuclear components affect its mechanics. We then review the physiological contexts of nuclear deformations and highlight the importance of physical connections between the nuclear envelope and the cytoskeleton in the transmission of forces to the nucleus and driving its deformations. We also consider the emerging role of nuclear deformations in cellular mechanosensing and mechanotransduction.

Nuclear organization

The extent of nuclear deformations is determined by the balance between the mechanical properties of the nucleus and the mechanical forces acting on it. Nuclear mechanical properties are dependent on the various components constituting the nuclear structure. The forces acting on the nucleus are primarily derived from the cytoskeleton, which establishes physical connections with the nuclear envelope (FIG. 1), although some forces can also originate from the outside of the cell.

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Box 1 | **Nuclear mechanosensing**

Although it is now well recognized that nuclear deformations have both rapid and long-lasting consequences on nuclear and cellular function, the precise mechanisms by which nuclear deformations are translated into biochemical signals, and to what degree the nucleus itself serves as a cellular mechanosensor, remain incompletely understood. As a note of caution, many nuclear changes in response to external mechanical stimuli (for example, altered nuclear shape, chromatin organization, gene expression) cited as indicators of nuclear mechanosensing may reflect, at least in part, downstream effects of signalling pathways initiated in the cytoplasm or cell surface, rather than direct nuclear mechanosensing. In the following, we highlight recent findings and novel insights into established and proposed nuclear mechanosensing mechanisms. For a more detailed discussion, we refer the reader to some excellent recent reviews[32,194,218,219].

Stretch-activated opening of channels in the nuclear membranes

Nuclear pore complexes allow passage of small molecules while excluding larger molecules that do not contain nuclear localization sequences or are transported by other proteins. Recent live cell imaging, electron microscopy and cryo-electron tomography studies found that nuclear pore complexes are highly sensitive to nuclear membrane tension[15,198,199], increasing their diameter in response to elevated nuclear membrane tension and thus facilitating nuclear import, including of the mechanoresponsive transcription factor[198]. The nuclear envelope and endoplasmic reticulum (ER) membranes (which are continuous with the nuclear envelope) contain various other stretch-sensitive ion channels such as Piezo1 and inositol triphosphate receptor (InsP3R). Increased nuclear membrane tension, in response to cell compression, osmotic swelling or stretching application, may trigger opening of these channels and calcium release from the ER and perinuclear space, which can lead to increased cell contractility[17,127] as well as to the uptake of calcium into the nucleus, resulting in changes in chromatin organization and nuclear softening driven by loss of heterochromatin[16]. However, it remains unclear whether opening of these ion channels in response to cellular deformation occurs at the nuclear envelope, ER or the plasma membrane. One interesting hypothesis is that all three locations contribute to cellular mechanotransduction, depending on the context. As such, spatial coordination between ion channels in the different membranes would allow cells to distinguish between different sources of nuclear membrane strain such as osmotic swelling and compression[3,127].

Mechanosensing by the nuclear membranes and nuclear envelope proteins

Changes in the tension or curvature of the nuclear membranes can alter the packing and/or composition of nuclear membrane phospholipids, which, together with increased intranuclear calcium concentrations, promote binding of nucleoplasmic phospholipase A2 (cPLA2) to the inner nuclear membrane[192–194], where it can initiate cell signalling events related to actomyosin contractility and inflammation.

Besides altering protein interactions with the nuclear membranes, forces acting on the nucleus can also lead to local unfolding, conformational changes and increased phosphorylation of lamins[105,109,220–222], although the functional relevance of these changes remains to be fully characterized. Furthermore, force application to the nucleus via nesprins leads to phosphorylation of emerin via Src kinases, resulting in the recruitment of lamins to the nuclear envelope and nuclear stiffening[223]. Although it remains unclear whether the increased phosphorylation is due to mechanically induced activation of nuclear Src kinase or emerin becoming more accessible to the kinase, this study, which was conducted on isolated nuclei, provided some of the most direct evidence for nuclear mechanosensing.

Force-induced changes in chromatin organization

Several studies have demonstrated mechanically induced changes in chromatin organization that could affect gene expression, including in neutrophils that had migrated through tight constrictions[208], macrophages under spatial confinement[179] and a 3D chemo-mechanical model of the nuclear interior and its connections to the cytoskeleton. However, these studies did not completely address whether the effects were nucleus-intrinsic or mediated by cytoplasmic signals. Support for direct involvement of chromatin remodelling in nuclear mechanosensing comes from two recent studies, which found that force application to the cell surface leads to near instantaneous chromatin deformation, visualized by tracking multiple GFP–LacI-labelled genomic loci, and rapid (<15 s) increase in transcription of the corresponding transgene and other genes[204,205]. The magnitude of the response was directly related to the extent of chromatin deformation and histone methylation status. Of note, the chromatin 'stretching' reported in these studies likely does not reflect stretching of the DNA itself but rather partial unpacking of the chromatin, which may promote access to transcriptional regulators or polymerases[205]. Depletion of lamins, emerin or linker of nucleoskeleton and cytoskeleton (LINC) complex components abolished the force-induced gene expression[204], pointing to the importance of nucleo-cytoskeletal coupling in nuclear mechanosensing. The effect of LINC complex disruption on the activation of mechanoresponsive genes contrasts with a previous study in which LINC complex disruption did not alter the expression of several mechanoresponsive genes despite reducing nuclear deformation[36], possibly reflecting differences in cell type, the mode of force application or the extent/type of nuclear deformation resulting from the applied force.

Another intriguing thought is that liquid–liquid phase separation, which is a central player in the assembly of membraneless compartments within the nucleus, could contribute to nuclear mechanosensing. Indeed, significant mechanical forces through attractive and repulsive interactions between protein droplets and chromatin can alter chromatin organization and rearrangements[84,90]. One could therefore speculate that externally applied forces and resulting nuclear deformation could affect intranuclear biomolecular condensates, which are highly dynamic structures that may condense or dissolve under specific nuclear deformations, and thereby regulate nuclear functions.

Mechanotransduction
In its literal sense, mechanotransduction refers to the molecular process in which mechanical stimuli are converted (or transduced) into biochemical signals, that is, equivalent to the 'mechanosensing' defined below. However, mechanotransduction is commonly used to more broadly refer to cellular responses to changes in the mechanical environment, including forces, deformations or mechanical properties. In this article, we use this broader definition of mechanotransduction.

Mechanosensing
Molecular process through which cells or cellular components translate mechanical forces or deformations into biochemical signals.

The nuclear envelope. The nuclear envelope serves multiple pivotal functions: it controls access of cytoplasmic proteins to the genome, provides structural stability to the nucleus, and physically connects the nuclear interior and cytoskeleton (FIG. 1; see next sub-section). The nuclear envelope comprises nuclear membranes, the nuclear lamina and nuclear pore complexes (NPCs). The inner and outer nuclear membranes (INM and ONM, respectively) are two concentric lipid bilayers, each ~4 nm thick, separated by the ~20–50 nm-wide perinuclear space[10] (FIG. 1a).

Stress
Expression of the mechanical loading in terms of force applied per cross-sectional area of an object. Units of stress are $N\,m^{-2}$ (or Pa).

Rhabdomyosarcoma
Highly aggressive form of cancer mostly observed in children and adolescents that usually develops in soft tissues, such as the muscles, from mesenchymal cells that have failed to fully differentiate.

Segmental premature ageing disease
Pathological condition that reflects some but not other phenotypes of the normal ageing process at a much earlier age. For example, children with Hutchinson–Gilford progeria syndrome develop severe cardiovascular disease (heart attacks and strokes) in their early teens but lack neurodegenerative defects such as dementia and are not more prone to cancer.

The ONM is contiguous with the endoplasmic reticulum (ER) and can expand by the addition of lipids from the ER, allowing the nuclear surface area to adapt in response to deformation (although membrane recruitment to the nuclear envelope may be limited by physical resistance from the ER). Furthermore, the nuclear membrane is wrinkled and folded at low tension, which provides an additional membrane reservoir for adjusting nuclear shape[11]. NPCs are homogeneously distributed over the nuclear membrane surface[12] and regulate the active nuclear transport of macromolecules larger than ~50 kDa into and out of the nucleus[12,13]. The size of the NPCs can change in response to mechanical stress, which accounts for up to 10% of nuclear surface expansion during nuclear deformations[14–16]. The nuclear envelope and ER additionally contain mechanosensitive ion channels

Box 2 | Human pathologies associated with nuclear deformations

Abnormalities in nuclear and chromatin organization are hallmarks of many diseases, ranging from heart disease to premature ageing and cancer[224], where they can indicate, for example, metastatic potential[8,225,226]. Hundreds of mutations and variants have been found in genes encoding nuclear envelope components, including inner and outer nuclear membrane proteins (for example, nesprins, emerin and SUN (Sad1p, UNC-84) proteins) and lamins, and the diseases resulting from these mutations[227] are collectively called nuclear envelopathies. Mutations in the *LMNA* gene, which encodes lamins A/C, alone cause over 13 human diseases, including congenital dilated cardiomyopathy[228,229], various types of muscular dystrophy[230] and progeria[231], with altered nuclear stability and mechanotransduction thought to contribute, at least in part, to the disease mechanism.

LMNA mutations associated with muscular dystrophy and dilated cardiomyopathy often result in more deformable and more fragile nuclei[55]. This leads to extensive nuclear envelope damage in skeletal muscle cells in vitro and in vivo, resulting from mechanical stress on the more fragile nuclei[119]. Lamin mutations associated with muscular dystrophy can also impair linker of nucleoskeleton and cytoskeleton (LINC) complex function[55,232,233] and other cellular processes. Furthermore, abnormal YAP (Yes-associated protein) activity, known to be responsive to nuclear deformation and lamin A levels[27,198], has been reported in muscular dystrophy and rhabdomyosarcoma[234]. In *LMNA*-related congenital muscular dystrophy, lamin mutations increase YAP nuclear localization via increased nuclear import, implicating YAP as a potential pathogenic contributor in muscular dystrophies caused by nuclear envelope defects[235].

Hutchinson–Gilford progeria syndrome (HGPS) is an exceptionally rare and severe segmental premature ageing disease caused by mutations in the *LMNA* gene. Most cases of HGPS result from a mutation that leads to alternative splicing, causing a truncated form of prelamin A (LAΔ50) that remains farnesylated. Cells from patients with HGPS have irregular nuclear shapes[236], increased nuclear stiffness and increased sensitivity to mechanical stress[237–240], which may be responsible for the progressive loss of vascular smooth muscle cells in HGPS. The structural abnormalities of the mutant lamins and their stronger interaction with other lamins reduces the ability of the nuclear envelope to dissipate mechanical stress[240]. In addition to perturbing nuclear lamina organization, the mutant lamins also alter chromatin organization. Restoring the loss of heterochromatin alone in HeLa cells expressing LAΔ50 and in cells from patients with HGPS is sufficient to restore normal nuclear shape, suggesting that heterochromatin loss may be responsible for many of the phenomena associated with HGPS[64,91,241].

Deficiency of lamin B1 and lamin B2, but also increased expression of lamin B1, are associated with neurodevelopmental defects and distinct nuclear shape abnormalities in neurons[242,243]. Loss of B-type lamins interferes with proper nucleokinesis, a nuclear translation process required during neuronal development[73]. Lamin B1-deficient and lamin B2-deficient mouse embryos have defective migration of cortical neurons[242–244], leading to neuronal layering abnormality in the cerebral cortex along with neonatal mortality. The neuronal migration abnormality may be explained by a weakened nuclear lamina (in particular as developing neural tissue lacks expression of A-type lamins) as preliminary work shows that B-type lamin depletion may affect nuclear mechanical properties[245]. Duplication of the gene encoding lamin B1 results in autosomal dominant leukodystrophy, which is characterized by widespread loss of myelin in the central nervous system[246], although the molecular mechanisms underlying these defects remain unclear.

In addition to mutations in nuclear envelope proteins, cytoplasmic proteins can also result in nuclear defects and diseases. Tauopathies refer to a class of neurodegenerative diseases involving the aggregation of Tau protein, a neuronal microtubule-associated protein, into neurofibrillary or gliofibrillary tangles in the brain. Pathological accumulation of Tau, known as Tau nuclear rods or Tau-positive nuclear indentations[247], have been identified in several neurodegenerative disorders, including Alzheimer disease, frontotemporal dementia and Huntington disease[248,249]. However, the mechanism underlying Tau-mediated pathogenesis is still unclear. Mutations in the Tau-encoding gene *MAPT* result in Tau mislocalization to the cell bodies rather than to the neuronal axon. This leads to abnormal microtubule organization, which can potentially deform the nuclear envelope via LINC complex-based coupling[250], causing large nuclear lamin invaginations and defects in nucleocytoplasmic trafficking[251,252].

Although the pathological mechanisms underlying the diverse envelopathies are still not fully understood, various hypotheses have been put forward. The key role of the nuclear envelope in regulating nuclear mechanics and mechanotransduction suggests that defects in nuclear envelope/lamina proteins can result — directly (by changing nuclear physical properties) or indirectly (for example, via changes in chromatin organization or nucleo-cytoskeleton coupling) — in impaired nuclear stability, increased nuclear fragility and perturbations of mechanotransduction pathways, which could explain some of the tissue-specific phenotypes. This hypothesis is supported by numerous in vitro and in vivo observations of abnormalities in nuclear morphology (for example, wrinkling, irregularities, blebs and invaginations) associated with *LMNA* mutations linked to dilated cardiomyopathy, muscular dystrophy and HGPS as well as the increased DNA damage found in several laminopathies[26,187,253]. Besides their mechanical function, lamins have a key role in tethering and organizing chromatin as well as in signalling involved in transcriptional regulation. In support of this, laminopathic nuclei often display alterations in the organization of chromatin and signalling as well as broad alterations in gene expression[7,254–258], which could contribute to tissue-specific phenotypes.

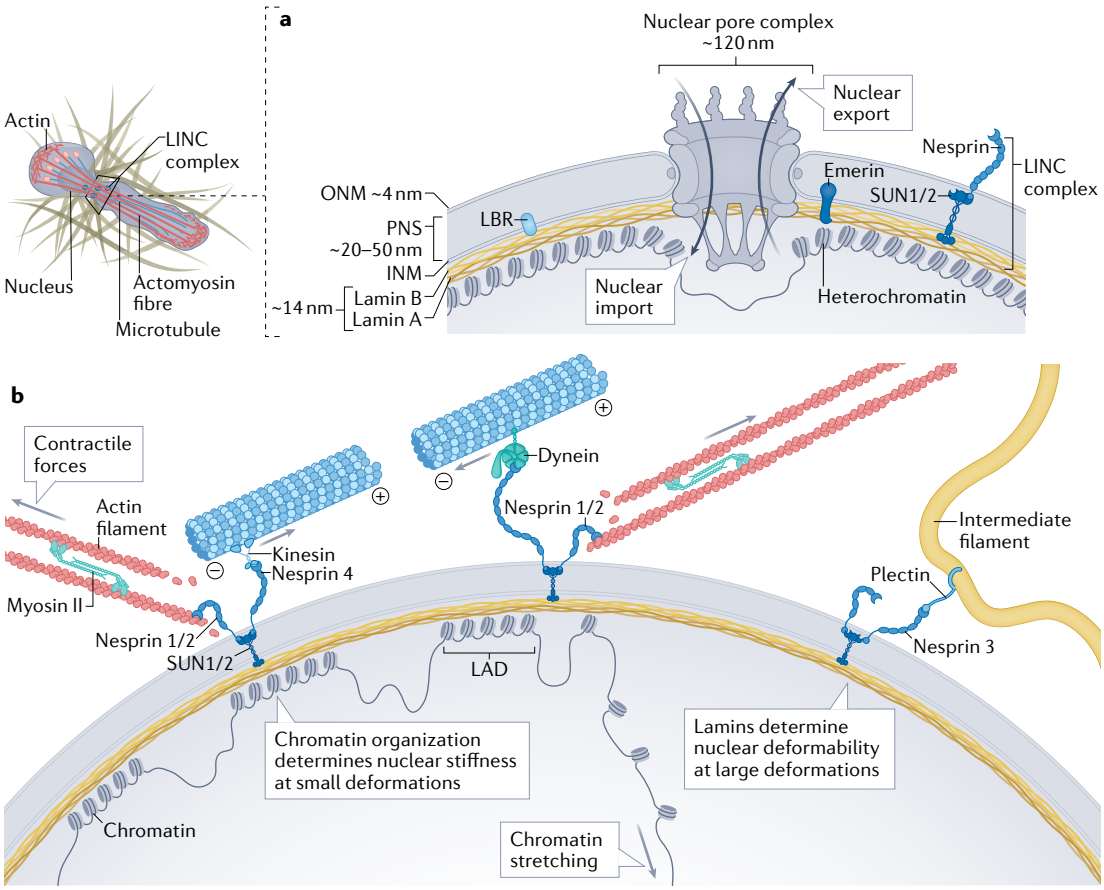


Fig. 1 | **The nuclear envelope and nucleo-skeletal interactions. a** | The nuclear envelope is composed of the inner (INM) and outer (ONM) nuclear membranes, which form a double lipid bilayer separated by the perinuclear space (PNS), and the proteinaceous nuclear lamina, which is attached to the INM and in close contact with condensed chromatin. The nuclear lamina meshwork is composed of A-type and B-type lamins. Nuclear pore complexes span the nuclear envelope and are surrounded by less condensed chromatin, and allow controlled nuclear import and export of large molecules. Lamins, along with other INM proteins, such as the lamin B receptor (LBR) and emerin, anchor chromatin to the nuclear envelope. Nesprins, ONM, SUN (Sad1p, UNC-84) domain proteins and INM together form the linker of nucleoskeleton and cytoskeleton (LINC) complex. The LINC complex provides a direct physical connection between cytoskeletal filaments and the nuclear interior, which allows the transfer of extracellular and cytoskeletal forces to the nucleus. **b** | The nuclear interior is connected to cytoskeletal filaments by nesprins and SUN domain proteins (SUN1/2). Nesprin 1 and nesprin 2 bind to actin filaments, whereas nesprin 3 interacts with intermediate filaments. Nesprins 1, 2 and 4 can interact with microtubules via kinesin and dynein molecular motors. Interactions between molecular motors and cytoskeletal filaments generate forces that are directly transmitted to the nucleus through LINC complexes. The genomic regions connected to the lamina are lamina-associated chromatin domains (LADs), which have low transcriptional activity.

such as Piezo1 (REF.[16]) and inositol triphosphate receptors (InsP3Rs)[17] that can respond to nuclear membrane tension (BOX 1). The nuclear lamina, a dense protein network underlying the INM, is primarily composed of lamins, a family of nuclear intermediate filaments. Lamins assemble into 300–400 nm-long and ~3.5 nm-thick nonpolar filaments, and form a ~14–30 nm-thick meshwork[18,19]. In mammalian somatic cells, the nuclear lamina is predominantly composed of four lamin isoforms: two A-type lamins (A and C) and two B-type lamins (B1 and B2)[20]. The *LMNA* gene encodes lamin A and lamin C and some rare isoforms that arise from alternative splicing, and the *LMNB1* and *LMNB2* genes encode lamin B1 and lamin B2, respectively[20]. Each lamin isoform forms separate but interacting meshworks[21,22]. B-type lamins are permanently modified by farnesylation and are thus primarily located at the nuclear membranes (FIG. 1a), whereas A-type lamins either lack farnesylation sites completely (lamin C) or have their farnesylated C terminus removed post-transcriptionally (lamin A) and can be localized at both the nuclear lamina and the nuclear interior[23], with the intranuclear distribution of lamins mediated by lamina-associated polypeptide 2α (LAP2α) and other proteins[24]. Lamins interact with various binding partners, including NPC proteins, INM proteins, chromatin and various transcription regulators[20]. Accordingly, the lamina has many structural and other functions, including contributing to nuclear shape, mechanical stability, nucleo-cytoskeletal coupling, nuclear positioning, genome organization and mechanosensing[25–27].

The nuclear interior. The nuclear interior primarily consists of chromatin and nuclear bodies such as nucleoli, Cajal bodies and promyelocytic leukaemia bodies, which

Intermediate filaments
Large family of nuclear and cytoskeletal filaments that includes keratins (types I and II), desmin and vimentin (type III), neurofilaments (type IV) and lamins (type V). Intermediate filaments form dimers that then assemble into larger nonpolar filament structures that are characterized by their ability to extend substantially under mechanical stress.

are membraneless structures with specific signalling and processing functions[28]. Chromatin is composed of DNA and DNA-binding proteins, particularly histones (FIG. 2). Chromatin can be classified into two categories, depending on its level of compaction, transcriptional activity and histone modifications. The loosely packed

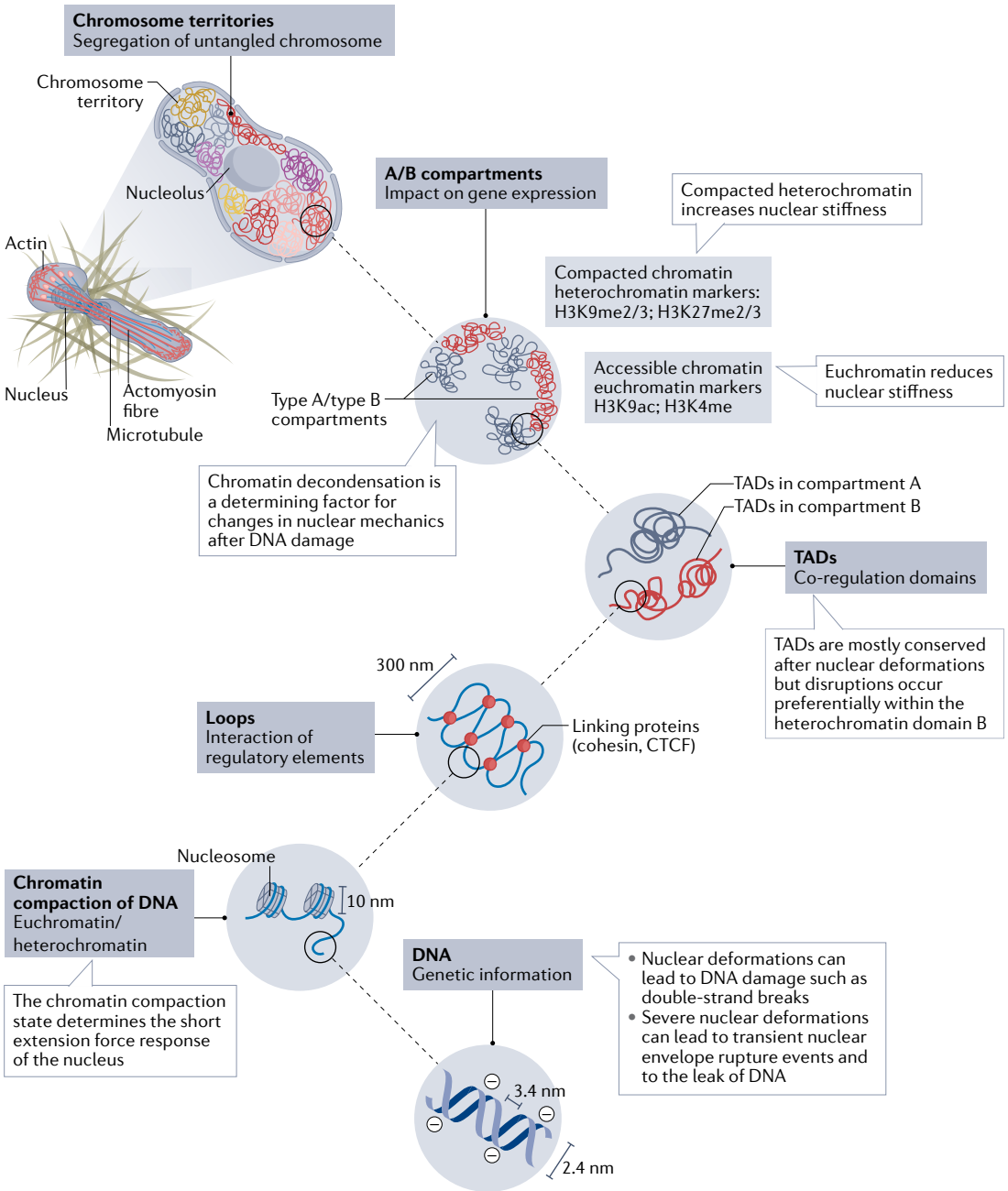


Fig. 2 | **Chromatin organization and its impact on nuclear mechanics.** The figure illustrates the different levels of chromatin organization, from bottom to top. Chromosomal DNA is packaged inside the cell nucleus with the help of histones. At the simplest level, chromatin is a double-stranded helical structure of DNA. The negatively charged DNA double helix is complexed with histones, which are positively charged proteins, to form nucleosomes. Inside the interphase nucleus, chromosomes occupy distinct territories (highlighted by different colours). Within each chromosome territory, the chromatin is folded into multiple loops and segregated into two distinct compartments: compartment A, clustered around the nucleolus and nuclear bodies (permissive region), and compartment B (repressive region), located at the nuclear periphery. Within compartments, chromatin is further partitioned into topologically associating domains (TADs), which have preferential intradomain interactions compared with interdomain interactions with the neighbouring *cis* chromatin domains. Histone methylation, particularly at residues H3K9 and H3K27, is often associated with heterochromatin, whereas histone acetylation, particularly at residue H3K9, or histone methylation at residue H3K4, is typically associated with euchromatin. In addition to lamins, chromatin is a major mechanical component that determines nuclear size and stiffness. Chromatin is particularly important in resisting small nuclear deformations, whereas lamins dominate for large nuclear deformations. Chromatin modifications associated with euchromatin typically lead to reduced nuclear stiffness, while chromatin modifications associated with the more compacted heterochromatin increase nuclear stiffness.

Farnesylation
Post-translational modification of proteins catalysed by the enzyme farnesyltransferase, which adds a 15-carbon unsaturated hydrocarbon chain to a cysteine residue via a thioether linkage, thus anchoring the protein to a lipid membrane.

Lamina-associated polypeptide 2α
One of six alternatively spliced isoforms of the mammalian *LAP2* gene that is functionally and structurally different. LAP2α shares only the NH_2 terminus with the other isoforms and contains a unique COOH terminus. LAP2α is localized throughout the nucleus and is a specific binding partner of nucleoplasmic A-type lamins.

euchromatin is transcriptionally accessible and mostly localized in the nuclear interior and near NPCs. Densely packed heterochromatin is considered transcriptionally repressed and tends to be located at the nuclear periphery and around the nucleoli, with likely connections in between[29]. The physical connections between chromatin and the nuclear envelope not only provide control over gene expression but also increase nuclear stiffness and stability, akin to the mechanical reinforcement used in composite materials or cross-linked polymer networks[30–32]. Although chromatin generally displays solid-like properties at the mesoscale, at high cation concentrations it can undergo liquid–liquid phase separation (LLPS) and, locally, chromatin can behave like a phase-separated condensate[33,34]. These physical properties of chromatin need to be considered when studying the contribution of chromatin to the mechanical properties of the nucleus (see next section).

Physical connections between the nucleus and the cytoskeleton. Force transmission between the cytoskeleton and the nucleus is required for nuclear movement and positioning, for example, during cell migration, nucleokinesis and muscle fibre regeneration[35] (FIG. 3). Cytoskeletal connections to the large and rigid nucleus are also important for cytoskeletal organization, affecting the organization of stress fibres, focal adhesions and cell–cell adhesions[36,37]. The physical coupling between the cytoskeleton and the nuclear interior is achieved by linker of nucleoskeleton and cytoskeleton (LINC) complexes that span the nuclear envelope[35,36] (FIG. 1a), although additional mechanisms, such as molecular motors binding to NPCs[38] or microtubules connecting to emerin and other nuclear envelope proteins[39], may further contribute to nucleo-cytoskeletal coupling. LINC complexes are composed of nesprins (nuclear envelope spectrin repeat proteins) localized within the ONM

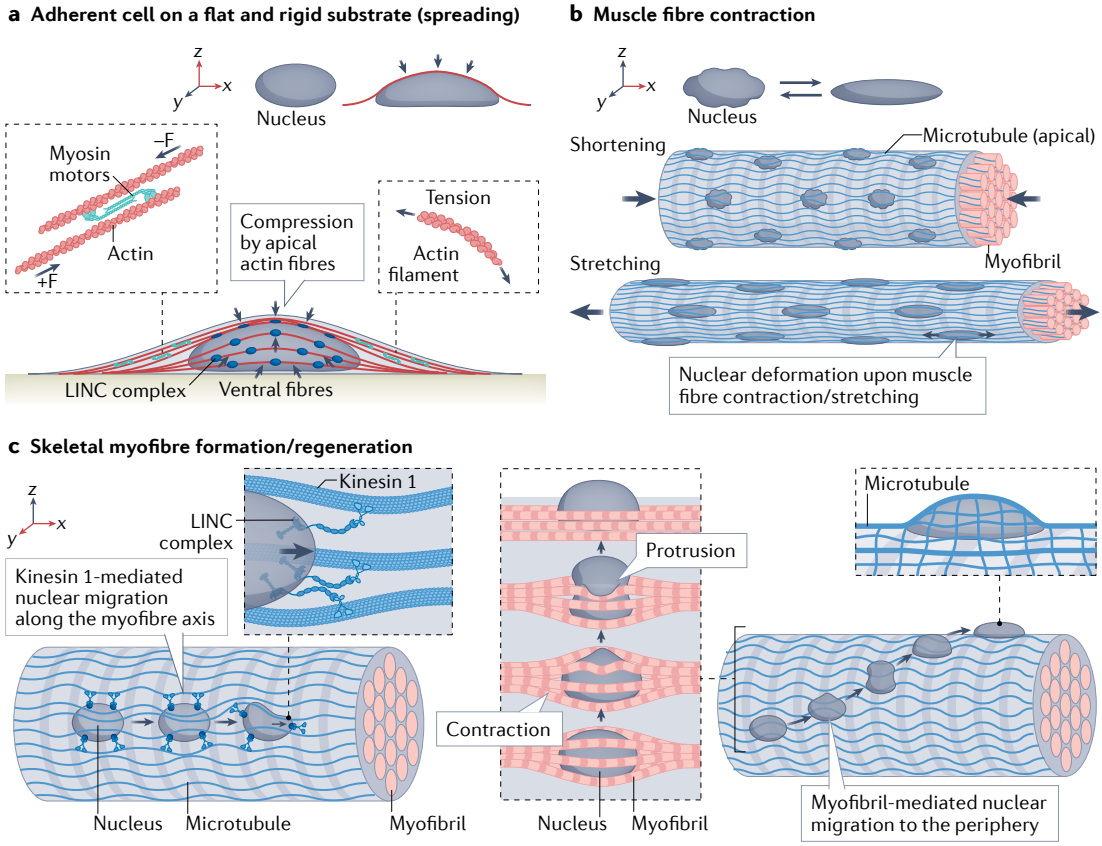


Fig. 3 | **Physiological sources of nuclear deformations. a** | Actomyosin contraction produces tension in actin fibres (in red) spanning the nucleus, which are connected to the nuclear envelope via linker of nucleoskeleton and cytoskeleton (LINC) complexes (in blue). In polarized adherent cells, such as epithelial cells, the contact to the basement membrane through transmembrane integrins defines a basal membrane, whereas the apical side has an exposed surface corresponding, for instance, to the lumen of internal cavities. Tension in apical actomyosin fibres generates vertical compressive forces that result in nuclear flattening. **b** | Contraction and stretching of myofibres induce nuclear deformations, including nuclear envelope wrinkling and expansion, respectively. Microtubules (in light blue) form a cage-like structure around nuclei that may provide additional mechanical support to the nuclei in contracting muscle fibres. **c** | Formation and regeneration of skeletal muscle fibre require migration of nuclei along the muscle fibre axis to the muscle fibre periphery, which involves LINC complexes and microtubule-associated motors, such as kinesin 1, that can pull on the nucleus, causing its movement and deformation. In addition, myofibril contraction drives nuclear movement to the fibre periphery during muscle fibre maturation. This process requires myofibrils to exert contractile forces on the nucleus, resulting in large nuclear deformations. This process is highly dependent on nuclear stiffness and lamin A/C levels.

Topologically associating domains
(TADs). Self-interacting megabase-scale genomic blocks in which DNA sequences exhibit significantly higher interaction frequencies with other DNA sequences within the domain than with those outside of the block.

Liquid–liquid phase separation
Physicochemical process leading to the formation of membraneless compartments or cell structures. This process is based on multivalent macromolecular interactions, including π–π interactions, cation–anion interactions, dipole–dipole interactions and π–cation interactions, that drive the transition of some proteins into another phase with different physiochemical properties to induce the formation of membraneless organelles or cell structures.

Nucleokinesis
Translation of the nucleus within the cell, often neurons, which may or may not be coupled to cell migration.

Stress fibres
Actin filament assembly resulting from the interaction and merging of pre-existing radial fibres and transverse arcs (10–30 filaments). Stress fibres can reach a diameter of several hundreds of nanometres and are under constant tensile stress owing to actomyosin contractility.

Focal adhesions
Integrin-mediated cell–substrate adhesion structure anchoring the ends of stress fibres. Focal adhesions mediate strong attachments to substrates and function as an integrin-based signalling platform.

Tensile force
Pulling force resulting in the extension of an object.

Viscoelastic
Rheological property of natural or synthetic materials with viscous and elastic properties that allows for timescale-dependent deformation when subjected to mechanical stress.

that bind across the perinuclear space to SUN (Sad1p, UNC-84) domain-containing proteins located on the INM via their C-terminal KASH (Klarsicht, ANC1, Syne homology) domain[35,40,41]. This interaction appears to be at least in part responsible for controlling the spacing between the INM and the ONM[35]. On the cytoplasmic side, nesprin 1 and nesprin 2 bind to actin filaments[42] and — via kinesins[43] and dynein[44] — to microtubules (FIG. 1b). Nesprin 3 binds to intermediate filaments via plectin[45]. Nesprin 4, which is found in polarized epithelial cells, plays an important role in nuclear positioning via kinesin 1 (REF.[46]). KASH5 is a germ cell-specific KASH-domain protein required for proper meiosis[47]. On the nucleoplasmic side, SUN-domain proteins bind to the nuclear lamina, NPCs and chromatin. The current model considers that LINC complexes balance part of the cytoskeletal tensile force exerted on the ONM, with maximal stress values at nuclear extremities/poles[48].

LINC complex localization at the nuclear envelope is associated with specific cellular functions. For example, LINC complex proteins are organized along apical stress fibres interacting with the cell nucleus[49,50] and at the front of the nucleus as cells squeeze their nuclei through small pores[51]. Although our current understanding of how LINC complex localization and force transmission are regulated is still incomplete, recent findings indicate that disulfide bonds between the SUN and KASH domains can serve as a crucial modulator of nucleo-cytoskeletal coupling[35,41]. Several additional components have been identified that mediate LINC complex function and force transmission, including FHOD1 (Formin homology 2 domain-containing protein 1)[52], torsinA[53], Samp[54] and lamins A/C[55]. Nesprins can also contribute to nucleo-cytoskeletal coupling independently of their actin and KASH domains via their spectrin repeats[56]. Nonetheless, many questions remain regarding the precise regulation of LINC complex formation and function.

Nuclear mechanics

The mechanical properties of the nucleus, including its size and stiffness, are one of the key pieces of information for understanding how nuclear deformations mediate cellular functions: the stiffer the nucleus, the more resistant to deformations it becomes.

The physical properties of the nucleus. Insights from various experimental assays[57] indicate that the nucleus behaves as a viscoelastic material, that is, it exhibits both elastic and viscous behaviour when subjected to external forces[58]. Elastic materials are defined by an instantaneous and reversible deformation, like a spring that extends under an applied force and snaps back to its original length when the force is removed. By contrast, viscous materials are liquid-like, exhibit flow and undergo irreversible deformation when subjected to force.

Numerous assays have been developed to quantitatively capture the rheological properties of the nucleus, ranging from micropipette aspiration and microindentation to stretching intact cells or isolated nuclei[59]. A major challenge lies in the fact that the viscoelastic response of the nucleus reflects a complex coupling between chromatin, lamins and other nuclear components, and thus the exact behaviour can vary depending on the nature of the applied force/deformation and the molecular composition and organization of the cells being examined. Illustrating this challenge, some studies using micropipette aspiration found that the nucleus gradually deformed under an applied pressure before reaching a plateau, whereas, in other cases, the nucleus continued to deform under applied pressure, exhibiting a fluid-like behaviour[58,60–63]. Stretching isolated nuclei at physiologically relevant strain rates revealed that, for small deformations (<30% of the original length of the nucleus), the nuclear resistance is dominated by chromatin organization, whereas resistance to larger deformations is dominated by the expression levels of lamins A/C[64]. Furthermore, the nucleus undergoes strain stiffening, that is, it becomes stiffer and more difficult to deform upon larger deformations[64,65].

After the removal of a mechanical strain, the elongated nucleus can relax with a nearly elastic response[66–69] or with a delayed response and even exhibit residual plastic deformation, characteristic of viscoelastic material properties[70,71]. The elastic response requires the presence of lamins A/C, SUN-domain protein linkages and vimentin[67]. Overall, these nuclear shape change dynamics may be explained by variations in nuclear lamina composition, chromatin organization, and cytoskeletal structure, composition and remodelling.

Regulation of mechanical properties of the nucleus by its components. Although A-type and B-type lamins share similar biochemical properties and filament structure, it is primarily the levels and assembly status of A-type lamins that determine nuclear stiffness and viscoelastic properties. Nonetheless, B-type lamins also contribute to nuclear stiffness and stability[72,73], and loss of either lamin type results in abnormal nuclear shape and an increased propensity for nuclear envelope rupture[66,74–77]. Besides lamins, chromatin histone modification state and composition are major determinants of the mechanical properties of the nucleus, particularly for low nuclear deformation regimes[64,78]. Increasing the euchromatin content with histone deacetylase inhibitors, decreasing heterochromatin with histone methyltransferase inhibitors or disrupting dynamics of the linker histone H1, all lead to softer nuclei and more nuclear blebbing events — indicative of disturbed nuclear stability — independently of lamin levels[64,78]. New evidence also suggests that chromatin-associated proteins, such as HP1a, WDR5, BAF and NuMa, provide mechanical support to chromatin and regulate nuclear shape[79–82]. Interactions between chromatin and the nuclear envelope further contribute to nuclear stiffness by forming an interconnected network.

Furthermore, the physical properties of chromatin itself need to be considered when studying the contribution of chromatin to the mechanical properties of the nucleus. Although chromatin behaves as a solid at larger length scales, locally, chromatin can behave like a fluid[33,34]. It is now increasingly recognized that LLPS of nucleoplasmic components may serve as a key principle governing nuclear organization, with several nuclear

components, such as the nucleolus or heterochromatin, showing properties of biomolecular condensates[83–87]. The propensity to form liquid droplets is enhanced in the vicinity of regions of low chromatin density because the higher mechanical energy required to deform the dense chromatin to create space for a growing protein droplet would generate an energetic penalty[88]. The growth of liquid droplets within the low chromatin density areas can lead to two distinct mechanical effects[89]. First, chromatin can be repelled as the drops grow by creating an effective repulsive interaction. In this case, the formation of protein condensates can be inhibited by the forces generated by the elastic chromatin network. A second effect can be driven by the tendency of neighbouring droplets to merge to minimize their surface energy. Indeed, regions of chromatin initially far apart and in separate droplets can be brought into proximity when the droplets merge, creating an effective attractive interaction that brings together different chromatin regions. The different types of interaction (repulsive versus attractive) between LLPS and chromatin are thus able to generate significant mechanical forces that can result in the structural rearrangement of chromatin[90]. Nonetheless, the relative contributions of LLPS versus other molecular mechanisms in determining the static and dynamic organization of chromatin within the nucleus remain to be fully elucidated. Additionally, the contribution of condensed chromatin to the mechanical integrity of the nucleus and its ability to respond to extranuclear forces are difficult to reconcile with a liquid state. Indeed, nuclear chromatin is mechanically responsive and can resist significant applied forces[91], which is more consistent with a solid or gel state. Further studies that consider chromatin fibres as viscoelastic filaments that can behave as both a viscoelastic solid and a viscous liquid at different time and length scales may reconcile some of the apparently contradictory observations and ultimately provide a physical framework for understanding genome organization in space and time.

Determinants of nuclear volume. The initial observation that the ratio between cellular and nuclear volumes is largely constant across various cell sizes was made over 100 years ago[92], and it is now well recognized that nuclear volume changes with chromatin organization and DNA content. Interestingly, accumulating evidence shows a close relationship between changes in cell morphology and nuclear deformations that often leads to modifications of nuclear volume, which can affect DNA synthesis[93], gene transcription[94,95] and downstream signalling[27]. Yet, the precise mechanisms underlying nuclear volume regulation remain incompletely understood. The nuclear volume is determined by the balance between outward pressures that originate from the nucleoplasm and tend to expand the nucleus and inward pressures that originate from the cytoplasm and compress the nucleus. The outward pressures include contributions from both the chromatin and the fluid inside the nucleus. Notably, despite the presence of NPCs that facilitate flow of fluid either into or out of the nucleus, cells can establish hydrostatic pressure differences between the nucleoplasmic and cytoplasmic compartments[96,97]. On the basis of the concept that the interior of living cells is 'crowded', changes in nuclear volume, such as inflating the nucleus, can be explained by the differences in colloid osmotic pressure between the nucleoplasm and cytoplasm[98]. Preliminary, theoretical works indeed suggest that the dominant pressure within the nucleus and cytoplasm originates from the osmotic pressure of the macromolecules preferentially localized to these compartments rather than from the effects of the mechanical properties of large complexes such as chromatin and the cytoskeleton[99,100]. The nuclear to cell volume ratio is determined by the number of macromolecules in the nucleoplasm and cytoplasm and increases when nuclear export is impaired owing to the accumulation of macromolecules in the nucleus[100], demonstrating an active role of nucleo-cytosolic transport in the regulation of the osmotic pressure that controls nuclear size. More sensitive subcellular osmometers[100], such as genetically encoded biosensors, are needed to establish definitive physiological values of colloid osmotic pressure and to determine how crowding inside cells is regulated as a function of the subcellular localization of macromolecules and physiological inputs.

Adaptive changes in nuclear mechanics. Deformation of cells and the nucleus can lead to changes in chromatin organization and compaction. These changes alter the mechanical properties of the nucleus as discussed above, providing a mechanism to prevent further deformations and protect the nucleus from mechanical stress[16,101]. Furthermore, mechanical force application can lead to the phosphorylation of emerin and subsequent recruitment of lamins to the nuclear envelope, causing rapid stiffening of the nucleus. In addition to binding to lamins, emerin is a recognized actin-binding protein that promotes actin polymerization at the nuclear envelope[102]. Emerin has also been recognized as a force sensor, relocating from the INM to the ONM in response to nuclear strain, leading to increased perinuclear actin polymerization[103], which could alter nuclear deformability and protect it from damage[104]. By contrast, reducing cytoskeletal tension can soften the nucleus by increasing lamin phosphorylation and turnover[105], highlighting the importance of the interplay between the nucleus and the cytoskeleton.

The difference in lamin expression between various cell types and tissues affects the deformability and mechanical stability of nuclei and may indicate tissue-specific adaptations to particular mechanical demands of the local microenvironment[26,106–111]. For example, nuclei in neutrophils have a particular lobulated morphology with characteristic low lamin A/C levels and elevated condensed chromatin level[112]; this nuclear organization promotes transit through tight spaces[113] such as lung capillaries that are only a few microns in diameter or even smaller gaps between endothelial cells. However, it is still under debate whether individual cells can dynamically adapt their nuclear stiffness on short timescales to promote migration through tight spaces. Confocal Brillouin microscopy revealed nuclear softening during transendothelial migration of breast cancer cells[114]. However, the origin and timing of such nuclear

Elastic
Property of a material that instantaneously deforms in response to a stress and recovers its size and shape after deformation. It is usually represented by a spring that stores energy in the form of elastic potential energy. Units of an elastic modulus are Pa (or $N\,m^{-2}$).

Viscous
Property of liquid of high viscosity, which corresponds to the resistance of a fluid to deform under either shear or extensional stress, defined as the ratio of shear stress to shear flow. Viscous fluids are usually depicted by a dashpot, which represents the internal friction within the fluid that dissipates energy over time. Units of viscosity are $Pa\,s$ (or $N\,s\,m^{-2}$).

Strain
Geometric measure of the amount of deformation in the direction of the applied force divided by the initial length of the object (unitless number).

Strain stiffening
Mechanical material property corresponding to a sudden increase of the elastic modulus under strain, that is, an increase in resistance to further deformation.

Plastic deformation
Ability of a solid material to undergo permanent deformation (that is, irreversible change of shape) without rupture in response to applied forces.

Linker histone H1
Histone protein family responsible for DNA compaction, whose members are located at the base of a nucleosome adjacent to the DNA entry/exit site to regulate the higher-order chromatin structure.

Blebbing
Dynamic protrusion of the plasma or nuclear membrane, often characterized by a spherical morphology. At the cytoplasm, blebbing results from actomyosin contraction of the cortex that causes either transient detachment of the cell membrane from the actin cortex or a rupture in the actin cortex. The cytosol streams out and inflates the bleb. Nuclear blebs arise from increased intranuclear pressure and detachment of the nuclear membranes from the nuclear lamina.

BAF
Barrier-to-autointegration factor is an essential 10 kDa chromatin-binding protein that is highly conserved in metazoa and helps DNA anchoring to the nuclear envelope. BAF is involved in multiple pathways, including nuclear envelope reassembly (after mitosis and nuclear envelope rupture), chromatin epigenetics and DNA damage response. BAF function is controlled by phosphorylation/dephosphorylation waves that drive nuclear envelope disassembly.

Biomolecular condensates
Micron-scale compartments often formed by liquid–liquid phase separation that lack surrounding membranes and concentrate functionally related components such as proteins and nucleic acids.

Colloid osmotic pressure
Pressure generated by solutions of macromolecules in contact with pores that are permeable to water and ions but not to macromolecules. Colloid osmotic pressure generates depletion forces that push macromolecules together in crowded solutions and thus promotes aggregation and phase separation.

Confocal Brillouin microscopy
Optical technique combining Brillouin spectroscopy with confocal microscopy to provide a non-contact and direct read-out of the mechanical properties of a material (that is, stiffness, temperature or strain) at the micrometre scale. Spontaneous Brillouin light scattering arises from the interaction between photons and acoustic phonons (that is, propagation of thermodynamic fluctuations) and permits quantification of the intracellular longitudinal modulus without disturbing the cell.

softening remain poorly understood. Interestingly, inhibition of metalloproteinases that remodel the extracellular matrix (ECM) leads to nuclear softening via lamin A/C phosphorylation, which is essential for migration through ECM pores with a subnuclear diameter (confined cell migration; see also next section)[115,116]. This response requires an intact connection between the nucleus and the centrosome via the LINC complex protein nesprin 2 and the dynein adaptor Lis1 (REF.[116]). Chromatin remodelling can further modulate nuclear stiffness and cell migration in 3D environments[80]. These findings suggest that dynamic chromatin modification and changes in lamin levels and organization can mediate nuclear mechanics and promote cell migration in confined 3D environments[117,118]. However, reducing lamin A/C levels below a critical threshold may reduce cell survival under mechanical stress[75,119,120].

Sources of nuclear deformations

The nucleus is constantly exposed to forces from the surrounding cytoskeleton, including from active positioning of the nucleus during cell polarization[121], migration[121] or differentiation[122]. Recent advances in intravital imaging and modelling physiological microenvironments in vitro have documented large-scale nuclear deformations related to contraction and relaxation of striated muscle[123,124] and during confined cell migration[75,76,125,126], although similar nuclear deformations and functional consequences are expected to also occur during numerous other important situations, including developmental cell migration[127,128] and nucleokinesis events[129]. Here, we discuss several physiological and pathological situations associated with nuclear deformations and how these deformations arise.

Nuclear deformations in cells adhering to flat and rigid substrates. Actin stress fibres and actomyosin contractility can impose vertical and lateral inward compressive forces on the nucleus. Lateral actin fibres can lead to nuclear deformations when cells migrate or are stretched[130,131]. Vertical compressive forces are exerted by apical actin stress fibres that form a dome-like structure across the nucleus and that are physically attached to the nuclear lamina through LINC complexes[132]. On flat rigid substrates, these forces flatten the nucleus during cell spreading (FIG. 3a) and can cause nuclear envelope rupture[133–135]. By contrast, the nucleus remains more rounded in cells on soft substrates[136] that are associated with lower cytoskeletal tension and fewer actin stress fibres[137], or when the actin cytoskeleton or LINC complexes are disrupted[135]. Indeed, ventral actin fibres, which are thick actomyosin bundles connected from both ends to focal adhesions at the bottom of the cell, can exert lateral compressive forces on both nuclear sides[93]. The high level of tension in ventral actin stress fibres can lead to nuclear indentations. These indentations can measure a few microns and are characterized by local enrichment of LINC complexes and segregated domains of condensed chromatin, indicating that the nucleus responds to compression by adjusting its architecture[50,138]. Collectively, these findings suggest that the amount of tension within the perinuclear actin fibres is an important source of nuclear deformations and nuclear mechanotransduction.

Nuclear deformations in skeletal and cardiac muscle. Actomyosin contractility also has an important role in nuclear deformations in striated muscle cells (FIG. 3b). Large nuclear deformations were recently visualized in cardiac and skeletal muscle contraction in living fly larvae[124]. Increased expression of lamins A/C in muscle cells is essential to protect their nuclei from mechanical damage caused by muscle contraction[26] and during nuclear movement associated with myoblast elongation[139]. Another, more surprising mechanism responsible for mechanical stress on the nucleus are the cytoskeletal forces required to position muscle nuclei along the length of the muscle fibre and the nuclear periphery during myotube maturation[140,141]. LINC complex proteins such as nesprin 1, together with the microtubule associated motors kinesin 1 and dynein as well as other nuclear envelope proteins such as emerin, have been implicated in this process[140,142,143]. Generally, the physical stress associated with the motors pulling on the nucleus results in nuclear rotation and nuclear deformations[144–146] (FIG. 3c, left). In lamin A/C-deficient or mutant cells, which have mechanically weaker nuclei, the kinesin-mediated forces can result in large-scale nuclear deformations and damage[119]. In addition to the role of motor proteins, myofibril contraction was shown as a mechanism to move skeletal muscle nuclei to the periphery of muscle fibres, also incurring nuclear deformations in the process (FIG. 3c, right). Both a reduction and an increase in nuclear stiffness (by lamin A/C depletion or overexpression) perturbed the nuclear repositioning. Additionally, lamin A/C deficiency was associated with particularly pronounced nuclear deformations, suggesting an important role of nuclear mechanical properties in regulating this nuclear repositioning event[143]. Intriguingly, in lamin A/C-deficient and mutant mouse models that develop severe muscular dystrophy and dilated cardiomyopathy (BOX 2), reducing the cytoskeletal forces acting on the fragile muscle cell nuclei by disrupting the LINC complex prevents nuclear damage and results in improved muscle function and muscle cell viability in vitro and in vivo[119,147], pointing to promising new therapeutic approaches for these devastating diseases. However, given that mutations in nesprins and SUN proteins can lead to muscular dystrophy and heart disease[148], further studies will need to evaluate the long-term risks and consequences of LINC complex disruption using, for example, inducible LINC complex disruption models[149].

Nuclear deformations in developing tissues. In early *Drosophila* embryo, pronounced nuclear deformations occur during cellularization — a process during which somatic nuclei at the periphery of the syncytial embryo move as the plasma membrane invaginates to form membranes around each nucleus. The nuclear deformations are caused by the formation of microtubules into bundles that run across the nuclear envelope[150]. These nuclear deformations may be particularly pronounced because A-type lamins are not expressed in *Drosophila* during cellularization, leading to more

deformable nuclei[151]. Nuclear movement during development also results in substantial nuclear deformations in the nematode *Caenorhabditis elegans*, which require cytoskeletal force transmission to the nucleus via the LINC complex[152].

In epithelial systems, cellular intercalation is a common process occurring throughout development, whereby neighbouring cells exchange their place to maintain epithelium integrity. Depending on the cell density, cellular intercalation can lead to transient squeezing and nuclear deformations in the intercalating cell (FIG. 4a) likely due to compression by neighbouring cells and cytoskeletal remodelling that transmits forces onto the nucleus[153,154].

Another phenomenon occurring during development that is associated with nuclear deformations is nucleokinesis in the central nervous system. One such nucleokinesis event is interkinetic nuclear migration in neural progenitor/stem cells around cell divisions[155,156] as is nucleokinesis of newborn neurons that migrate to their final destination in the tissue[157]. Both actin and microtubules have been involved in these nucleokinesis processes, depending on the system and cell type[158]. Microtubules can exert pulling forces on the nuclear lamina through LINC complexes that move the nucleus towards the centrosome, whereas actomyosin could push the nucleus from behind (FIG. 4b). Neuroepithelia are densely packed with cells, necessitating the nuclei to squeeze through narrow spaces. Thus, these cytoskeletal forces, together with the need for the nucleus to navigate the dense neuroepithelial tissue, result in nuclear deformations. Notably, developing neural tissues lack the expression of lamins A/C, which makes the nuclei less rigid, thereby supporting nuclear deformability[159]. At the same time, developing neural tissue requires lamin B to maintain nuclear integrity during nucleokinesis. For example, in the developing brain, loss of either lamin B1 or lamin B2 causes defective migration of cortical neurons and leads to severe nuclear architectural abnormalities (for example, chromatin protrusions) and nuclear membrane ruptures, likely explaining the severe brain development defects and reduced neuronal survival associated with B-type lamin deficiency[73]. It remains to be determined whether these defects are caused by disrupted transmission of force during nuclear movement or by a more fragile nucleus unable to bear the stress generated during nucleokinesis.

Besides nucleokinesis, live imaging studies have found remarkable nuclear deformations and rotation during the migration of cerebellar granule cells through narrow intercellular spaces in neural tissues[144]. During this process, microtubules steer the nucleus and drive its rotation and deformation through a dynamic interaction of nesprins with kinesin 1 and dynein. Given the apparent diversity of cytoskeletal organization in neuron species, further studies are needed to obtain a better understanding of nuclear dynamics and nuclear shape regulatory mechanisms in neural tissues.

Nuclear deformations during confined migration. Nuclear deformation is a hallmark of important physiological and pathological situations involving cell migration. For instance, immune cells or invasive cancer cells must navigate through small interstitial spaces ranging from 1 to 20 µm in diameter[160,161], which requires cells to deform their nucleus to squeeze through the available spaces (FIG. 4c,d). In the absence of matrix metalloproteinases that digest the ECM and widen migratory tracks, the nucleus is often the main physical hindrance to cell migration through confined spaces[75,125]. Leukocytes can insert basolateral protrusion within (paracellular) or between (transcellular) endothelial cells to breach the endothelial barrier (FIG. 4c) and use actomyosin forces to push the nucleus through the pore, resulting in substantial nuclear deformations.

Tumour cells face similar challenges when invading tissues and intravasating and extravasating blood vessels to metastasize to distant tissues[114] (FIG. 4d). One of the primary sources of cytoskeletal forces to translocate and deform the nucleus is actomyosin contractility. This contractility can cause both tension and compression of the nucleus by actin stress fibres pulling or pushing on the nucleus[146,162,163]. However, build-up of actomyosin contractility can also increase the cytoplasmic hydrostatic pressure, which results in the influx of cytoplasmic content into the nucleus causing its volume expansion and blebbing, which hinders motility[97]. An additional, actin-based mechanism has been observed in dendritic cells, whose nuclei are rigid owing to high expression of lamina A/C. These cells use Arp2/3 complex, a central actin nucleator, to generate a perinuclear actin network. These perinuclear actin filaments accumulate around the constriction site and exert a lateral pushing force on the nucleus, facilitating migration through narrow ECM pores[164]. Alternatively to actomyosin contractility, mechanisms for propelling the nucleus may involve microtubule-associated motors, kinesins and dyneins[165], which directly attach to the nucleus via nesprins and other proteins at the nuclear envelope, dragging the nucleus along the microtubule tracks. Whether the nucleus is pulled and/or pushed during confined migration is still debated[166], although it is likely that cells can use multiple independent mechanisms, depending on the particular context (FIG. 4d). Hence, the nuclear deformation pattern can be expected to vary in different in vivo scenarios of confined migration.

Nuclear deformations during confined migration may also involve dynamic or persistent changes in nuclear mechanical properties. For example, transient nuclear softening has been reported during transendothelial migration of cancer cells[114]; neutrophils develop highly lobulated and deformable nuclei during granulopoiesis, which facilitates passages through tight spaces[113]; and highly invasive breast cancer cells are characterized by increased nuclear deformability and low lamin A/C levels[115]. Notably, the physical properties of the large nucleus can directly influence confined migration. The microtubule-mediated 'frontward' positioning of the nucleus in amoeboid cell migration was shown to allow cells to use their nucleus as a mechanical gauge to determine the path of least resistance when encountering bifurcations of the path with pores of different sizes[162]. This provides an example of how deformation of the nucleus aids cells in their 'decision-making' during migration through confined environments.

Interkinetic nuclear migration
Periodic movement of the nucleus between apical and basal surfaces of neuroepithelial progenitor cells as they progress through the cell cycle. Interkinetic nuclear migration results in all mitoses taking place at the apical side of the neuroepithelium. As a consequence, most newborn neurons resulting from division of neuroepithelial progenitors must move their soma from the apical side to more basal locations where they function.

Cerebellar granule cells
Among the smallest and the most numerous neuron type that form dense and distinct layers of the cerebellar cortex.

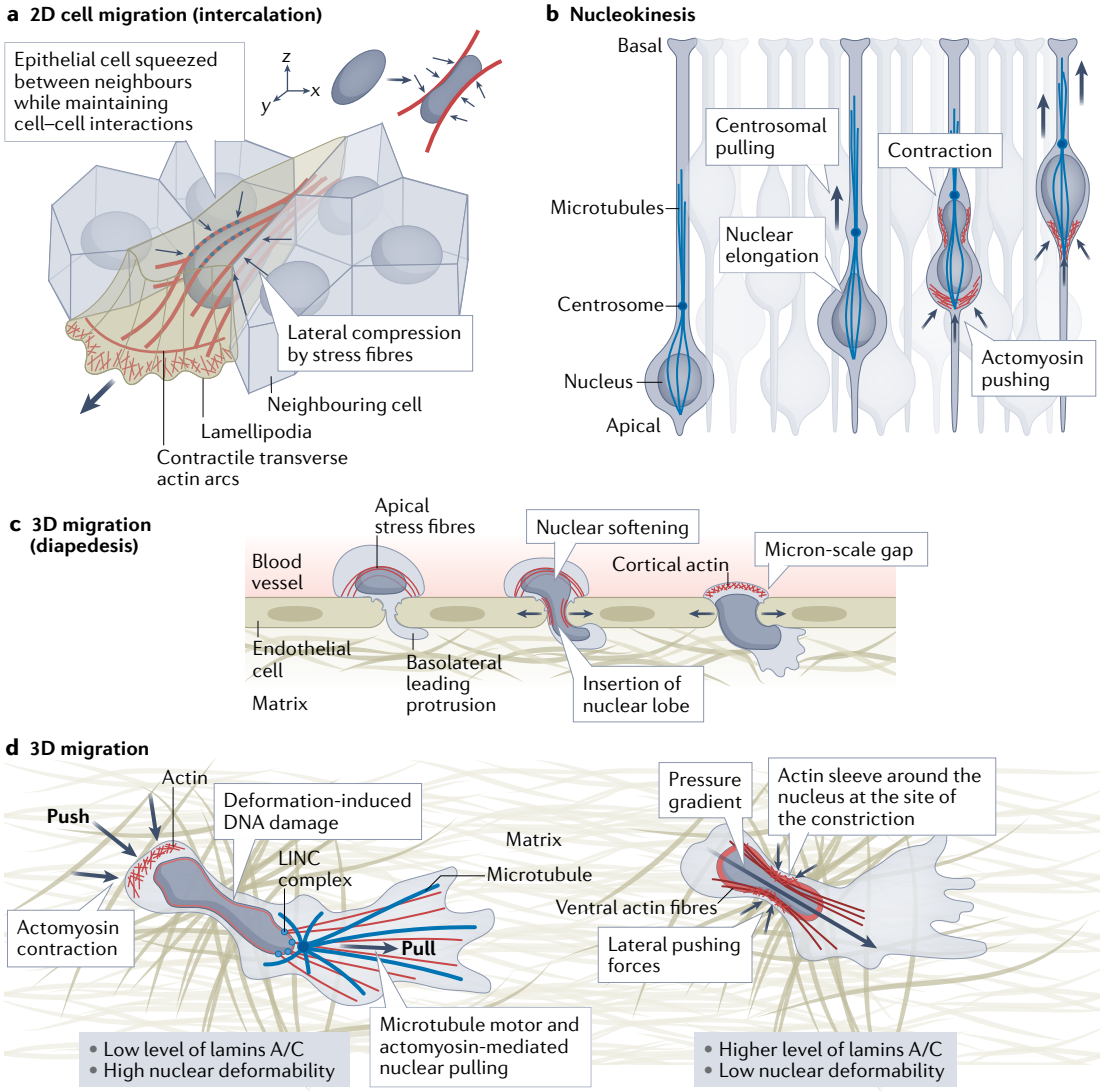


Fig. 4 | **Migration-associated nuclear deformations. a** | Epithelial cell intercalation within dense bidimensional tissues requires cellular elongation and nuclear deformations. Lateral compressive forces are exerted on both nuclear sides by ventral fibres, which are thick actomyosin bundles connected from both ends to focal adhesions. **b** | Nucleokinesis events are observed during development of the neuroepithelium of the central nervous system and are accompanied by considerable nuclear deformations. One of these events is the migration of early-born neurons, which reposition their soma from the apical to the basal side of the neuroepithelium to reach their final destination. This event occurs in densely packed, neuroepithelial tissue and involves pulling forces on the nucleus exerted by a microtubule cage towards the centrosome and pushing forces at the cell rear generated by actomyosin contraction, depending on the system and the neuronal cell type. In mammals, microtubules exert pulling forces on the nuclear lamina through linker of nucleoskeleton and cytoskeleton (LINC) complexes that move the nucleus towards the centrosome. Together with stresses instigated by neighbouring cells, these cytoskeletal forces deform the nucleus. **c** | Immune cells and tumour cells can breach the endothelial barrier of blood vessels by inserting protrusion between or inside endothelial cells. Migration through the small openings in the endothelium (a few micrometres in diameter) is associated with large nuclear deformations and may be linked to nuclear softening. **d** | Migration of cells in vivo requires them to squeeze through narrow spaces, navigating often very complex and dense structures of the extracellular matrix as well as moving in between cells. Actomyosin contraction leads to pushing and pulling forces and cooperates with microtubule motors at the front, which are recruited to generate pulling forces. Together, the balance of forces results in the forward movement of the nucleus through the narrow constriction. Nuclear deformations result from the balance between the amount and direction of the applied cytoskeletal force, the mechanical properties of the nucleus and the degree of external confinement. Cells with low levels of lamin A/C expression, and thus more deformable nuclei, can more easily move through tight spaces as seen in neutrophils and some metastatic cancer cells. However, reduced lamin expression makes cells more prone to nuclear envelope rupture (FIG. 5). Cells that express high levels of lamins A/C (for example, dendritic cells) can use a perinuclear, actin 'sleeve' that is recruited at the site of the constriction to locally deform the stiffer nucleus.

Laminopathy
Over 450 mutations have been reported in the genes encoding lamins, in particular the *LMNA* gene, causing diseases termed laminopathies. The number of identified laminopathies has steadily increased in recent years, currently including 13 known conditions. Most of these diseases are rare but *LMNA* mutations are the second most common cause of congenital dilated cardiomyopathy. Although lamins are nearly ubiquitously expressed, many of the laminopathies exhibit tissue-specific phenotypes, for example, primarily affecting striated muscles and tendons, hence the suggestion of a mechanical connection.

LEM-domain proteins
The LAP2, emerin and MAN1 (LEM) domain is a ~40-residue helix–loop–helix fold conserved both in eukaryotes and in prokaryotic DNA/RNA-binding proteins. Except for LAP2 proteins, which have a second LEM domain that binds DNA, the function of a eukaryotic LEM domain is to directly bind the conserved chromatin protein BAF.

TREX1
Three prime repair exonuclease 1 is the major 3′→5′ DNA exonuclease in mammalian cells and metabolizes preferentially single-stranded DNA. It cleans the cytosol from DNA fragments coming from endogenous elements. Unless degraded, the accumulation of these DNA fragments can activate innate immune signalling.

ATR kinase
Serine/threonine protein kinase activated in S phase and involved in sensing DNA damage and activating DNA damage checkpoint upon genotoxic stresses (for example, ionizing radiation or ultraviolet light), thereby acting as a DNA damage sensor.

Epithelial–mesenchymal transition
Transcriptionally governed process over which epithelial cells establish a front-rear polarity while acquiring a mesenchymal and motile phenotype.

Consequences of nuclear deformations

Given the central role of the cell nucleus in cellular function, it is easy to imagine how nuclear deformations can lead to various transient or persistent consequences, including downstream signalling, altered nucleo-cytosolic transport and genome regulation as well as loss of nuclear envelope integrity and DNA damage (FIGS 5,6). Notably, although these outcomes of deforming the nucleus are now well established, the molecular mechanisms responsible and whether the nucleus itself senses mechanical signals and translates these into biological responses (BOX 1) often remain unresolved and a matter of active research.

Deformation-associated nuclear envelope rupture and repair. Nuclear envelope rupture describes the transient loss of nuclear membrane integrity at localized sites rather than global breakdown of the nuclear envelope as occurs in vertebrate cells during mitosis. Spontaneous nuclear envelope rupture events, persisting typically for between a few minutes and several dozens of minutes, were first observed in vitro in cells expressing the HIV protein VPR[167] and subsequently in fibroblasts from patients diagnosed with laminopathy[168] and in cancer cells[146]. Since then, it has become apparent that physical stress on the nucleus and the associated nuclear deformations can lead to transient nuclear envelope rupture events, particularly during migration through confined environments, and that the probability of nuclear envelope rupture increases with the degree of confinement[75,76,163,169].

Nuclear envelope rupture events have been documented in vitro and in vivo. These ruptures are often associated with loss of A-type or B-type lamins[168,170,171], lamin mutations[172–174], peripheral heterochromatin disruption[91] or high-level mechanical stress resulting from tensile or compressive forces on the nucleus[74–76,164,175–178]. On the basis of super-resolution imaging and computational modelling, the nuclear envelope rupture sites are estimated to be ~100 nm in diameter[73,74,179]. A current hypothesis proposes that nuclear envelope ruptures occur at pre-existing gaps or defects in the nuclear lamina, particularly where the lamin B meshwork is weaker and thus cannot sufficiently support the nuclear membranes. This mechanical fragility causes the membrane to form a bleb that expands under continued mechanical stress and ultimately ruptures[169,180] (FIG. 5). However, nuclear envelope ruptures and membrane blebs have also been observed in the absence of nuclear lamina gaps; they may thus generally arise when the nuclear membranes peel off the underlying nuclear lamina in response to increased nuclear pressure resulting from cytoskeletal forces[75,181,182]. A better understanding of the mechanisms that drive nuclear envelope rupture will require study of the dynamics of the heterogeneous lamina meshwork and its interaction with the nuclear membranes during nuclear deformations.

In line with the observations that most nuclear envelope rupture events are transient, cells have robust mechanisms to repair their nuclear membrane during interphase and even more persistent rupture events (a few hours) can eventually be repaired[183]. The mechanisms involved in interphase nuclear membrane repair are largely shared with those during resealing of the nuclear envelope after mitosis. The nuclear membrane repair mechanism is based on the recruitment of specific proteins to the sites of nuclear envelope rupture, particularly BAF, LEM-domain proteins, A-type lamins and membrane remodelling proteins, including endosomal sorting complexes required for transport (ESCRT)-III remodelling complex and its binding recruiting factor CHMP7 (REFS[76,177,183–185]). The extent of rupture is correlated with the amount of cytoplasmic BAF entering the nucleus and accumulating at the rupture site[76,183,185]. A current model of nuclear membrane repair considers that the binding of cytosolic BAF to the exposed chromatin initializes recruitment of both new ER membranes to repair the membrane hole and the ESCRT-III complex to reseal the remaining gaps (FIG. 5). BAF also recruits cytoplasmic lamins A/C to the rupture site, further contributing to the restoration of nuclear envelope integrity. Interestingly, some nuclear processes, such as transcription and DNA replication, can be disturbed after nuclear envelope rupture events, leading, for instance, to aneuploidy or extensive DNA damage such as persistent double-stranded DNA breaks[134].

Mechanically induced DNA damage. Severe nuclear deformations occurring, for example, during confined migration, external compression or nuclear repositioning in dense tissues can induce DNA damage upon nuclear envelope rupture[72,73,171,186] and even in the absence of rupture[187] (FIG. 5). Nuclear envelope rupture can cause DNA damage by allowing access of the ER-associated exonuclease TREX1 into the nucleus[186] or by loss of DNA damage repair factors from the nucleus via nuclear efflux[171,182]. Nuclear envelope rupture-associated DNA damage occurs throughout all phases of the cell cycle, more often in cells deficient for the DNA damage sensor ATR kinase[188]. By contrast, deformation-induced DNA damage (DNA damage in the absence of nuclear envelope rupture) occurs primarily in S/G2 phases, that is, during active DNA replication. This damage is linked to increased replication stress, possibly due to torsional stress on DNA resulting from the nuclear deformation during confined migration or mechanical compression of cells[187]. Interestingly, different cell lines exhibit different propensities for these modes of DNA damage[186,187], but the exact molecular underpinnings for these cell type-specific differences remain to be elucidated.

What are the long-term consequences of DNA damage and nuclear envelope rupture for cells and tissues homeostasis? Repeated migration through tight constrictions can lead to the accumulation of DNA damage and changes in chromosome copy number, which may drive the emergence and evolution of malignant cells[182]. Furthermore, TREX1-dependent DNA damage following nuclear envelope rupture may favour tumour cell invasion by inducing a partial epithelial–mesenchymal transition, including increased degradation of collagen and increased invasive potential[172]. The precise mechanisms linking TREX1 and collagen degradation activity is still unknown but is believed to be downstream of the DNA damage response pathway initiated by ATM kinase[189,190].

ATM kinase
Serine/threonine protein kinase that is recruited and activated to sites of DNA double-strand breaks and signals to various downstream targets to initiate cell cycle arrest and DNA repair.

Nuclear envelope rupture can also lead to activation of the pro-inflammatory cGAS–STING DNA-sensing pathway, as it allows access of cytosolic cGAS to the genomic DNA at sites of rupture[75,76,191]. A recent study found that increased cGAS–STING signalling can drive cancer metastasis in a mouse breast cancer model[191], although, in this case, cGAS–STING activation was primarily due to nuclear envelope rupture in micronuclei and not in primary nuclei.

Nuclear deformation-associated signalling. Confinement of cells below a critical threshold, typically a fraction of the uncompressed nuclear height, results in nuclear flattening, an increase in nuclear membrane tension and unfolding of nuclear membrane invaginations[17,127]. Unfolding of the nuclear envelope under increasing membrane tension allows the nucleus to deform without exceeding critical membrane tension in the nuclear membranes[186] but may also trigger downstream signalling events. This nuclear mechanosensing of cellular confinement has been referred to as 'cellular proprioception'. One example is the increased uptake of calcium into the nucleus, which is promoted by calcium release from the ER — an event that is also mechanically triggered, resulting from confinement, nuclear flattening and expansion of the nucleus/ER–plasma membrane contact area (FIG. 6a). Increased nuclear membrane tension, further amplified by the increased intranuclear

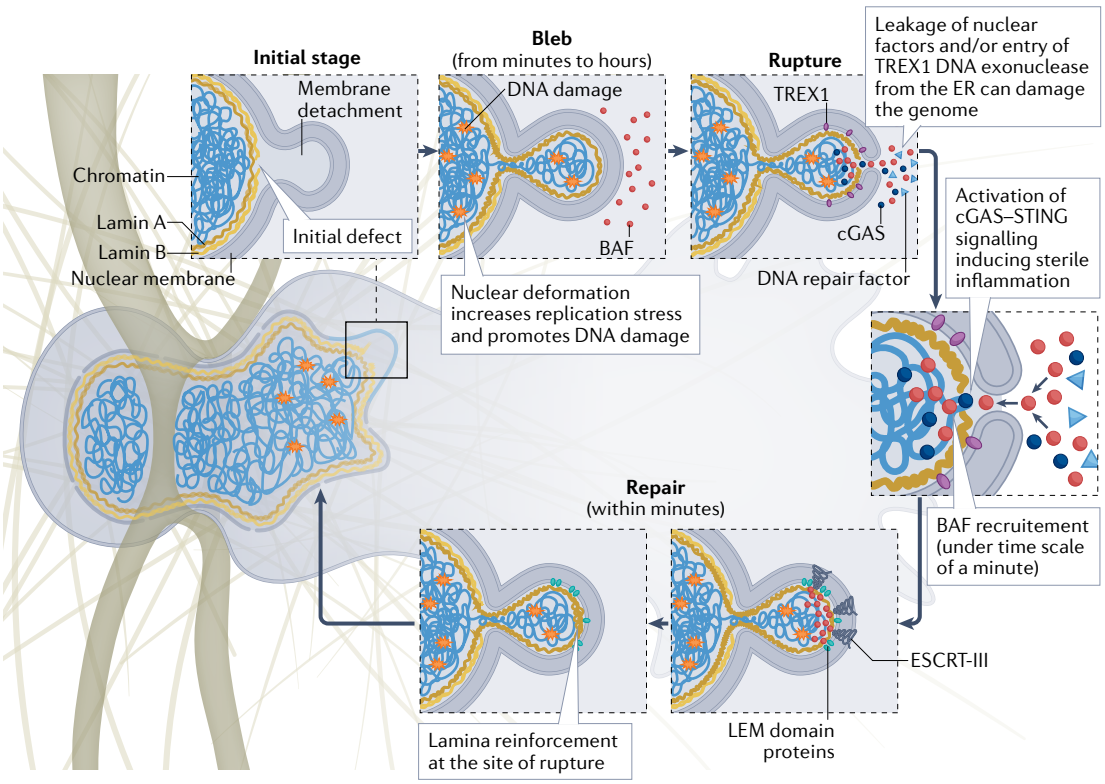
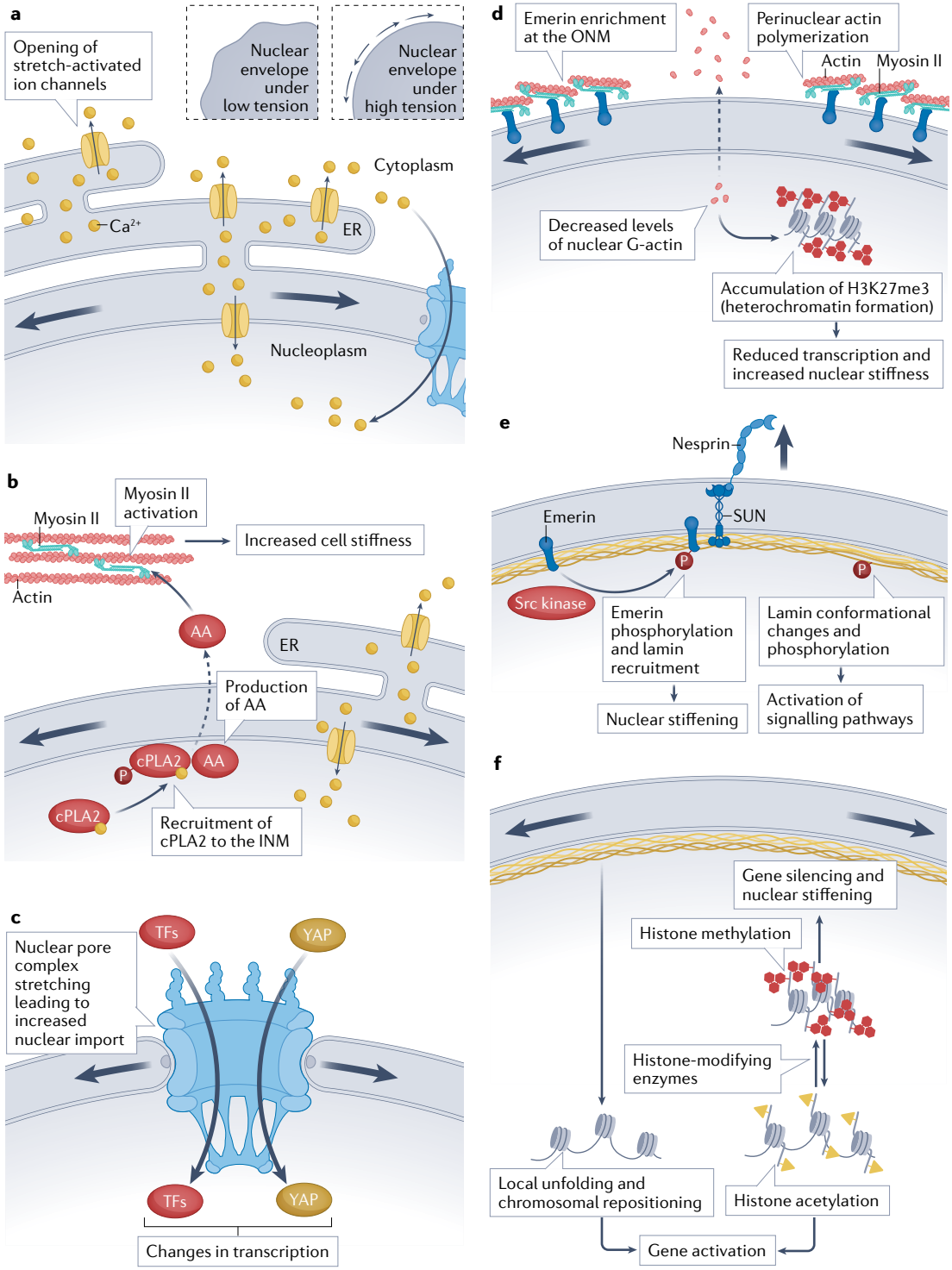


Fig. 5 | **Nuclear envelope rupture and repair.** Migration through confined environments or external compression of cells can result in nuclear envelope ruptures. The rupture process is typically initiated by the formation of a nuclear membrane extrusion, or bleb, where the nuclear membranes detach from the underlying lamina. Blebs are driven by increased hydrostatic pressure within the nucleus. Blebs form at sites with high nuclear membrane curvature and where an initial defect (weakening) in the nuclear lamina exists. Blebs can have varying size and can contain chromatin or can just be filled with fluid. They typically lack lamin B and nuclear pore complexes, whereas lamins A/C and chromatin can enter the bleb. Continued nuclear compression by confinement from the extracellular matrix, apical actin stress fibres, cell contractions or external compression results in bleb expansion until the nuclear membranes in the bleb exceed a critical strain threshold and rupture, leading to the leakage of soluble proteins from the nucleoplasm into the cytoplasm and uncontrolled influx of cytoplasmic proteins into the nucleus. The lifetime of blebs can range from minutes to hours, but the rupture itself is usually quite short, on the order of minutes. Following nuclear envelope rupture, BAF is rapidly (within minutes) recruited to initiate nuclear envelope repair. The recruitment of endosomal sorting complexes required for transport (ESCRT)-III complexes further contributes to resealing the nuclear membranes. The process of repair/rescue is typically completed within 10–15 min and often associated with recruitment of nucleoplasmic lamins A/C to the site of rupture. Although the rupture is resealed, the bleb/protrusion often persists and is not fully resorbed. Severe nuclear deformation can sensitize cells to DNA damage. This can be caused by nuclear envelope rupture, which has been linked to the translocation of exonuclease TREX1 from the endoplasmic reticulum (ER) to the inner nuclear membrane. Nuclear rupture may also cause depletion of DNA repair factors, promoting damage, and can also induce sterile inflammation by exposing nuclear DNA to the cytosolic DNA sensor cGAS–STING. In cells undergoing S phase, nuclear deformation can promote DNA damage even in the absence of nuclear envelope rupture, likely by inducing torsional stress and interfering with DNA replication.



calcium concentrations[192–194], results in the recruitment of nucleoplasmic phospholipase A2 (cPLA2) to the INM, where it catalyses the production of arachidonic acid (an omega-6 polyunsaturated fatty acid) and lysophosphatidic acid, which are then released to the cytoplasm[192,194,195] (FIG. 6b). Recruitment of cPLA2 to the INM can be triggered by osmotic swelling associated with cell and tissue injury, inducing inflammatory signalling[192], or by physical confinement of cells[17,127]. Arachidonic acid has been implicated in regulating myosin II activity, both directly[196] and indirectly via protein phosphorylation[197], which results in the increase in cortical actomyosin contractility (FIG. 6b). Thus, the higher nuclear membrane tension resulting from nuclear deformations modulates cell morphology and promotes migration through narrow constrictions[17,127].

Nuclear deformations and nuclear transport. Recent structural evidence indicates that nuclear membrane tension is associated with an open state of the NPCs and that reduced tension causes NPC constriction[198,199]. Hence, it is conceivable that forces acting on the nucleus

Sterile inflammation
Immune response that is typically associated with the recognition of intracellular contents released from damaged and necrotic cells by inflammatory signalling receptors or triggered by exogenous material that can injure cells. This process occurs in the absence of microorganisms.

◀ Fig. 6 | **Examples of functional consequences of nuclear deformations. a** | High tension exerted on the nuclear envelope during nuclear deformations induces straightening and unfolding of the wrinkled nuclear envelope, which may lead to the opening of stretch-activated ion channels. The nature of these channels remains to be established, but it was suggested that a key mechanosensitive calcium channel Piezo1 localizes to the nuclear envelope and the endoplasmic reticulum (ER) in addition to the plasma membrane. As the nuclear envelope is continuous with ER membranes, the stress on the nuclear envelope may also propagate to the ER, leading to the opening of mechanosensitive channels in that location. **b** | Increased nuclear membrane tension, coupled with calcium release from the ER that increases intranuclear calcium concentrations, promotes the recruitment of cytosolic phospholipase A2 (cPLA2) from the nucleoplasm to the inner nuclear membrane (INM), where cPLA2 synthesizes arachidonic acid (AA) that is subsequently released to the cytoplasm. The activation of the cPLA2–AA pathway leads to RhoA activation and increased myosin II recruitment to the cell cortex, increasing actomyosin contractility. **c** | Increased nuclear membrane tension promotes stretching of nuclear pore complexes, leading to increased nuclear import of transcription factors (TFs) and mechanoresponsive transcriptional activators, such as YAP (Yes-associated protein)/TAZ (transcriptional coactivator with PDZ-binding motif). **d** | Deformation of the nucleus induces enrichment of emerin at the outer nuclear membrane (ONM). Relocalization of emerin to the ONM promotes perinuclear actin polymerization that leads to decreased levels of intranuclear free monomeric actin (G-actin). This perturbs the activity of several chromatin modifiers that bind to G-actin, such as HDAC1/2, Tip60, INO80, SWR1, SWI/SNF and RSC100, resulting in increased heterochromatin formation (accumulation of histone H3 Lys27 and Lys9 trimethylation (H3K27me3, H3K9me3)). By increasing compaction of the genome, these epigenetic changes reduce global transcriptional activity and impact the mechanical properties of the nucleus. **e** | Nuclear deformations transduced by linker of nucleoskeleton and cytoskeleton (LINC) complexes induce phosphorylation of emerin, which is mediated by Src family kinases, and confer nuclear adaptation to force by promoting lamin recruitment, thereby causing nuclear stiffening. Nuclear deformations can also induce conformational changes in lamins A/C and/or modulate the phosphorylation status of lamins A/C, which can alter the interaction of lamins with their binding partners and influence lamin distribution, dynamics and degradation, initiating further signalling events and promoting changes in genome organization. **f** | Forces acting on the nucleus may reposition or locally unfold chromatin domains, altering their transcriptional activity, and modulate the methylation level of histones by methyltransferases and deacetylases, regulating transcriptional activity. SUN, Sad1p, UNC-84.

and the resulting nuclear deformations will have a considerable impact on nucleo-cytosolic transport, including import–export dynamics of important transcription and epigenetic regulators. For instance, nuclear deformations can modulate the balance of nuclear and cytoplasmic pools of two key mechanoresponsive transcription regulators, YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif)[200] (FIG. 6c), which have crucial roles in regulating a wide range of key biological processes[201]. In mouse embryonic fibroblasts, mechanical signals from ECM rigidity are transmitted to the nucleus via LINC complexes. These forces cause nuclear envelope stretching, likely opening nuclear pores and promoting nuclear import of YAP[198]. By contrast, during differentiation of myoblasts into myotubes, nuclear elongation (see discussion above) promotes YAP nuclear export to drive cell differentiation[139]. More recently, YAP nuclear export was associated with substrate curvature changes that impose nuclear deformations. Nuclei located on convex zones (that is, crests) were flattened with an elevated nuclear presence of YAP and chromatin was less condensed, whereas nuclei on concave zones (that is, valleys) were highly elongated, contained more condensed chromatin, and YAP was predominantly cytoplasmic[202]. These findings support the notion of a control of YAP/TAZ by nuclear deformations and highlight the importance of mechanical and cytoskeletal regulation of the nuclear shape in modulating YAP/TAZ signalling. Several lines of evidence indicate that similar effects can be observed by imposing nuclear deformations with higher cell density[203] or various external forces[27,132,198,200], without changing the mechanical properties of ECM. However, precisely how the intracellular localization of YAP is modulated by nuclear shape and volume changes[198], and how this observation relates to known regulators of YAP nuclear translocation, remain to be elucidated.

Mechanically induced genome regulation. Recent evidence suggests that the cytoskeleton can modify not only the physical state of the nucleus but also the chromatin state and gene expression. For example, local stresses applied to integrins can propagate to the LINC complex through the actin cytoskeleton and lead to chromatin unpacking[204] and epigenetic changes in chromatin (such as H3K9me3 demethylation)[205] that promote force-induced transcription in the nuclear interior. At the nuclear envelope periphery, local cytoskeletal forces, such as actin fibre-based indentation of the nucleus, can severely deform the nuclear envelope and trigger reversible formation of heterochromatin[50,93,206]. Nuclear deformations during confined migration can also induce increased activity of histone methylases and histone deacetylases (HDACs). This results in an increase in H3K9me3 and H3K27me3 heterochromatin marks (FIG. 6d) and promotes cell migration through mechanisms that are yet to be defined[118,207]. This increase in heterochromatin abundance can last from hours to days[207]. In addition to local changes in chromatin architecture and organization, dynamic nuclear deformation could be an underlying driving force of spatiotemporal genomic reorganization. Indeed, suppression of nuclear deformation in the mouse retinal photoreceptors results in impairment of heterochromatin clustering into chromocentres[94]. There is also evidence that confined cell migration leads to rearrangements in 3D genome organization in neutrophils and cancer cells[208,209].

Chromatin modifications can also arise from changes in the nuclear actin pool. Increased perinuclear actin polymerization, mediated by re-localization of emerin to the ONM in response to nuclear deformations (FIG. 6e), can result in increased facultative heterochromatin formation by depleting monomeric actin from the nucleus, reducing transcription and activating Polycomb repressive complex 2 (PRC2)[103]. Mechanically induced depolymerization of actin can also lead to translocation of HDAC3 from the cytoplasm into the nucleus, resulting in increased heterochromatin formation[210]. Spatial confinement can similarly reduce actin polymerization, thereby reducing nuclear translocation of megakaryoblastic leukaemia 1 protein (MKL1), a mechanoresponsive coactivator of the serum response factor (SRF), which regulates many physiological processes, including pro-inflammatory macrophage differentiation[179]. Likewise, emerin-mediated actin polymerization can modulate nuclear translocation of MKL1 (REF.[211]). Sustained activity of MKL1 results in reduced nuclear volume and globally reduced chromatin accessibility[49].

cGAS–STING DNA-sensing pathway
Cellular cytosolic double-stranded DNA sensor, allowing innate immune response to infections, inflammation and cancer.

Micronuclei
Small DNA-containing nuclear structures that are spatially isolated from the main nucleus. Micronuclei form from lagging chromosomes or chromosome fragments following mitotic errors or DNA damage, respectively.

Chromocentres
Dense aggregation of heterochromatin formed during interphase.

Facultative heterochromatin
Condensed, transcriptionally silent chromatin region that can decondense and adapt to allow transcription within temporal and spatial contexts. Facultative heterochromatin is not characterized by repetitive sequences so, at the DNA sequence level, it is entirely different from constitutive heterochromatin.

Polycomb repressive complex 2
(PRC2). Major repressive chromatin complex formed by Polycomb group (PcG) proteins.

Serum response factor
(SRF). Transcription factor that plays a key role in the transduction of mechanical signals from cytoplasmic actin and extracellular matrix proteins to the nucleus. SRF is involved in various cellular processes, from cell proliferation to differentiation and development.

Mechanically induced epigenetic changes can have a functional impact on gene expression and cell fate regulation (FIG. 6f). For example, human mesenchymal cells respond to matrix stiffening by increasing nuclear membrane tension and histone acetylation via deactivation of HDACs, leading to osteogenic fate determination[212]. By contrast, LINC complex disruption, which presumably reduces nuclear membrane tension, leads to upregulation of HDACs and inhibits osteogenic differentiation[212]. Similarly, persistent differentiation of fibroblasts to myofibroblasts relies on increased chromatin compaction mediated by nuclear mechanosensing of cytoskeletal forces via LINC complexes (FIG. 6f) that results in increased activity of HDACs[213]. In macrophages, spatial confinement can suppress the acquisition of a pro-inflammatory phenotype and associated transcriptional programmes (for example, expression of IL-6, CXCL9, IL-1β and iNOS) by inducing epigenetic alterations (such as an increase in H3K36me2) and promoting chromatin compaction[179]. In cardiac myocytes, peripheral heterochromatin characterized by H3K9me3 marks, which closely correlates with intranuclear deformations and reducing nuclear deformations by LINC complex disruption, results in loss of peripheral H3K9me2/3 marks and reduced expression of cardiac developmental genes[214].

The molecular details by which mechanical deformation of the cell and nucleus result in chromatin modification and reorganization remain incompletely understood, but two major contributors have emerged to date: an increase in intracellular cations (calcium and/or magnesium) by activation of stretch-activated ion channels and remodelling of the nuclear and/or perinuclear actin network. Repetitive stretching of mesenchymal stem cells activates mechanosensitive ion channels, such as Piezo1, leading to increased intracellular calcium levels and increased heterochromatin formation (marked by H3K9me2 and H3K9me3), ultimately promoting mesenchymal differentiation[215,216]. In epithelial cells, cyclic mechanical stretch triggers immediate nuclear deformation that leads to Piezo1-mediated calcium release from the ER, reducing lamina-associated heterochromatin (H3K9me3 marks) within a ~30 min window[16]. This results in nuclear softening that decreases stress and DNA damage in the stretched cells[16]. Long-term (8–12 h) cyclic uniaxial stretch application causes transcriptional repression, increased heterochromatin (H3K27me3) and silencing of differentiation gene expression[16]. Intriguingly, activation of mechanosensitive ion channels by increasing extracellular multivalent ion concentrations, even in the absence of cell stretching or compression, is sufficient to trigger a similar increase in heterochromatin[91]. The increased heterochromatin content mechanically strengthened the nucleus, rescued abnormal nuclear morphology in *LMNA*-mutant and breast cancer cells, reduced nuclear envelope ruptures and prevented DNA damage[91]. Collectively, these findings demonstrate that mechanosensitive ion channels respond to mechanical stimuli causing an increase in intracellular calcium that leads to chromatin modifications, which mechanically protect the nucleus and influence cell fate decisions. These stretch-sensitive ion channels can be found on the plasma membrane, the ER and, potentially, the nuclear envelope itself, with the contribution of specific channels and their locations likely depending on the particular cellular context and the mechanical cue.

Conclusions and perspectives

Considerable efforts in recent years have started to shed light on the fascinating roles of nuclear deformations in cell function, whereby chromatin organization, compaction, stretching and modifications that arise from nuclear deformations control the downstream expression of genes and cell fate decisions. Altogether, these discoveries have revealed the remarkable mechanoresponsive nature of the nucleus and the key role of nuclear proteins in the cellular response to mechanical stimuli. However, many open questions remain. For example, although potential mechanisms have been proposed (BOX 1), how the nucleus senses the different forces and deformations that it is subject to in different contexts and how it transduces this signal for specific responses remain elusive. Although substantial progress has been made in the understanding of nucleo-cytoskeletal coupling, the precise mechanisms for the spatiotemporal regulation of force transmission across the LINC complex required for many cellular functions has yet to be fully elucidated. Connections between the nucleus, other organelles and the plasma membrane have received far less attention and should be investigated in more detail. Inside the nucleus, a better understanding of the role of nuclear F-actin and associated motor proteins as well as LLPS processes in the maintenance of the nuclear structure, genomic organization and chromatin remodelling will require deeper investigation.

Deciphering the complex mechanical interplay between chromatin, the nuclear envelope, cytoskeletal filaments and the cell surface in mechanobiology will benefit from interdisciplinary and integrative approaches, combining live-cell imaging with high spatial and temporal resolution, genetic manipulation and precise mechanical manipulation. Much of our knowledge about nuclear mechanotransduction has come from innovative technologies. Addressing current challenges in this field will require further technological innovations, for instance, to visualize gene expression in live cells while exerting subcellular deformations, ideally on a genome-wide scale and yet with single-cell resolution. In addition to these experimental breakthroughs, mechanochemical models of the nucleus developed by theoretical modelling will be essential to explore how the cooperation between mechanical and biochemical parameters regulates feedback loops[217] in nuclear signalling pathways. A better understanding of the molecular mechanisms governing nuclear mechanobiology would not only clarify how the various cellular mechanotransduction pathways are combined to determine downstream cellular function but may also guide the development of novel therapeutic strategies to treat human diseases that arise from impaired nuclear mechanics, mechanotransduction and disturbed nucleo-cytoskeletal force transmission (BOX 2).

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