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Sizing and shaping the nucleus: mechanisms and significance

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Abstract

The size and shape of the nucleus are tightly regulated, indicating the physiological significance of proper nuclear morphology, yet the mechanisms and functions of nuclear size and shape regulation remain poorly understood. Correlations between altered nuclear morphology and certain disease states have long been observed, most notably many cancers are diagnosed and staged based on graded increases in nuclear size. Here we review recent studies investigating the mechanisms regulating nuclear size and shape, how mitotic events influence nuclear morphology, and the role of nuclear size and shape in subnuclear chromatin organization and cancer progression.

Introduction

Many structural components of the nucleus control nuclear size and shape. The nuclear envelope (NE) is a double lipid bilayer consisting of the outer nuclear membrane (ONM), continuous with the endoplasmic reticulum (ER), and inner nuclear membrane (INM). The nuclear pore complex (NPC) embedded in the NE mediates nucleocytoplasmic transport. The nucleoplasmic face of the INM is lined by the nuclear lamina, a meshwork of intermediate lamin filaments that structurally supports the NE and mediates connections with chromatin. Linker of nucleoskeleton and cytoskeleton (LINC) complexes connect the nuclear lamina with the cytoskeleton through the NE, mediated by interactions between INM SUN-domain proteins and ONM KASH-domain proteins (reviewed in [1,2]).

The nucleus is a dynamic organelle, particularly during mitosis in metazoans when the NE breaks down to facilitate mitotic spindle assembly. Reassembly of the NE, nuclear lamina, and NPCs occurs after chromosome segregation [1], and recent studies show that these post-mitotic events are important in determining proper nuclear morphology in the subsequent interphase. Yeast studies have also elucidated the regulation of nuclear size and shape, however in contrast to the open mitosis of animal cells, many yeasts undergo a closed mitosis that necessitates dramatic cell cycle regulated changes in nuclear morphology [3-6].

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Changes in nuclear size and shape are associated with cell differentiation, development, and disease. Of note, nuclear morphology is frequently altered in cancer cells [7,8]. By and large the physiological consequences of altered nuclear size and shape are not known but could potentially impact chromatin organization and gene expression, particularly in the context of tumor development and cancer progression. Therefore, it is important to understand the mechanisms that regulate nuclear size and shape as well as the function of proper nuclear morphology control.

In this review we focus on recent studies addressing mechanisms of nuclear size and shape regulation, in particular the roles of nuclear structural elements, the cytoskeleton, membrane, and the extracellular matrix (ECM). We then discuss how mitotic events impact nuclear morphology and how nuclear size and shape might impact subnuclear structure and function. We conclude with recent studies investigating the contributions of nuclear morphology to cancer and some future directions.

Mechanisms of nuclear size regulation

Nucleocytoplasmic transport, nuclear structural components, and post-mitotic nuclear assembly can all impact nuclear size. Although genome size scales with nuclear size across a wide range of species, DNA content tends to be a less important contributor to nuclear size regulation in a variety of experimental systems, primarily establishing a minimum nuclear size (reviewed in [9-11]). Here we will integrate results from older studies with newer findings on the roles of the nuclear lamina, LINC complexes, and NPCs in the regulation of nuclear size (Table 1).

Several studies support a role for nuclear lamins in nuclear size regulation. In *Xenopus* egg extracts, the lamin Ig-fold motif was required for post-mitotic lamina assembly and NE growth [12], lamin B3 depletion resulted in small nuclei that failed to expand [13], and ectopic addition of lamin B3 increased the rate of nuclear growth [14] (Fig. 1a). In tissue culture cells and *Xenopus* oocytes, NE growth was promoted by the C-terminal domain from B-type lamins, which contains a farnesylated CaaX motif required for lamin interaction with the INM [15,16]. Lamin B overexpression in zebrafish embryos and tissue culture cells resulted in extranuclear cisternae-like lamin/membrane arrays, dependent on farnesylation [16]. Furthermore, in *Arabidopsis thaliana*, deletion of genes encoding lamin-like nuclear matrix proteins, LITTLE NUCLEI 1/2, resulted in decreased nuclear size and altered nuclear morphology [17].

The lamina-associated polypeptides (LAPs) establish connections between the lamins and chromatin [18]. Addition of the nucleoplasmic chromatin-binding domain of human LAP2β to *Xenopus* extract blocked nuclear lamina assembly, inhibited nuclear growth, and resulted in a scalloped NE phenotype, demonstrating a role for LAP2 in postmitotic nuclear size determination [19]. Additionally, LAP2 was mislocalized upon depletion of TPX2, an important regulator of spindle assembly, resulting in dramatically smaller, but functional, interphase nuclei [20] (Fig. 1b).

LINC complexes also contribute to the regulation of nuclear size. In HaCaT cells, F-actin depolymerization resulted in small, highly dysmorphic nuclei, while microtubule

depolymerization increased nuclear size. Notably, depolymerization of both cytoskeletal components decreased nuclear size, suggesting that nuclear connections with the actin cytoskeleton may be dominant [21]. These effects may be mediated through the actin-binding domain (ABD) of the ONM KASH-domain protein nesprin-2. Expression of nesprin-2ΔABD, the ABD alone, or the KASH domain alone increased nuclear area. Conversely, expression of nesprin-2-mini, a fusion protein consisting of only the KASH domain and ABD and lacking the large central spectrin-repeat rod domain, resulted in reduced nuclear size [21,22] (Fig. 1c).

During normal interphase, nuclear volume and NPC number nearly double, however distinct mechanisms seem to regulate these two processes because disruption of interphase NPC assembly in HeLa cells by cyclin-dependent kinase inhibition negligibly affected nuclear growth [23,24]. Nonetheless, altered NPC composition can affect nuclear size. In budding yeast, a RSC chromatin remodeling complex mutant exhibited NPC mislocalization, accumulation of nuclear membrane sheets, and altered nuclear morphology [25]. In *Xenopus* egg extract, a dominant-negative fragment of the nucleoporin POM121 blocked NE growth when added to intact nuclei [26], while depletion of Nup188 led to the formation of enlarged nuclei with intact NPCs that exhibited increased import of INM proteins [27].

Mechanisms of nuclear shape regulation

Recent studies support previous research demonstrating that nuclear lamins modulate nuclear shape [11,28,29]. During granulopoesis, neutrophils developing lobulated nuclei increase expression of lamin B receptor (LBR) and downregulate lamin A. Reducing LBR in neutrophil-differentiated HL-60 cells resulted in hypolobulated nuclei, while lamin A overexpression caused both nuclear hypolobulation and impaired neutrophil migration [30,31] (Fig. 1d). Cortical neurons in lamin B1 knock-out mice exhibited abnormally shaped nuclei with blebs and irregular lamin B2 distribution, while lamin B2 deficiency resulted in neurons with elongated nuclei accompanied by severe defects in brain development [32]. Abnormal nuclear shape and premature senescence of Ataxia telangiectasia cells were rescued by reducing lamin B1 levels [33].

Diseases caused by mutations in nuclear lamin genes, collectively termed laminopathies, are frequently associated with altered nuclear shape [34]. Lamin A mutations give rise to muscular dystrophies, familial partial lipodystrophy, dilated cardiomyopathy, and Hutchinson-Gilford progeria syndrome (HGPS). HGPS misshapen nuclei are caused by an inappropriately farnesylated form of lamin A, called progerin, that improperly incorporates into the lamina (Fig. 1e). Inhibition of farnesyltransferase or farnesylcysteine methylation improved nuclear morphology and phenotypes of progeroid mice [35,36]. Similarly, inhibiting prelamin A farnesylation significantly reduced nuclear shape abnormalities in HGPS patient fibroblasts [37]. Strikingly, reducing levels of the INM protein Sun1 in laminopathy mouse models and HGPS patient cells rescued defects in nuclear shape and cellular senescence [38], as did inhibition of the mTOR pathway which reduced progerin levels and nuclear blebbing, detected by a novel automated and high-throughput image analysis method that quantifies NE curvature [39,40].

NE components other than the lamina also influence nuclear shape [11,28]. Mutations in budding yeast nucleoporins that cause NPC clustering are frequently associated with altered nuclear shape [41,42]. Deletion of yeast proteins Mlp1p and Mlp2p, structural components of the NPC basket thought to link and properly distribute neighboring NPCs, led to increased NPC mobility and clustering and the formation of fragile, misshapen nuclei that frequently exhibited NE blebs [43]. *Arabidopsis thaliana* expresses a plant-specific nucleoporin, Nup136, a functional homolog of vertebrate Nup153. Nup136 overexpression increased nuclear size and elongation in many tissues, whereas reducing Nup136 expression resulted in smaller, more spherical nuclei [44,45] (Fig. 1f). *Arabidopsis* also expresses LINC complex proteins that regulate nuclear shape. Knockdown of AtSUN1 and AtSUN2 produced round nuclei in root hairs, compared to highly elongated wild-type nuclei [46]. Furthermore, *Arabidopsis* WIPs, plant-specific KASH-domain proteins, interact with SUN1/2 proteins, and disrupting these interactions reduced nuclear elongation [47].

Recent studies highlight an important role for perinuclear actin caps in controlling nuclear shape and positioning [48]. The multi-lobed, elongated nuclei of embryonic stem cells lack a perinuclear actin cap. During differentiation, these nuclei were observed to take on a more smooth, rounded morphology concomitantly with the appearance of a perinuclear actin cap, which wrapped around the nuclear surface making contacts across the NE with lamin A/C through LINC complex proteins [49] (Fig. 1g). Intriguingly, in mouse models of progeria and muscular dystrophy, the perinuclear actin cap was disrupted or absent and nuclei assumed deformed shapes [50].

There is growing evidence that physical properties of the ECM modulate nuclear shape. The actin-myosin cytoskeleton transmits mechanical force from focal adhesions at the cell membrane/ECM junction to nuclear LINC complexes and the lamina (reviewed in [29]), and the actin cytoskeleton was also shown to be important in coordinating nuclear shape with cell shape [51]. Rigidity of the substrate on which NIH 3T3 cells were grown modulated nuclear shape, such that soft substrates produced cells with round nuclei while stiff substrates led to flattened nuclei [52]. Dermal fibroblasts from laminopathy patients exhibited round nuclei on soft substrates but misshapen or ruptured nuclei on stiff substrates [53] (Fig. 1h). Intriguing interactions between lamin A levels, ECM stiffness, and cell differentiation have also recently emerged [54], as well as a novel role for keratin filaments in regulating nuclear shape [55]. Taken together, nuclear shape is determined by structural elements of the nucleus (Table 1), cytoplasmic and extracellular structures, and cytoskeletal tension transduced from the ECM. In the case of disease, weakened nuclei may contribute to abnormal nuclear morphology.

Cell cycle events that influence nuclear morphology

Events that occur during mitosis are important in establishing normal interphase nuclear morphology [1]. Depletion of microtubule-binding ER proteins REEP3/4 caused inappropriate ER accumulation on metaphase chromosomes, leading to NE defects during interphase [56] (Fig. 2a). In addition to clearance of ER membrane from metaphase chromosomes, mitotic microtubule dynamics also influence interphase nuclear morphology. In *Xenopus* egg extract, chromatin-binding protein Dppa2 inhibits post-mitotic microtubule

polymerization, and depletion of Dppa2 led to the formation of small, misshapen nuclei with decreased nuclear lamin and NPC assembly. Strikingly, these nuclear morphology defects could be rescued by ectopically depolymerizing microtubules, suggesting that precisely tuned microtubule dynamics are required for proper nuclear assembly [57] (Fig. 2b). Also important for establishing correct nuclear shape are interactions between chromatin-bound BAF and LEM family INM proteins that mediate nuclear assembly (Fig. 1). LEM4 depletion or mutation caused misshapen, multi-lobed nuclei in *C. elegans* [58] (Fig. 2c), and in *Schizosaccharomyces japonicus*, the conserved LEM-domain protein Man1 was required for equal partitioning of nuclear membrane and NPCs to daughter nuclei [59]. During the closed mitoses of many yeasts, spindle pole bodies inserted into the NE drive intranuclear spindle formation. Elongation of the internally-forming spindle profoundly alters nuclear shape, as the intact nucleus expands along the mother-daughter axis prior to cytokinesis [3-6].

The regulation of phospholipid biosynthesis is important in maintaining normal nuclear structure and dynamics. In fission yeast, a temperature-sensitive RanGEF mutant exhibited asymmetric cell divisions, reduced post-mitotic nuclear growth, and frequent NE breakage, phenotypes that could be rescued by slowing spindle elongation, increasing proliferation of ER membrane, or increasing the relative proportion of ER sheets [60]. In budding yeast, expression of a dominant negative SUN-domain protein, Mps3, led to over-proliferation of the INM that could be rescued by altering lipid homeostasis [61]. Upregulating lipid biosynthesis in yeast led to ER and NE membrane proliferation and the formation of misshapen nuclei in which the NE expanded specifically in the region adjacent to the nucleolus, forming a structure termed a "flare" [28,62,63]. More irregular nuclear shapes were observed if endosome to late Golgi trafficking was also disrupted, but a normal nuclear/cell volume ratio was maintained [64]. Mitotic delay induced similar nucleolar flares that could be rescued by inhibition of phospholipid synthesis [65], and ER-NE lipid partitioning controlled NE assembly and growth in higher eukaryotes as well [66,67]. In *C. elegans*, downregulation of lipin homolog LPIN-1 altered ER composition, NE breakdown, chromosome segregation, and nuclear morphology [68]. Mutations affecting trafficking through the ER-Golgi intermediate compartment also affected NE structure, disrupting transport of NE proteins and nucleoporins [69].

During interphase different mechanisms promote the maintenance of proper nuclear morphology. Inappropriate condensin II activity in interphase, caused by depletion of the ubiquitin ligase SCF^{Slimb}, resulted in chromatin compaction and deformed, ruffled nuclei [70] (Fig. 2d). Early in development in some fish and amphibian embryos, post-mitotic NE assembly is initiated around individual chromosomes, forming structures called karyomeres that eventually fuse to form an intact nucleus. The zebrafish protein brambleberry was shown to be required for fusion of karyomeres into a mononucleus and for the regulation of normal nuclear morphology in early development [71] (Fig. 2e).

Nuclear morphology, chromatin organization, and gene expression

An important function of nuclear architecture is to organize chromatin and regulate gene expression. Some factors that structure and modify chromatin also influence nuclear morphology and size. Whether nuclear size directly impacts subnuclear function remains an

open question. Recent studies have quantified chromatin positioning and gene expression during development and differentiation, processes associated with changes in nuclear size (reviewed in [72,73]), and modeling studies suggest that nuclear volume could drive chromatin organization [74,75].

In immortalized mammary epithelial cells, knockdown of a chromatin-remodeling enzyme, BRG1, resulted in nuclear periphery grooves [76]. During neuronal cell maturation, the chromatin-associated protein MeCP2 was required for normal developmental nuclear growth and gene transcription [77]. RNAi of soybean GmFWL1 resulted in decreased nuclear size, likely due to altered heterochromatization [78]. During *C. elegans* embryogenesis, reductions in nuclear size were shown to correlate with increased mitotic chromosome condensation [79] and interphase genome reorganization resulting in activated genes shifting towards the nuclear lumen and silenced genes localizing to the NE [80]. Interestingly, increasing the size of *Xenopus* embryonic nuclei did not result in increased mitotic chromosome length or width [81]. During T-cell activation, both actin-mediated nuclear elongation and activation of signaling intermediates were required to alter gene expression [82].

Changes in histone modifications have also been linked to nuclear size and shape. Bone marrow mesenchymal stem cells placed under mechanical strain by microtopographic patterning exhibited elongated nuclei and increased histone acetylation and gene transcription [83,84]. During myotube formation in human primary myoblasts, nuclei became smaller and more flattened, accompanied by altered histone modifications, chromatin remodeling, and gene expression silencing [85]. In mouse myoblasts, increased histone H3 acetylation correlated with increased nuclear size and F-actin cytoskeleton content [86], which has been shown to be required in large nuclei to stabilize subnuclear organization against gravitational forces [87]. Null mutations in the mouse cannabinoid receptor type 1 resulted in spermatozoa with elongated nuclei, reduced histone retention, and poor chromatin quality, which could be rescued by estrogen treatment [88].

Osmotic stress is known to induce global changes in gene expression. Articular chondrocytes under hyper-osmotic conditions showed increased nucleocytoplasmic transport, decreased nuclear size, and a more convoluted NE morphology. Conversely, under hypo-osmotic stress, nuclei swelled, assuming a smooth spherical shape limited by NE stiffness, with no effect on nucleocytoplasmic transport [89,90]. Osmotic stress may be a useful system for elucidating the relationship between nuclear morphology and gene expression [91].

Some structural components of the NE that regulate nuclear size have also been shown to affect chromatin structure. During *Drosophila* embryogenesis, the NE protein Kugelkern and dynamic microtubules were necessary to maintain normal NE morphology and chromatin dynamics and to activate zygotic gene transcription [92,93]. During differentiation of human embryonic stem cells, increased expression of lamin A/C and emerin were associated with increased nuclear size, the appearance of nuclear invaginations or lobes, and large-scale chromatin reorganization [94]. Overexpression of budding yeast Esc1, a NE protein with roles in chromatin organization and gene expression, led to NE

extensions into the cytoplasm [95]. In *Arabidopsis thaliana*, seed germination increased expression of lamin-like nuclear matrix proteins, resulting in independently regulated nuclear growth and chromatin decondensation [96].

Nuclear morphology in cancer

Nuclear size differs between normal and cancer cells, and nuclear atypia is a common diagnostic and prognostic marker [7,8]. In lung cancer cells and adenocarcinomas, increased p53 expression and decreased expression of p16INK4A, a regulator of Rb, correlated with increased nuclear size and chromatin density as well as distortion of the NE [97]. In mucinous ovarian cancer, LINE1 DNA hypomethylation and increased nuclear area correlated with greater cell proliferation rates, aneuploidy, and reduced survival probability [98]. Lamin A was identified as a potential new biomarker for prostate cancer progression, which is associated with altered nuclear size, shape, and heterochromatin organization. Compared to benign samples, lamin A was downregulated in low grade tumors and upregulated in high grade tumors [99,100]. Tumor regression in response to treatment of breast cancer with anti-estrogen therapy was associated with decreased nuclear size in tumor cells, suggesting that reductions in nuclear size might be used to assess treatment efficacy [101].

Micronuclei, extranuclear structures generated by chromosome missegregation during mitosis, are common in cancer cells and may be degraded by nucleophagy [102]. Micronuclei were observed to generate extensively fragmented chromosomes that could be distributed to daughter nuclei, potentially contributing to chromosomal rearrangements and aneuploidy associated with cancer progression [103]. Micronuclear disruption, triggered by NE collapse and lamina disorganization, was frequently observed in cancer cells and may represent a general characteristic of genomic instability useful in diagnosis or prognosis [104,105] (Fig. 2f). Nuclear blebs are also common pathological features in cancers and laminopathies. Modeling studies indicated that separation of lamin fibers within the meshwork of the lamina is required for bleb formation, suggesting a possible approach to preventing these NE deformations in disease [106,107].

Recent diagnostic advances relevant to altered nuclear size in cancer have been reported. High grade urothelial carcinomas exhibited increased nuclear size, relative to low grade cases, that correlated with increased numbers of centromeres, detected by FISH using centromere enumeration probes (CEPs). Such CEPs may be applied to diagnosis of bladder carcinomas [108]. Tomographic imaging performed on fibrocystic and malignant mammary epithelial cells revealed abnormal nuclear shape, increased nuclear volume, greater numbers of nucleoli, and increased chromatin density and clumping, compared to normal cells [109]. Digital image analysis performed on melanocytic lesions comparing 62 features, including nuclear area, shape, and texture, allowed for effective differentiation of melanoma stages and subtypes [110]. Taken together, automated quantitative 3D nuclear morphometry could be useful as a novel diagnostic tool. These and future advancements in the analysis of digital histological images promise to improve diagnosis and provide for more individualized therapeutic interventions.

Conclusions

Some common mechanistic themes in the regulation of nuclear morphology are beginning to emerge. NE structural components, especially nuclear lamins, lamin-associated and lamin-like proteins, LINC complex proteins, and NPCs, are frequently involved, as is regulated nuclear import of these components. Perinuclear elements also influence nuclear morphology, such as ER structure and mechanical forces transduced by the actin and microtubule cytoskeletons, sometimes through ECM associations. In many systems, DNA amount appears to not be a primary determinant of nuclear size, while chromatin structure and modification can affect nuclear morphology. It is also becoming evident that mitotic events determine interphase nuclear morphology, where clearance of ER and microtubules from chromosomes and proper lipid homeostasis are important.

Open questions remain regarding the functional significance of nuclear morphology and how steady-state nuclear morphology is determined. The regulation of nuclear size and shape may be intimately linked, for instance it was recently proposed that changes in nuclear shape that maintain a constant karyoplasmic ratio may in fact be manifestations of altered nuclear size [28,64]. Although factors that influence nuclear size and shape are known, an integrated model of the mechanisms controlling nuclear morphology has yet to emerge, and upstream regulatory determinants and/or signals of nuclear size regulation remain to be identified. Emerging technologies, such as microfluidics [111], cell encapsulation [112], advances in microscopy [113], and 3D cell culture systems [114], broaden the possibilities for studying mechanisms of organelle scaling. In one recent example, microfluidic devices were used to encapsulate mitotic *Xenopus* extract within microdroplets of defined and tunable size, demonstrating how cytoplasmic volume contributes to mitotic spindle length scaling [115,116] and offering evidence for limiting-component models of organelle size regulation [117-119]. Similar approaches may be applied to study mechanisms regulating nuclear size and shape. Coupled with emerging technologies, *Xenopus* has been, and will continue to be, a powerful system to investigate intrinsic mechanisms of organelle size regulation [120].

Higher order chromatin organization is usually perturbed in cancers and can affect mutation frequencies [121,122], but the cause and effect relationships between increased nuclear size and altered subnuclear organization remain to be elucidated. One hypothesis is that nuclear size directly affects chromatin organization and gene expression. Enlarged nuclei are often observed in cells adjacent to a tumor, and these cells appear otherwise normal by histology. An explanation for this “field effect” is that genetic alterations leading to cancer occur in a stepwise fashion and cells in the field around the tumor represent a clonal population arising from an early genetic change that was a precursor to carcinogenesis [123]. By this model, precancerous alterations in nuclear size might disrupt chromatin positioning, thereby influencing transcriptional profiles and priming cancer development or promoting additional genetic alterations that contribute to cancer progression.

Development, differentiation, and disease progression are associated with changes in nuclear size, nuclear morphology, chromatin organization, and gene expression. Determining how these parameters relate to one another can now be accomplished using new techniques for

mapping global chromatin organization coupled with massively parallel sequencing technologies (reviewed in [72,73,124]). Elucidating how developmentally regulated changes in nuclear size affect gene expression will help to clarify the relationship between aberrant nuclear morphology and diverse disease states such as cancer, progeria and other laminopathies, and neuronal disorders [77,125]. Answering fundamental questions about nuclear size and shape regulation promises to provide novel approaches to disease diagnosis, prevention, and treatment.

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Highlights

- Mechanisms of nuclear size and shape regulation
- Cell cycle events that influence nuclear morphology
- Nuclear morphology, chromatin organization, and gene expression
- Nuclear morphology in cancer

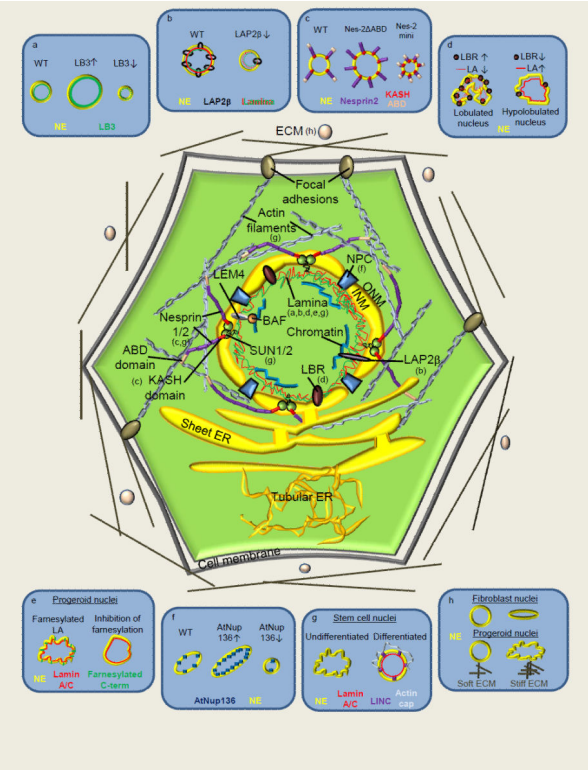

Figure 1. Mechanisms of nuclear size and shape regulation

The central diagram depicts the major cellular components involved in regulating nuclear morphology. The blue boxes around the edge depict specific examples where mechanisms determining nuclear size and/or shape have been identified. (a) In *Xenopus* egg extracts, lamin B3 (LB3) depletion reduces nuclear size [13], while supplementing extract with LB3 increases the rate of NE expansion [14]. (b) Mislocalization of LAP2 or addition of a dominant negative fragment of LAP2 to *Xenopus* egg extract inhibits nuclear growth [19,20]. (c) Expression of nesprin-2 lacking the ABD increases nuclear size, while expression of nesprin-2-mini decreases nuclear size [21,22]. (d) Altered LBR and lamin A (LA) expression in neutrophils affects nuclear lobulation [30,31]. (e) Progerin expression leads to the formation of misshapen nuclei that can be rescued with farnesylation inhibitors [34]. (f) Altered expression of *Arabidopsis thaliana* Nup136 affects both nuclear size and elongation [44,45]. (g) Stem cell differentiation is associated with acquisition of a perinuclear actin cap that regulates nuclear morphology through LINC and lamina interactions [49]. (h) ECM stiffness modulates nuclear shape [53].

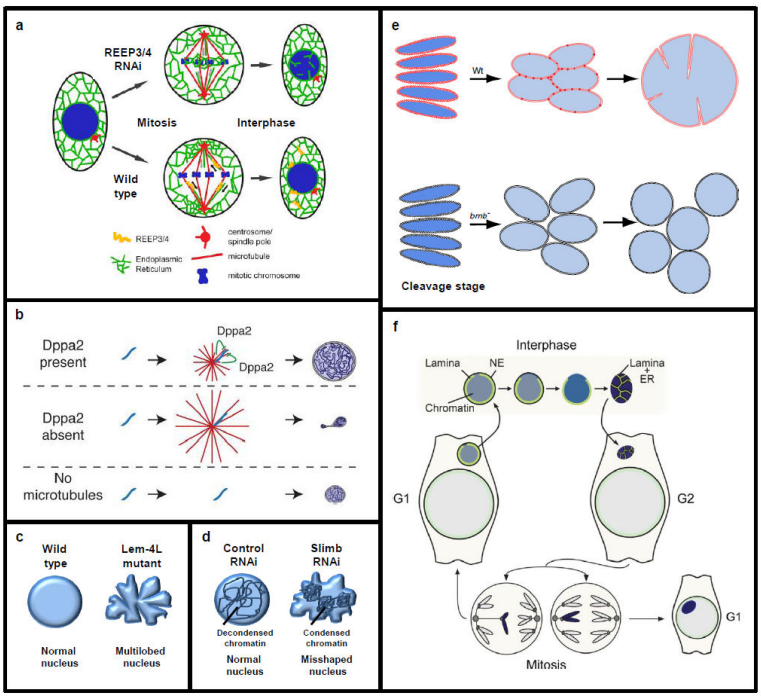

Figure 2. Cell cycle events that influence nuclear morphology

(a) REEP3/4 are required to clear ER membrane from metaphase chromatin. Failure to do so leads to intranuclear membrane invaginations extending into the interphase nucleus. Image adapted with permission from [56]. (b) Post-mitotic suppression of microtubule (red) polymerization by Dppa2 (green) is required for the formation of a nucleus with normal morphology. Chromatin is shown in blue. Image adapted with permission from [57]. (c) Depletion of LEM4 in *C. elegans* leads to misshapen, multi-lobed nuclei [58]. (d) Depletion of the ubiquitin ligase SCF^{Slimb} leads to increased condensin II activity in interphase, chromatin compaction, and deformed nuclear morphology [70]. (e) The brambleberry protein (red) is required for karyomere fusion during early zebrafish development. In the absence of brambleberry (bmb) multiple micronuclei form. Image adapted with permission from [71]. (f) The process of micronuclear formation and disruption is depicted. A micronucleus forms around a lagging chromosome at the end of mitosis. During interphase, disorganization of the nuclear lamina leads to NE collapse, chromatin compaction, and intercalation of tubular ER. Image adapted with permission from [104].

Table 1

Nuclear envelope structural elements that regulate nuclear morphology.

Protein	Organism/ System	Function	Alteration and nuclear phenotype
Lamin A/C	Vertebrates	Structural support to the nucleus, roles in DNA replication and gene expression	Mutations in LMNA gene cause diseases with misshaped nuclei [34-40]
Lamin A/C	Neutrophil-differentiated HL-60 cells	As above	Overexpression causes hypolobulated nuclei [30,31]
Lamin B1	Mammals Cortical neurons	As above	Deficiency causes misshaped nuclei, nuclear blebs [32]
Lamin B2	As above	As above	Deficiency leads to elongated nuclei [32]
Lamin B2	Zebrafish embryo	As above	Overexpression causes lobulated nuclei with intranuclear membranes [16]
Lamin B3	*Xenopus* egg extract	As above	Depletion decreases nuclear size [13] Ectopic addition increases nuclear size [14]
Lamin-like nuclear proteins	*Arabidopsis thaliana*	Should have similar functions to vertebrate lamina	Deletions of LINC1/2 genes result in smaller and more round nuclei [17]
LBR	Neutrophil-differentiated HL-60 cells	Binds lamins and chromatin	Depletion causes hypolobulated nuclei [30,31]
Lap2β	*Xenopus* egg extract	Binds lamins and chromatin	Addition of truncated Lap2β causes small scalloped nuclei [19]
LEM4	*Caenorhabditis elegans*	Interacts with lamina and chromatin	Depletion causes misshapen, multilobed nuclei [58]
AtSun1/2	*Arabidopsis thaliana*	Components of LINC complex	Depletion causes nuclear rounding [46]
AtWIPs	*Arabidopsis thaliana*	Plant specific KASH domain proteins, components of LINC complex	Mutations that disrupt LINC interactions cause nuclear rounding [47]
Nesprin2	HaCaT cells	KASH domain protein; binds to actin cytoskeleton and SUN proteins; part of LINC complex	Nes2ΔABD overexpression increases nuclear size; Nes2-mini overexpression decreases nuclear size [21,22]
Pom121	*Xenopus* egg extract	Nucleoporin, structural component of NPC	Addition of dominant negative fragment blocks NE growth [26]
Nup188	*Xenopus* egg extract	As above	Depletion increases nuclear size [27]
AtNup136	*Arabidopsis thaliana*	As above	Overexpression increases nuclear size and nuclear elongation; Depletion decreases nuclear size and causes nuclear rounding [44,45]