Review

The Nucleus and Its Physiological Role

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Article

The Nucleus and Its Physiological Role

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Abstract: The nucleus, serving as a pivotal regulatory and control hub within the cell, governs numerous aspects of cellular functions, including DNA replication, transcription, RNA processing and so on. Therefore, any deviations in nuclear morphology, structure or organization can profoundly impact cellular activities. In this review, we provide an updated perspective on the structure and function of nuclear components, with a specific focus on the linker of nucleoskeleton and cytoskeleton complex, the nuclear envelope, the nuclear lamina and chromatin. It is crucial to note that nuclear size should not be overlooked but rather considered as a fundamental parameter for cellular state. Its regulation is tightly linked to environmental changes, development and various diseases, including cancer. Hence, we also provide a concise overview of different mechanisms by which nuclear size is determined, the emerging role of the nucleus as a mechanical sensor, and the implications of altered nuclear morphology on the physiology of diseased cells.

Keywords: nucleus; nuclear components; cellular functions; nuclear size; mechanical function

1. Introduction

The key feature that distinguishes eukaryotic from prokaryotic cells is the presence of a well-defined nucleus within the former. The nucleus serves as the repository for genetic information and functions as the primary regulatory hub within the cell, controlling diverse aspects of cellular function. Alterations in the standardized structure, morphology or organization of the nucleus have been linked to a wide range of pathological conditions. To establish and maintain proper cellular functions, the majority of nuclear components are typically situated in their designated positions, present in precise quantities and functioning at appropriate times. Given the evidence that nuclear components are functionally important and subject to precise quantitative and spatiotemporal regulation, what are the intricate structure of these components, and what specific roles do they play in cellular functions? In this review, we discuss recent studies that have shed lights on the main nuclear constitutes and their respective functions, focusing on the linker of nucleoskeleton and cytoskeleton (LINC) complex, the nuclear envelope (NE), the nuclear lamina and chromatin.

Since the appropriate nuclear size is crucial for maintaining optimal cellular function, we are particularly interested in exploring the mechanisms governing nuclear size and its impact on cellular function. Here we summarize recent advances in the mechanisms that regulate nuclear size, with a specific focus on regulators such as the nuclear lamina, chromatin, osmotic pressure and others. While our primary concern is on nuclear size, we also address the factors influencing nuclear shape, as alterations in nuclear shape may be indicative of alterations in nuclear size.

Interestingly, recent studies increasingly suggest that nuclei can function as a mechanical sensor, capable of modifying their morphology and regulating cellular behaviors in response to environmental pressure. Herein, we examine recent advances describing how nuclei are involved in nuclear mechanics and how impairment in nuclear mechanics leads to multiple disorders. Furthermore, we will briefly touch upon how alterations in nuclear morphology may potentially contribute to the development of certain diseases.

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2. Nuclear Components and Their Cellular Functions

Any abnormal changes in the nuclear structure can result in functional issues, including genetic instability, aberrant chromosomal numbers, altered gene expression and metabolic imbalance [1].

2.1. The LINC Complex Structure and Its Cellular Functions

The LINC complex spans both inner and outer nuclear membranes of the NE, transmitting the force between cytoplasm and nucleoplasm. Its core components are SUN and KASH domain containing proteins [2]. Specifically, nesprin-1 and nesprin-2. which contain KASH domains, are anchored at the outer nuclear membrane and interact with SUN domain-containing proteins which are embedded in the inner nuclear membrane [3]. The canonical structure of the LINC complex typically consists of six SUN and six KASH proteins, with SUN proteins forming homotrimers to interact with KASH [4]. However, recently obtained crystal structures have reported that the SUN-KASH complex adopts a 9:6 configuration *in vivo* recently, suggesting the feasibility that SUN-KASH complexes can assemble asymmetrically. Additionally, some *in vitro* studies proposed that the self-locked structure of SUN proteins can form trimers without the involvement of KASH proteins and the formed SUN trimers can interact with chromatins independently [5]. Furthermore, the CH domain of nesprin can interact with cytoskeletal networks, thereby facilitating force transduction from cytoplasm to nucleus and ultimately promoting nuclear movement [6]. The mechanism involves KASH proteins interacting with microtubules and then recruiting dynein to outer nuclear membrane, generating the force needed to move the nucleus towards the microtubules [7]. Based on these findings, it can be concluded that the LINC complex plays a crucial role in promoting nuclear migration by connecting the cytoskeleton with the nuclei. For example, P cells are the vulval and neuronal precursor cells of *Caenorhabditis elegans* (*C. elegans*), which proceed migration from lateral positions to the ventral cord during larval development via the LINC complex and then they will differentiate to form the vulva and GABA neurons [8]. Researchers analyzed the absence of GABA neurons to assess cell migration, which could indirectly reflect nuclear migration. When MET-2, a homolog of mammalian methyltransferase, is knocked out in *C. elegans*, heterochromatin is observed to detach from the NE without any loss of GABA neurons. However, animals with both the LINC complex defects and MET-2 deficiency exhibit an enhanced loss of GABA neurons compared to those with only the LINC complex defects, indicating the potential that the LINC complex to interact with perinuclear heterochromatin in regulating the nuclear movement [9].

Interestingly, researchers have discovered that the suppression of H3K9-specific histone methyltransferase SUV39H1 causes the Golgi apparatus to scatter, a process mediated by the LINC complex [10]. It is likely that the loss of H3K9me3 promotes the formation of SUN2-nesprin2 complex, which connects with the plus end kinesin KIF20A and thereby activating its dynein activity [11]. As we know, the steady state of Golgi complex is maintained by the minus end directed MT motor [12]. Therefore, the activation of KIF20A can disrupt the balance between Golgi complex and MT dynamics, ultimately causing the Golgi complex to disperse. It indicates that the LINC complex facilitates bidirectional interactions between the cytoplasm and nucleus.

2.2. The NE Structure and Its Cellular Functions

The NE, composed of a double membrane with inner and outer layers, serves to separate the nucleus from the cytoplasm. The nuclear pore complexes (NPCs) are large protein assemblies embeded into the NE, controlling the transport between nucleus and cytoplasm and ensuring precise gene regulation by facilitating the exchanges of necessary substance [13,14]. Intriguingly, NPCs have the ability to regulate the genome in response to environmental mechanical stress [15]. In order to gain a deeper understanding of the function of NPCs, it is necessary to conduct a thorough investigation into their structure. NPCs are composed of three layers: the cytosolic ring, the inner ring and the nuclear ring, and contain more than 1000 protein subunits [16]. Currently, it has been discovered that *Saccharomyces cerevisiae* (*S. cerevisiae*) has two distinctive types of NPCs in the same nucleus: one harbors basket-like structure on the nuclear face, while the other does not [17]. Novel

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methods have been developed to isolate the NPCs from *S. cerevisiae* nucleus for further investigation of their heterogeneous components, associated proteins, and functions. Researchers tagged GFP to nucleoporin 133 (Nup133) in basket-less NPCs and protein A to Mlp1 in basket-containing NPCs, respectively. Then, they used different beads to distinguish the tagged proteins and successively pulled down two distinct NPCs to analyze their compositions and associated proteins [18]. The subsequent step involves investigating the newly identified components of NPCs and their respective functions.

Nucleoporins (Nups), identified as the functional subunits of NPCs, are the primary components of NPCs [19]. The integrity of NPCs ensures the stability of nuclear circumstance, while the deficiency of NPCs can lead to cell dysfunction and even severe diseases attributed to the imbalance of cellular homeostasis. For instance, Focal Segmental Glomerulosclerosis (FSGS), which is caused by deficient podocytes, is now believed to be associated with mutations in Nup93, Nup205 [20]. Recently, scientists have found that sufficient and proper nuclear localization of YAP and TAZ is required for cell homeostasis, a process that largely depends on the accurate expression of Nup205 to facilitate the shuttling of YAP and TAZ through the NE into the nucleoplasm. Therefore, the decrease of YAP and TAZ leads to low transcriptional activity and increased oxidative stress in podocytes, which may help explain the potential molecular mechanism underlying FSGS [21]. Additionally, the deficiency of Nup protein Seh1 in Schwann cell impairs neurons integrity by altering the gene expression [22]. Potentially, the depletion of Seh1 results in attenuated H3K9me3 modification, which subsequently triggers the ZBP1-RIPK3-MLKL pathway and leads to neuron necroptosis. Consequently, it activates the immune response, recruits the macrophages to peripheral nerves, and results in pathological inflammation.

Additionally, Nups play a crucial role in maintaining genome stability by regulating its distribution. For instance, the Nup protein Elys predominantly tethers chromatin within the lamina-associated domains (LADs) region, ensuring the proper distribution of peripheral chromatin [23]. Once the Elys is diminished, peripheral chromatin will move toward the interior, causing some compacted domains to unfold, which can lead to the de-repression of several inactive genes in LADs. Moreover, Nup170, located in the inner ring of the NE in *S. cerevisiae*, has been reported as an important factor for tethering telomere and repressing subtelomeric genes [24]. The ablation of Nup170 leads to the upregulation of subtelomeric genes due to the reduction in proliferating cell nuclear antigen (PCNA) levels on DNA. When researchers delete the Elg1 to elevate PCNA levels on DNA, the abnormal expression of subtelomeric genes caused by the deletion of Nup170 is rescued. This is likely due to the increased level of PCNA, which can interact with CAF-1, a protein complex responsible for promoting the formation of heterochromatin [24]. However, the mechanisms by which Nups interact with chromatins are still not fully understood. One reported mechanism is that Nup98 interacts with chromatin through a histone deacetylases (HDAC)-dependent pathway. After inhibiting HDAC activity, researchers found that the signal of Nup98 at its chromatin biding sites is declined [25]. Nups communicate not only with chromatin but also with components surrounding the NE. Recently, researchers have proposed that NPCs may cooperate with the LINC complex to form a cohesive unit, contributing to the distribution of centromere. In some Nup mutants of *Arabidopsis thaliana*, such as Nup85-1, Nup85-2, Nua-2 and Nua-3, the location of centromeres tends to rearrange, leading to their accumulation near the nuclear membrane compared to the wild types [26]. These findings suggest that Nups play a crucial role in maintaining genome stability by regulating its distribution.

NPCs, which serve as pathways for transporting molecules between the nucleus and cytoplasm, contain repetitive sequences of phenylalanine-glycine (FG) that can assist in the movement of proteins with nuclear localization signal (NLS) into the nucleus or proteins with nuclear export signal (NES) out of the nucleus. Moreover, particles exceeding the exclusion limit of approximately 40 nm of the NPCs, can be transported through nuclear budding, similar to the transport of herpesvirus [27]. Similarly, large macromolecules, such as RNA granules and aggregated proteins can be transported through NPCs via NE budding [28]. The NLS signal is recognized by karyopherin, which then facilitates the import of proteins into the nucleus by forming an NLS-karyopherin-FG complex

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[29]. It has been reported that nuclear import is considered to have two processes [30]. First, there is fast cargo transport via the exclusion zone. Second, FG domains will unfold, releasing cargos into nucleoplasm as slow cargo transport. Recently, ^{781}KKRK^{784} has been considered as the core of NLS in Pif1, which is a DNA helicase [31]. In *S. cerevisiae*, Pif1 has been discovered important for maintaining both nuclear and mitochondrial DNA integrity [32]. As *Δpif1* cells are hard to culture, the *Δpif1* strain is not ideal for investigating functions of nuclear Pif1. Therefore, knocking out the NLS part of Pif1 could be a feasible way to mimic the *Δpif1* strain. It suggests a novel approach to characterize the functions of lethal-depletion karyopherin proteins. It's intriguing that upon osmotic stress changes, the diameters of NPCs can either constrict or dilate in response to hyperosmotic or hypoosmotic pressure, respectively, and there changes positively correlated with the fluid flow rate across NPCs [33]. However, their permeability barriers for macromolecules in the fluid are still intact, indicating that NPCs have adaptive mechanisms to regulate their permeabilities for macromolecules. This result indicates that nuclei are capable of adapting to changes in osmotic pressure while maintaining their functionality.

The NE proteins ensure nucleus homeostasis in various ways. For instance, nuclear membrane proteins like Lem2 and Bqt4 are thought to prevent the NE from rupture though lipid synthesis processes [34]. Bqt4 can recruit the phosphatidic acid to the rupture site through its intrinsically disordered regions (IDRs), creating a microenvironment that facilities the formation of the ESCRT-III complex, which helps seal the ruptures and repair the NE [35]. Furthermore, the nuclear cargo adaptor Atg39 mediates nucleophagy by transporting nuclear metabolites from the nucleus to the vacuole (in yeast and plants) for degradatation [36], thereby preventing the nucleus from progeroid syndromes [37].

In summary, each component of the NE has its own function, and maintaining the proper state of the NE is considered essential for cellular processes, such as transcription, cell division and spermiogenesis [38]. Therefore, researchers are urgently needed to investigate the factors leading to the NE deformation and its implications.

2.3. The Nuclear Lamina Structure and Its Cellular Functions

The nuclear lamina, composed of lamins (Lam), is located beneath the inner nuclear membrane of the NE, and plays vital roles in maintaining the stability and integrity of the nucleus [39]. The aberrant arrangement of lamins is closely associated with nuclear rupture and blebbing. In vertebrates, lamins are classified into A and B-type. Lam A and Lam C, encoded by the LMNA gene, belong to A-type and Lam B1 and Lam B2, encoded by LMNB1 and LMNB2 genes, respectively, belong to B-type [40]. Interestingly, despite the independent formation of the Lam A and Lam B meshwork, progerin (a mutant form of Lam A) induces irregularities and large openings in both Lam A and Lam B meshwork. These defects can be effectively restored by the expressing Lam B1 [41]. This indicates that the Lam A and Lam B meshwork somehow are interconnected and dependent on each other.

The depletion or phosphorylation of Lam A can impact the distribution of the NE proteins, possibly by altering the self-assembly of Lam A/C [42]. In mouse embryo fibroblasts (MEFs), the absence of Lam A/C can result in mislocalization of emerin and NPCs [43]. Furthermore, the phosphorylation of Lam A can affect cellular function. Lam A R564P mutant causes Nups to accumulate at both the NE and in the cytoplasm in *Drosophila*, leading to defects in protein homeostasis, slow larval motility, and muscle amyotrophy [44]. Another crucial role of Lam A is to maintain the integrity of the nuclear structure. One report showed that the depletion of Lam A, Lam C or Lam A/C in MEFs causes varying levels of nuclear blebbing. Interestingly, only the loss of Lam A results in increased nuclear blebbing, indicating that although Lam A and C are encoded by the same gene, they have distinct effects on the NE [45]. Those results demonstrate that Lam A is important for nuclear morphology, which is consistent with the role of A-type lamins in repairing the nuclear lamina after the NE rupture in the mammalian nucleus [46]. Furthermore, TGFβ, known to play critical roles in epithelial-mesenchymal transition (EMT), has recently been shown to activate Smad3 signaling pathway, leading to the phosphorylation of AKT2 on the Ser390 at Lam A in A549

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cells [47]. The abolishment of Ser390 phosphorylation prevents nuclear deformation, suggesting that phosphorylation of Lam A at Ser390 contributes to proper nuclear modelling.

Lam B participates in numerous biological processes, and any abnormalities in Lam B modification, whether in expression or localization, can lead to alternations in chromatin organization and gene expression. Lam Dm0 is a B-type lamin in *Drosophila*, and its normal distribution is impaired in the muscle cells of PIGB-deficient mutants [48]. Researchers have found that the abnormal distribution of Lam Dm0 leads to an increase in the number of LADs, accompanied by a decrease in their average size. This alternation ultimately results in changes in gene expression, which contributes to muscle defects. Additionally, Autosomal Dominant Leukodystrophy (ADLD) is a lethal neurological disorder characterized by demyelination in the central nervous system (CNS), and it is thought to be caused by tandem genomic duplications of Lam B1. Recently, Nmezi et al. have shown that there is a 19 kb silencer region specifically in oligodendrocytes, which downregulates the transcription of Lam B1 [49]. The silencer region maintains the homeostasis of Lam B1, protecting individuals with tandem duplications of Lam B1 from developing ADLD. The discovery suggests that the possibility of additional silencer factors may be absent or dysregulation in ADLD patients. In summary, both deficiency and overexpression of B-type lamins can have severe consequences on neural development. Hence, B-type lamins play critical roles in maintaining chromatin stability, thereby preventing abnormal transcription and ensuring proper cellular function [50].

Although lamins are considered specific to metazoan cells and have evolved to adapt to diverse environments, numerous Lam-like sequences have been identified in non-metazoan species [51]. Thus, researchers sought to investigate the functions of these related proteins to better understand their roles across different species [52]. They selected the Dictyostelium Lam-like protein NE81 as a target and expressed either NE81 or Lam A in *Lmna*$^{-/-}$ MEFs and triple lamins knockout (TKO) MEFs, which lack all lamins, to investigate the function of NE81. They found that the expression of NE81 in both *Lmna*$^{-/-}$ MEFs and TKO MEFs partially rescues nuclear deformability, but it is not as effective as Lam A in restoring normal function. This indicates that there are differences in self-assembly or -interactions between non-metazoan lamins and metazoan lamins. Lam-like proteins CRWN1 and CRWN2 in Arabidopsis have been shown to interact with RAD51D and SNI, undergo liquid–liquid phase separation (LLPS), and promote DNA repair response to DNA Damage [53]. This suggests that lamins may facilitate the dynamic process of chromatin undergoing LLPS. These results indicate that Lam-like proteins exhibit similar functions, though not identical to canonical lamins.

Nuclear constituents are not isolated entities; rather, they are extensively interconnected as part of integrated network. It's known that chromatins can interact with lamina via LADs [54]. LADs are almost inactive and rich in repressive histone modifications, such as H3K9me2/3, H3K27me3 [55]. However, the precise role of the crosstalk between chromatin and the nuclear lamina within LADs regions remains incompletely elucidated. To answer this question, researchers have found that Lam B involves in the suppression of DNA transcription. Using the Auxin-inducible degron technology to ablate Lam B1 and Lam B2, researchers observed a movement of peripheral chromatin into the interior, as detected by Partial Wave Spectroscopic (PWS) microscopy. They also identified distinct alterations in gene expression within both LADs and non-LADs domains. Specifically, the differentially expressed genes (DEGs) in LADs are primarily associated with laminopathies and chromatin structural disorders, such as scoliosis, while the DEGs in non-LADs are linked to malignancies [56]. These results indicate that B-type lamins are essential for maintaining the three-dimensional genomic architecture within LADs.

Additionally, chromatin itself is crucial for preserving the structure of LADs. Researchers deleted specific regions ranging from 150 kb to 1.3 Mb within LADs region on chromosome 9 in mouse embryonic stem cells (mESCs) [57]. They observed that the deletion region of LADs exhibits varying potential for autonomous association with the nuclear lamina. Interestingly, those remaining LADs regions after rearrangements are able to connect with nearby intervening inter-LAD (iLAD) and subsequently facilitate the establishment of new connections between iLAD and the nuclear lamina, indicating that LADs have the ability to drag neighboring iLAD sequences towards the

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nuclear lamina. Furthermore, certain iLAD regions that acquire the capability to interact with the nuclear lamina show elevated levels of H3K9me3, while others do not. It indicates that H3K9me3 deposition could be a marker of LAD-nuclear lamina interaction, but there are other mechanisms that can also affect LAD-nuclear lamina interaction.

In conclusion, lamin is crucial for numerous cellular functions, particularly in maintaining chromatin structure. Alterations in lamin modification or expression can result in abnormal gene expression, leading to cellular dysregulation and severe diseases.

2.4. Chromatin Structure and Its Cellular Functions

Over the past decade, researchers have discovered that except for traditional membrane-bound organelles, varieties of membrane-less organelles composed of biomolecules can undergo phase separation. Moreover, proteins containing IDRs are capable of performing a similar phenomenon known as LLPS [58]. Although the dynamics of macromolecules are not yet fully understood, *Xenopus* extract offers a robust system for studying the biochemistry and biophysics of living systems [59]. Interestingly, chromatin exhibits notable Brownian diffusion during interphase, albeit its movement restricted to specific subregions referred to as chromosome territories [60,61]. Specifically, on a larger scale, there are two types of territories: euchromatin with low DNA density and heterochromatin with high DNA density [62]. Namely, the region can be sorted into A (active) and B (inactive) compartments, which almost correspond to euchromatin and heterochromatin, respectively [63]. These regions are believed to result from interactions between chromatin and the nuclear lamina, as well as interactions within the chromatin itself, which may be influenced by various proteins or RNA factors [64]. Those abundant protein and RNA factors in the nucleus can interact with each other via LLPS to promote the formation of B compartments [65]. For instance, H3K9me3 is a marker of heterochromatin, which can bind to the chromodomain of heterochromatin protein 1 (HP1) and suppressor of variegation 3-9 homolog 1 (SUV39H1) [66]. When the HP1-SUV39H1 complex connects with H3K9me3 and undergoes LLPS, it can induce chromatin compartmentalization B mentioned above [67]. Furthermore, the chromatin states could also be changed by histone posttranslational modifications (PTMs) [68]. For example, researchers substituted H3.3 K9 for A in mESCs and generated a new line known as K9A. They observed a significant reduction in H3K9me3 signals within heterochromatin and an increase in overlapping H3K27ac signals within the same region in K9A mESCs [69]. Consequently, cryptic cis-regulatory elements at endogenous retroviruses sequences in heterochromatin become active, inducing the expression of immune-related genes. In sum, the chromatin state is closely linked to the level of gene expression.

Recently, researchers start to develop new techniques to investigate chromatin dynamics, which exhibit features reminiscent of LLPS. For instance, researchers have applied the VECTOR (ViscoElastic Chromatin Tethering and ORganization) system to explore the movement of telomere loci, providing a novel platform for viewing chromatin dynamics [70]. To be more specific, researchers can reposition telomere loci by fusing both synthetic light-controlled condensates and telomere loci with the same phase separation-prone IDRs. Thus, the interaction between the IDRs can connect two elements together through capillary forces, allowing nucleic acids at telomere loci to follow the movement of light-controlled condensates. What's more, because both the sequences and charges of synthetic condensates differ from those of telomere loci, it could prevent the mixing of these two elements [71]. Using this system, researchers can calculate the dynamic parameters of chromatin and find that the viscoelastic resistance of internal locus is lower than that of its peripheral partner locus, indicating that chromatin possesses both dynamic and stable properties [72]. In addition, varying chromatin densities result in distinct nonequilibrium processes, with lower density leading to a sol-like network and higher density leading to gel-like networks [73]. It's intriguing that chromatin dynamics is affected by condensates capillarity, like transcription factors, which have the ability to remodel chromatin and subsequently activate or repress gene expression [74].

Since chromatin contains the majority of cell DNA, proper dynamics and state of chromatin are essential for maintaining nuclear homeostasis [75]. First, chromatin dynamics in the nucleus plays important roles in many aspects of nuclear function. For instance, during cell mitosis, chromatin

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undergoes intense compaction to avoid DNA replication and transcription [76]. Interestingly, a recent study reported that the transcription factor Ace2 can bind to the promoter Peng1 to decompact local chromatin during cell mitosis, allowing DNA activation in fission yeast [77]. It is possible that chromatin assembly through chromatin dynamics limits the accessibility of DNA and thereby hinders nuclear events like transcription, DNA replication, and DNA repair, consequently affecting cellular function. For instance, a recent study found that nuclear actin can regulate the rearrangement of heterochromatin by altering chromatin accessibility [78]. The multipotent bone marrow mesenchymal stem cells (MSCs) were exposed to CK666 or CytoD. It was observed that treatment with CK666 results in a decreased level of nuclear F-actin, leading to increased chromatin accessibility and adipogenesis of the cells. Conversely, treatment with CytoD leads to an increased level of branched nuclear F-actin, decreased chromatin accessibility, and osteoblastogenesis. Furthermore, H3K27ac levels in chromatin regions increase upon β-actin depletion [79]. A possible mechanism involves lncRNA Meg3, which could increase chromatin transcription through interacting with chromatin modifying enzymes or transcription factors [80]. It has been reported that the level of H3K27ac in Meg3 promoter is upregulated on β-actin depletion, which can increase the accessibility of Meg3 promoter and its expression. Subsequently, expressed Meg3 will move and accumulate at sites harboring increased the level of H3K27ac levels to regulate chromatin organization. Remarkably, computer simulations of chromatin dynamics have highlighted the crucial role of nucleosome spacing in chromatin organization and accessibility [81]. Second, the state of chromatin regulates various cellular processes, particularly transcription. For instance, treatment of Beta pancreatic cells with bone morphogenetic protein-2 (BMP-2) decreases insulin release in response to glucose, which is attributed to PTMs [82]. This effect is caused by BMP-2 induced reductions in H3K27ac levels, leading to heterochromatin formation and downregulation of NeuroD1 binding sites. The diminished binding sites of NeuroD1, a transcription factor that interacts with the promoters of crucial genes for Beta pancreatic cell determination, result in a decline in Beta pancreatic cells numbers and consequently insulin secretion. Another study revealed that the precise concentration and location of H3K27ac ensure the normal process of early human embryogenesis. During early human embryogenesis, a large portion of the genome is enriched with H3K27ac, predominantly localized in promoters and partially methylated domains before the 8-cell stage, due to the dynamics of H3K27ac [83]. Right after zygotic genome activation at the 8-cell stage, the majority of H3K27ac is removed by histone deacetylases. This dynamic modulation of H3K27ac within chromatin leads to alterations in gene expression, indicating the importance of temporal gene regulation for the early embryonic development. Interestingly, the length of cell cycle can influence both the erasure and re-accumulation of H3K9me3 during early development in medaka, zebrafish and Xenopus embryos [84]. It is reported that prolonged cell cycle permits the accumulation of Setdb1, subsequently initiating the onset of H3K9m3 deposition for heterochromatin formation. Over all, these results indicate that the alteration of chromatin dynamics or state can regulate DNA expression, ultimately influencing cellular functions.

3. Mechanisms of Nuclear Size Regulation

The size of the nucleus is a critical factor that influences various processes, including development, migration, and disease progression [85–87]. Hence, numerous studies have attempted to elucidate the regulatory mechanisms governing nuclear size. A variety of factors have been identified as key regulators, including nuclear transport [88–90], NPCs [91–93], endoplasmic reticulum (ER) [94], cytoskeleton [95], limiting components [96], the nuclear lamina [97–99], chromatin [100] and more. In this section, we review some recent advancements in understanding the mechanisms by which these regulatory factors control nuclear size.

Phosphorylation of lamins is crucial in regulating nuclear size, and defects in lamin proteins results in the NE rupture during mitosis. Specifically, researchers found that the Lam A R249Q mutation in human induced pluripotent stem cell-derived cardiomyocytes(iPSC-CMs) leads to a significant reduction in Lam A/C levels at the NE compared to healthy controls, resulting in an increased nuclear cross-sectional area and disruption of the NE [101]. Furthermore, mechanical

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stretching of muscle cells can induce the recruitment of esmin and plectin to the nuclear periphery via Lam A/C, thereby maintaining nuclear morphology. However, in Lam A/C-deficient cells, the absence of interactions between Lam A/C and esmin and plectin leads to nuclear deformation [102]. The findings suggest that Lam A/C plays a critical role in the cellular response to mechanical strain. Mostafazadeh et al. recently proposed a mathematical model to elucidate a physics modulus expressing the mechanical behaviors of the nuclear lamina, in which the stretching ability of Lam A is similar to that of macromolecules with coiled-coils and extended helical motifs, such as DNA [103].This physics modulus could assist in calculating the precise density and shear modulus of lamin network, providing a deeper understanding of how nuclear mechanics change in laminopathies. Interestingly, the interaction of Lam A and histone H3 is proposed as a determinant of nuclear size and shape. For instance, scientists have found that Lam A monomers can bind directly to histone H3, which is influenced by histone PTMs [104]. Specifically, Lam A is more likely to bind to H3 with a methyl-methyl modification such as H3R8me2/K9me2 than to H3 with only a single methyl modification such as H3K9me2. Furthermore, when H3 undergoes oncogenic mutations, such as those in histone H3.3 that impair H3K27 methylation, it results in a decrease in both circularity and size of the nucleus, and can even cause severe diseases like pediatric glioma and chondrosarcomas [105]. These findings suggest that lamin interacts with chromatin to jointly regulate nuclear size and shape.

The alternations in chromatin organization are closely related to changes in nuclear shape and disease. First, the levels of chromatin compaction can alter nuclear morphology [106,107]. Viola et al. found that the compactness of chromatin makes difference in membrane invagination during mitosis [108]. They treated cells with calyculin A to induce the chromatin condensation and found that cells have reduced nuclear radius and increased NE invagination events. Rather, the decompaction of chromatin could lead to the formation of nuclear bleb [109]. Similarly, in TSA treatment cells, heterochromatin is going to loosen, promoting the nuclear bleb formation [110]. Second, an increase in the amount of DNA contributes to nuclear size enlargement in a cell-free system [111]. In tetraploid cells commonly found in human tumors, the G1 phase is too short for adequate replication factors formation [112]. This causes an increase of γH2AX foci in chromatin, which is an early marker of DNA damage, making the cells unstable and prone to DNA damage, particularly in the S phase. The double amount of DNA is densely packed within the limited nuclear space, which restricts access for DNA repair molecules, further exacerbating the damage. Therefore, chromatin, as a major component in the nucleus, plays an important role in the NE remodeling. One of the mechanisms of how chromatin regulates the nuclear size could be through the alternation of chromatin-lamina interaction. In the *Xenopus* egg extract system, nuclear expansion preferentially occurred at sites of high-density chromatin and lamin addition, suggesting that peripheral chromatin-lamin incorporation generates forces pushing against the NE, which may promote nuclear growth [90].

However, a comprehensive mechanism for regulating nuclear size has yet to be fully elucidated. From our perspective, as with others, nuclear size is maintained through a balance of forces exerted on the outer and inner nuclear membranes; stronger pushing forces compared to pressing forces induce nuclear expansion, and vice versa [113]. For instance, there is a tug-of-war relationship between the membranes of the NE and ER, and the ER is continuous with the out membrane of the NE [114]. Increasing perinuclear ER contributes to the growth of the nuclear surface, potentially by enhancing the pulling force on the NE. In addition, elevated nuclear influx or inhibited nuclear efflux is accompanied by nuclear volume expansion, potentially through the augmentation of intranuclear pushing force exerted by osmotic pressure [115]. Similarly, the elevation of nuclear osmotic pressure induced by proteins and mRNA is responsible for driving nuclear expansion [113]. Conversely, hyperosmotic pressure drives chromatin compaction, resulting in small and stiff nuclei in Arabidopsis root meristems [116]. It is possible that the force pressing on nuclei from hyperosmotic pressure is stronger than the intranuclear pushing force generated from compact chromatin, resulting in smaller nuclei. One mechanosensitive senor that has been discovered is Piezo channel, which can detect fluid-stress in the environment [117]. However, further evidence is required to substantiate

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this model, such as the sensor utilized by nuclei to detect intranuclear forces, methods to detect those forces on nuclei and other related factors.

4. The Nuclear Mechanical Function

The nucleus is a key sensor of the local microenvironment. When a cell is confined or subjected to mechanical stress, the unfolding of the NE triggers a signaling cascade for actomyosin contractility, enabling the cell to migrate out of confinement [118,119]. Additionally, the nuclei can act as a piston, exerting pressure on the front of the cell [120], thus influencing cell migration efficiency [121]. Deformation of the nucleus under mechanical stress can reorganize the chromatin state and increased condensation of proteins in the nucleoplasm, thus influencing cellular function [122]. Decompaction of chromatin, conversely, can enhance cellular adhesion strength and contractility via RhoA activation, showing a reverse mechanotransduction pathway from the nucleus to the cell surface [123]. It is argued that the mutation E145K of Lam A, which leads to the phenotype of Hutchinson-Guildford progeria in humans, is due to the different mechanical properties of the lamina layer [124]. Thus, this highlights a clear link between the mechanics of the nucleus and the development of disease.

When cells are subjected to the compression from surrounding tissues, the physical force is transmitted from the extracellular environment through extracellular matrix to cytoskeleton and then to the nucleus, potentially causing the deformation of the NE [125]. For instance, reduced Arp2/3 activity, low substrate adhesiveness or rigidity, and high contractility promote bleb formation, while the expansion of bleb is driven by hydrostatic pressure regulated by contractility [126]. Moreover, FLN-2 works alongside the LINC complex and CDC-42/actin-dependent pathways to preserve the integrity of the NE and facilitate the movement of P-cell nuclei through narrow spaces [127]. Therefore, nuclear morphology is typically modified by mechanical stimuli during cellular migration. One potential mechanism by which mechanical forces impact cellular function is through the modification of chromatin states within the nucleus. A recent study delivered different mechanical strain to MSCs cultured on a flexible membrane by sine or brachial waveforms at different frequency (0.1 Hz, 1 Hz). It found out that MSCs under moderate strain amplitudes (7.5% - 12.5%) are suitable for chromosome unwinding and expressing regenerative properties, while strain amplitude below 7.5% or high amplitude can't unwind the chromosome sufficiently or cause chromosome damage, respectively [128]. Interestingly, cellular pressure can affect nuclear position as well. During *C. elegans* gonadogenesis, the position of nucleus is crucial for maintaining leader cell integrity [129]. Overall, both nuclear morphology and position are important factors for the mechanical role of the nucleus.

5. Nuclear Morphology and Disease

Since the nucleus is the largest and stiffest organelle in the cell, nuclear deformation is thought to be related to cell migration through narrow channels, including embryonic development, wound healing, immune responses, neurodegenerative disorders, and cancer metastasis [87,130,131]. Furthermore, the link between actin and the nucleus is essential for efficient cell invasion by providing the necessary forces for cell movement [132].

Cancer cells with high levels of nuclear deformability can more easily gain access to other tissues in the body. A recent study has shown that WDR5 could affect the metastasis of acute lymphoblastic leukemia (ALL) cells in dense 3D conditions [133]. After inhibition of WDR5 expression, nuclear deformability is abrogated and the infiltration of ALL cells into other tissues (*in vivo* experiments) is decreased, indicating the potential role of WDR5 in controlling ALL cells' metastasis through changes in nuclear morphology. A study focused on colorectal cancer cells revealed that high expression of ErbB4 leads to activation of the ErbB4-Akt1-Lam A/C pathway, resulting in phosphorylation of Lam A/C [134]. Consequently, this promotes nuclear lamina disassembly and increases nuclear deformability, ultimately leading to metastasis. Intriguingly, another investigation reported that tumor cells with high levels of Lam A are more likely to metastasize to the lymph nodes, while tumor cells with low levels of Lam A are more prone to entering apoptosis, possible because low levels of Lam A lead to fragile the NE [135]. Emery-Dreifuss muscular dystrophy (EDMD) is collectively

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known as a nuclear envelopathies and laminopathies disorder. One of its subtypes has now been related with the downregulation of the NE protein Net39, which then affect NE integrity and induce DNA damage [63]. Thus, by gaining a deeper understanding of NE deformation, it will potentially lead us in the direction of identifying specific targets for treating disorders related to NE morphology

To gain a more intuitive insight and understand the molecular details of nuclear morphology and mechanobiology, 3D models have been developed [136,137]. Compared to traditional 2D projections, 3D models overcome limitations of losing important parameters, such as curvedness, shape index, and fractal dimension, thus providing further mechanistic insights into cells phenotypes during migration. For instance, in a 3D culture device, using agarose as a base for sustaining long-term cell confinement could help scientists investigate cell behaviors throughout the entire cell cycle in a simulated *in vivo* environment [138]. In a mouse model, one research found that prolonged exposure to external adverse stimulus can lead to the NE deformation, which in turn causes cells to deteriorate [139]. It suggests that nuclear deformation can arise not only from intrinsic cellular factors, but also from external severe environmental conditions. In summary, understanding the normal traversal of nuclei through constricted spaces can help improve our understanding of metastasis.

Based on the aforementioned model that nuclear size is regulated through force equilibration, it is conceivable that additional forces may be exerted on the NE by nuclear constituents, the surrounding cytoplasm or others, disrupting equilibrium and consequently resulting in deformation of the NE. For example, increased chromatin compaction may result in greater intranuclear force, ultimately leading to deformation of the NE [90]. However, the detailed mechanism underlying NE deformation and its implications for related diseases remain unclear.

6. Conclusions

The proper nuclear architecture, including NE associated protein, nuclear transport, nuclear-cytoskeletal contacts, the nuclear lamina meshwork and chromatin organization, is critical for cell function. In this review, we discuss the impact of certain nuclear components on nuclear morphology and cellular function, potential mechanisms of nuclear size regulation and the mechanical role of the nucleus in cell migration. While the underlying mechanisms that regulate nuclear morphology have been elucidated in different systems, there remain substantial gaps in our knowledge. Advanced microscopy technology, proteomics and genomics, single-cell technology, and other emerging technologies will provide insights into the impact of nuclear functional architecture on nuclear mechanics, chromatin organization, gene expression and cellular functionality. Moreover, expanding the study to *in vivo* models to investigate nuclear mechanistic function during cell migration would provide valuable insights. Since the size and shape of the nucleus can significantly impact various human disorders, such as cancer, accelerated aging, and different types of neuro-muscular diseases, it would be highly intriguing to investigate whether nuclear morphology could serve as a novel therapeutic target, particularly in cancer treatment.

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