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How nuclear envelope dynamics can direct laminopathy phenotypes

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Abstract

The nuclear envelope separates the genome from the cytoplasmic environment. However, the nuclear envelope is also physically associated with the genome and exerts influence on gene expression and genome modification. The nucleus is dynamic, changing shape and responding to cell movement, disassembling and assembling during cell division, and undergoing rupture and repair. These dynamics can be impacted by genetic disease, leading to a family of diseases called laminopathies. Their disparate phenotypes suggest that multiple processes are affected. We highlight three such processes here, which we believe can be used to classify most of the laminopathies. While much still needs to be learned, some commonalities between these processes, such as proteins involved in nuclear envelope formation and rupture repair, may drive a variety of laminopathies. Here we review the latest information regarding nuclear dynamics and its role in laminopathies related to mutations in the nuclear lamina and linker of nucleoskeleton and cytoskeleton complex (LINC) proteins.

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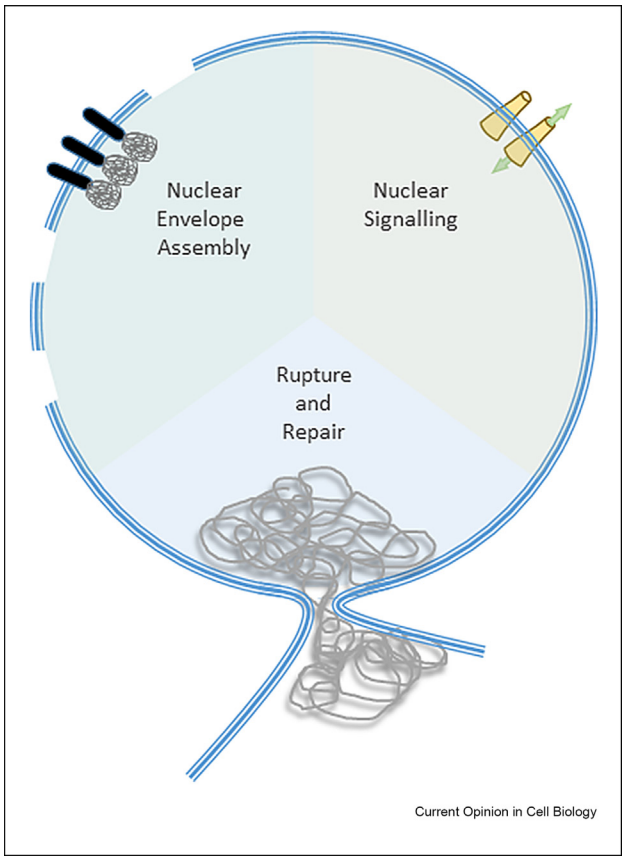
Introduction

Defects in nuclear lamina proteins in laminopathies cause a range of diseases, such as muscular dystrophies, progerias, infertility, and lipodystrophies. Nuclear envelope proteins include the constituents of the linker of nucleoskeleton and cytoskeleton complex (LINC), the nuclear lamina filaments lamin A/C and lamin B, and lamina-associated proteins [1–4]. A recent study highlighted the complexity of laminopathies by linking mutations in these proteins to specific diseases, showing that there are singular mutations in lamin A that can be linked to a number of diseases presenting in different tissues [5*]. The nuclear envelope is mainly responsible for the protection of the genome. However, in recent years, it has become clear that the nuclear envelope also acts as an integrating platform between the genome, the cytoplasmic, and the extracellular environments through linkages to the cytoskeleton and as a regulator of gene expression. This linkage of the genome to the nuclear envelope and the cytoskeleton is modulated, for instance, in migrating cells, where physical strain results in altered gene expression and epigenetic modification.

The cellular defects in laminopathies that cause the ultimate disease presentation remain unclear in many cases. Thirty-five different medical conditions affecting skeletal muscle, cardiac muscle, metabolism, and the nervous system have been linked to mutations in the Lamin and LINC proteins. Lamin A/C is commonly mutated in such diseases, although there is no clear correlation between specific groups of mutations and diseases. However, clusters of mutations in exons 1 and 6 seem to be correlated to striated muscle disease, some of which have been linked to increased nuclear rupture or delayed and impaired repair [5*], while others are linked to problems with cell division, especially in gametogenesis.

However, from our current understanding, we believe three major groups of laminopathies can be distinguished, defined by: (1) defects in post-mitotic/meiotic nuclear envelope formation; (2) alterations in nuclear shape-regulated gene expression; (3) increased nuclear rupture as well as decreased nuclear rupture repair (Figure 1). Evidence for this hypothesis remains scattered, but cases pointing to these three paths to pathology are present. In this review, we will briefly discuss the latest knowledge on nuclear envelope formation, nuclear-regulated gene expression, and nuclear envelope rupture and repair. We further demonstrate how certain diseases would fit within the three groups of laminopathies.

Figure 1



The three major effects postulated to occur at a cellular level as a result of a laminopathy; 1) defects in cell division, 2) changes in nuclear dependent gene expression, and 3) changes in nuclear rupture and repair.

We hypothesize that laminopathies are caused by mutations in nuclear lamina-associated proteins that result in either defects cell division, nuclear rupture, or in changes in gene expression regulated by nuclear shape.

The dynamics of nuclear envelope formation after cell division

The LINC complex lies at the heart of the physical interaction between the genome, the nuclear lamina, and the cellular cytoskeletons and is ultimately connected to the plasma membrane via structures such as focal adhesions. The laminar network consists of Lamin A/C, found in most differentiated cells, along with lamin B. The nuclear lamina binds to chromatin and, in turn, is connected to the LINC complex at the inner nuclear membrane (INM) [6]. At the INM, Sad1-UNC-84 domain containing protein 1 (SUN1) and 2 proteins interact with the lamina while they project into the perinuclear space, where they connect to nesprins. A number of associated proteins, such as emerin, barrier to autointegration factor (BAF), and four and a half lim domain protein 1 (FHL1), interact with the core LINC complex at the INM, while at the cytoplasmic face, nesprins connects to the cytoskeletons. Specifically, nesprin-3 connects to the intermediate filament system [7], nesprin 1 and 2 to the actin cytoskeleton [8], and nesprin-1 also connects to the microtubule network [9,10].

The mechanisms and efficacy of nuclear assembly upon mitotic exit play a vital role in nuclear integrity. During entry into mitosis, the nuclear envelope, along with the integrated membrane proteins such as SUN proteins, is disassembled and integrated within the endoplasmic reticulum (ER) [11,12]. VRK1-dependent phosphorylation of nuclear BAF during mitotic entry enables chromatin relaxation, while other kinases phosphorylate lamin A/C, leading to their release from the membrane and the chromatin [13], readying the genome for division. After division, during anaphase, chromatin organizes into disc-like structures that act as nuclear envelope nucleation points and undergo multiple phosphorylation events (for review, see Ref. [14]). The chromatin attracts INM proteins embedded in the ER membrane, resulting in the extension of the ER membrane to become the new nuclear envelope [15,16*]. Subsequently, BAF is dephosphorylated by Ankle2/PP2A [17] to increase its affinity for chromatin while binding to the lap-emerin-man domain protein (LEM) proteins, making it an essential mediator of the NE assembly process [13]. At the same time, emerin aids in the even distribution of A-type lamins in the assembling nucleus [18]. Finally, nuclear assembly is brought to a close by spastin, which severs the microtubules at the kinetochores, and the ESCRTIII complex, which seals the nuclear membrane to form a continuous envelope [19]. Interestingly, the nucleoporin Nup153 has been shown to aid in the continued incorporation of B-type lamins, lamin B receptors, and SUN1 after nuclear assembly. This suggests that there are further mechanisms of nuclear assembly succeeding nuclear envelope sealing that are still to be elucidated [20].

To enable meiotic recombination during meiosis, chromosomes must migrate along the still intact INM to form a meiotic bouquet, which brings the homolog chromosomes into close proximity. This process requires force to move the chromosomes, which is mediated by LINC complexes through force generation by Dynein. Dynein binds to KASH5 and to the chromosomes via SUN1 and 2, along with dynactin which is recruited via LIS1 [21]. The movement of the telomeres during this process is mediated by SUN1, which is regulated by cyclin dependent kinase 2 (CDK2) via the protein complex Speedy/Ringo [22]. Mutations in gamete-specific LINC proteins can affect cell division, which leads to defects in meiosis and spermatogenesis. For instance, testis-specific KASH5 and ubiquitous SUN1 proteins have been shown to be essential for spermatogenesis since knockouts of either protein cause sterility [23,24].

Moreover, SUN1 mutations such as p.Tyr221X have been associated with familial nonobstructive azoospermia. This mutation leads to a reduction in KASH5 expression and impaired telomeric attachment to the INM during prophase I [25]. Clinically, mutations in SUN1 and KASH5 have been linked to nonobstructive azoospermia and diminished ovarian reserves, suggesting that common pathways are regulated by these proteins in male and female gamete production [26]. LINC complexes also regulate sperm formation structurally. Testis-specific SUN4 heterodimerises with SUN3 and binds to lamin B3 in the nucleus. Loss of SUN4 leads to defects in sperm head formation [27]. Indeed, SUN3 loss is also associated with misshapen flagella due to the absence of manchette microtubules [28]. Similarly, SUN5 mutations cause acephalic spermatozoa syndrome, which is characterized by disruption of head-to-tail linkages. SUN5 mutations lead to the misdirection of nesprin-3 away from the anterior and posterior of the nuclear envelope, where it is normally localized, which is important for the head-to-tail linkage [29]. Thus, mutations in LINC proteins in the gametes affect proper genetic material division and the physical formation of sperm, suggesting that the nuclear envelope plays a central role in directing proper gamete formation.

The influence of nuclear mechanotransduction on transcriptional regulation

The nuclear envelope's ability to regulate protein entry and exit can be modulated by nuclear shape, cell migration, and nuclear deformation, which in turn will influence transcription. Such nuclear morphology-mediated mechanotransduction is often mediated via the yes associated protein (YAP)/tafazzin (TAZ) complex. For example, nuclear compression due to cytoskeletal and osmotic changes leads to increased YAP nuclear translocation [30] and directs transcription factors such as transcription enhancer factor (TEAD) and AP-1 to alter gene expression [31,32]. YAP signaling is regulated by pathways such as the RhoA/ROCK and Wnt/β-catenin pathways [33,34], while the extracellular regulated kinase (ERK) and NF-κB pathways have also been associated with nuclear deformation-dependent regulation of gene expression [35].

The induction of senescence is a common result of nuclear signaling through YAP/TAZ after nuclear deformation, which is also often seen in laminopathies. For instance, an endothelium-specific progeria mouse model exhibited increased expression of senescence-associated secretory phenotype proteins, while the endothelium-specific miR34a-5p positively impacted the p53-pathways and p16-pathways to maintain the senescence phenotype linked to progeria cardiovascular pathology [36]. Moreover, analysis of gene expression shows that progerias share many differentially expressed genes with aging [37]. Strain-mediated activation of YAP may explain the phenomenon of the same laminopathy-related mutations resulting in differential gene expression in different tissues. For example, in patients with Werner syndrome, transcriptomic analysis of fibroblasts from the torso (less physical strain) showed decreased adipogenic and chondrogenic gene expression, while fibroblasts from the feet (more physical strain) exhibited increased osteogenic gene expression compared to healthy individuals, suggesting that tissue-specific differences in strain-dependent transcriptional regulation occur [38].

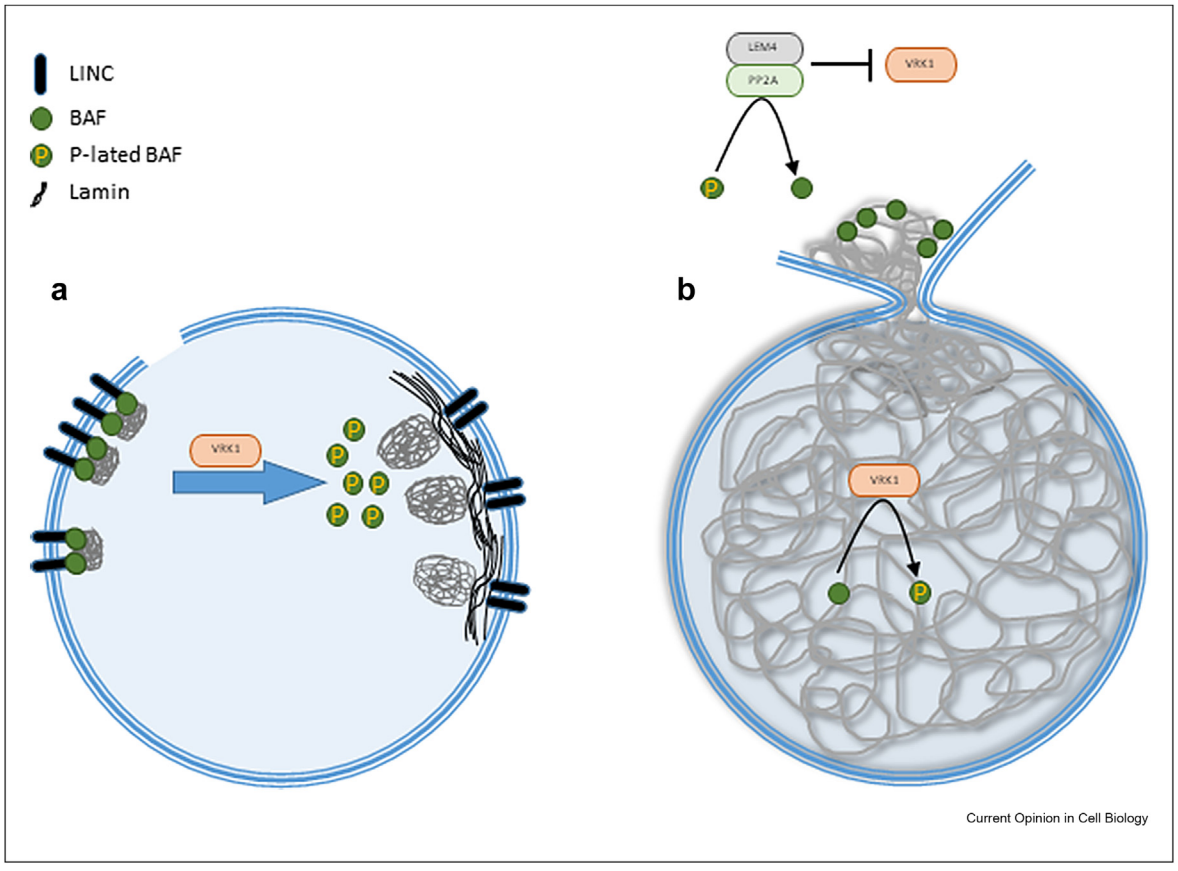
The aetiology and effects of nuclear rupture

Nuclear rupture can occur in virus-infected cells, in cells from patients with laminopathies, or in cancer cells [39]. Nuclear rupture starts when a gap in the nuclear lamina appears, leading to membrane blebbing, chromatin herniation, or both. With additional mechanical stress, this bleb will rupture, spilling genomic DNA into the cytoplasm and allowing unregulated access to the nuclear interior, and vice versa. Most ruptures are repaired within minutes, but even those persisting for hours can be repaired, although ruptures on micronuclei are not always repaired [39–41]. Gaps in the lamina can result from reduced lamin A/C expression, mutations in these proteins, or chromatin disruption at the membrane. Recently, it was shown that cancer cells harboring mutations leading to reduced DNA damage repair exhibit nuclear rupture without physical causes such as deformation. This is mediated by ATR-dependent phosphorylation of Lamin A/C, which impacts lamina assembly [42*]. However, it is still not clear how these gaps themselves induce rupture and what the role of peripheral chromatin as well as mechanical stress is in the development of nuclear ruptures.

Nuclear rupture repair

Nuclear rupture repair requires the recruitment and integration of membrane sheets from the ER or the outer nuclear membrane to close the gap left by the rupture. Interestingly, ER proteins involved in nuclear envelope formation such as BAF and LEM domain proteins, seem to be simultaneously involved in rupture repair [43] (Figure 2). Several diseases, including muscular dystrophies, cardiomyopathies, and partial lipodystrophy, are linked to mutations in the binding motifs of lamin A/C for BAF and emerin and vice versa, leading to increased nuclear rupture, possibly through the loss of lamin A/C chromatin crosslinking [44*,45,46]. Nuclear BAF is dynamically regulated in interphase cells via VRK1 to reduce its affinity for chromatin, preventing aberrant DNA compression and nuclear deformation [44*,47,reviewed in 48]. Interestingly, there is also a cytoplasmic pool of BAF that acts as

Figure 2



BAF is involved in nuclear envelope assembly and nuclear rupture repair. a) nuclear envelope assembly is depicted, showing the role of BAF in linking the chromatin to the emerging nuclear membrane via the LINC complex. BAF binds to chromatin, which attracts the LINC complex-bound membrane from the ER to generate the new nuclear envelope. Upon completion of nuclear envelope formation, BAF is phosphorylated and released from the chromatin. b) dephosphorylated BAF detects chromatin in the cytoplasm and binds to it to initiate the nuclear repair process. Once the rupture is repaired and chromatin is once again inside the nucleus, BAF is phosphorylated and removed to the cytoplasm. LINC, linker of nucleoskeleton and cytoskeleton complex.

a sentinel for the presence of dsDNA in the cytoplasm. This can occur upon viral infection but also during nuclear rupture. Cytoplasmic BAF will concentrate at nuclear rupture sites through its binding to chromatin, which leads to the recruitment of LEM2, Chmp7, Lamin A/C, and ESCRTIII [49*,50]. Interestingly, if Chmp7 and ESCRT-III are not recruited to the rupture site, repair can still be carried out, albeit delayed [51]. During this process, LEM-4/ANKLE-2 activates PP2A to dephosphorylate and activate cytosolic BAF, while VRK1 is inactivated [4,52], inducing enhanced chromatin binding by BAF. When the chromatin is once again ensconced in the nucleus through the repair of the nuclear envelope rupture, BAF is phosphorylated and can dissipate into the cytoplasm. In this way, BAF is seen as the nucleation point for nuclear rupture detection and repair initiation.

Mutations of BAF have been shown to lead to an increase in nuclear envelope rupturing. For instance, the Nestor–Guillermo progeria syndrome (NGPS)-associated A12T mutation leads to increased nuclear rerupture by limiting BAF-lamin A/C interactions [53*,54]. Other mutations (R75W, H7Y, N70T) have been found to affect BAF binding to DNA, although this doesn't appear to alter BAF localization [55*]. Also, diminished rupture repair through the loss of BAF, ANKLE2, or PP2A have been implicated in the cytoplasmic accumulation of insoluble Tau protein, while overexpression of LEM2D is protective, suggesting that nuclear envelope rupture repair may be important for the prevention of Tau phosphorylation and accumulation [56*]. Overexpression of lem domain containing protein 2 (LEMD2), ANKLE1, and emerin have also been associated with advanced malignancy and a poor prognosis in prostate cancer [57], while LEMD2 mutations are also associated with cardiomyopathy [58] and a mild form of NGPS. Thus, efficient nuclear repair seems to be important in averting several diseases and depends on the proper regulation of BAF.

Table 1

Examples of mutations related to the three major groups of laminopathies.

Mutation	Gene	Effect	Disease type	Refs
p.Tyr221X	*SUN1*	Attenuated KASH5 expression and impaired telomere attachment to INM during prophase 1	Impaired cell division	[24]
p.Arg424Thrfs*20	*KASH5*	Inhibits KASH5 expression leading to nonobstructive azoospermia	Impaired cell division	[26]
A12T	*BANF1*	Induces Nestor-Guillermo progeria syndrome, an early-onset aging condition. Causes a greater incidence of nuclear re-rupture due to limited BAF-l	Impacted nuclear rupture and repair	[53*,54]
R75W, H7Y, N70T	*BANF1*	Diminishes BAF binding to DNA	Impacted nuclear rupture and repair	[55]
p.L13R	*LEMD2*	Causes nuclear membrane invaginations and decreased nuclear circularity, resulting in DNA damage and senescence that ultimately induce cardiomyopathy	Impacted nuclear rupture and repair	[58]
c.1824C > T	*LMNA*	Activation of the cryptic donor splice site, leading to progerin protein lacking 50 amino acids, induces aging-associated symptoms including a lack of subcutaneous fat, alopecia, swollen veins, and cardiovascular pathology	Effects on nuclear expression	[36]

INM, inner nuclear membrane.

Conclusion

Laminopathies and mutations in LINC-related proteins are responsible for a wide array of diseases, with some even emanating from the same mutation (Table 1). However, we believe many can be classified as diseases of deleterious cell divisions, nuclear rupture, or altered nuclear-regulated gene expression. We highlighted some of the latest knowledge gained in nuclear rupture and repair, as we believe this to be the major impact of many laminopathies related to cell and tissue maintenance and homeostasis, while also showing how mutations in nuclear gamete-specific LINC proteins can cause different forms of infertility due to effects on cell division. Importantly, processes such as nuclear repair and nuclear envelope formation seem to make use of very similar cellular machinery, further complicating the phenotypic outcomes of many genetic diseases. While much is known about nuclear shape-regulated gene expression, how these feed into laminopathies needs to be better elucidated. Overall, nuclear integrity and dynamics are clearly important for normal homeostasis and seem to be often affected by disease, and thus, we need to better understand the overlapping mechanisms underlying these processes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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