

Review

Structure-Function Relationships of Nuclear Lamins

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Abstract: Nuclear lamins are type V intermediate filament proteins that form a filamentous meshwork beneath the inner nuclear membrane. Additionally, a sub-population of A-type and B-type lamins is localized in the nuclear interior. The nuclear lamina protects the nucleus from mechanical stress and mediates nucleo-cytoskeletal coupling. Lamins form a scaffold that partially tethers chromatin at the nuclear envelope. The nuclear lamina also stabilizes protein-protein interactions involved in gene regulation and DNA repair. The lamin-based protein sub-complexes are implicated in both nuclear and cytoskeletal organization, the mechanical stability of the nucleus, genome organization, transcriptional regulation, genome stability, and cellular differentiation. Here we review recent research in the field of nuclear lamins and their role in modulating various nuclear processes and their impact on cell function.

Keywords: Nucleus, Nuclear envelope, Lamins, Genome organization, Chromatin, Gene expression.

1. Introduction

Spatial genome organization and subnuclear compartmentalization are essential for the maintenance of normal cellular physiology. One of the critical subnuclear structures is the nuclear lamina; which along with the nuclear membrane forms a barrier that protects the nucleus and the genome [1]. The nuclear lamina is a protein meshwork at the nuclear envelope of ~15–20 nm thickness in mammalian cells [2]. Lamins contribute to the integrity of the nuclear envelope in various cell types [3,4]. Nuclear lamins belong to the type V intermediate filament family of proteins, which has complex roles in the maintenance of normal cellular physiology [5,6]. A large number of nuclear proteins are associated with nuclear lamins and are implicated in modulating various cellular processes and tissue-specific cell functions [7,8]. There is growing evidence suggesting the role of nuclear lamins in a wide range of structural processes such as maintaining mechanical stability of the nucleus, nuclear and cytoskeletal organization, chromatin organization, nuclear assembly/disassembly as well as cellular processes such as transcription, replication, DNA damage repair, genome stability, differentiation and senescence [5,9–12]. Lamins provide binding sites for regulatory proteins such as pRb and c-fos, among others [9,13]. Furthermore, lamins are involved in the coupling of the nucleus with the cytoskeleton, the destabilization of which severely impacts the cytoskeletal organization, and the position of the nucleus within cells [14,15]. The broad spectrum of diseases caused by mutations or altered expression of lamins, namely laminopathies provide crucial insights into the structure-function relationships of lamins across mammalian cells [16]. Research in the past two decades demonstrates that lamins are not only the structural components of the nucleus but are also involved in the maintenance of nuclear architecture, facilitate cell signalling and perform regulatory roles at the nuclear envelope.

2. Physical properties of Nuclear Lamins

Lamins are evolutionarily conserved and belong to the intermediate filament (IF) superfamily, and are classified as type V intermediate filament proteins [17,18]. Lamins are structural proteins of the nuclear envelope that are unique to metazoans. Like all intermediate filament proteins, lamin monomers have a tripartite structural organization consisting of a short globular N-terminal (head)

domain followed by a central α -helical coiled-coil (rod) domain and a globular C-terminal (tail) domain (Figure 1A) [2,19]. Unlike cytoplasmic IF proteins, the tail domain of lamins harbors lamin-specific motifs; a nuclear localization signal (NLS), an immunoglobulin (IgG) fold motif, and a C-terminal -CAAX (C, cysteine; A, aliphatic amino acid; X, any amino acid) motif (Figure 1A) [19]. NLS is essential for directing lamins into the nucleus, where they assemble into the nuclear lamina; a fibrous proteinaceous meshwork beneath the inner nuclear membrane (INM) [2]. The -CAAX motif is a site of extensive post-translational modifications involving sequential farnesylation (at the cysteine residue), proteolysis, and carboxymethylation of the -AAX sequence [20,21].

Figure 1

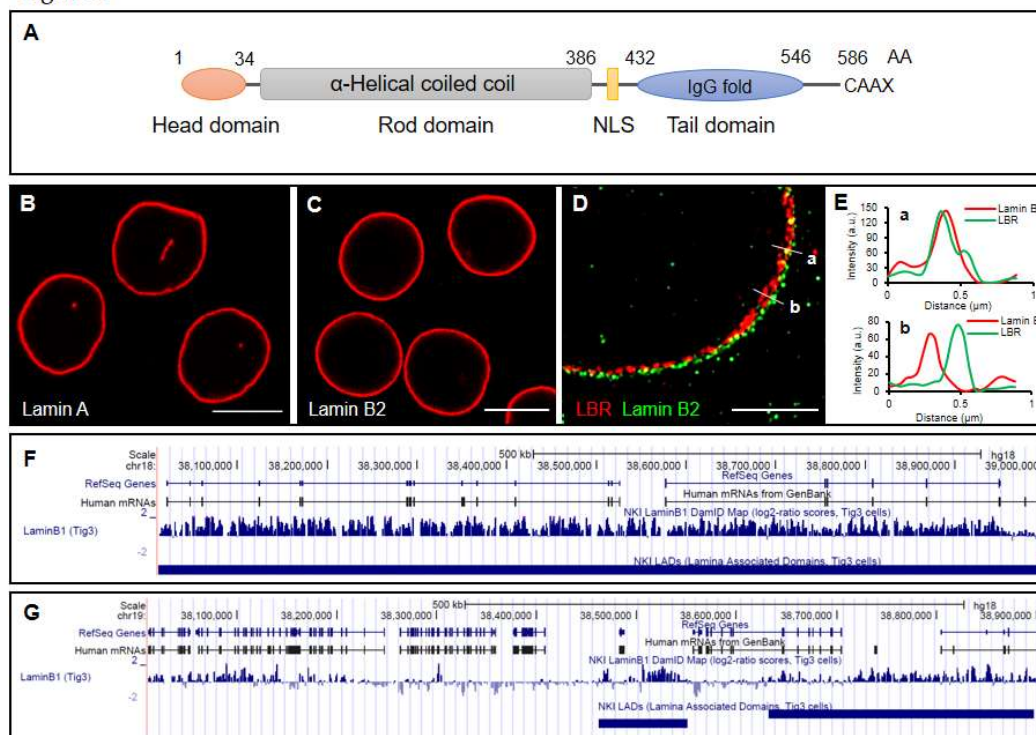


Figure 1: Structure, localization, and chromatin binding of nuclear lamins (A) The domain organization of a lamin monomer showing the N-terminal head domain, central rod domain, and the C-terminal tail domain which includes nuclear localization signal (NLS), IgG fold, and -CAAX motif. Schematic represents amino acid positions for lamin B1 protein. (B) and (C) Confocal microscopy images of colorectal cancer cells (HCT116) immunostained with Lamin A and Lamin B2 respectively, Scale bar $\sim 10\mu\text{m}$. (D) Structured Illumination Microscopy (SIM) image of colorectal cancer cells (SW480), co-immunostained with Lamin B2 (green) and LBR (red). Scale bar $\sim 3\mu\text{m}$. (E) Line scan profiles across the nuclear envelope in D representing Lamin B2 and LBR showing (a) overlapping and (b) non-overlapping regions. (F) and (G) UCSC Genome Browser view of LADs identified by lamin B1 DamID-seq in a region of (F) chr18q12.3 and (G) chr19q13.11 (Source: [183]). Note that human gene-poor chromosome 18 shows higher lamina associations as compared to gene-rich chromosome 19.

Lamins are of two major subtypes: A-type and B-type lamins. In mammals, A-type lamins are encoded by a single gene *LMNA*, which upon alternate splicing, result in lamin A, and lamin C - both of which are found in terminally differentiated somatic cells. *LMNA* also generates the less abundant somatic lamin A Δ 10 and germ cell lamin C2 isoforms [22]. The B-type lamins, which are expressed in all cell types, are encoded by two different genes. *LMNB1* encodes for lamin B1 protein, whereas *LMNB2* encodes for somatic lamin B2, and lamin B3 is specific to male germ cells [23]. B-type lamins are tightly associated with the nuclear envelope and the inner nuclear membrane by virtue of a permanently farnesylated and carboxy-methylated CAAX motif [21]. Mature lamin A and lamin C are generated from enzymatic cleavage of C-terminal amino acids of pre-lamin A, that includes the -

CAAX motif, due to which A-type lamins are more soluble during mitosis and interphase stages of the cell cycle [20].

Lamins form coiled-coil parallel dimers that assemble into higher-order filamentous structures similar to other intermediate filament proteins, such as keratin and vimentin [24,25]. The detailed structure of the nuclear lamina has been challenging to elucidate, owing to its refractory nature. Electron microscopy (EM) studies on purified mammalian and avian lamins revealed that these proteins associate to form ~50 nm rod-shaped homodimers, which spontaneously assemble *in vitro* into intermediate-like filaments [24,26]. 3D Structured Illumination Microscopy (3D-SIM) and cryo-Electron Tomography (cryo-ET) studies of the lamina meshwork revealed that different lamin isoforms assemble into distinct yet interlinked filamentous networks with unique properties of assembly to build up the nuclear lamina [27,28]. A-type and B-type lamins assemble into head-to-tail polymers of tetrameric filaments of ~3.5 nm thickness. These filaments are arranged in a partially staggered conformation wherein, the immunoglobulin (IgG) domain repeats every 20 nm alongside the lamin filament [27]. Stochastic Optical Reconstruction Microscopy (STORM) visualization of the nuclear lamina in mammalian cells reveals that lamin B1 and lamin A/C form overlapping concentric networks; wherein lamin B1 shows curvature dependent localization in the outer concentric ring and restrains the outward protrusions of the lamin A/C network [29,30]. The organization of the nuclear lamina is complex and cell-type specific.

Furthermore, lamins also exist in the nucleoplasm with functions that are novel and distinct from that of the nuclear envelope [9,31]. A sub-population of A-type lamins upon phosphorylation (Ser22, Ser390, Ser392), dissociate from the nuclear lamina during interphase, and redistribute throughout the nucleoplasm; whereas B-type lamins are largely membrane-associated throughout the cell cycle (Figure 1B and 1C) [32,33]. Lamin phosphorylation and other post-translational modifications complement lamin function in terms of the stability of the lamina, lamin-protein interactions, chromatin binding, and gene regulation. Fluorescence Correlation Spectroscopy (FCS) performed on fluorescently tagged lamins revealed that nucleoplasmic lamin complexes are considerably more mobile than the lamins associated with the nuclear envelope [34]. The relative stoichiometry of A-type and B-type lamins is often cell-type specific and exists in a dynamic equilibrium [35]. Additionally, the ratio of A:B-type lamins modulates tissue-specific gene expression and determines mechanical properties of the nucleus [35,36].

3. Interacting partners of Nuclear Lamins

Lamins interact with various proteins both at the INM and nucleoplasm (Figure 2). Among the first identified mammalian lamin-binding proteins are: lamina-associated polypeptide 1 (LAP1) and the LEM domain-containing proteins (LAP2, emerin, MAN1) in the INM [37,38]. The bi-helical LEM domain interacts with an evolutionarily conserved DNA-associated protein termed Barrier to Autointegration Factor (BAF) [39,40]. Lamins and LEM proteins in the INM together anchor heterochromatin to the nuclear lamina by associating with BAF and via direct interaction with DNA (Figure 2) [41,42]. Another lamin interacting INM protein is the Lamin B Receptor (LBR) - composed of eight transmembrane domains and a sterol reductase activity (Figure 1D and 1E) [43]. The chromatin binding domain of LBR associates with and tethers chromatin closer to the nuclear envelope. Further, LBR recognizes the histone modification - H4K20Me2 (histone-4 lysine-20 dimethylation) and is involved in the compaction of associated chromatin by the recruitment of HP1 α , MeCP2, and B-type lamins collectively involved in transcriptional silencing [44,45]. Loss of both Lamin A/C and LBR in rod cells of mouse retina showed an inverted nuclear architecture with heterochromatin localized towards the nuclear interior, while euchromatin was closer to the nuclear envelope [46]. Lamins interact with nuclear envelope transmembrane proteins (NETs) in a tissue-specific manner [47,48]. The differences in the composition of nuclear lamina and stoichiometry of A-

type and B-type lamins potentially manifest cell-type-specific differences in binding partners for lamins. Lamin interactomes define tissue-specific functions of nuclear lamins.

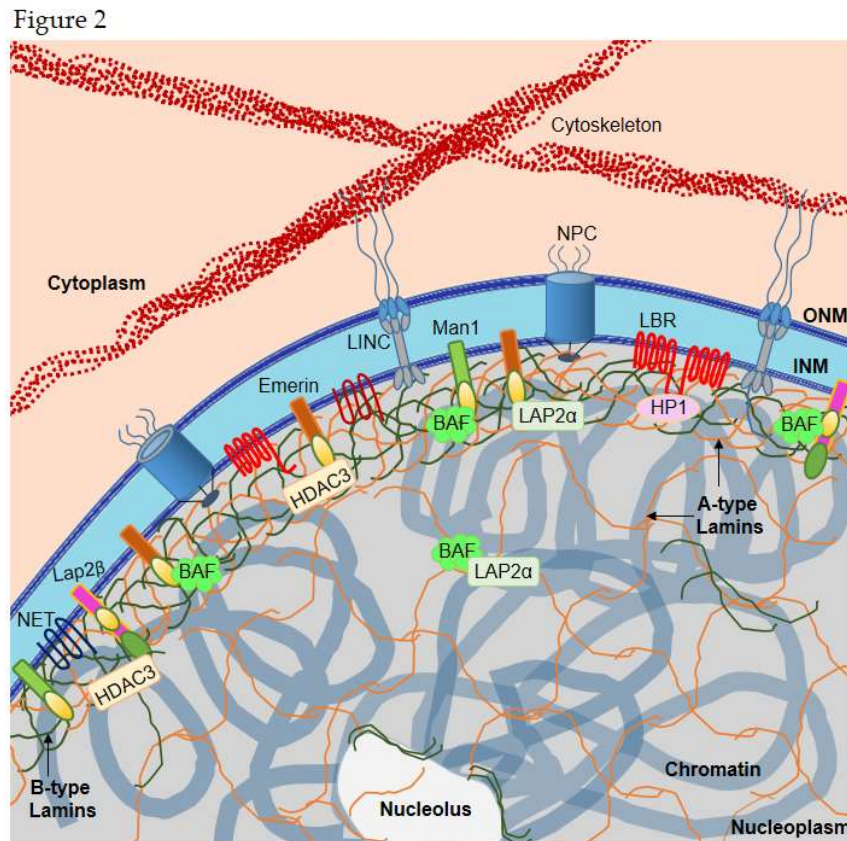


Figure 2: Organization of the nuclear envelope The nuclear envelope (NE) is composed of the outer nuclear membrane (ONM), inner nuclear membrane (INM), nuclear lamina, nuclear pore complex (NPC), and nuclear envelope transmembrane proteins (NET). A-type lamins and B-type lamins together form a filamentous meshwork of nuclear lamina at the NE and are also localized in the nucleoplasm. The linker of nucleoskeleton and cytoskeleton (LINC) complex connects the nucleus to the cytoskeleton. This schematic shows a subset of INM proteins interacting with the nuclear lamina such as LEM domain NETs (Lap2 β , Emerin, Man1), Lamin B Receptor (LBR) and their chromatin interacting partners such as barrier to autointegration factor (BAF), histone deacetylase 3 (HDAC3) and heterochromatin protein 1 (HP1). The nuclear lamina and associated proteins modulate the spatial organization of chromatin, heterochromatinization, gene expression, nuclear stability, and mechanotransduction.

The LINC (linker of nucleoskeleton and cytoskeleton) protein complex couples the nuclear lamina to the components of the cytoskeleton (Figure 2), composed of SUN domain proteins in the INM and KASH domain proteins in the outer nuclear membrane (ONM) [49]. The nucleoplasmic domain of the SUN protein interacts with lamins, whereas its transluminal domain interacts with the KASH domain proteins [50]. LINC complex mediates interactions between nuclear lamins and chromatin with various components in the cytoplasm such as actin filaments, microtubules, centrosomes, and cytoplasmic organelles [14,51,52].

Filamentous networks of A-type and B-type lamins provide attachment sites for nuclear pore complexes (NPCs) and regulate the symmetric distribution of NPCs; however, lamin C shows preferential association with the NPC over lamin A [53,54]. Lamins, along with NETs and NPCs interact with DNA, histones, chromatin organizer proteins, epigenetic chromatin marks, and transcriptional regulators [11,55,56]. These interactions largely influence chromatin organization and function. Lamin-binding proteins contribute to nuclear architecture, mechanics, and signalling [57,58]. The difference in the composition of lamin-interacting proteins in different tissues can

potentially modulate tissue-specific lamin functions [47]. In summary, the lamin meshwork emerges as a complex network of interactions at the nuclear envelope, further modulated by cell- and tissue-specific functions.

4. Lamins maintain integrity of the nucleus

Lamins are the major structural components that contribute to the shape, rigidity, and mechanical integrity of the nucleus [36,59]. Nuclear morphology is strikingly altered upon lamin depletion in *C. elegans*, *D. melanogaster*, Lamin A/C knockout mice, and Lamin B1 knockdown HeLa cells [60–62]. Loss of lamins is frequently associated with nuclear blebs, invaginations, and transient ruptures of the nuclear envelope [63]. Nuclear stiffness increases with the ratio of A:B-type lamins [35]. Lamin A/C deficient human fibroblasts have relatively fragile nuclei that are more deformable under mechanical strain and exhibit altered mechanotransduction [62,64,65]. Lamin A/C and lamin B1 both contribute to nuclear stiffness; wherein B-type lamins impart elastic properties to the nuclear envelope and nuclear viscosity is specified by lamin A/C [66–68]. These differences in the function of A-type and B-type lamins are due to the ability of A-type lamins to form a thicker meshwork (~15 nm) than B-type lamins (~7 nm) [69]. Additionally, the relative stoichiometry of A-type and B-type lamins determines mechanical stiffness of the nucleus [36].

Lamin depletion alters nucleo-cytoskeletal coupling, as lamin deficient cells induce a separation of the microtubule-organizing center from the nuclear envelope, impairing centrosome positioning [15]. Moreover, mouse fibroblasts deficient in A-type lamins show altered cytoskeletal organization and reduced cytoplasmic stiffness [15,70]. Interestingly, during cell migration through narrow constrictions, the nuclear envelope was ruptured at the leading edge of cells, facilitated by reduced lamin levels [36,71]. B-type lamins are essential for the forward movement of the nucleus during neuronal migration; further, lamin B1 deficient neurons showed nuclear rupture accompanied by DNA damage and cell death [72,73].

Lamin pools within the nucleoplasm contribute to normal cellular processes by associating with various nuclear and nucleolar structures [74]. Lamin A/C associates with nuclear components such as the nuclear pore complex and promyelocytic leukemia nuclear (PML) bodies [75,76]. Lamin A is required for the compartmentalization of PML bodies, which also accumulate within nuclear blebs and the nuclear envelope in lamin A-deficient cells [77]. While lamin B2 is enriched as punctae at the granular component (GC) of the nucleolus in colorectal cancer cells, lamin A is localized in the nucleolar interior [78]. Interestingly, lamin B2 showed a separation of function at the nuclear envelope and nucleolus of colorectal cancer cells. The N-terminal head domain of lamin B2 maintains discrete, spherical nucleolar morphology; while, a stretch of seven amino acids (SLSATGR) in the C-terminal tail domain of lamin B2 is essential for bleb-free morphology of the nucleus [78]. Membrane-associated fractions of B-type lamins also contribute to nuclear envelope assembly and chromosome organization post-mitosis [79]. Needless to mention, the development of new imaging and molecular approaches is essential for unravelling the structure and function of nucleoplasmic lamins.

5. Lamins modulate chromatin organization

The genome is non-randomly organized as chromosome territories that occupy a distinct sub-volume and non-random spatial positions in the interphase nucleus [80,81]. Chromatin at the nuclear periphery associates with the nuclear lamina through lamina associated domains (LADs), characterized by the presence of lamina associated sequences (LASs) (Figure 1F) [82,83]. The association of chromosomes with the lamina is largely dependent on DNA sequences and shows a greater propensity to associate with repetitive sequences typically enriched, for instance, in gene-poor chromosome 18 as compared to gene-rich chromosome 19 (Figure 1F and 1G). Interactions of the genome with the nuclear lamina are dynamic and modulated across developmental stages [84–86]. For example, during adipogenic differentiation, a large number of lamin-genome associations are remodeled globally that alters associated transcriptional outputs [87]. Lamins directly interact with DNA, chromatin, and histones *in vitro*, and are required for chromatin organization *in vivo* [44,88,89]; since depletion of mammalian lamin B1 and lamin A/C, or lamin in *C. elegans* shows

chromatin reorganization and alters chromatin dynamics [90]. In human fibroblasts, for instance, ~40% of the genome comprises LADs that range from ~10 kb to ~10 Mb in size and this region is enriched for (i) heterochromatin marks (ii) gene-poor chromatin (iii) low transcriptional activity and (iv) late replication timing [82,91]. Borders of LADs are enriched in H3K9Me_{2/3} (histone 3 lysine 9 di-trimethylation), H3K27Me₃ (histone 3 lysine 27 trimethylation) and are flanked by the insulator and genome organizer - CTCF (CCCTC binding factor) [83,84]. LADs show higher enrichment on intergenic regions, and silent or weakly expressed genes in mammals, nematodes, and fruit flies [85,92].

Chromatin-association of the nuclear lamina is mediated by protein complexes formed between lamins and lamin-binding proteins at the INM, via direct chromatin-binding or the recruitment of intermediate factors [93,94]. Studies on mammalian cells and *D. melanogaster* have demonstrated that heterochromatin is tethered to the nuclear lamina by lamins and lamin-interacting NET proteins via their mediators - HP1 α , BAF, PRR14 or repressive histone marks such as H3K9Me_{2/3}, H3K27Me_{2/3}, and H4K20Me₂ [82,92]. Lamins significantly contribute to the maintenance of LADs, however, these interactions are stabilized by lamin interactors at the nuclear interior (Lamin A/C with LAP2 α , BAF) and nuclear envelope (Lamin A/C with Emerin, SUN1, SUN2, Nesprin-1 α , Nesprin-2 and B-type Lamins with LBR, LAP2 β , HP1 α) respectively [9,95–97]. LADs bound by B-type lamins are proximal to the nuclear envelope encompassing heterochromatin, while those bound by A-type lamins exist both at the nuclear envelope and nuclear interior, involving heterochromatin and euchromatin respectively [95,98]. LADs at the nuclear envelope are more compact also due to their proximity to the lamin meshwork, which hinders chromatin mobility [11]. Spatial organization of LADs in the nucleus is an important factor in the functional compartmentalization of the genome.

A comparison of LADs from different cell lineages derived from mouse embryonic stem cells (mESCs) showed that LADs are of two types; (a) facultative LADs (fLADs) and (b) constitutive LADs (cLADs) [83]. Lamin-B1 derived DamID readouts in different cell lineages showed that cLADs were consistently associated with the nuclear lamina, whereas fLADs were detached from the lamina in a cell-type-specific manner [99,100]. This suggests altered localization and function of cLADs and fLADs, depending on their genomic features in the interphase nucleus [94,101,102]. The fLADs are associated with differentiation, as they harbor cell-type-specific genes that are released from lamins for the activation of tissue-specific gene expression upon lineage commitment [103,104]. For example, during Jurkat T-cell activation, genomic loci (*CBLP* and *IL2*) and enhancers specific to T-cell function are released from the nuclear lamina, but are constrained in an active compartment proximal to the lamina [99]. The binding of A-type lamins to LADs is altered during adipogenic differentiation in response to metabolically regulated O-GlcNAcylation of histone H2B, thereby contributing to differentiation-specific repression of genes [105].

The aberrant splicing of the *LMNA* gene is associated with Hutchinson-Gilford Progeria Syndrome (HGPS), which shows striking changes in chromatin architecture [20,106]. Imaging HGPS fibroblasts reveals the loss of heterochromatin tethering to the nuclear lamina [106,107]. Depletion of B-type lamin in S2 cells of *D. melanogaster* showed a repositioning of the testis-specific gene cluster (*60D1* locus) toward the nuclear interior and impaired the segregation of chromatin into active and inactive compartments [108,109]. Moreover, lamin depletion alters the spatial positions of chromosome territories in mammalian cell lines [97,110]. For instance, CT18 was repositioned away from the nuclear envelope in lamin B1 knockout murine cells [111], whereas fibroblasts derived from laminopathies showed a mislocalization of the gene-poor CT13 and CT18 respectively away from the nuclear envelope [112]. Lamins, with emerin, nuclear actin, and myosin constitute intra-nuclear complexes that are involved in the spatial localization of gene-rich chromosome territories as well as individual gene loci in the interphase nucleus [113–115]. Additionally, co-depletion of lamin A/C and emerin showed altered sub-cellular localization of NM1 (nuclear myosin-1), chromosome territory positions and enhanced chromatin mobility in colorectal cancer cells [115]. However, how the relative stoichiometry of A-type and B-type lamins, and its cell-cell variability impacts chromosome territory positions and LAD organization in a tissue-specific manner remains unclear.

6. Lamins modulate gene expression

The nuclear envelope is largely a transcriptionally repressive region. However, certain regions are nevertheless transcriptionally permissive [116]. This is consistent with the finding that anchoring genes to the nuclear lamina correlates with tissue-specific gene repression, and this tethering mechanism is vital for stable repression of genes during differentiation [102,117,118]. For example, in neuronal progenitor cells of *D. melanogaster*, tethering of the hunchback (hb) gene to the nuclear lamina is required for its stable repression [119]. Nuclear lamins are implicated in regulating transcriptional activity by modulating chromatin structure and organization at the nuclear periphery [120,121]. Overexpression of Lamin A/C shows a reduction in RNA polymerase II-mediated transcription and disrupts the spatial organization of RNA polymerase II speckles in the interphase nucleus [122]. Furthermore, lamins function as a scaffold for RNA polymerase II and associated transcription factors [34,122]. Activation of tissue-specific gene transcription during cell differentiation is frequently associated with the movement of gene loci away from the nuclear lamina to the nuclear interior, at sites that are enriched for transcription factors [123,124]. For instance, the immunoglobulin heavy chain (*IgH*) locus, repositions away from the nuclear envelope during B-cell development [123].

Figure 3

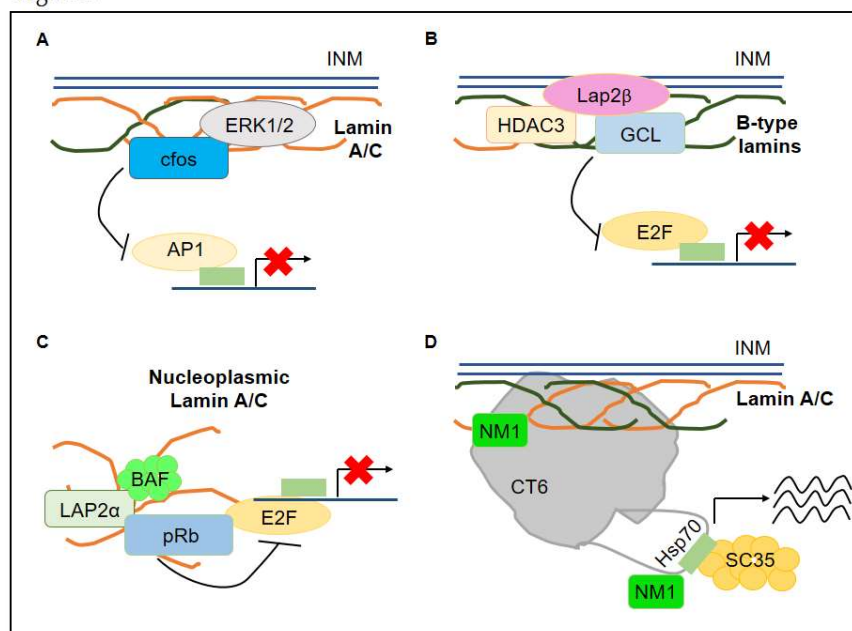


Figure 3: Mechanisms of lamin mediated gene regulation (A) The c-Fos protein is associated with the nuclear envelope through interaction with A-type lamins in serum-deprived conditions. AP-1 responsive genes are OFF under these conditions. Lamin A bound ERK1/2 functions as a molecular switch for the mitogen dependent activation of AP-1 by releasing c-Fos from the lamina. **(B)** Transcriptional repressor germ-cell-less (GCL) is localized at the nuclear envelope by associating with B-type lamins and LAP2 β . This interaction reduces the transcriptional activity of E2F. **(C)** Interaction of pRb with lamin A/C and LAP2 α anchors the pRb/E2F complex in the nucleoplasm, reducing the pool of available E2F, arresting cell cycle at the G1 pRb-dependent checkpoint. **(D)** A novel regulatory role for lamin A/C and nuclear myosin (NM1) in the modulation of the heat shock response. The Hsp70 gene locus moves away from the nuclear envelope and shows enhanced contact with SC35 nuclear speckles upon heat shock, which enhances its gene expression levels.

Nuclear lamins interact with various transcription factors that affect cell proliferation, differentiation, and apoptosis (Figure 3) [125]. A-type lamins interact with transcription factors such as pRb, c-Fos, AP-1, SREBP1, ERK1/2, MEL18, and GCL [126]. Many of the transcription factors bound

by lamin A are sequestered at the nuclear envelope in inactive complexes [127,128]. These factors are released from the lamin anchor upon specific signalling cues leading to the activation of target genes. For instance, the transcription factor c-Fos is sequestered at the nuclear envelope by A-type lamins and released during mitogen-activated protein kinase (MAPK) signalling to facilitate cell proliferation (Figure 3A) [129]. A-type lamins function as transcriptional repressors when targeted to promoters [130]. Robust transcriptional repression of promoters with Gal4 binding sites was observed upon expressing human lamin A as a fusion protein to the Gal4 DNA-binding domain in yeast and cultured human cells [130,131]. Promoters of transcriptionally active genes positioned at the nuclear envelope are often excluded from the nuclear lamina-association, further reiterating the significance of promoter-lamina interactions in gene repression [132]. The B-type lamins are involved in transcriptional repression through their interacting partner LAP2 β at the INM, which shows a direct interaction with the transcription regulator (GCL) and epigenetic modifier (HDAC3) (Figure 3B) [126]. B-type lamins regulate Oct-1 dependent genes; since the disruption of the interaction between lamin B1 and Oct-1 resulted in the down-regulation of oxidative stress response genes and elevated reactive oxygen species levels [133].

Gene expression profiling of lamin A/C or lamin B2 depleted colorectal cancer cells showed transcriptional deregulation [97]. Additionally, a candidate gene locus *ZNF570* repositioned away from the nuclear lamina in lamin B2 depleted cells, which correlated with a significant increase in its transcript levels [97]. Lamin C (LamC, *D. melanogaster* A-type lamin) and the transcription factor Hey partner to maintain nuclear architecture unique to differentiated enterocytes (ECs), as loss of Hey or aberrant lamin expression shows loss of EC identity [134]. Interestingly, transcriptionally active chromatin can also associate with lamin B1, forming dynamic euchromatin-lamin B1-associated domains in murine cells [135]. The depletion of lamin B1 from the euchromatin fraction massively alters the expression profile of EMT (epithelial to mesenchymal transition)-associated genes (*CDH1*, *FN1*, *ZEB1* and *TWIST2*), thereby resulting in impaired EMT [135,136]. Furthermore, nuclear lamins also contribute to altered gene expression during heat shock [137]. Lamin A/C depletion prevented the translocation of Hsp70 (a key transcription factor driving the expression of heat shock-induced genes during heat shock) into the nucleus upon heat shock (Figure 3D). This uncovered a novel function for lamin A/C in modulating gene expression and the nuclear localization of the genomic locus of Hsp70 upon heat shock [137].

7. Lamins in mechano-signalling

Nuclear lamina impacts gene expression by serving as a docking site for transcription factors and downstream signalling molecules [128]. Additionally, the nuclear lamina functions as a mechanosensor as it senses external mechanical signal, and functions as a mechanotransducer by relaying the signal that elicits appropriate cellular responses [35,138]. External mechanical stimulus results in the rearrangement of lamin filaments, which enables the transduction of external mechanical signals into the genome to elicit appropriate mechanosensitive transcriptional responses [139]. Lamina associated LEM domain-containing nuclear envelope proteins are implicated in the regulation of signalling at the nuclear periphery and mechanotransduction into the nucleus [42]. For instance, lamin-binding proteins regulate TGF- β -signaling in *D. melanogaster*, *X. laevis*, and mammals [140,141]. LEM protein - Man1, directly binds and inhibits R-SMAD, regulating BMP and TGF- β signalling in early vertebrate development [141,142]. The lamin A, LAP2 α , and pRb complex regulates nucleoplasmic anchoring of pRb and modulates E2F-dependent transcription in cell proliferation (Figure 3C) [8,143].

Phosphorylation of lamins regulates their solubility resulting in lamina assembly or disassembly, also as a response to external mechanical signals [144]. Lamins show enhanced phosphorylation and solubility in cells cultured on softer matrices [138]. This was consistent with enrichment in nucleoplasmic lamin levels in cells cultured on softer matrices. Remarkably, lamins were restored to the nuclear envelope in cells transferred from softer to stiffer substrates [145]. Taken together, lamins respond to external mechanical signals in a phosphorylation-dependent mechanism. Stem cells grown on substrates of differing elasticity showed differential lamin A levels, altering cell

fate decisions [35,36]. For example, stiffer substrates promoted osteogenic differentiation of mesenchymal stem cells, while softer substrates promoted adipogenesis of the same cells [35].

A-type lamins show a greater diversity of function than B-type lamins. Lamin A impacts cellular growth and proliferation by participating in mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, wherein activated ERK1/2 interacts and co-localizes with Lamin A at the nuclear periphery (Figure 3A) [129,146]. Phosphorylated ERK1/2 activates c-Fos, which heterodimerizes with c-Jun to initiate transcription [129]. A-type lamins are also implicated in protein phosphatase 2A (PP2A) mediated inhibition of TGF- β signalling [147]. Aberrant activation of TGF β signalling hyperactivates the MAPK/ERK signalling pathway in a murine model for EDMD - a disorder caused by a mutation in *LMNA* or *EMD* [148]. Additionally, lamin A tethers SKIP - a co-activator of Notch-dependent target genes, essential in the differentiation of mesenchymal stem cells [149]. Involvement of lamins in cell signalling highlights the ability of cells to utilize structural proteins as a signal processing unit by modulating lamin localization. This depends on post-translational modifications of lamins, facilitating the integration of mechanical and architectural cues.

8. Lamins and genome stability

Genome instability is a hallmark of cancer. Cells encounter genomic instability typically due to defects in i) DNA damage repair pathways ii) DNA replication iii) chromosome segregation during mitosis [150,151]. Nuclear lamina proteins are implicated in various cellular processes that regulate genome stability, such as mitotic progression, cell cycle regulation, and nuclear assembly post-mitosis [152,153]. Disassembled components of nuclear lamina play a critical role in chromosome segregation that impact chromosome ploidy and post-mitotic nuclear assembly [154]. Additionally, a transient loss in the integrity of nuclear envelope during cell migration through confined spaces contributes to the genomic instability, as nuclear envelope rupture induces DNA double-strand breaks [155].

B-type Lamins are a part of the mitotic spindle matrix in *X. laevis* and mammalian cells [156]. Loss of lamin B2 perturbs chromosome segregation in colorectal cancer cells. Therefore, this function of lamin B2 is required to prevent chromosomal instability [157]. Furthermore, in HeLa cells, Lamin A/C, LAP2 α and BAF form a protein complex that localizes at the spindle and cell cortex during mitosis, for regulating mitotic spindle assembly and positioning [158]. Partial loss of lamin B1 expression in cancer cell lines resulted in delayed cell cycle and accumulation of cells in the early S phase [159]. Interestingly, the maintenance of lamin B1 levels was essential for DNA replication and repair via regulation of the expression of key factors *BRCA* and *RAD51* [159]. Another study showed that disruption of lamin B1 led to nuclear blebbing and cytokinesis failure generating bi-nucleated and multinucleated cells [111,136]. Imaging GFP-histone 2B labelled in lamin A/C depleted ovarian epithelial cells followed by monitoring of narrow protrusions of nuclear materials, revealed that nuclear herniations break off from the main nucleus to form micronuclei, which were gradually degraded, leading to aneuploidy [160]. These observations emphasize the key role of lamins in maintaining the numerical stability of chromosomes.

Laminopathies caused by mutations in the *LMNA* gene are associated with genome instability with cells displaying high incidences of aneuploidy, DNA damage, and chromosome abnormalities [107,161]. Ectopic expression of lamin A mutant - progerin resulted in heterochromatin loss; further causing enhanced DNA replication defects, telomeric DNA damage, and impaired DNA damage response [107]. Lamins are also involved in DNA damage repair pathways, either to recruit factors involved in DNA repair or in epigenetically modulating the transcription of genes involved in DNA repair [162,163]. *LMNA*-null mouse fibroblasts show enhanced genomic instability, as observed by an increase in chromosome breaks, and γ H2AX foci [162]. In summary, lamins are essential in regulating both structural and numerical stability of chromosomes. 3D-SIM has uncovered that ~50% of telomeres are associated with the nuclear lamina [164]. Interestingly, telomeres are stabilized by lamin-binding, and alterations in nuclear lamins lead to defects in telomere compartmentalization, homeostasis, and function, contributing to the genomic instability [165]. It is unclear if genomic rearrangements found in cancers and other developmental disorders, alter lamina-chromatin interactions and associated epigenetic regulatory pathways.

9. Nuclear lamins in cell proliferation and cancer

Lamins function in both tumour-suppressive and oncogenic pathways and are also involved in the regulation of apoptosis [112]. Nucleoplasmic lamins in progeroid cells govern growth-regulating functions of LAP2 α to either enhance or inhibit cell proliferation, relative to the levels of A-type lamins in the nuclear interior [166]. Lamin B1 foci remain associated with major nuclear components such as chromatin, nucleoli, and nuclear speckles during mitosis [154]. These remnants of nuclear lamina potentially provide a structural memory that allows key features of nuclear architecture to be inherited from one cell cycle to the next [154]. B-type lamin levels are downregulated during physiological ageing in both humans and fruit flies [167,168]. However, oncogene-induced senescence is associated with the depletion of both A-type and B-type lamins, along with NETs (including LBR), which implies the disruption of heterochromatin tethers [169]. Furthermore, calcification of vascular smooth muscle cells was induced via activation of the senescence-associated secretory phenotype upon expression of pre-lamin A [170].

Nuclear envelope morphology is a biomarker of tumour grade and prognosis in cancer patients [171]. Recent studies have demonstrated the context-dependent role of nuclear lamins in human malignancies. Depletion of lamin A/C in a human lung cancer cell line elevated *in vivo* tumour growth rate in a xenograft model [172]. Conversely, independent knockdown of lamin A/C and lamin B1 in primary human diploid fibroblasts resulted in G1 arrest and premature senescence respectively, revealing cell-type-dependent effects of lamin levels on proliferation [143,173]. Nuclear lamins are downregulated in breast, colon, prostate, ovarian, gastric cancers, and are often associated with increased tumour aggressiveness and poor prognosis [174–178]. In contrast, colorectal and prostate tumours demonstrated an association between increased expression of lamin A/C and disease progression [179,180]. Studies on B-cell activation revealed that lamin B1 acts as a negative epigenetic regulator of somatic hyper-mutation in normal B-cells and suppresses the aberrant mutations that drive lymphoid malignancy [181]. Lamin B2 is highly expressed in non-small cell lung cancer cells and promotes tumour proliferation and migration by silencing of E-cadherin via the upregulation of H3K9Me2 (dimethylation of histone-3 lysine-9) [182]. Taken together, the functions of lamins in cancer cells and the mechanisms that determine the profile of lamin expression during tumorigenesis strongly implicate nuclear lamins as biomarkers for the early detection and prognosis of cancers.

10. Conclusion

Lamin filaments play essential roles as structural elements in the maintenance of nuclear stability; however, lamin filaments and lamin oligomers both are involved in mechano-transduction in cells. The solubility of nuclear lamins, lamina meshwork, the localization and sequestration of lamin interactors are regulated by phosphorylation and other post-translational modifications. Nuclear lamins, together with lamina associated proteins are key modulators of heterochromatin organization, the spatial organization of the genome, gene expression, genome stability, and mechanosignalling. These functions are exhibited by dynamic association with the heterochromatin, euchromatin, and promoter sub-domains, thereby affecting chromatin accessibility and epigenetic regulatory pathways. Differences in the expression patterns and membrane-association properties of A-type and B-type lamins also suggest unique and non-overlapping roles of A-type and B-type lamins in the maintenance of nuclear structure-function relationships.

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Abbreviations

IF	Intermediate Filament
INM	Inner Nuclear Membrane
NET	Nuclear Envelope Transmembrane protein
NPC	Nuclear Pore Complex
LINC	LInker of Nucleoskeleton and Cytoskeleton
LBR	Lamin B Receptor
BAF	Barrier to Autointegration Factor
HP1	Heterochromatin Protein 1
LAP2	Lamina Associated Polypeptide 2
LAD	Lamina Associated Domain
CT	Chromosome Territory
DamID	DNA adenine methyltransferase IDentification

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