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Review

Dynamic interactions of nuclear lamina proteins with chromatin and transcriptional machinery

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Abstract. The nuclear lamina is a filamentous nuclear structure intimately connected to the inner nuclear membrane. It is composed of lamins, which are also present in the nuclear interior, and lamin-associated proteins. The nuclear lamina is involved directly or indirectly in many nuclear activities, including DNA replication and transcription, nuclear and chromatin organization, cell cycle regulation, cell development and differentiation, nuclear migration and apoptosis. Mutations in nuclear lamina genes cause a wide range of heritable human diseases, the molecular mechanisms for which are not well understood. This review describes our current knowledge of interactions between nuclear lamina proteins and chromatin, chromatin-remodeling factors, specific transcription factors and RNA polymerase II transcription machinery. Recent studies provide new insights into the nature and regulation of these interactions and suggest additional roles for the nuclear lamina.

Key words. BAF; GCL; heterochromatin; lamins; lamin-associated proteins; LEM-domain; transcriptional regulation.

Introduction

The separation of nuclear and cytoplasmic compartments by the nuclear envelope is the most remarkable characteristic of the eukaryotic cell. The nuclear envelope is a complex structure composed of the outer and inner nuclear membranes, nuclear pore complexes (NPCs) and the nuclear lamina. The two lipid bilayer membranes are separated by a lumen and joined at the nuclear pore complexes. The outer nuclear membrane (ONM) is continuous with the endoplasmic reticulum (ER) and is covered with ribosomes, whereas the inner nuclear membrane (INM) faces the chromatin and contains a unique set of proteins. NPCs are large complex protein structures that mediate bidirectional transport of macromolecules between the cytoplasm and the nucleus. The nuclear lamina is a protein meshwork located between the INM and the peripheral chromatin. However, some nuclear lamina components are also present in the nuclear interior (fig. 1). The components of the nuclear lamina are lamins, which are nuclear intermediate filament proteins [1], plus a growing number of lamin-associated proteins such as emerin, lamina-associated polypeptides 1 and 2 (LAP1, LAP2), nesprin-1, lamin-B receptor (LBR), MAN1, otefin and young arrest (YA) [2–5]. Other integral proteins of the INM, including UNC-84, UNC-83, nurim and ring finger binding protein (RFBP), are also considered to be part of the nuclear lamina, as they interact directly or indirectly with lamins [6, 7]. The nuclear lamina is evolutionarily conserved in metazoa. However, the number and complexity of nuclear lamina proteins increased during metazoan evolution [8, 9].

Many functions have been attributed to the nuclear lamina. These functions include the maintenance of nuclear morphology [10, 11], correct spacing of the NPCs [12, 13] and the provision of docking sites for chromatin at the

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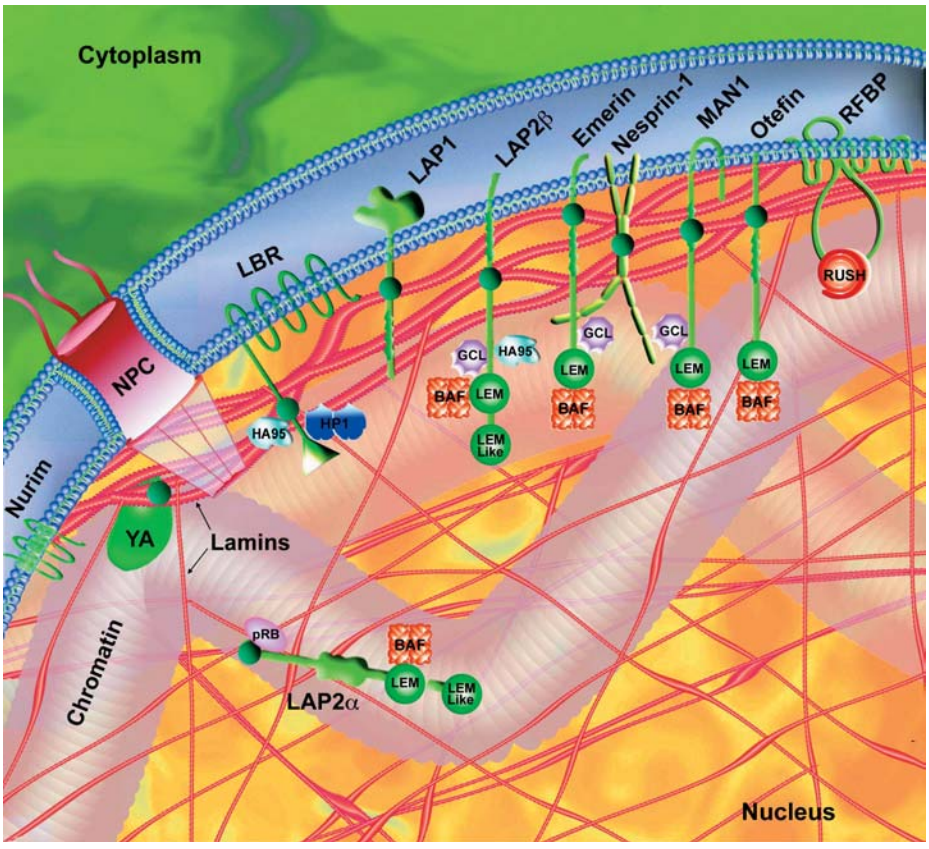

Figure 1. Schematic view of the nuclear envelope, lamina and chromatin. The inner and outer nuclear membranes are joined at the nuclear pore complexes (NPC) and are separated by the nuclear lumen. Lamins (both A- and B-types) are shown as thicker filaments at the nuclear periphery and as thinner filaments in the nucleoplasm. However, the filamentous nature of the lamins, especially in the nucleoplasm, remains hypothetical. Also shown are selected proteins of the inner nuclear membrane and proteins that interact with lamins in the nuclear interior. The green circles represent interactions with lamins. Also depicted are the LEM domain and the LEM-like domain. Chromatin at the nuclear periphery is structurally condensed, since it is mostly transcriptionally silent.

nuclear periphery [12, 14, 15]. The lamina is also involved in the mitotic disassembly and reassembly of the nuclear envelope [16], apoptosis [17, 18], DNA replication and transcription [14, 19–21], cell cycle regulation [10], chromosome segregation [10], programmed nuclear migration [22, 23] and differentiation [24, 25].

Interactions between the nuclear lamina and chromatin

The intimate association between the nuclear lamina and the peripheral chromatin, which includes a large fraction of the transcriptionally silent chromatin, is seen in electron micrographs of metazoan nuclei [26]. Three-dimensional analyses of *Drosophila* interphase and polytene nuclei revealed that centromeres, telomeres and intercalary heterochromatin juxtapose the nuclear lamina [27]. Associations between the nuclear envelope, telomeres and centromeres were also shown in other organisms, including plants, budding yeast, fission yeast and mouse meiotic cells [28]. However, these associations are not maintained in somatic mammalian nuclei. Understanding the interactions and possible protein complexes that the nuclear lamina forms with chromatin is an important goal for future studies. Insights into these protein complexes are beginning to emerge [29].

Nuclear lamins and their interactions with chromatin

Lamins are type V intermediate filament (IF) proteins. They are classified as either A- or B-type according to their primary sequence, expression pattern and biochemical properties. A-type lamins are predominantly expressed in differentiated cells, have a neutral isoelectric point and are solubilized and dispersed during mitosis. B-type lamins are expressed in all somatic cells, have an acidic isoelectric point and remain mostly associated with membranes during mitosis [1]. The differences in membrane attachment between A- and B-type lamins can be explained by specific sequences in their C-terminal (tail)

domain and by the presence or absence of a CaaX box in the C-terminus, which undergoes posttranslational modifications including proteolysis of the last three residues, methyl-esterification and farnesylation [1]. Some B-type lamins may be also both palmitoylated and farnesylated [30].

Like other IF proteins, lamins contain a short N-terminal head domain, an α-helical rod domain and a long globular tail domain. The coiled-coil (rod) domain mediates dimerization; thus, the fundamental 'unit' of lamins is the dimer. At their next level of structural organization, lamin dimers associate as polar head-to-tail polymers [31, 32]. These polymers associate laterally to form 10-nm thick filaments, which can further associate to form 50–200 nm thick lamin fibers [1, 33]. The number of lamin genes increased during evolution. There is only a single B-type lamin gene in *Caenorhabditis elegans* [34] and one B-type lamin and one A-type lamin gene in *Drosophila* [35, 36]. Mammals have three different A-type and B-type lamin genes that give rise to at least seven different spliced isoforms [37–40].

Nuclear lamins are not exclusively located within the nuclear lamina meshwork underlying the inner nuclear membrane but are also found inside the nucleus, as shown in mammalian cells [41–43] and *C. elegans* [10]. Belmont et al. [44], used a combination of sophisticated techniques to show that the in vivo distribution of lamin B is highly correlated to the underlying chromatin distribution and that lamin B directly covers the surface of nuclear envelope-associated large-scale chromatin domains.

Lamins can bind directly to DNA both in vivo and in vitro. Photocrosslinking experiments showed that *Drosophila* interphase lamins, but not mitotic lamins, are associated with nucleic acid in vivo [45]. In vitro, lamins bind matrix attachment/scaffold-associated regions (MARs/SARs) [46] and centromeric and telomeric sequences [47, 48] with high affinity. MARs/SARs are regions of AT-rich DNA that are organized into topologically constrained loops and attach to the nuclear matrix/scaffold [49, 50]. Lamins can also bind single-stranded DNA, but with lower affinity than MARs/SARs sequences [51]. Lamin binding to DNA is mediated through the rod domain and requires lamin polymerization [52]. It is currently unclear whether lamin-DNA interactions are significant in vivo. In particular, it is not known whether the nucleoplasmic lamins bind to DNA directly.

In vitro, lamins from different species interact with chromatin from other species [53–57], suggesting that these interactions are evolutionarily conserved. Lamins can bind in vitro assembled chromatin [57], isolated mammalian mitotic chromosomes [55, 58], polynucleosomes [54] and isolated mammalian and *Xenopus* histones (table 1) [56, 59]. While lamin binding to DNA is mediated by its rod domain, its binding to chromatin requires the tail domain. Two separate regions are required for *Drosophila* lamin Dm_0 (a B-type) binding to mitotic chromosomes: strong binding involves residues 425–473, and weaker binding involves residues 572–622 [56]. Human lamin A/C binding to chromosomes involves residues 396–430, located immediately adjacent to the rod domain [59]. Similarly, *Xenopus* lamin B2 binding to chromosomes involves residues 404–419, located eleven residues downstream of the rod domain, and residues 432–467 [53]. These chromatin binding regions of different lamins have conserved stretches in the tail domain, including the RAT/S (single letter code) and the nuclear localization signal (NLS) motifs, which are probably involved in the binding to chromatin [A. Mattout-Drubezki and Y. Gruenbaum, unpublished]. Interestingly, these sequences are just outside the Ig globular domain in an unstructured region of the lamin tail [60, 61]. Lamins from *Drosophila*, turkey and humans interact in vitro with polynucleosomes [54, 56, 59]. The binding affinities of the human lamin-A tail for both polynucleosomes and purified core histones are similar, in the range of 0.12–0.3 µM [59]. *Drosophila* lamin Dm_0 binds specifically the histone H2A/H2B dimer, with an affinity of ~1 µM [56]. Lamin Dm_0 can bind the tail domain of histone H2B. Acetylation of histone H2B does not affect this binding [62]. However, lamin Dm_0 binds the histone H2B tail more weakly than full-length H2B, and it remains to be seen if the histone tail is the target in vivo for lamin binding to H2B. The interactions between lamins, chromatin and DNA are intriguing because they have the potential to influence higher-order chromatin organization structure and to help direct lamin binding proteins to the chromatin.

Lamin-associated proteins and their interactions with chromatin

Lamin-associated proteins also interact with chromatin (table 1). LBR is a 58-kDa protein with eight putative transmembrane segments and a nucleoplasmic amino terminal domain. LBR interacts with B-type lamins and has a sterol C14 reductase activity [63–66]. LBR also binds chromatin [67], dsDNA [68], heterochromatin protein HP1 [69], histone H3/H4 tetramer [70] and the chromatin-associated protein HA95 [71]. HP1 contains both a chromodomain and a chromo shadow domain and is a key heterochromatin protein originally identified in *Drosophila*, where it functions as a suppressor of position-effect variegation [72]. HP1 is conserved in evolution and regulates gene expression by binding to the methylated lysine 9 residue in histone H3 (H3K9) [73]. The interaction between LBR and HP1 requires the N-terminal domain of LBR [69] and the chromo shadow domain of HP1. The chromo shadow domain is also necessary for the self-association of HP1 [69]. LBR can form a quater-

Table 1. Summary of known interactions between nuclear lamina proteins and chromatin. The major binding sites related to these interactions within the nuclear lamina proteins are mentioned.

Nuclear lamina proteins	Chromatin binding partners	Major binding site(s)	References
Lamin	ssDNA, MARs/SARs	lamin rod domain	45, 46, 51
	telomeric and centromeric DNA		47, 48
	interphase chromatin	lamin C-terminal domain	45, 53
	mitotic chromosomes		55, 58
	core histones H2A and H2B		56, 59
LBR	chromatin	N-terminal nucleoplasmic domain	67
	dsDNA	residues 1–53	68, 69
	HP1	residues 97–174	69
	histone H3/H4	ND	70
	HA95	ND	71
LAP2α	DNA	LEM-like domain (residues 1–50)	86
	chromatin	residues 1–85	146
		C-terminal LAP2α-specific domain (residues 270–615)	91
	BAF	LEM domain (residues 111–152)	78, 79
LAP2β	DNA	LEM-like domain (residues 1–50)	86
		residues 244–296	147
	Chromatin	residues 1–85	146
	BAF	LEM domain (residues 111–152)	78, 79
	HA95	residues 137–242; 299–373	71, 88
Emerin	BAF	LEM domain (residues 1–50)	80
MAN1	BAF	N-terminal domain	141
RFBP	RUSH	RFBP conformationally flexible loop	76
YA	Interphase chromatin		24
	polytene chromosomes	Binding requires four domains:	102
	mitotic chromosomes	residues 1–117; 270–396; 397–472	
	dsDNA	and 506–696	
	histone H2B		103

nary complex with HP1 and core histones H3/H4 [70]. Supporting the role of LBR in chromatin organization is the Pelger-Huet anomaly (PHA), caused by mutations in the LBR gene. PHA is an autosomal dominant disorder characterized by abnormal chromatin organization and nuclear lobulation in blood granulocytes [74]. It remains to be tested whether LBR-HP1 interaction directly mediates the peripheral localization of heterochromatin or has a nonstructural role. The recent discovery that homozygous mutations in LBR also cause the Greenberg skeletal dysplasia/HEM demonstrates roles for LBR in a variety of tissues [75]. The fetal death involves elevated levels of cholesta-8,14-dien-3 -ol, indicating that the sterol C-14 reductase activity of LBR is essential for its functions.

Another chromatin-associated INM protein is RFBP [76]. RFBP contains the structural features of type IV P-type ATPase proteins but lacks the domain required for pump activity. RFBP binds RUSH, which belongs to the SWI2/SNF2 RING-finger motif-containing transcription factors that bind to the uteroglobin promoter and are involved in chromatin remodeling [76].

The lamina proteins LAP2, emerin, MAN1, otefin and several other uncharacterized proteins contain an ~40-residue-long motif, termed the LEM domain [6, 77]. All lamina-associated LEM-domain proteins probably interact with barrier-to-autointegration factor (BAF) [78–80] [Y. Gruenbaum, unpublished]. BAF is a small, conserved metazoan protein that was first identified for its role in retroviral DNA stability and integration [81, 82]. BAF binds DNA without any detectable sequence specificity. The protein forms dimers and has the ability to bridge ds-DNA in vitro [15, 83].

The LAP2 gene is alternatively spliced to give rise to at least six different products [84]. Four of these products (LAP2β, LAP2γ, LAP2δ and LAP2ε) are type II integral proteins of the INM, whereas two others (LAP2α and LAP2ζ) are soluable proteins [84, 85]. All isoforms of LAP2 have the same N-terminal 'constant' domain,

which includes both a LEM domain and a LEM-like domain. The LEM domain is essential for binding BAF and BAF-DNA complexes [79, 86], while the LEM-like domain binds directly to DNA [86]. Interestingly, LAP2β has higher affinity for BAF-DNA complexes than for BAF dimers alone [79]. LAP2β also interacts with B-type lamins, germ cell-less (GCL) [87], a transcriptional repressor (discussed below) and HA95. This latter interaction has been recently demonstrated to be required for the initiation of DNA replication [88].

LAP2α is the major nucleoplasmic isoform of the LAP2 gene that binds only A-type lamins [89, 90]. During interphase, newly synthesized LAP2α first binds to an unidentified chromosomal protein through its α-specific domain and subsequently binds BAF through its LEM domain [91].

Emerin is a type II integral membrane protein that is about 40% homologous to LAP2β outside the LEM domain [92, 93]. Mutations in the emerin gene cause X-linked Emery-Dreifuss muscular dystrophy [94, 95]. Emerin binds to both A and B-type lamins [96, 97]. Nuclear envelope localization of emerin requires an intact lamina, since reduced amounts of lamin A in humans and reduced Ce-lamin in *C. elegans* causes emerin to be mislocalized to the ER [98, 99]. Emerin binds directly to BAF through its LEM domain [80], and emerin LEM-BAF interactions are critical for membrane recruitment and chromatin decondensation during postmitotic nuclear assembly [15].

YA is an essential *Drosophila* gene that is required for the transition from meiosis to early embryonic mitotic divisions [100]. The maternally encoded YA protein is a peripheral protein of the INM during the first two hours of zygotic development, where it binds lamin Dm_0 [101]. During this developmental period, YA is essential for proper chromatin condensation [24]. Ectopically expressed YA associates with polytene chromosomes in vivo and with mitotic chromosomes in vitro [102]. This binding involves interactions with dsDNA and core histone H2B, but not other core histones [103]. Four domains of YA, including two zinc fingers, a Ser/Thr-rich region, and a potential DNA-binding motif (SPKK), are required to bind chromosomes, DNA and H2B [103].

Posttranslational modifications regulate the nuclear lamina-chromatin interactions

The nuclear lamina is a dynamic structure that disassembles during mitosis and that is involved in nuclear growth during G1. Posttranslational modifications of lamina proteins regulate these dynamic changes. Mitotic phosphorylation by CDK1 causes lamins to depolymerize and dissociate from chromatin [104, 105]. During interphase, lamin Dm_0 is phosphorylated on serine 25 and on one of the threonine residues in the sequence TRAT (single letter code) [106, 107]. The latter phosphorylation could be involved in lamin Dm_0 binding to core histones [56] [A. Mattout-Drubezki and Y. Gruenbaum, unpublished]. The binding of LBR to chromatin is enhanced by interphase phosphorylation of a region rich in arginine-serine repeats (residues 1–53), whereas mitotic phosphorylation at different residues in the same region probably suppresses this binding [108]. LAP2α and LAP2β also interact with chromosomes in a phosphorylation-dependent manner [89, 109].

Acetylation of core histones regulates their binding to HP1 and LBR, since acetylated H3/H4 cannot bind HP1 or LBR, whereas nonacetylated histones can bind [70]. Likewise, HP1 binds specifically to methylated H3K9, but acetylation of K9 inhibits that binding [73, 110], suggesting that LBR-HP1 binding to chromatin is sensitive to histone modifications that determine its accessibility.

Regulation of gene expression by nuclear lamina proteins

Interactions between the nuclear lamina, DNA and chromatin-associated proteins at the nuclear periphery and nucleoplasm are proposed to tether chromatin to the nuclear envelope and organize chromatin, respectively. These interactions also have functional significance for regulation of gene expression.

Heterochromatin at the nuclear periphery

Heterochromatin, including centromeres, telomeres and repetitive DNA, is preferentially positioned near the nuclear envelope. Boyle et al., used chromosome painting to show that in human lymphoblastoid cells, gene-poor chromosomes are preferentially positioned near the nuclear periphery, whereas gene-rich chromosomes are positioned more centrally in the nucleus [111], indicating that the genes are not randomly distributed with respect to the nuclear lamina. The inactive condensed (heterochromatic) X chromosome is also localized to the nuclear periphery of interphase female mammalian cells, while the active X chromosome is localized in a more interior position [112, 113], suggesting a silencing role for the nuclear periphery. Several experiments support this role. For example, insertion of a heterochromatin region into the *brown* locus in *Drosophila* causes its association with other heterochromatic regions on the same chromosome and targets the *brown* locus to the nuclear envelope [114]. When a functional enhancer is inserted near a silenced transgene, it activates the transgene by displacing it from centromeric peripheral heterochromatin to a more interior nuclear domain [115]. Likewise, targeting of the VP16 acidic activation domain to a specific locus initi-

ates transcription in that region and causes the redistribution of this locus from predominantly peripheral to a more internal nuclear domain [116]. These data suggest that the INM may be a repressive environment for transcription of many genes. However, there is still no direct evidence that the association of the heterochromatin with the nuclear envelope causes gene silencing, and some active genes are also located near the INM, so the situation is unclear.

Transcriptional silencing in yeast also correlates with perinuclear localization of the chromatin. For example, when the yeast transcription activator Gal4 fused to a transmembrane protein is targeted to the nuclear membrane, the Gal4 binding sites become anchored to the nuclear periphery, leading to silencing of a nearby reporter gene [117]. This silencing requires the activity of the yeast silent information regulators (*SIR*) as well as the *yKU, RAP1, MLP1, MLP22* and *ESC1* genes [118; reviewed in 119]. Intriguingly, yeast does not contain any known metazoan nuclear lamina genes [6]. Therefore, nuclear periphery-dependent transcriptional repression in yeast probably occurs by a mechanism different from metazoans or is mediated by an unidentified lamina homologous structure in yeast.

Direct evidence for nuclear lamina involvement in chromatin organization comes from genetic analysis of lamina genes. Chromatin attachment to the peripheral nuclear lamina is abnormal in human emerin-deficient cells [120], in mouse cells lacking lamin A/C [121, 122], in *Drosophila* cells lacking lamin Dm_0 [123] and in *C. elegans* cells lacking Ce-lamin [12].

The nuclear lamina and the regulation of specific transcription factors

The interaction of transcription factors or chromatin-remodeling factors with the nuclear lamina supports a role for the nuclear lamina in gene regulation. There are now many examples of specific transcription factors that bind lamins or lamin-associated proteins.

GCL is a BTB/POZ-domain transcriptional repressor first identified in *Drosophila* and is required for germline specification [124]. The *gcl* gene is conserved in evolution, and the mouse *gcl* (mGcl) can complement a *Drosophila gcl* mutation [125]. The GCL protein was localized to the vicinity of the NPCs in *Drosophila* [126] and at the nuclear envelope and nucleoplasmic speckles in mammalian cells [127]. mGcl was independently isolated as a binding partner of the DP3α subunit of the E2F-DP transcriptional complex [128] and as a binding partner for LAP2β [127]. Both LAP2β and GCL can directly repress the E2F-DP complex in transient transfection assays. However, full repression of the E2F-DP complex requires both LAP2β and GCL, suggesting that these repressors act cooperatively [127].

LAP2β binds GCL through its β-specific domain [127]. GCL also binds directly to emerin. GCL co-immunoprecipitates with emerin from HeLa cells and forms stable complexes with emerin and lamin A [129]. Interestingly, BAF competes with GCL for binding to emerin, suggesting that emerin forms at least two distinct types of nuclear complexes in vivo [129].

The retinoblastoma $p110^{Rb}$ (pRb) protein controls progression through the cell cycle by repressing E2F transcriptional complexes in a phosphorylation-dependent manner and by recruiting histone deacetylase complexes [130]. The pocket C domain in the hypophosphorylated (repressive) form of pRb binds to the coil 2 domain of lamin A/C both in vivo and in vitro [131–133]. The same domain in lamin A/C binds the MOK2 transcription factor [134] (see below), suggesting that A-type lamins provide docking sites for many transcription factors.

LAP2α binds lamin A/C and also binds tightly to the pocket C (and weakly to the pocket B) regions of pRb. Reduced levels of LAP2α mislocalize pRb. Also, aberrant localization of lamin A/C or LAP2α causes similar redistribution of hypophosphorylated pRb [133], suggesting that hypophosphorylated pRb is anchored by binding to LAP2α-lamin A/C complexes.

MOK2 is a transcription factor with a Krupper/TFIIIA-related zinc-finger domain that binds DNA and RNA and represses the interphotoreceptor retinoid-binding protein gene [135, 136]. Human MOK2 also binds lamin A/C in vitro and colocalizes with lamin A/C in vivo [134]. It remains to be seen if repression by MOK2 requires its colocalization with lamins.

Familial partial lipodystrophy (FPLD) is an autosomal dominant inherited disease caused by mutations in the tail domain of lamin A [137, 138]. Sterol regulatory element binding proteins 1 and 2 (SREBP1 and SREBP2) are activators of the complete program of cholesterol and fatty-acid biosynthesis in the liver [139]. The N-terminal domain of SREBP1 (residues 227–487) can bind in vitro to the tail domain of lamin A. Lipodystrophy-causing mutations in lamin A reduce that binding [140]. It is important to test whether the SREBP1-lamin A interaction occurs in vivo, and whether this might explain the disease mechanism.

The *C. elegans* MAN1 gene (Ce-MAN1) binds both Ce-lamin and Ce-BAF. Ce-MAN1 is an essential gene. Elimination of Ce-MAN1 together with Ce-emerin causes chromatin condensation in interphase and anaphase chromatin bridges in mitosis [141], leading to early embryonic lethality. In *Xenopus*, the MAN1 homolog (XMAN1) has an important role in antagonizing the bone morphogenetic protein (BMP) pathway [142].

Several other transcription factors show a correlation between nuclear peripheral localization and transcriptional activity. In young or immortalized cells, Oct-1 represses the collagenase gene and colocalizes with B-type lamins

[143]. During senescence, Oct-1 dissociates from the nuclear periphery, and collagenase gene expression is highly induced. It was therefore suggested that Oct-1 must associate with the nuclear lamina to be repressive [143]. In pancreatic beta cells, the insulin promoter factor-1 (IPF-1/PDX-1) transactivates the insulin promoter. At low extracellular glucose concentration, the inactive IPF-1/PDX-1 is localized to the nuclear periphery, whereas at high glucose levels it rapidly translocates to the nucleoplasm and stimulates the transcription of the insulin gene [144]. Sp3 is a GC box-binding transcription factor that can function as either a transcriptional activator or a repressor, depending on the gene. Sp3-dependent transcriptional activity is repressed by SUMO-1 (small ubiquitin-like midifier 1) modification of Sp3. Endogenous Sp3 is sumoylated and localized to the nuclear periphery and in nuclear dots, whereas removal of the SUMO-1 modification converts Sp3 to a strong activator with a nucleoplasmic distribution [145].

Interestingly, in all known cases the association of the transcription factor with lamins leads to transcriptional repression. Further studies are needed to understand the mechanism of repression conferred by the nuclear lamina.

RNA polymerase II activity requires nuclear lamins

Recent studies provided direct evidence for nuclear lamina involvement in RNA polymerase II (Pol II)-dependent transcription [21, 43]. Expression of a dominant-negative lamin mutant lacking the head domain disrupts lamin A filaments and inhibits Pol II activity in both mammalian cells and transcriptionally active embryonic nuclei from *Xenopus laevis*. This transcriptional inhibition is specific to Pol II, does not affect Pol I or Pol III, and involves redistribution of the TATA-binding protein [21]. Likewise, expression of modified lamin A or C in HeLa cells affects the distribution of internal lamins and down-regulates Pol II transcription [43]. In addition, treatment of HeLa cells with the Pol II inhibitors α-amanitin or 5,6-dichlorobenzimidazole riboside (DRB) causes lamin A to aggregate, whereas subsequent removal of DRB allows Pol II to reactivate and causes nucleoplasmic, but not peripheral, lamins to properly re-localize [43]. The latter results suggest that Pol II transcription is organized by internal (nucleoplasmic) lamins and does not involve the peripheral lamins.

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