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COMMENTARY

Lamins in the nuclear interior – life outside the lamina

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ABSTRACT

Nuclear lamins are components of the peripheral lamina that define the mechanical properties of nuclei and tether heterochromatin to the periphery. A-type lamins localize also to the nuclear interior, but the regulation and specific functions of this nucleoplasmic lamin pool are poorly understood. In this Commentary, we summarize known pathways that are potentially involved in the localization and dynamic behavior of intranuclear lamins, including their post-translational modifications and interactions with nucleoplasmic proteins, such as lamina-associated polypeptide 2α (LAP2α; encoded by *TMPO*). In addition, new data suggest that lamins in the nuclear interior have an important role in chromatin regulation and gene expression through dynamic binding to both hetero- and euchromatic genomic regions and promoter subdomains, thereby affecting epigenetic pathways and chromatin accessibility. Nucleoplasmic lamins also have a role in spatial chromatin organization and may be involved in mechanosignaling. In view of this newly emerging concept, we propose that the previously reported cellular phenotypes in lamin-linked diseases are, at least in part, rooted in an impaired regulation and/or function of the nucleoplasmic lamin A/C pool.

KEY WORDS: Lamins, LAP2α, LAP2, TMPO, Chromatin regulation, Lamina-associated domain, Lamin-linked diseases

Introduction

Lamins are intermediate filament proteins in the nucleus of metazoan cells (Gruenbaum and Foisner, 2015), which – together with inner nuclear membrane proteins (Korfali et al., 2012; Wilson and Foisner, 2010; Worman and Schirmer, 2015) – form the nuclear lamina, a filamentous protein meshwork at the nuclear periphery. The lamina defines the mechanical properties of the nucleus (Dahl et al., 2004; Lammerding et al., 2006; Swift et al., 2013, and reviewed in Cho et al., 2017; McGregor et al., 2016; Osmanagic-Myers et al., 2015) and is involved in chromatin organization (Guelen et al., 2008; Kind et al., 2015; Meuleman et al., 2013; Peric-Hupkes et al., 2010; and reviewed in Amendola and van Steensel, 2014; Gonzalez-Sandoval and Gasser, 2016).

Mammals express A-type- and B-type-lamins. The main B-type lamins, lamin B1 and B2, are encoded by *LMNB1* and *LMNB2*, respectively, and the main A-type lamins, lamins A and C, by a single gene, *LMNA* (Gruenbaum and Foisner, 2015). B-type lamins are ubiquitously expressed in embryonic and adult cells (Yang et al., 2011), whereas A-type lamins are only expressed at low levels in embryonic stem cells and in the inner cell mass of blastocysts (Eckersley-Maslin et al., 2013), but are significantly upregulated during differentiation (Constantinescu et al., 2006; Rober et al., 1989; Stewart and Burke, 1987). All lamins exhibit an intermediate filament protein-type domain organization with an N-terminal head, a central rod and a globular C-terminal tail (Gruenbaum and Medalia, 2015), which contains a nuclear localization signal, an IgG fold and – for B-type lamins and lamin A, a Caax motif (where C is Cys, a is an aliphatic amino acid and x can be any amino acid) at the C-terminus. The Caax motif undergoes several sequential post-translational modifications (Rusinol and Sinensky, 2006), including addition of a farnesyl group to its Cys by a farnesyltransferase, cleavage of the aax tripeptide by the zinc metalloprotease Zmpste24, and carboxy-methylation of the C-terminal farnesylated Cys by isoprenylcysteine carboxyl methyltransferase (Icmt). Whereas B-type lamins remain permanently farnesylated and carboxy-methylated and, are thus, tightly associated with the nuclear membrane (Gerace and Blobel, 1980), lamin A undergoes an additional cleavage step that is catalyzed by Zmpste24 and removes the 15 C-terminal amino acids including the farnesylated Cys. Thus, mature lamin A and lamin C, which lacks a C-terminal Caax motif, are not farnesylated and carboxy-methylated, rendering them more soluble during mitosis and interphase (Dechat et al., 2004, 2000; Kochin et al., 2014; Moir et al., 2000).

Although some studies reported that B-type lamins (Moir et al., 1994; Shimi et al., 2008) and *Caenorhabditis elegans* lamin (Liu et al., 2000; Wiesel et al., 2008) can form stable structures in the nuclear interior, A-type lamins in particular were shown to exist in different states within distinct nuclear compartments as 3.5-nm-thick lamin filaments at the peripheral lamina, as resolved by cryo-electron tomography (Turgay et al., 2017), as well as a highly dynamic pool in the nucleoplasm (Dechat et al., 2010; Gesson et al., 2014). These non-lamina-associated lamins in the nuclear interior have long been observed and considered to be a transient pool of lamins before their assembly into the lamina but more-recent studies reported important novel functions of nucleoplasmic lamins that are fundamentally different from those they exert within the lamina. In this Commentary, we discuss recent advances in the understanding of how the lamina-independent pool of lamins is regulated, and highlight their newly emerging functions in chromatin organization, gene expression, mechanical regulation, differentiation and disease.

Dynamics and assembly state of lamins in the nuclear interior

Whereas lamins at the nuclear periphery form a meshwork of filaments (Goldberg et al., 2008; Shimi et al., 2015, 2008; Turgay et al., 2017; Xie et al., 2016), the assembly state of nucleoplasmic lamins remains elusive. Early electron microscopic studies suggested the existence of lamin filaments throughout the nucleus (Hozak et al., 1995). However, fluorescence microscopy using antibodies or fluorescently tagged lamins revealed a rather unstructured nucleoplasmic 'veil' of A-type lamins (Broers et al., 1999; Dechat et al., 2000; Moir et al., 2000; Naetar et al., 2008), or the presence of intranuclear lamin foci and short fibrous structures (Bridger et al., 1993; Kennedy et al., 2000; Shimi et al., 2008).

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Fluorescence recovery after photobleaching (FRAP) (Broers et al., 1999; Moir et al., 2000) or fluorescence correlation spectroscopy (FCS) (Shimi et al., 2008) of fluorescently tagged lamins showed that nucleoplasmic lamin complexes are considerably more mobile than peripheral lamins. Indeed, a recent study, in which continuous photobleaching of GFP-lamin A in the nuclear interior was performed, concluded that ∼60% of lamin A is highly mobile, while the remaining ∼40% is immobile and likely to be bound to stable structures (Bronshtein et al., 2015). Furthermore, biochemical analyses have shown that intranuclear A-type lamins can be easily extracted with detergents (Kolb et al., 2011; Naetar et al., 2008), indicating that their assembly state is less complex, possibly comprising dimers and short polymers, as compared with lamin filaments at the nuclear periphery. On the basis of FCS diffusion coefficients, the molecular mass was estimated to be ∼1.3 MDa for a fast-moving, and ∼2.9 GDa for a slow-moving lamin A fraction in the nuclear interior (Shimi et al., 2008), but these molecular masses probably correspond to lamins in complex with other intranuclear binding partners. Together, the current data suggest that the majority of A-type lamins in the nuclear interior exist in a mobile low-assembly state, which is very different from the filamentous, interwoven, static structures they form at the nuclear periphery (Turgay et al., 2017).

As much as the exact assembly state of nucleoplasmic A-type lamins is unclear, the molecular mechanisms that regulate lamina-independent lamins are poorly understood and many questions remain open, such as: where does this intranuclear lamin pool originate, what molecular marks or modifications define lamins in the nucleoplasm, what prevents them from being assembled into the peripheral lamina? We will address these questions in the following sections.

Origin of lamins in the nuclear interior

As for the origin of the nucleoplasmic lamin pool, several non-exclusive scenarios can be envisaged. The first scenario is linked to the highly dynamic behavior of lamins during cell division (Fig. 1). The lamina disassembles at the onset of mitosis through phosphorylation of lamins by mitotic kinases at sites that flank the central rod (Heald and McKeon, 1990; Kuga et al., 2010; Peter et al., 1990; Ward and Kirschner, 1990). In anaphase/telophase, lamins start to re-assemble around segregated sister chromatids in a (de-)phosphorylation-dependent manner (Steen and Collas, 2001; Thompson et al., 1997). However, B-type lamins stay membrane-associated throughout the cell cycle, whereas A-type lamins are dispersed throughout the cytoplasm in mitosis (Gerace and Blobel, 1980) and accumulate in the nuclear interior in early G1 phase before they assemble into the lamina throughout G1 (Dechat et al., 2004, 2007; Moir et al., 2000). Thus, the lamin A/C pool in the nuclear interior is most prominent during G1 and remains low in S and G2 phase. Interestingly, A-type lamins are undetectable in the nuclear interior in non-cycling, quiescent, senescent or terminally differentiated cells (Markiewicz et al., 2005; Naetar and Foisner, 2009; Naetar et al., 2007). Overall, in this cell-cycle-linked pathway, the lamina-independent pool of lamins observed in G1 is generated in the preceding mitosis and a fraction of it is prevented to assemble into the lamina throughout the cell cycle. Mechanisms that may prevent lamin assembly involve post-translational modifications and specific interactions as discussed below.

Although nucleoplasmic lamin A generated in the preceding mitosis represents fully processed, mature lamin A, it is conceivable that also newly synthesized pre-lamin A contributes to the nucleoplasmic lamin pool (Fig. 1). This model is supported by studies showing that microinjected recombinant pre-lamin A accumulates in nucleoplasmic foci before it assembles at the peripheral lamina (Goldman et al., 1992), and ectopically expressed GFP-tagged pre-lamin A accumulates in nucleoplasmic foci upon treatment with farnesyltransferase inhibitors (Barrowman et al., 2008; Casasola et al., 2016; Lutz et al., 1992). These observations are consistent with the idea that processing of pre-lamin A, including farnesylation and concurrent recruitment to the nuclear membrane as well as subsequent modifications at the membrane, occurs mainly in the nucleus (Barrowman et al., 2008). Zmpste24 and Icmt1 are endoplasmic reticulum (ER) membrane proteins, but they also reside in the inner nuclear membrane (Barrowman et al., 2008). Altogether, non-farnesylated pre-lamin A may initially localize to the nuclear interior before its recruitment to the membrane, final processing and assembly into the lamina. However, because antibodies that specifically recognize pre-lamin A only detect very low levels of endogenous pre-lamin A in the absence of farnesyltransferase inhibitors (Casasola et al., 2016), unprocessed pre-lamin A is unlikely to contribute significantly to the nucleoplasmic pool of A-type lamins throughout interphase.

A third mechanism, possibly explaining the origin of lamins in the nuclear interior, is the dynamic exchange of lamins between the nucleoplasmic pool and the lamin filaments of the lamina during interphase. However, as lamins in the lamina show only very low levels of fluorescence recovery in FRAP experiments (Broers et al., 1999; Moir et al., 2000), this scenario appears to be unlikely, although a slow exchange of lamin subunits between these pools cannot be completely excluded.

Regulation of A-type lamins in the nuclear interior

Independently of the origin of nucleoplasmic lamins, their localization is likely to be tightly regulated, raising the question: which pathways are involved in this regulation and what prevents incorporation of nucleoplasmic lamins into peripheral filaments?

Lamins have been shown to undergo several types of post-translational modification, including phosphorylation, *O*-GlcNAcylation, sumoylation, acetylation and ubiquitylation (Simon and Wilson, 2013), and these represent obvious potential mechanisms to regulate lamins (Fig. 1). Phosphorylation of human lamin A/C at Ser22 in the N-terminal head and Ser392 proximal to the C-terminal end of the rod (and analogous sites in lamin B) is required for lamina disassembly during mitosis (Heald and McKeon, 1990). These amino acid residues are targeted by cyclin-dependent kinase 1 (Cdk1) (Ward and Kirschner, 1990) and, possibly, other kinases, including Cdk5 (Chang et al., 2011), Cdk4 and Cdk6 (Moiseeva et al., 2016), as well as extracellular signal-regulated kinases 1 and 2 (Erk1 and Erk2; officially known as MAPK2 and MAPK1, respectively) (Peter et al., 1992), which may target these sites also during interphase (Kochin et al., 2014). Furthermore, lamin A variants with phosphomimetic Ser-to-Asp mutations at these sites localized to the nuclear interior in interphase cells and were highly mobile and easily extractable with non-ionic detergents (Kochin et al., 2014), suggesting that phosphorylation at previously known mitosis-specific sites regulates lamin assembly state and intranuclear localization also during interphase. As phosphorylation of A-type lamins in interphase has been linked to a lamin-mediated mechanosignaling response (Buxboim et al., 2014) (see below), it is tempting to hypothesize that phosphorylation of lamin A/C regulates the amount of nucleoplasmic lamins, depending on both cell-intrinsic (e.g. phase of the cell cycle, differentiation), as well as environmental (e.g. matrix stiffness) cues.

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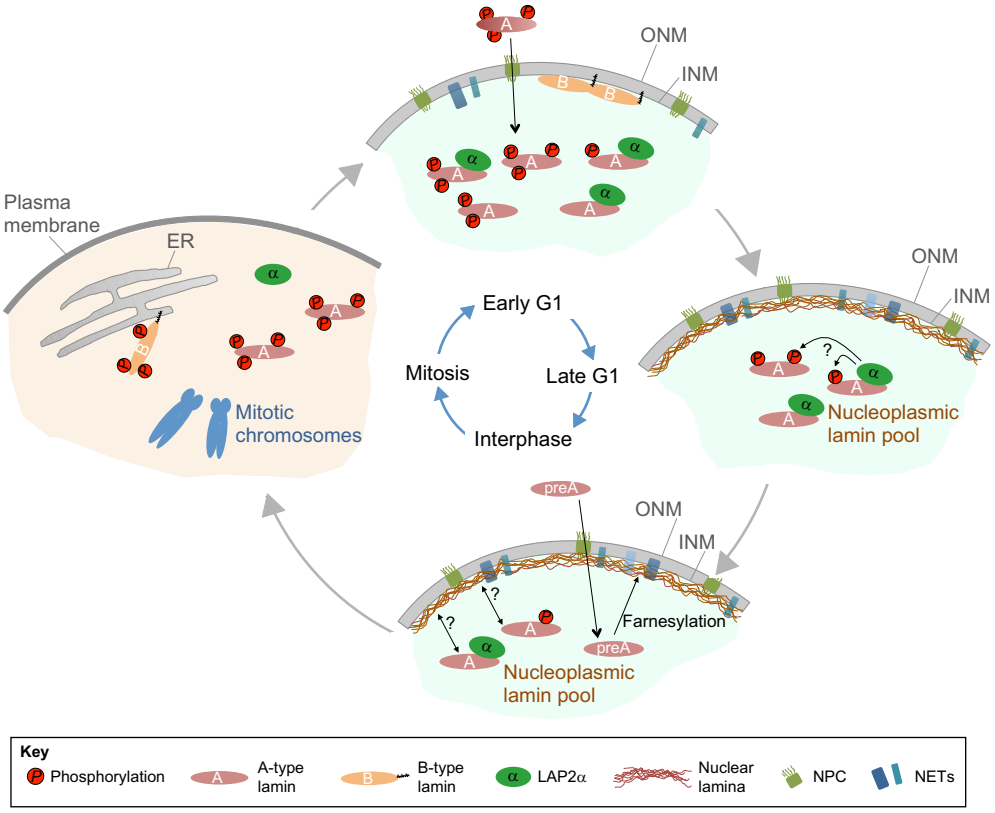

Fig. 1. Possible origin and regulation of nucleoplasmic lamins. Nucleoplasmic lamins A/C could be generated during mitosis by phosphorylation-dependent disassembly of the lamina. Soluble lamins A/C re-enter the newly forming nuclei in early G1, initially localizing to the nuclear interior, where they might begin to form complexes with LAP2α (α). Subsequently, a pool of A-type lamins is prevented to assemble in late G1 and in interphase, possibly involving their post-translational modification and/or binding to LAP2α. A dynamic exchange of lamins A/C between the lamina and the nucleoplasmic pool cannot be entirely excluded. Alternatively, newly synthesized pre-lamin A (preA) might transiently localize to the nuclear interior before its farnesylation, and further processing and assembly at the periphery. ER, endoplasmic reticulum; NPC, nuclear pore complex; ONM, outer nuclear membrane; INM, inner nuclear membrane; NETs, nuclear envelope transmembrane proteins.

For most of the other post-translational modifications of lamins, the functional implications remain unclear (Simon and Wilson, 2013). Sumoylation at Lys201 affects lamin A localization and assembly (Zhang and Sarge, 2008), and a SUMO-interacting motif in the lamin A IgG-fold that might mediate interaction with other sumoylated proteins is required for postmitotic dephosphorylation of lamin A and its accumulation on chromosomes (Moriuchi et al., 2016).

Localization of lamin A in the nuclear interior is also regulated by the specific lamin A/C-binding partner lamina-associated polypeptide 2 α (LAP2α; also known as thymopoietin alpha, TMPO) (Fig. 1). LAP2α is one of six splice variants encoded by the mammalian *LAP2* (*Tmpo*) gene (Berger et al., 1996). Unlike the other isoforms, which are integral inner nuclear membrane proteins, LAP2α localizes throughout the nucleus, where it interacts with A-type lamins (Dechat et al., 2004, 2000; Vlcek et al., 1999). Cells and tissues derived from LAP2α-knockout mice showed significantly reduced levels of lamin A/C in the nuclear interior (Gesson et al., 2016; Naetar et al., 2008) (Fig. 2), and siRNA-mediated knockdown of LAP2α in primary human fibroblasts decreased lamin levels in the nuclear interior (Pekovic et al., 2007). Moreover, low levels of nucleoplasmic A-type lamins in quiescent and differentiated cells correlate with a downregulation of LAP2α (Markiewicz et al., 2005; Naetar et al., 2007). Altogether, these data led to the hypothesis that LAP2α is necessary to maintain A-type lamins in the nucleoplasm in a soluble, mobile and low-assembly state, but the molecular mechanisms are not completely understood. One possibility is that binding of LAP2α to the lamin A/C tail (Dechat et al., 2000) may directly impair lamin assembly. Alternatively, binding of LAP2α to lamin A/C could be linked to post-translational modifications of lamins, which in turn also affect lamin assembly. Two scenarios are plausible in this regard: LAP2α binding could facilitate lamin A/C phosphorylation or, vice versa, phosphorylation of lamin A/C or LAP2α, could influence their mutual interaction. Another open question relates to when exactly during the cell cycle LAP2α–lamin A/C complexes form. Immunopreciptation analyses suggest that binding occurs only after mitosis (Dechat et al., 2000). Interestingly, the interaction of importin α with *Xenopus* lamin B3 was also found to inhibit lamin assembly *in vitro* (Adam et al., 2008) and was suggested to prevent assembly of lamins before their nuclear import after mitosis.

Overall, the lamina-independent lamins in the nuclear interior may have fundamentally different properties compared to lamins at the nuclear periphery, as well as specific modes of their regulation. As discussed below, their increased mobility, dynamic nature and

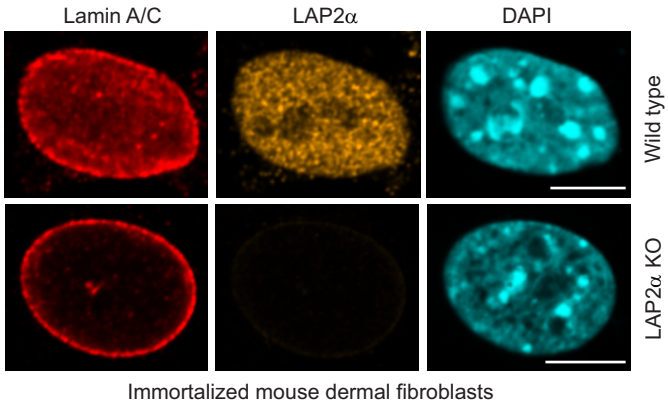

Fig. 2. LAP2α is necessary to maintain nucleoplasmic lamins A/C. Mouse immortalized dermal fibroblasts that are either wild type or knockout (KO) for LAP2α were processed for immunofluorescence microscopy by using antibodies against LAP2α and lamins A/C. DNA was stained using DAPI. Confocal microscopy images reveal a strong reduction of nucleoplasmic lamin staining in the absence of LAP2α. Scale bar: 10 µm.

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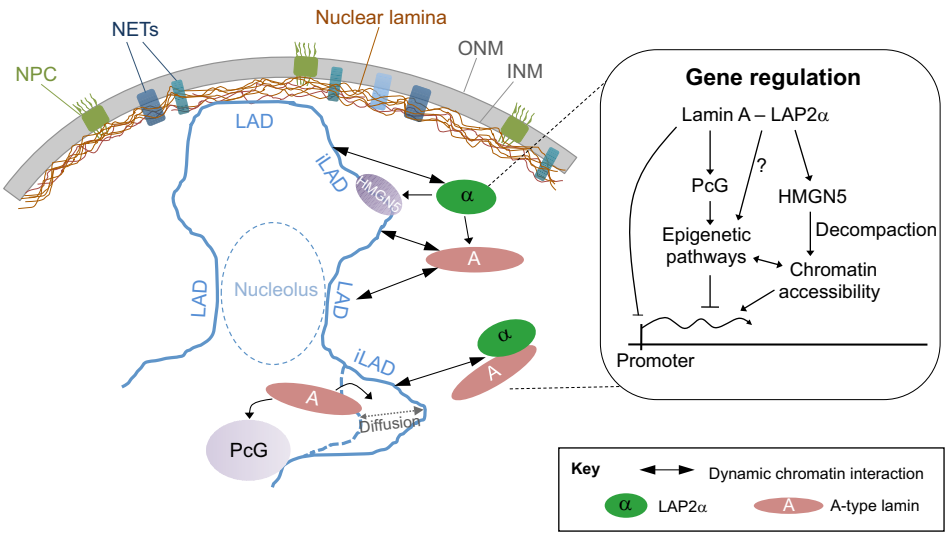

Fig. 3. Functions of lamins in chromatin organization and gene expression. Lamins in the lamina associate with heterochromatic genomic regions called lamina-associated domains (LADs). Lamins A/C in the nuclear interior interact with internal LADs, as well as with open genomic regions outside of LADs (iLADs), and regulate epigenetic pathways by affecting polycomb (PcG) complexes and/or chromatin compaction through high mobility group nucleosome binding domain 5 (HMGN5). Moreover, nucleoplasmic lamins also affect chromatin diffusion and sturdiness. Their role in regulation of gene expression could be either indirect, by affecting chromatin accessibility and epigenetic modifications or, alternatively, is exerted by a direct association with promoter regions (illustrated in the inset). iLAD, interLAD; NPC, nuclear pore complex; ONM, outer nuclear membrane; INM, inner nuclear membrane; NETs, nuclear envelope transmembrane proteins.

low-assembly state, therefore, enable a profoundly different set of functions for this pool compared to those at the nuclear periphery.

Peripheral and nucleoplasmic A-type lamins associate with and regulate chromatin

Many studies have shown direct binding of lamins to DNA (Luderus et al., 1992; Stierle et al., 2003; Zhao et al., 1996), chromatin, nucleosomes and histones (Goldberg et al., 1999; Mattout et al., 2007; Taniura et al., 1995; Yuan et al., 1991), but the physiological relevance of these interactions is still unclear. DNA adenine methyltransferase identification (DamID) studies using lamin-Dam fusion proteins, which add methyl groups to adenine at GATC sequences in genomic regions near the lamin fusion proteins, have identified large, up to 10 Mb long heterochromatic domains associated with lamins (Guelen et al., 2008; Kind et al., 2015; Meuleman et al., 2013; Peric-Hupkes et al., 2010; Pickersgill et al., 2006; van Steensel and Kind, 2014). These chromatin domains, termed lamina-associated domains (LADs) (Fig. 3), contain many intergenic regions and mostly transcriptionally inactive genes, and were enriched in the repressive histone marks H3K9me2/3 and H3K27me3. LADs were initially reported to localize at the nuclear periphery, but single-cell analyses revealed that only a subset of LADs in the mammalian genome localizes to the lamina, whereas they are stochastically redistributed during the cell cycle between the lamina and the nuclear interior, where they tend to localize around nucleoli (Kind et al., 2013; van Steensel and Kind, 2014). A number of studies have shown that anchoring genes to the lamina correlates with tissue-specific gene repression (Gonzalez-Sandoval et al., 2015; Mattout et al., 2011; Meister et al., 2010; Robson et al., 2016; Therizols et al., 2014; Towbin et al., 2010) and dosage compensation (Snyder et al., 2016), leading to the concept that tethering of genomic regions to the lamina is required for stable repression of genes during differentiation (Amendola and van Steensel, 2014; Harr et al., 2016; Mattout et al., 2015).

Although one study reported that the targeting of chromatin to the lamina requires A-type lamins (Harr et al., 2015), a second found that association of heterochromatic LADs to the nuclear periphery occurs in the absence of all lamins in embryonic stem cells (Amendola and van Steensel, 2015). This is not surprising as many proteins of the inner nuclear membrane bind to (hetero-)chromatin. These include the lamin B receptor (LBR) that, directly, binds to H4K20me2 through its Tudor domain (Hirano et al., 2012) and, indirectly, through heterochromatin protein 1 (HP1; officially known as CBX5) (Ye and Worman, 1996), as well as several nuclear envelope transmembrane proteins (NETs) (de Las Heras et al., 2017; Robson et al., 2016; Zuleger et al., 2013), including the LEM proteins (Brachner and Foisner, 2011; Lin et al., 2000). The latter comprise a protein family that is characterized by the presence of the LAP2–emerin–MAN1 (LEM) domain, a 40-amino-acid-long bi-helical region that binds to the DNA crosslinker barrier to autointegration factor (BAF) (Cai et al., 2001, 2007). Most of the LEM proteins are integral components of the inner nuclear membrane and some, such as emerin and LEM2, require lamin A for their correct localization (Brachner et al., 2005; Vaughan et al., 2001). Thus, the association of the lamina with chromatin is likely to be mediated by complexes formed between lamins and lamin-binding proteins at the inner nuclear membrane. This hypothesis is supported by a study that revealed redundant roles for LBR and for lamin A-LEM protein complexes in peripheral heterochromatin tethering (Solovei et al., 2013). However, there is probably a complex functional redundancy of LEM proteins in chromatin tethering, and other NETs might contribute to peripheral chromatin tethering as well (Thanisch et al., 2017).

In view of the fact that A-type lamins localize throughout the nuclear interior, where they interact with the non-membrane-bound LEM protein LAP2α (Dechat et al., 2000; Naetar et al., 2008), it is not surprising that they also associate with chromatin throughout the nucleus (Gesson et al., 2016) (Fig. 3). Nucleoplasmic lamin A/C could interact with intranuclear LADs, and, indeed, a study has proposed that interaction of LADs with lamin A/C in the nuclear interior modulates their frequency of association with lamins at the nuclear periphery (van Steensel and Kind, 2014). Furthermore, binding of A-type lamins to LADs has recently been shown to change during adipogenic differentiation in response to metabolically regulated O-GlcNAcylation of histones, thereby contributing to differentiation-specific repression of genes (Ronningen et al., 2015).

Surprisingly, we recently found that A-type lamins in the nuclear interior also associate with euchromatic genomic regions outside of LADs, which overlap with those that are bound by LAP2α (Gesson et al., 2016). Although DamID yielded mostly heterochromatic LADs associated with A-type lamin complexes (Guelen et al.,

2008), chromatin immunoprecipitation combined with deep sequencing (ChIP-seq) detected additionally euchromatic regions that were associated with A-type lamins (Gesson et al., 2016; Lund et al., 2015). It is still unclear why the use of different assays to assess chromatin association yields different results and, currently, one can only speculate about potential explanations; one possibility is that DamID favors the identification of stable interactions between lamins and chromatin that are likely to occur at the lamina. Interestingly, we found that – when used in ChIP – a lamin A/C antibody that preferentially binds to the mobile nucleoplasmic pool mostly pulls down euchromatic regions, whereas another antibody that prominently detects lamina-associated lamin A/C preferentially precipitates heterochromatin (Gesson et al., 2016). Furthermore, we also demonstrated that the procedure for preparation of chromatin for ChIP can greatly influence the results. Whereas moderate shearing of chromatin resulted in open euchromatic regions being enriched as analyzed by lamin A ChIP-seq, the precipitation of heterochromatin requires more-rigid chromatin shearing (Gesson et al., 2016). Similar differences have been reported in a lamin-A –ChIP-seq protocol that used chromatin sonication versus micrococcal nuclease (MNase) treatment (Lund et al., 2015).

What are the specific functions of the interaction between A-type lamins and chromatin in the nuclear interior? Although interactions with LADs may contribute to gene repression, similar to association of LAD and lamina at the periphery (van Steensel and Kind, 2014), the dynamic association of A-type lamins with euchromatic regions may serve more-complex functions in gene regulation (Fig. 3). Interestingly, loss of LAP2α has dramatic effects on the association of lamin A/C with chromatin, shifting the euchromatin-bound lamin A fraction towards heterochromatic LADs, which correlates with changes in active as well as repressive histone marks throughout the genome (Gesson et al., 2016). Thus, it is tempting to speculate that the dynamic pool of lamin A/C affects epigenetic pathways and chromatin accessibility, and that this role is affected by LAP2α. In line with this model, LAP2α has also been shown to influence genome-wide chromatin association of high mobility group nucleosome binding domain 5 (HMGN5), a nucleosome-binding protein involved in chromatin decompaction (Furusawa et al., 2015; Zhang et al., 2013). It remains unclear, however, whether the association to chromatin by lamin A/C or HMGN5 together with LAP2α actively generates accessible chromatin, or whether these proteins preferentially bind to “open” chromatin and keep it in an “open” state. Nucleoplasmic lamins are also required for the correct assembly of polycomb protein (PcG) foci, which are involved in epigenetic repression of developmentally regulated genes (Cesarini et al., 2015; Marullo et al., 2016), suggesting that lamins affect chromatin accessibility through the regulation of epigenetic modifier complexes. In addition to the potential role of nucleoplasmic lamin A/C in genome-wide chromatin organization, a study using lamin A ChIP combined with promoter array hybridization revealed the binding of lamin A/C to specific promoter subregions that regulate gene expression during adipogenic differentiation, depending on the epigenetic profiles at the promoter (Lund et al., 2013). Lamin A/C also binds to muscle-specific promoters in myoblasts (Athar and Parnaik, 2015), but the underlying mechanism for how this interaction contributes to gene regulation is unknown.

Besides these potential roles of nucleoplasmic lamins A/C in gene regulation, they may also be involved in the spatial organization of chromatin throughout the nucleus. In line with this notion, chromatin motion in the nuclear interior was shown to be restricted by lamin A/C complexes. Diffusion of several tested genomic loci was slow and anomalous in wild-type cells, but diffusion transformed to a faster and normal pattern in lamin A/C-deficient cells (Bronshtein et al., 2015), suggesting that nucleoplasmic lamin A-mediated crosslinking of chromatin restricts its diffuson. Similarly, lamin A expression upon embryonic stem cell differentiation regulates chromatin plasticity and dynamics (Melcer et al., 2012). Lamin A and LAP2α were also found to stabilize telomeres by affecting telomeric-repeat-binding factor 2 (TRF2)-dependent formation of interstitial t-loops (Wood et al., 2014), or by affecting telomere positioning and regulation (Chojnowski et al., 2015; Gonzalez-Suarez et al., 2009).

In summary, although essential functions have been ascribed to the peripheral lamina in the organization of chromatin, the specific functions of nucleoplasmic lamins in chromatin organization are only beginning to emerge. Although most previous studies did not specifically investigate these two lamin A/C pools, it seems clear that nucleoplasmic lamins bind to more transcriptionally active, open chromatin and may, thus, be more relevant for directly controling gene expression compared to the peripheral pool.

Mechanical functions of lamins

Several exciting studies demonstrate that A-type lamins in the nuclear lamina are involved in mechanosensing and mechanosignaling (Cho et al., 2017; Osmanagic-Myers et al., 2015). While B-type lamins are important for elasticity of the nucleus, A-type lamins contribute to nuclear stiffness (Stephens et al., 2017; Swift et al., 2013) and impair cell migration through micron-scale pores (Denais et al., 2016; Harada et al., 2014).

It is still unclear, whether and how A-type lamins in the nuclear interior contribute to the response of nuclei to mechanical forces, but there are some observations that point to such a function. The compactness of the genome affects nuclear sturdiness and deformability of the nucleus (Bustin and Misteli, 2016) Euchromatin and heterochromatin levels were shown to modulate the stiffness of isolated nuclei in response to small extensions (<3 µm), while peripheral lamin A controls nuclear strain stiffening at large extensions (Stephens et al., 2017). Furthermore, overexpression of nucleosome-binding HMGN5 in cardiomyocytes has been shown to cause decompaction of chromatin as well as nuclear deformation (Furusawa et al., 2015). As LAP2α and nucleoplasmic lamin A affect the association between HMGN5 and chromatin (Zhang et al., 2013) and also chromatin mobility (Bronshtein et al., 2015), it is tempting to speculate that structures comprising A-type lamins and LAP2α contribute to the mechanical properties of the nucleus indirectly through their effect on spatial chromatin organization. In line with this hypothesis, a study that used genetically engeneered designed ankyrin-repeat proteins (DARPins) that disassemble lamins in living cells showed that these cells have a higher nuclear stiffness compared to *LMNA*-knockout cells (Zwerger et al., 2015). However, this study also showed that nuclei with disassembled lamins are considerably softer than control nuclei in which the majority of lamins assembled at the nuclear lamina, suggesting that the peripheral lamina is particularly relevant for nuclear stiffness, whereas nucleoplasmic lamins can fine-tune the mechanical response of nuclei through changes in chromatin organization.

Interestingly, a reduction of mechanical strain applied to nuclei causes changes in lamin structure and phosphorylation (Bera et al., 2014; Buxboim et al., 2014) that, in turn, lead to an increase in lamin A levels in the nuclear interior. Thus, the strain-mediated reorganization of A-type lamins between the lamina and the nuclear interior might also fine-tune the response of cells to changes

in external strain and translate these into gene expression changes. At high mechanical strain, lamin A assembles at the nuclear lamina, thereby increasing stiffness, whereas at low mechanical strain, stiffness is reduced by solubilization of lamin A in order to reach the 'mechanostat equilibrium' (Osmanagic-Myers et al., 2015). In view of the different roles of the lamina and internal lamins in chromatin organization and gene regulation (see above), the mechanosensing-mediated lamin A reorganization might specifically affect expression of mechanoresponsive genes (Le et al., 2016). Taken together, although peripheral lamins clearly are the main players in mechanosignaling, there is emerging evidence that nucleoplasmic lamins also modulate and fine-tune the mechanical response of the nucleus.

Nucleoplasmic lamins in disease

Over 400 mutations have been described in *LMNA* that are linked to at least four different disease groups, including striated muscle diseases, lipodystrophies and metabolic diseases, peripheral neuropathies, as well as premature aging syndromes – which are collectively termed laminopathies (Schreiber and Kennedy, 2013; Worman, 2012). The molecular mechanisms underlying the different diseases are not fully understood but are, most likely, to be explained by a combination of effects, such as impaired mechanosignaling owing to changes in nuclear stiffness (Davidson and Lammerding, 2014), impaired tissue regeneration due to stem cell defects (Gotzmann and Foisner, 2006; Meshorer and Gruenbaum, 2008), changes in chromatin regulation (Mattout et al., 2015), impaired signaling pathways (Gesson et al., 2014) and genome instability (Gonzalez-Suarez and Gonzalo, 2010).

Disease-causing *LMNA* mutations can affect the functions of both the peripheral and nucleoplasmic pool of A-type lamins and/or cause changes in their respective distribution. When introduced into *C. elegans* lamin, several disease-linked mutations affected *in vitro* assembly of lamin and/or showed its abnormal localization *in vivo*, with some of them being more nucleoplasmic compared to wild-type lamin (Wiesel et al., 2008). In addition, some myopathic lamin mutants, such as the dilated cardiomyopathy-causing *LMNA*-N195K, showed increased nucleoplasmic localization in patient cells (Zwerger et al., 2013). Another prominent example of a dramatic defect in lamin assembly and a complete loss of lamin A/C at the lamina is the *LMNA* delK32 mutation (Bank et al., 2011; Bertrand et al., 2012) that has been linked to severe early-onset congenital muscular dystrophy. The exclusive localization of the lamin delK32 mutant in the nuclear interior causes mechanical defects (Bertrand et al., 2014) but does not affect the functions of nucleoplasmic lamin A/C-LAP2α complexes with regard to the regulation of tissue progenitor cells (Pilat et al., 2013).

In contrast, the heterozygous Hutchinson Gilford progeria syndrome (HGPS)-linked *LMNA G608G* mutation leads to the expression of an incompletely spliced and permanently farnesylated pre-lamin A, called progerin, that remains stably tethered to the peripheral nuclear membrane (Goldman et al., 2004; Vidak and Foisner, 2016). Interestingly, we have previously shown that the wild-type lamin A/C expressed from the unaffected allele is also relocalized to the nuclear periphery, resulting in a nearly complete loss of nucleoplasmic lamins in progeria cells (Vidak et al., 2015). A plethora of cellular and organismal defects in HGPS, including changes in nuclear shape, mechanosensing (Dahl et al., 2006; Verstraeten et al., 2008), epigenetic pathways, chromatin structure (McCord et al., 2013; Shumaker et al., 2006) and signaling (reviewed in Vidak and Foisner, 2016), as well as increased genomic instability (Gonzalo and Kreienkamp, 2015) have mostly been linked to the accumulation of progerin at the nuclear membrane. However, the loss of nucleoplasmic lamins might also contribute to some of these cellular phenotypes. Expression of progerin and reduction of the nucleoplasmic lamin pool correlate with the downregulation of LAP2α, and re-introduction of LAP2α into HGPS cells significantly ameliorates the proliferation defects of these cells (Vidak et al., 2015). Another study found that downregulation of LAP2α in HGPS cells leads to defects in telomere function, probably by changing the epigenetic pathways involved in telomere regulation (Chojnowski et al., 2015). The loss of nucleoplasmic lamin A/C could, like the complete loss of lamin A/C in *LMNA*-knockout cells, lead to increased DNA damage and genome instability (Ghosh et al., 2015; Gibbs-Seymour et al., 2015; Gonzalez-Suarez et al., 2009).

Furthermore, expression of progerin affects tissue stem cell proliferation and differentiation (Espada et al., 2008; Rosengardten et al., 2011; Sagelius et al., 2008; Scaffidi and Misteli, 2008) through impaired Notch (Scaffidi and Misteli, 2008) or Wnt-β-catenin signaling (Espada et al., 2008; Schmidt et al., 2012). Similarly, induced pluripotent stem cells (iPSCs) generated from progeria patient cells were undistinguishable from wild-type controls – probably because of the low or absent expression of lamin A/C and progerin in stem cells – but showed severe abnormalities upon differentiation into some but not all lineages (Zhang et al., 2011). None of these studies mentioned above looked specifically into the potential role that loss of nucleoplasmic lamins in progerin-expressing or lamin-A-knockout cells might have. However, on the basis of studies that used LAP2α-deficient mice, it appears highly likely that the nucleoplasmic complex between lamin A/C and LAP2α influences stem cell biology. We have shown that LAP2α-deficient tissue progenitor cells selectively lose the nucleoplasmic pool of lamin A/C, while leaving the peripheral lamin A/C unaffected (Naetar et al., 2008). Loss of nucleoplasmic lamins in these mice promotes proliferation of tissue progenitor cells and delays their differentiation in skin, colon and muscle (Gotic et al., 2010; Naetar et al., 2008), leading to mild tissue hyperplasia. These proliferation defects in stem and progenitor cells might be linked to impaired retinoblastoma protein pathways or impaired PcG-mediated epigenetic pathways, which were shown to be regulated by LAP2α and nucleoplasmic lamins (Dorner et al., 2006; Marullo et al., 2016). As these phenotypes are reminiscent of some of the above-described progerin-induced phenotypes, it is tempting to speculate that the absence of nucleoplasmic A-type lamins in progeria cells contributes, at least partially, to the observed stem cell phenotypes in HGPS.

In summary, the past decades have revealed many novel and important findings regarding the disease phenotypes and underlying mechanisms of laminopathies. Although most studies did not specifically address the role of nucleoplasmic versus peripheral lamins in the development of disease phenotypes, an increasing number of more-recent studies clearly point to a possible causative role of lamins in the nuclear interior.

Conclusions and perspectives

From the recent studies discussed here, it becomes increasingly clear that lamins have an important 'life' outside of the lamina, with exciting unique nuclear functions. Many of these functions, however, are only incompletely understood. A bottleneck for studying nucleoplasmic lamins is the lack of suitable cell and animal models. *Lmna*-knockout mice lack both peripheral and nucleoplasmic lamins, and it is difficult to assign the observed phenotypes to the loss of a specific pool. LAP2α-deficient mice

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(Naetar et al., 2008), mice that express assembly-deficient lamin A mutants (Bertrand et al., 2012) or cells that express lamin-disassembling DARPins (Zwerger et al., 2015), are probably the best experimental systems currently available, but these proteins or reagents might have additional lamin-independent or dominant-negative effects. Thus, the identification and development of new tools to specifically analyze lamins in the nuclear interior and their functions represent one of the key future challenges that are needed to unravel specific functions and roles of nucleoplasmic lamins in laminopathic diseases.

Competing interests
The authors declare no competing or financial interests.

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