Nuclear Lamins

Thomas Dechat¹, Stephen A. Adam¹, Pekka Taimen², Takeshi Shimi¹,
and Robert D. Goldman¹

¹Department of Cell and Molecular Biology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611

²Department of Pathology, University of Turku, Kiinamyllynkatu 10 20520 Turku, Finland

Correspondence: r-goldman@northwestern.edu

The nuclear lamins are type V intermediate filament proteins that are critically important for the structural properties of the nucleus. In addition, they are involved in the regulation of numerous nuclear processes, including DNA replication, transcription and chromatin organization. The developmentally regulated expression of lamins suggests that they are involved in cellular differentiation. Their assembly dynamic properties throughout the cell cycle, particularly in mitosis, are influenced by posttranslational modifications. Lamins may regulate nuclear functions by direct interactions with chromatin and determining the spatial organization of chromosomes within the nuclear space. They may also regulate chromatin functions by interacting with factors that epigenetically modify the chromatin or directly regulate replication or transcription.

A filamentous layer located between the inner nuclear membrane (INM) and peripheral heterochromatin was evident even in early electron microscopic studies of vertebrate cell nuclei (Fawcett 1966). This layer, later termed the nuclear lamina, is also found to be closely associated with nuclear pore complexes (NPCs) and contains three major structurally related polypeptides (Aaronson and Blobel 1975). These proteins are named nuclear lamins A, B, and C according to their molecular weights (Gerace and Blobel 1980). Further biochemical characterization and cDNA cloning of the nuclear lamins classifies them as type V intermediate filament proteins (Goldman et al. 1986; McKeon et al. 1986).

STRUCTURE AND BIOCHEMICAL PROPERTIES OF NUCLEAR LAMINS

Lamin Isoforms and Expression Patterns

Lamins are present in all metazoans examined to date ranging from hydra to human, but are not found in unicellular organisms and plants (Cohen et al. 2001; Melcer et al. 2007). Extensive characterization in several model organisms including humans, mice, frogs, fruit flies and nematodes shows that their properties are shared across species (Melcer et al. 2007; Dechat et al. 2008b). Based on their sequence homologies, expression patterns, structural features, and biochemical and dynamic properties, lamins are subdivided into A- and B-types. All

T. Dechat et al.

metazoans express at least one B-type lamin. Typically, invertebrates have only a single lamin gene of the B-type, with some exceptions such as *Drosophila*, which expresses one B-type (lamin Dm0) and one A-type lamin (lamin C) encoded by two distinct genes. Most vertebrates have one A-type lamin and two B-type lamin genes except for *Xenopus*, which has three B-type genes (Melcer et al. 2007).

The two major isoforms of vertebrate A-type lamins, lamins A and C, are derived from a single gene (*LMNA*) by alternative splicing (see Fig. 1) (Lin and Worman 1993). In some vertebrates, alternative splicing can also produce two less abundant isoforms, lamins A Δ 10 and C2, from *LMNA* (Nakajima and Abe 1995; Machiels et al. 1996). Lamins B1 and B2 are the two major B-type lamins in most vertebrates. They are encoded by the *LMNB1* and *LMNB2* genes, respectively (Peter et al. 1989; Vorburger et al. 1989). The latter also encodes the minor isoform lamin B3 (Furukawa and Hotta 1993). Although at least one B-type lamin is expressed in all cells throughout development, the expression of A-type lamins is developmentally regulated (Benavente et al. 1985; Schatten et al. 1985; Lehner et al. 1987). During mouse development, lamins A and C are not expressed until days 10–12 of mouse embryogenesis and then primarily in primordial muscle cells (Stewart and Burke 1987; Rober et al. 1989). Lamin A/C expression in other organs does not occur until after birth (Rober et al. 1989). Cells of hematopoietic lineage express only B-type lamins (Guilly et al. 1990; Rober et al. 1990). Similar patterns of expression of A and B-type lamins take place during the developmental

progression of other vertebrates (Benavente et al. 1985; Lehner et al. 1987; Prather et al. 1989) and *Drosophila* (Frasch et al. 1988; Riemer et al. 1995). The regulated expression of A- and B-type lamins is also evident during differentiation of stem cells in culture. For example, undifferentiated human and mouse embryonic stem (ES) cells lack lamins A and C, but express lamins B1 and B2 (Constantinescu et al. 2006). The minor mammalian isoforms, lamins C2 and B3, are expressed exclusively in germ cells (Furukawa and Hotta 1993; Machiels et al. 1995; Nakajima and Abe 1995), whereas small amounts of lamin A Δ 10 appear to be present in a variety of cell types (Machiels et al. 1995).

The importance of the developmental regulation of lamin expression is evident from studies in *LMNA* knockout (*LMNA*^{−/−}) and *LMNB1* mutant (*LMNB1*^{Δ/Δ}) mice. In mice null for the A-type lamins, no obvious embryonic defects can be detected, but these animals show severe postnatal growth retardation and muscular dystrophy (Sullivan et al. 1999). On the other hand, mice with an insertional mutation in *LMNB1* develop defects in their lungs and bones during embryogenesis and die at birth, even though they continue to express lamin B2 (Vergnes et al. 2004).

Structure and Assembly of the Nuclear Lamins

The nuclear lamins have the typical tripartite structure of intermediate filament (IF) proteins, consisting of a highly α -helical central rod domain flanked by a short globular amino-terminal “head” domain and a longer carboxy-terminal

Figure 1. Structure of nuclear lamins. Schematic drawing of mature lamin A and lamin C polypeptide chains. The lamin structure consists of a short amino terminal head domain, a central α -helical rod domain (red), and the carboxy-terminal domain containing the NLS and the Ig-fold (blue; the nine β -strands of the Ig-fold motif are depicted). Modified, with permission, from (Dechat et al. 2008b).

“tail” domain (Parry et al. 1986). The central rod domain is composed of four subhelical regions comprised of heptad repeats and designated as coil 1A, 1B, 2A, and 2B. These individual “coils” are separated from each other by three short linker segments, L1, L12, and L2, of which L12 is the most flexible (Parry et al. 1986). Although the head domain appears to be unstructured, the tail domain contains a highly conserved structural motif similar to a type s immunoglobulin fold (Ig-fold) (Dhe-Paganon et al. 2002; Krimm et al. 2002). A nuclear localization signal (NLS), required for transport into the nucleus, is present in all lamins between the carboxy-terminal end of the central rod domain and the Ig-fold (Loewinger and McKeon 1988) (Fig. 1).

In vitro, lamins self-assemble into higher order structures through a series of steps. The first step involves the formation of a coiled-coil dimer by the in register and in parallel association of two α -helical rod domains into a left handed superhelix (Heitlinger et al. 1991) (Fig. 2A). Next, the lamin dimers associate in a head-to-tail fashion (Heitlinger et al. 1991; Stuurman et al. 1996) and these polarized arrays interact in an antiparallel fashion to form apolar tetrameric protofilaments (Heitlinger et al. 1991) (Fig. 2B). The interaction of four lamin protofilaments leads to the formation of ~ 10 -nm filaments (Heitlinger et al. 1991; Stuurman et al. 1996; Ben-Harush et al. 2009) (Fig. 2C,D). Although the assembly of some invertebrate lamins appears to terminate at this stage of the assembly process, vertebrate lamins continue to assemble into well ordered paracrystalline arrays in vitro (Zackroff and Goldman 1979; Heitlinger et al. 1991; Stuurman et al. 1996; Ben-Harush et al. 2009) (Fig. 2E). The assembly of lamin proteins differs from their cytoplasmic counterparts in several ways. For example, lamin dimers associate by polar “head-to-tail” interactions to form protofilaments, which is very different from the half-staggered, antiparallel side-by-side association of cytoplasmic IF dimers, which assemble into 10 nm filaments (Strelkov et al. 2004). This difference is at least in part explained by the crystal structure of the coiled-coil dimer of the lamin A coil 2B region (Strelkov et al. 2004). Although

Figure 2. Assembly of the nuclear lamins in vitro. Lamins self assemble to form dimers (A) which then join to form linear head-to-tail polymers (protofilaments) (B). Bar = 100 nm; electron micrograph of rotary shadowed chicken lamin B2. These protofilaments further assemble into “beaded” filaments or fibers (C) which in turn associate laterally into thicker fibers (D), and eventually into paracrystalline arrays (E); C,D are negatively stained electron microscope preparations. Reprinted from Stuurman et al. (1998) with permission from Elsevier.

this structure appears to be similar to the overall structure of the homologous segment of the cytoplasmic IF protein vimentin, the distribution of charged residues varies causing significant changes in the patterns of intra- and interhelical salt bridges. Additionally, vertebrate lamins have six extra heptads in the central rod domain (McKeon et al. 1986), which may also help to explain assembly differences between cytoplasmic IF and lamins. The central rod domains of some invertebrates lamins contain fewer extra heptads and these lamins stop assembling into higher order structures at the 10-nm (IF) stage of assembly, similar to cytoplasmic IF proteins (Ben-Harush et al. 2009).

Posttranslational Processing and Modifications of the Nuclear Lamins

Lamins A, B1, and B2 are expressed as prelaminins that require extensive posttranslational modifications of their carboxy-terminal –CAAX box

T. Dechat et al.

to become mature lamins (Rusinol and Sinensky 2006; Davies et al. 2009). Modification of the –CAAX box takes place in a highly regulated temporal sequence starting with the farnesylation of the cysteine residue (Farnsworth et al. 1990; Lutz et al. 1992) by a farnesyltransferase (Zhang and Casey 1996). This modification initiates a sequence of processing steps (Beck et al. 1990) beginning with the removal of the –AAX by a CAAX prenyl protease. Two members of this zinc metalloproteinase family have been identified in humans: Rce1 (Ras-converting enzyme 1) and Zmpste24 (Zinc metalloprotease related to the STE24 homolog in yeast), also known as FACE1 (farnesylated-proteins converting enzyme) (Boyartchuk et al. 1997; Leung et al. 2001; Corrigan et al. 2005); followed by carboxymethylation of the carboxy-terminal

cysteine by isoprenylcysteine carboxyl methyltransferase (Icmt) (Winter-Vann and Casey 2005). In contrast to B-type lamins, which remain permanently farnesylated and carboxymethylated, an additional 15 amino acids are removed from the carboxyl terminus of farnesylated/carboxymethylated prelamins A by Zmpste24/FACE1 (Corrigan et al. 2005). This final processing step results in the production of mature lamin A lacking the carboxy-terminal farnesyl- and carboxymethyl-modifications (Fig. 3). This sequence of lamin processing steps is highly regulated and each step depends on the preceding modification (Kilic et al. 1997). Lamin C, which is 74 residues shorter than mature lamin A, does not possess a –CAAX box and therefore is not farnesylated or otherwise modified (see Fig. 1). The precise location

Figure 3. Posttranslational processing of the carboxyl terminus of prelamins A, B1, and B2. Processing takes place in a series of steps: (1) addition of a farnesyl group to the cysteine residue of the –CAAX box of pre-lamin A, prelamins B1 and prelamins B2 by a farnesyltransferase; (2) removal of the last three residues (–AAX) by an AAX endopeptidase; (3) methylation of the terminal carboxylic acid group (–COOH) by a carboxyl methyltransferase; (4) removal of the carboxyl terminal 15 amino acids of lamin A with the farnesyl attached by the metalloprotease Zmpste24/FACE1. This last proteolysis step does not occur on B-type lamins and therefore they remain farnesylated. Modified, with permission, from Dechat et al. (2008b).

of the intracellular post-translational processing sites for the lamins remains largely unknown. Although the enzymes required for processing the carboxyl terminus of the lamins are present in both the inner nuclear membrane and endoplasmic reticulum membranes, the complete processing of prelamin A can occur when the protein is confined either to the cytoplasm or to the nucleus (Barrowman et al. 2008). Even though the prelamins can be processed in the cytoplasm, it is more likely that all lamin processing occurs in the nucleus (Lutz et al. 1992), because lamins are rapidly transported into the nucleus after translation in the cytoplasm (Lehner et al. 1986).

In addition to farnesylation and carboxymethylation, lamins are also posttranslationally modified by phosphorylation (Ottaviano and Gerace 1985), sumoylation (Zhang and Sarge 2008), ADP-ribosylation (Adolph 1987), and possibly by glycosylation (Ferraro et al. 1989). Phosphorylation of serine and threonine residues proximal to the NLS by protein kinase C is known to play a role in the regulated import of lamins into the nucleus (Hennekes et al. 1993; Leukel and Jost 1995). At the onset of mitosis, the phosphorylation of lamins at specific sites by cyclin-dependent kinase (Cdk) 1 and protein kinase C (PKC) is required to drive disassembly of the lamina (Gerace and Blobel 1980; Dessev and Goldman 1988; Dessev et al. 1988; Dessev et al. 1989; Heald and McKeon 1990; Peter et al. 1990; Ward and Kirschner 1990; Dessev et al. 1991; Molloy and Little 1992; Goss et al. 1994; Collas 1999). Subsequently, dephosphorylation of the mitotic sites by protein phosphatase 1a is required for lamin/lamina assembly during the telophase/early G1 transition (Thompson et al. 1997).

Lamin Structure and Dynamic Properties within the Lamina and Nucleoplasm

Very little is known about the formation, composition, and structure of lamin polymers in vivo. The structures of the lamins within the lamina that have been described to date range from a regular meshwork of ~10–15 nm filaments observed in *Xenopus* oocyte germinal

vesicles and in sperm pronuclei assembled in vitro (Aebi et al. 1986; Zhang and Casey 1996; Goldberg et al. 2008a) (Fig. 4A), to a more irregular filamentous meshwork seen in mammalian cells (Belmont et al. 1993; Schermelleh et al. 2008; Shimi et al. 2008) (Fig. 4B,C). These meshworks have long been assumed to be stable structures based on the resistance of the nuclear lamins within the lamina to extraction in detergent containing high salt solutions, and the propensity of purified lamins to polymerize into higher order insoluble structures in vitro at relatively low critical concentrations (Aebi et al. 1986; Lourim and Lin 1989; Glass and Gerace 1990). In further support of this assumption, measurements of lamin mobility by fluorescence recovery after photobleaching (FRAP) reveal that GFP-tagged A- and B-type lamins do not appreciably exchange subunits within the lamina for up to several hours throughout most of interphase (Broers et al. 1999; Moir et al. 2000; Dahl et al. 2006).

Recently it has become apparent that the A- and B-type lamins form separate filamentous networks in the lamina. These structures can be identified by both high resolution light microscopy (Schermelleh et al. 2008; Shimi et al. 2008) and whole mount electron microscopy in lamin B containing *Xenopus* oocyte nuclei ectopically expressing A-type lamins (Goldberg et al. 2008b). Even though the A-type and B-type lamin networks appear to be mainly separate structures (Shimi et al. 2008), there is evidence that the individual networks overlap and interact to varying degrees. Evidence for interaction between these two lamin meshworks is based on studies using fluorescence resonance energy transfer (FRET) in combination with time domain fluorescence lifetime imaging and high resolution confocal immunofluorescence (Moir et al. 2000; Delbarre et al. 2006; Shimi et al. 2008).

Other evidence supporting the interactions between the A and B type lamins is derived from studies of nuclei in which either A or B type lamins are perturbed. Fibroblasts derived from *LMNA*^{-/-} mouse embryos (MEFs) or a limb girdle muscular dystrophy patient with a homozygous nonsense mutation in *LMNA*

T. Dechat et al.

Figure 4. The nuclear lamins form a meshwork of filaments within the lamina. (A) Spread nuclear envelope from *Xenopus* oocytes after detergent extraction and preparation for transmission electron microscopy by freeze-drying/unidirectional metal shadowing. The micrograph shows the nuclear lamina meshwork partially studded with nuclear pore complexes. (Inset) Higher-magnification view of a particularly well-preserved area clearly shows the near-tetragonal lamina meshwork. Bars, 1 μ m. Reprinted from Stuurman et al. (1998), with permission from Elsevier. (B) Structured illumination microscopy (SIM) reveals that there is an irregular meshwork of nuclear lamin B as revealed by immunofluorescence (green). This preparation is also stained with antibodies directed against nuclear pores and is stained with DAPI for DNA/chromatin. Pores (red), DAPI (blue). From Schermelleh et al. (2008). Reprinted with permission from AAAS. (C) Confocal immunofluorescence localization of lamin A/C (green) and lamin B1 (red) in HeLa cells. Lamins A/C and B1 in a single nucleus are seen in an equatorial section (left panels) and the nuclear surface (right panels). The areas indicated by white squares in the top panels are enlarged fivefold in the lower panels. These images demonstrate that lamins form mainly separate networks with some overlapping regions. Bar, 5 μ m. Adapted, with permission, from Shimi et al. (2008).

contain abnormally shaped nuclei containing blebs or lobules (Sullivan et al. 1999; Muchir et al. 2003). A significant number of these blebbed regions lack B-type lamins and NPCs. In addition, nuclei in *LMNB^{Δ/Δ}* MEFs are also highly lobulated, showing a dramatic increase in the mesh size of the lamin A/C network (Vergnes et al. 2004). HeLa cells depleted of lamin B1 by shRNA silencing frequently develop extensively enlarged lamin A/C meshworks and nuclear envelope blebs which lack lamin B2 and NPCs (Shimi et al. 2008). Many of these nuclear phenotypes are also found in cells endogenously or ectopically expressing either point mutations or truncations of lamins A/C (Ostlund et al. 2001; Vaughan et al. 2001; Vigouroux et al. 2001; Bechert et al. 2003; Favreau et al. 2003; Muchir et al. 2003; Goldman et al. 2004). It is also noteworthy that lamin A is more mobile in the nuclear lamina in nuclei with decreased amounts of lamin B1 (Tang et al. 2008).

The A- and B-type lamins have different disassembly and assembly properties during mitosis as revealed by biochemical fractionation, immunofluorescence, and live cell imaging analysis, further supporting the idea that the two types of lamins form separate networks in the lamina. As described earlier, depolymerization of the lamins is regulated by mitotic kinases and reassembly requires dephosphorylation by protein phosphatase 1a (Thompson et al. 1997; Ito et al. 2007). When the nuclear envelope is disassembled during late prophase, A-type lamins become dispersed throughout the cytoplasm in an apparently freely diffusible state whereas the majority of B-type lamins remain associated with the nuclear membranes, which appear to be mainly dispersed into the endoplasmic reticulum (Gerace and Blobel 1980; Stick et al. 1988). This association of B-type lamins with membranes during mitosis appears to be mainly attributable to their permanently farnesylated state (Rusinol and Sinensky 2006).

Further support for differences in the properties of the A- and B-type lamins is derived from studies revealing their spatial and temporal order of assembly into the nuclear lamina at anaphase/telophase and in the early stages of

G₁. For example, in mouse keratinocytes and hamster cells, lamin B1 accumulates along the entire periphery of the decondensing daughter chromosomes and assembles into a relatively stable polymer by mid- to late- telophase (Broers et al. 1999; Moir et al. 2000). In these cells, lamin A begins to accumulate within the nucleus mainly after the major components of the nuclear envelope including NPCs are assembled in daughter cells in late telophase. In HeLa cells, however, a small fraction of A-type lamins associates with chromosomes much earlier than in mouse cells, first assembling in the central or “core” region of chromosomes in close association with kinetochores (Dechat et al. 2004; Dechat et al. 2007; Haraguchi et al. 2008) (Fig. 5). The remainder of the A-type lamins is then transported into the nucleus after formation of an intact nuclear envelope. Later, other elements of the nuclear envelope begin to assemble in daughter cells (Dechat et al. 2004; Dechat et al. 2007; Haraguchi et al. 2008).

Although the major fraction of the various lamin isoforms is associated with the nuclear lamina, these proteins are also present

throughout the nucleoplasm, especially in interphase (Goldman et al. 1992; Lutz et al. 1992). These nucleoplasmic lamins are likely to have different functions, for example in DNA replication and transcription (Dechat et al. 2008b), and a small fraction may represent assembly intermediates that are subsequently incorporated into the nuclear lamina (Goldman et al. 1992). Interestingly, B-type lamins in the nucleoplasm appear to be relatively static, similar to those in the lamina, whereas the nucleoplasmic A-type lamins are much more dynamic. These differences in the properties of nucleoplasmic A- and B-type lamins are supported experimentally by their biochemical extractability and their dynamic properties as determined *in vivo* by FRAP analyses and fluorescence correlation spectroscopy (FCS) (Broers et al. 1999; Moir et al. 2000; Shimi et al. 2008). For example, FCS measurements of GFP-tagged lamins A/C and lamins B1/B2 showed that nucleoplasmic lamins A/C are highly mobile, whereas lamin B1 and lamin B2 are mainly immobile (Shimi et al. 2008). This latter observation suggests that nucleoplasmic B-type lamins are either assembled into some type of

Figure 5. Association of lamin A with chromosomes during mitosis. HeLa cells expressing GFP-lamin A were followed by time-lapse microscopy from the metaphase/anaphase transition (far left panels) into early G₁ (far right panels). GFP-lamin A first associates with the core regions of chromosomes during telophase and spreads to cover the entire chromatin surface by early G₁. DIC images of the same series are shown in the bottom row (Dechat et al. 2007).

T. Dechat et al.

structure or are tightly associated with other unknown immobile structural components. Interestingly, decreasing the amount of nucleoplasmic lamin B1 by shRNA silencing increases the rate of mobility for a large fraction of nucleoplasmic lamin A (Shimi et al. 2008). Taken together, these FCS results suggest that, as in the case of the lamina, the A- and B-type lamins form separate yet interacting structures within the nucleoplasm. Obviously, it will be of great interest in the future to determine the specific functions of these nucleoplasmic lamins.

FUNCTIONS OF THE LAMINS

Regulation of Nuclear Shape and Mechanical Stability

It is becoming increasingly obvious that some of the functions of nuclear lamins are analogous to those of cytoskeletal intermediate filament proteins, which are known to be involved in the determination and maintenance of cell shape and mechanical properties (Goldman et al. 2008). In support of this, the nuclei of *LMNA*^{-/-} MEFs display increased deformability and impaired viability under mechanical strain compared to the nuclei in control MEFs (Houben et al. 2007). Increased nuclear deformability is also observed in human ES cells lacking A-type lamins as compared to nuclei in differentiated cells expressing the A-type lamins (Pajeroski et al. 2007). In addition, cells either deficient in lamins or expressing mutant lamin proteins often contain misshapen nuclei (Ostlund et al. 2001; Vaughan et al. 2001; Vigouroux et al. 2001; Bechert et al. 2003; Favreau et al. 2003; Muchir et al. 2003; Goldman et al. 2004). Quantitative rheological measurements, particle tracking methods and differential interference contrast microscopy reveal that in vitro reconstituted lamin B1 networks are extremely porous, with elastic stiffness providing resistance to shear deformations (Panorchan et al. 2004a; Panorchan et al. 2004b). Interestingly, measurements made by atomic force microscopy show that germinal vesicles isolated from *Xenopus* oocytes, which normally contain only B-type lamins, display a significant

increase in stiffness on the ectopic expression of lamin A (Schape et al. 2009).

Nuclear Lamins and the Regulation of Chromatin Positioning and Gene Expression

Lamins may regulate transcription by organizing chromatin into active and inactive domains. For example, electron microscopic and light microscopic observations show that there is a close association between peripherally localized heterochromatin and the nuclear lamina (Fawcett 1966; Paddy et al. 1990) (Fig. 6). This suggests that lamins may be involved in anchoring or organizing interphase chromosomes (Sullivan et al. 1999; Goldman et al. 2004; Nikolova et al. 2004; Galiova et al. 2008). Additional support for this idea comes from biochemical experiments showing that lamins A/C bind to mitotic chromosomes and to polynucleosomal particles in vitro (Burke 1990; Glass and Gerace 1990; Yuan et al. 1991). The interaction of lamins with chromatin could be mediated either by their direct binding to histones (Taniura et al. 1995; Goldberg et al. 1999; Mattout et al. 2007), or to specific DNA sequences in the matrix attachment/scaffold-associated regions (MARs/SARs) (Luderus et al. 1992; Luderus et al. 1994; Baricheva et al. 1996; Zhao et al. 1996).

The Role of Lamins in Mitosis

In addition to nuclear disassembly, several lines of evidence suggest a direct role for lamins in nuclear assembly following mitosis. The

Figure 6. The nuclear lamina is a fibrous network (fibrous lamina) located between peripheral heterochromatin and the inner nuclear membrane. A transmission electron micrograph of a thin section showing a portion of a smooth muscle nucleus in guinea pig epididymis. Adapted from Fawcett (1966), copyright 1995, Wiley-Liss, Inc. Reprinted with permission of John Wiley & Sons, Inc. American Journal of Anatomy, Vol. 119, No. 1, pg. 140.

microinjection of lamin antibodies into mitotic cells causes arrest in a telophase-like state with the chromosomes remaining condensed (Benavente and Krohne 1986). In addition, decreased expression of lamin Dm0 in *Drosophila* inhibits nuclear membrane assembly and causes an enrichment of NPCs in cytoplasmic annulate lamellae (Lenz-Bohme et al. 1997). In *Caenorhabditis elegans*, the down-regulation of the single lamin leads to a loss of chromosomes, defects in chromosome separation into daughter cell nuclei, and abnormal condensation of chromatin (Liu et al. 2000). In vitro nuclear assembly in frog egg extracts can be inhibited by addition of the C-terminal tail fragment of lamin B3, in part because of the Ig-fold motif in the lamin tail, which can inhibit lamin polymerization in vitro (Shumaker et al. 2005). Lastly, the expression of the mutant lamin A which causes Hutchinson-Gilford Progeria Syndrome (HGPS) leads to defects in cell division including a delay in cytokinesis, delayed completion of nuclear reassembly at the end of mitosis and an increase in mitotic cells (Cao et al. 2007; Dechat et al. 2007).

B-type lamins also play a role in the formation of the mitotic spindle. In cultured cells, a diffuse localization of B-type lamins can be observed associated with the mitotic spindle (Georgatos et al. 1997; Maison et al. 1997; Moir et al. 2000; Beaudouin et al. 2002; Tsai et al. 2006). In frog egg extracts, a mitotic spindle can be induced to form around added DNA or on beads coated with a variety of factors important for mitotic spindle formation (Tsai and Zheng 2005). In these lysates, lamin B3, the major lamin in frog eggs, is required to organize a “spindle matrix” structure. This matrix contains membrane vesicles and proteins known to regulate the assembly and dynamic properties of the microtubules comprising the mitotic spindle (Tsai et al. 2006). Depletion of lamin B3 from the egg extracts with antibodies or the addition of dominant negative fragments of lamin B3 known to disrupt lamin assembly, also disrupt the formation of the mitotic spindle. Furthermore, lamin B3 is associated with several spindle assembly factors within the spindle matrix such as

NuMA and Nudel and it appears to play an important role in regulating the activity of these proteins during mitosis (Tsai et al. 2006; Ma et al. 2009).

The Role of Lamins in DNA Replication and Repair

Several lines of evidence suggest that lamins play a role in DNA replication. In cultured cells, sites of DNA replication can be visualized as discrete early or late replication foci in the nucleoplasm. These foci can be detected by incorporation of bromodeoxyuridine into sites of replication (Moir et al. 1994) or by immunolocalization of replication-associated proteins such as proliferating cell nuclear antigen (PCNA) (Shumaker et al. 2008). It has been shown that lamin B1 colocalizes with these replication foci during late S phase in mouse 3T3 cells (Moir et al. 1994) and that lamins A/C are present at sites of early replication in normal human fibroblasts (Kennedy et al. 2000). Furthermore, DNA replication in *Xenopus* nuclei assembled in vitro is inhibited by depletion of lamin B3 or by the addition of a dominant-negative fragment of lamin B3, which drives the disassembly of the endogenous lamin network (Lopez-Soler et al. 2001; Shumaker et al. 2005; Shumaker et al. 2008). There is evidence that the lamins play a direct role in regulating replication by their binding to DNA replication factors such as PCNA. The lamin binding site for PCNA resides within the highly conserved Ig-fold motif located in the carboxyl terminus of both the A- and B-type lamins (Shumaker et al. 2008). In addition, there is a close association between lamin B3 and PCNA at the surface of sperm head chromatin during the earliest stages of nuclear assembly in *Xenopus* interphase egg extracts (Shumaker et al. 2008).

Nuclear lamins have also been implicated in DNA repair, although the mechanistic basis of this remains unclear. For example, the expression of disease-causing mutant lamins impairs the formation of DNA repair foci (Liu et al. 2005; Manju et al. 2006). Furthermore, genetic instability because of defects in telomere

T. Dechat et al.

function and DNA repair has been implicated in progeria, the premature aging syndrome (Gonzalez-Suarez et al. 2009a; Gonzalez-Suarez et al. 2009b).

The Role of Lamins in Transcription

Several lines of experimental evidence support the possibility that lamins play a role in transcription. An amino-terminally deleted dominant negative lamin A, which disassembles lamin networks, specifically inhibits RNA pol II activity in hamster cells or in nuclei isolated from *Xenopus* embryos (Spann et al. 2002). In addition, over-expression of lamins A/C or silencing of lamin B1 leads to a significant inhibition of pol II transcription in HeLa cells (Kumaran and Spector 2008; Shimi et al. 2008; Tang et al. 2008).

Lamins also associate with several transcription factors leading to the suggestion that they are involved in specific regulatory pathways (Heessen and Fornerod 2007; Andres and Gonzalez 2009). For example, the association of Oct-1 with lamin B1 at the nuclear envelope appears to be important for the oxidative stress response in MEFs, as lamin B1 deficiency leads to a dysregulation of Oct-1-dependent genes and to an increase in reactive oxygen species (Malhas et al. 2009). Lamins A/C also interact with the transcription factors c-Fos, MOK2, and sterol response element binding protein 1 (SREBP1) (Dreuillet et al. 2002; Lloyd et al. 2002; Ivorra et al. 2006; Dreuillet et al. 2008; Harper et al. 2009). In the case of c-Fos, its interaction with lamins A/C at the nuclear envelope appear to suppress AP-1 (activating protein 1) binding to DNA and transcriptional activity in an extracellular signal-regulated kinase (ERK) 1/2 activity-dependent fashion (Ivorra et al. 2006; Gonzalez et al. 2008). In addition to regulating transcription factor function by direct interaction, lamins are also associated with transcription factors indirectly via several lamin-binding proteins including emerlin, LAP2 β and pRb. Although the evidence supporting a role for the lamins in regulating transcription is convincing, it remains unclear

whether this regulation involves direct or indirect binding to transcription factors.

Lamins as Regulators of the Positioning and Organization of Chromatin

The positioning of genes near or in contact with the nuclear lamina may be a mechanism for modulating gene expression. Inactive genes and gene-poor chromatin are frequently found in association with the lamina region, which suggests that the nuclear lamina may be a transcriptionally silent microdomain (Boyle et al. 2001; Cremer et al. 2001). Furthermore, lamins may play a role in establishing this microdomain by directly interacting with chromatin. The interactions of lamins with chromatin/DNA at the nuclear lamina can be identified in more detail by DamID labeling (Pickersgill et al. 2006). In this technique, an expression vector encoding a potential chromatin/DNA binding protein fused to the *Escherichia coli* enzyme DNA adenine methyl transferase (Dam) is expressed in cells. DNA methylated by the lamin Dam fusion protein is then analyzed by sequencing. In *Drosophila* Kc cells, lamin D_{m0} seems to mainly associate with transcriptionally inactive, mid-to-late replicating genome regions, lacking active histone marks and enriched in large intergenic regions (Pickersgill et al. 2006). In human lung fibroblasts lamin B1-associated domains (LADs) are present along chromosomes in a distinct pattern interspersed with “lamin B1 poor” regions (Guelen et al. 2008). These LADs are ≥ 1 Mb in size, are mostly heterochromatic. Genes present within LADs are 5–10-fold less active than genes outside LADs.

The lamina appears to have gene or chromatin-specific effects on activation or repression of transcription. Evidence for the lamina constituting a repressive environment for transcription comes from studies localizing inactive gene loci to the nuclear periphery (Kosak et al. 2002; Zink et al. 2004; Williams et al. 2006). For example, the inactive Ig-heavy and Ig- κ loci are preferentially positioned at the nuclear periphery in non-B-cell lineages, but are centrally located in B-cell nuclei where

they are actively engaged in transcription (Kosak et al. 2002). In addition, transcriptionally inactive testis-specific gene clusters are frequently associated with lamin Dm0 in the lamina of *Drosophila* S2 cells. Upon down-regulation of lamin Dm0, these gene clusters relocate from the lamina to the nuclear interior and become transcriptionally active (Shevelyov et al. 2009). Artificial tethering of a reporter gene to the nuclear envelope using the membrane spanning domain of the inner nuclear membrane protein emerin results in the transcriptional inactivation of the gene in mouse cells (Reddy et al. 2008). However, the relocalization of chromosomes from the nuclear interior to the nuclear periphery using the inner membrane protein Lap2 β inactivates some genes, but not others (Finlan et al. 2008). The idea that the nuclear lamina is not repressive to all transcription is further supported by the finding that targeting a genetic locus to the nuclear lamina by artificial tethering to lamin B1 does not interfere with its transcriptional activation (Kumaran and Spector 2008). In addition, lamin A can act as a transcriptional repressor in mammalian cells and in yeast when artificially targeted to specific promoters (Lee et al. 2009). This latter finding is intriguing because yeast do not contain lamin genes. These somewhat conflicting results demonstrate that more research is required to determine the role of lamins in transcription both in the region of the lamina and throughout the nucleoplasm.

Lamins are Involved in the Epigenetic Regulation of Chromatin

The dramatic loss of peripheral heterochromatin in the nuclei of cells expressing one of the mutant forms of lamin A, progerin, that causes the premature aging disorder HGPS emphasizes the important role of lamins in the modification and/or the organization of chromatin (Shumaker et al. 2006) (Fig. 7). A partial loss of peripheral heterochromatin is also seen in *LMNA*^{-/-} MEFs (Sullivan et al. 1999; Nikolaeva et al. 2004). Furthermore, down-regulation of lamin B1 in HeLa cells results in lamin A/C-rich and lamin B2 deficient nuclear blebs

or microdomains characterized by the absence of heterochromatin (Shimi et al. 2008). These changes in chromatin organization related to lamin expression are reflected in alterations in histone modifications including reductions in trimethylated H3K9, trimethylated H3K27 and an increase in trimethylation of H4K20 in HGPS cells (Scaffidi and Misteli 2006; Shumaker et al. 2006; Shimi et al. 2008) (Fig. 7). These studies demonstrate that the interaction of chromatin with lamins, whether direct or indirect, has strong effects on the epigenetic modification of histones, and that lamin-associated microdomains in the nucleus might regulate modification of chromatin (Pegoraro et al. 2009). One potential link between lamins and chromatin modification may involve the tumor suppressor ING1. This protein, which interacts with histone acetyltransferases and histone deacetylases, appears to be stabilized and targeted to the nucleus by its interaction with A-type lamins (Han et al. 2008). HGPS cells have reduced ING1 levels and the expression of ING1 protein lacking its lamin interacting domain causes a loss of peripheral heterochromatin in normal cells.

Lamins and Interphase Chromosome Organization

The organization of chromosome territories and domains is influenced by the expression of lamins. For example, in *LMNB* ^{Δ/Δ} MEFs and in cells derived from patients suffering from some types of laminopathies, gene-poor chromosome 18 is positioned away from its normal location at the nuclear periphery toward the nuclear interior (Malhas et al. 2007; Meaburn et al. 2007). Furthermore, in HeLa cells silenced for the expression of lamin B1, the lamin A/C rich and lamin B2-deficient nuclear envelope blebs that form are associated predominantly with gene-rich chromosome regions (Shimi et al. 2008) (Fig. 8). Together, these findings suggest that A-type lamins are preferentially associated with gene-rich chromatin regions and B-type lamins are preferentially associated with gene-poor regions of chromosomes. It must be emphasized that these studies are of a

T. Dechat et al.

Figure 7. The association of the nuclear lamina with chromatin in normal and progeria patients' cells. (A) Thin section electron micrograph of a late passage blebbed nucleus in an HGPS patient's skin fibroblast (*left* and *center* panels) and normal human fore-skin fibroblasts (*right* panel). A high-magnification view of the nuclear envelope in a normal human fore-skin fibroblast shows a normal array of heterochromatin adjacent to the nuclear envelope, making any lamina structure difficult to detect (*right* panel). A higher-magnification view of a HGPS cell showing a loss of peripheral heterochromatin and a prominent electron-dense lamina region associated with the inner nuclear envelope membrane (the nucleus is to the left in *center* and *right* panels) (Goldman et al. 2004). (B) Alterations of histone methylation patterns in HGPS fibroblasts. Normal and HGPS fibroblasts from female donors were double-labeled with antibodies against lamins A/C (red) and trimethylated Lys 9 in histone H3 (H3K9me3), Lys 27 in histone H3 (H3K27me3), or Lys 20 in histone H4 (H4K20me3) (all green). Note the decrease of H3K9me3 and H3K27me3 and the increase of H4K20me3 in the lobulated HGPS nuclei compared with normal nuclei. The decrease in H3K27me3 is best observed at the inactive X chromosome, which is normally enriched in this histone modification (see arrowhead in center left panel). Bars, 10 μ m. Reprinted, with permission, from Dechat et al. (2008b).

preliminary nature and that much more work is required to establish the precise relationships between the different types of lamins and gene rich/gene poor chromosome domains within the interphase nucleus.

Lamins may also play a role in the localization and function of centromeres and telomeres in the nucleus. Centromeres are typically arranged near the nuclear periphery in an interphase nucleus (Solovei et al. 2004). However, the lamin A/C-rich, lamin B2-deficient nuclear envelope blebs that form in lamin B1-silenced cells are devoid of centromeres, suggesting that B-type lamins are involved in anchoring these

heterochromatic structures at the nuclear lamina (Shimi et al. 2008). Telomeres are also influenced by the composition and structure of the lamina, because in *LMNA*^{-/-} MEFs, the distribution, length and structure of telomeres is altered leading to increased genomic instability compared to control MEFs (Gonzalez-Suarez et al. 2009a). Human fibroblasts ectopically expressing HGPS lamin A mutant proteins show rapid telomere shortening and an accelerated replicative senescence phenotype (McClintock et al. 2006; Huang et al. 2008). Furthermore, the proliferative defects seen in normal dermal fibroblasts expressing progerin can be overcome

Figure 8. Localization of specific gene rich chromosomal regions in nuclear blebs in LB1-silenced HeLa cells. Chromosomes are detected by fluorescence in situ hybridization. DNA is counterstained with Hoechst 33258 (blue). Chromosome 6p (or 19), and chromosome 6q (or 18) are shown in green and red, respectively. Bars, 5 μ m. Adapted, with permission, from Shimi et al. (2008).

by expression of the catalytic subunit of telomerase or the inactivation of p53 (Kudlow et al. 2008). Other support for the involvement of lamins in telomere function comes from the finding that the D4Z4 human subtelomeric repeat can localize an adjacent telomere to the nuclear periphery probably by interacting with A-type lamins and CTCF (CCCTC-binding factor) (Ottaviani et al. 2009a; Ottaviani et al. 2009b). The D4Z4 repeat acts as a CTCF and A-type lamin-dependent transcriptional insulator, suggesting that nuclear lamin architecture may organize specific regions of chromatin and influence gene expression (Ottaviani et al. 2009a).

Strong support for the role of the lamins in interphase chromosome organization comes from a study of cells obtained from patients with a form of atypical HGPS (Taimen et al. 2009b). Unlike the most common form of HGPS, which results in only defective lamin A, these patients have a mutation resulting in the expression of a point mutation, E145K, in the 1B segment of the central rod domain of both lamins A and C (see Fig. 1). The cells from these patients have a flower-shaped nucleus with centrally clustered centromeres and abnormal peripherally displaced telomeres (Fig. 9). This abnormal configuration of chromosomes requires a round of cell division and persists throughout interphase. The multilobulated

Figure 9. Mislocalization of heterochromatin and centromeres in HGPS E145K cells. Control and E145K patient cells were stained with anti-lamin A (red), CREST antiserum (green), and Hoechst (white). Maximum projections of series of z-sections spanning the entire nucleus and side projections are shown. Centromeres are clustered in the central region of the nucleus in E145K cells, while they are either closely associated with the peripheral lamina region or elsewhere in the nucleoplasm in control cells. Inset shows an example of the close association of one centromere with the lamina in a single confocal section. In the right hand panels, side projections from merged images are shown. Centromeres are distributed throughout the nuclei in normal cells. In E145K cells centromeres are clustered in the middle of one region of the nucleus (Taimen et al. 2009a).

nuclei are therefore unlikely to correctly establish normal interphase chromosome territory arrangements. Both the abnormal nuclear shapes and chromosome configurations in E145K cells appear to be due to the aberrant assembly of the nuclear lamina by the mutant lamin A. In vitro analysis of E145K lamin A polymerization shows that this mutant lamin forms disorganized higher-order structures, a defect not seen in the more common form of progeria resulting from a truncation near the carboxyl terminus (Taimen et al. 2009b).

Lamins in Cell Proliferation and Differentiation

Deficiencies in A-type lamins or the expression of mutant A-type lamins both lead to an array of proliferative defects because of cell cycle

T. Dechat et al.

acceleration, cell cycle arrest and/or premature senescence (Verstraeten et al. 2007; Dechat et al. 2008a). There is evidence that lamins A/C are involved in the regulation of the pRb/E2F pathway responsible for the G1/S cell cycle transition. One current model suggests that pRb in its suppressive hypophosphorylated state is in a complex with lamins A/C and LAP2 α , and that the loss of lamins A/C leads to the degradation of pRb (Ozaki et al. 1994; Markiewicz et al. 2002; Johnson et al. 2004). In addition to pRb, cyclin D3, another critical regulator of G1 progression, interacts directly with lamins A/C (Mariappan et al. 2007).

The findings that lamins are involved in the regulation of cell cycle progression and that they are differentially expressed during development, suggest that they also function in the regulation of cell differentiation. In support of this, during myoblast differentiation there is a decrease in the soluble nucleoplasmic lamin A/C pool, most likely in a pRb and cyclin D3-dependent manner (Muralikrishna et al. 2001; Mariappan and Parnaik 2005). Furthermore, the down-regulation of lamins A/C or the expression of lamin A/C mutants associated with Autosomal Dominant Emery Dreifuss Muscular Dystrophy (AD-EDMD) lead to impaired myoblast differentiation possibly by disrupting the Rb-MyoD pathway (Bakay et al. 2006; Frock et al. 2006). As further evidence for the importance of the lamin A/pRb interaction, the expression of either an AD-EDMD lamin A mutant protein or the HGPS lamin A mutant protein, progerin, results in the inhibition of the phosphorylation of pRb (Markiewicz et al. 2005; Dechat et al. 2007). In the case of the AD-EDMD mutation, a further decrease in pRb levels along with the failure to hyperphosphorylate the available pRb inhibits myoblast differentiation (Favreau et al. 2004; Kandert et al. 2009). In adipocyte differentiation, the overexpression of either wild-type lamin A or a lamin A mutant associated with familial partial lipodystrophy impairs the potential of mouse fibroblasts to differentiate into mature adipocytes; and *LMNA*^{-/-} mouse embryonic fibroblasts differentiate more readily into fat-containing cells compared to control cells

(Boguslavsky et al. 2006). There is also evidence that lamins A/C regulate adipocyte differentiation in a complex with the inner nuclear membrane protein emerin, by influencing the nucleocytoplasmic distribution of β -catenin (Tilgner et al. 2009). In addition, lamins A/C appear to be involved in osteoblast differentiation, as silencing their expression causes impaired osteoblastogenesis and accelerated osteoclastogenesis in human bone marrow stromal cells (Akter et al. 2009; Rauner et al. 2009). Lamin A may also be involved in adult stem cell differentiation as the expression of progerin causes defects mouse stem cell populations (Espada et al. 2008) in the differentiation potential of human mesenchymal stem cells, probably by affecting the Notch-signaling pathway (Espada et al. 2008; Scaffidi and Misteli 2008).

Another aspect of the involvement of the lamins in differentiation is related to aging. In this regard, progerin can be detected in cells from healthy individuals and the protein appears to accumulate with increasing age (McClintock et al. 2006; Scaffidi and Misteli 2006; Cao et al. 2007; Rodriguez et al. 2009). Furthermore, dermal fibroblasts from older individuals (Scaffidi and Misteli 2006), and cells in aged *C. elegans* (Haithcock et al. 2005) display changes in nuclear shape similar to those found in premature aging.

The Lamins are Connected to the Cytoskeleton

There is evidence that the nuclear lamins are connected to the cytoskeleton through a complex of proteins called the LINC complex (linker of nucleoskeleton and cytoskeleton) (Crisp et al. 2006; Ketema et al. 2007; Stewart-Hutchinson et al. 2008; Burke and Roux 2009). In this complex the integral proteins of the inner nuclear membrane, Sun1 and Sun2, interact with the outer nuclear membrane proteins, nesprin-1, nesprin-2, and nesprin-3 α , in the luminal space between the inner and outer nuclear membranes. Although the Sun proteins bind to the lamins (Crisp et al. 2006), the nesprins are associated with both the microfilament and intermediate filament cytoskeletons

via direct actin binding and plectin (Tzur et al. 2006). Another lamin binding protein of the inner nuclear membrane, emerin, binds directly to nesprin isoforms, providing additional linkages between the lamins and the cytoskeleton (Wheeler et al. 2007; Zhang et al. 2007). These interactions between the nuclear lamina and the cytoskeleton may have important functional significance. For example, nuclei in fibroblasts deficient in lamin B1 rotate at a higher frequency than nuclei in control cells (Ji et al. 2007). *LMNA*^{-/-} MEFs, on the other hand, are reported to show a decrease in mechanical stiffness, defects in mechanotransduction resulting in impaired strain-induced signaling, defects in cell polarization and cell migration, and a disturbed organization of microfilaments, vimentin IF networks and microtubules (Houben et al. 2007; Lee et al. 2007; Dahl et al. 2008; Houben et al. 2009).

CONCLUSIONS AND FUTURE PERSPECTIVES

Over the past decade it has become clear that the nuclear lamins are one of the key players in determining nuclear architecture and function. There is growing evidence that these Type V IF proteins provide a filamentous scaffold built from interconnecting A- and B-type lamin networks that pervade the entire nucleus. This scaffold not only determines the shape and mechanical properties of the nucleus, but also serves as a docking site for chromatin and for numerous proteins involved in chromatin organization and various nuclear functions. Besides the extensive lamin structures located within the lamina, smaller and more dynamic lamin polymers appear to be components of large protein complexes known to be involved in a wide range of nuclear housekeeping functions such as DNA replication, DNA repair and RNA PolII transcription.

We have learned much about the nuclear lamins from the analysis of the changes in nuclear form and function that take place in cells from patients suffering from the remarkably large number of diseases attributable to hundreds of mutations in the *LMNA* gene.

However, the precise roles that normal lamins play in nuclear functions remain largely unknown. To gain more insights into their specific functions we need a better understanding of their normal structure at the highest levels of resolution. To date only a few subdomains of the lamins have been shown to be amenable to analysis by X-ray diffraction, because of the well known difficulties inherent in crystallizing IF proteins. Other challenges for future studies include determining the steps in lamin polymerization and depolymerization in vivo and determining how complex networks of the A- and B-type lamins are assembled and interact with each other both at the nuclear periphery and within the nucleoplasm throughout the cell cycle. Finally, it will be of great interest to determine the different roles of the A- and B-type lamins in determining the overall architecture of the nucleus and the mechanisms involved in their linkages to other nuclear structures, such as the nuclear membrane and pore complexes.

ACKNOWLEDGMENTS

Work in the Goldman lab on nuclear lamins is funded by the National Institute on Aging and the National Cancer Institute. PT received a fellowship from Sigrid Juselius Foundation, Orion-Farmos Research Foundation, Cancer Society of Southwestern Finland, and Finnish Cultural Foundation.

REFERENCES

- Aaronson RP, Blobel G. 1975. Isolation of nuclear pore complexes in association with a lamina. *Proc Natl Acad Sci* **72**: 1007–1011.
- Adolph KW. 1987. ADPribosylation of nuclear proteins labeled with [3H]adenosine: changes during the HeLa cycle. *Biochim Biophys Acta* **909**: 222–230.
- Aebi U, Cohn J, Buhle L, Gerace L. 1986. The nuclear lamina is a meshwork of intermediate-type filaments. *Nature* **323**: 560–564.
- Akter R, Rivas D, Geneau G, Drissi H, Duque G. 2009. Effect of lamin A/C knockdown on osteoblast differentiation and function. *J Bone Miner Res* **24**: 283–293.
- Andres V, Gonzalez JM. 2009. Role of A-type lamins in signaling, transcription, and chromatin organization. *J Cell Biol* **187**: 945–957.

T. Dechat et al.

- Bakay M, Wang Z, Melcon G, Schiltz L, Xuan J, Zhao P, Sartorelli V, Seo J, Pegoraro E, Angelini C, et al. 2006. Nuclear envelope dystrophies show a transcriptional fingerprint suggesting disruption of Rb-MyoD pathways in muscle regeneration. *Brain* **129**: 996–1013.
- Baricheva EA, Berrios M, Bogachev SS, Borisevich IV, Lapik ER, Sharakhov IV, Stuurman N, Fisher PA. 1996. DNA from *Drosophila melanogaster* β -heterochromatin binds specifically to nuclear lamins in vitro and the nuclear envelope in situ. *Gene* **171**: 171–176.
- Barrowman J, Hamblet C, George CM, Michaelis S. 2008. Analysis of prelamin A biogenesis reveals the nucleus to be a CaaX processing compartment. *Mol Biol Cell* **19**: 5398–5408.
- Beaudouin J, Gerlich D, Daigle N, Eils R, Ellenberg J. 2002. Nuclear envelope breakdown proceeds by microtubule-induced tearing of the lamina. *Cell* **108**: 83–96.
- Bechert K, Lagos-Quintana M, Harborth J, Weber K, Osborn M. 2003. Effects of expressing lamin A mutant protein causing Emery-Dreifuss muscular dystrophy and familial partial lipodystrophy in HeLa cells. *Exp Cell Res* **286**: 75–86.
- Beck LA, Hosick TJ, Sinensky M. 1990. Isoprenylation is required for the processing of the lamin A precursor. *J Cell Biol* **110**: 1489–1499.
- Belmont AS, Zhai Y, Thilenius A. 1993. Lamin B distribution and association with peripheral chromatin revealed by optical sectioning and electron microscopy tomography. *J Cell Biol* **123**: 1671–1685.
- Ben-Harush K, Wiesel N, Frenkiel-Krispin D, Moeller D, Soreq E, Aebi U, Herrmann H, Gruenbaum Y, Medalia O. 2009. The supramolecular organization of the *C. elegans* nuclear lamin filament. *J Mol Biol* **386**: 1392–1402.
- Benavente R, Krohne G. 1986. Involvement of nuclear lamins in postmitotic reorganization of chromatin as demonstrated by microinjection of lamin antibodies. *J Cell Biol* **103**: 1847–1854.
- Benavente R, Krohne G, Franke WW. 1985. Cell type-specific expression of nuclear lamina proteins during development of *Xenopus laevis*. *Cell* **41**: 177–190.
- Boguslavsky RL, Stewart CL, Worman HJ. 2006. Nuclear lamin A inhibits adipocyte differentiation: implications for Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* **15**: 653–663.
- Boyartchuk VL, Ashby MN, Rine J. 1997. Modulation of Ras and a-factor function by carboxyl-terminal proteolysis. *Science* **275**: 1796–1800.
- Boyle S, Gilchrist S, Bridger JM, Mahy NL, Ellis JA, Bickmore WA. 2001. The spatial organization of human chromosomes within the nuclei of normal and emerin-mutant cells. *Hum Mol Genet* **10**: 211–219.
- Broers JL, Machiels BM, van Eys GJ, Kuipers HJ, Manders EM, van Driel R, Ramaekers FC. 1999. Dynamics of the nuclear lamina as monitored by GFP-tagged A-type lamins. *J Cell Sci* **112**: 3463–3475.
- Burke B. 1990. On the cell-free association of lamins A and C with metaphase chromosomes. *Exp Cell Res* **186**: 169–176.
- Burke B, Roux KJ. 2009. Nuclei take a position: Managing nuclear location. *Dev Cell* **17**: 587–597.
- Cao K, Capell BC, Erdos MR, Djabali K, Collins FS. 2007. A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. *Proc Natl Acad Sci* **104**: 4949–4954.
- Cohen M, Lee KK, Wilson KL, Gruenbaum Y. 2001. Transcriptional repression, apoptosis, human disease and the functional evolution of the nuclear lamina. *Trends Biochem Sci* **26**: 41–47.
- Collas P. 1999. Sequential PKC- and Cdc2-mediated phosphorylation events elicit zebrafish nuclear envelope disassembly. *J Cell Sci* **112**: 977–987.
- Constantinescu D, Gray HL, Sammak PJ, Schatten GP, Csoka AB. 2006. Lamin A/C expression is a marker of mouse and human embryonic stem cell differentiation. *Stem Cells* **24**: 177–185.
- Corrigan DP, Kuszczak D, Rusinol AE, Thewke DP, Hrycyna CA, Michaelis S, Sinensky MS. 2005. Prelamin A endoproteolytic processing in vitro by recombinant Zmpste24. *Biochem J* **387**: 129–138.
- Cremer M, von Hase J, Volm T, Brero A, Kreth G, Walter J, Fischer C, Solovei I, Cremer C, Cremer T. 2001. Non-random radial higher-order chromatin arrangements in nuclei of diploid human cells. *Chromosome Res* **9**: 541–567.
- Crisp M, Liu Q, Roux K, Rattner JB, Shanahan C, Burke B, Stahl PD, Hodzic D. 2006. Coupling of the nucleus and cytoplasm: Role of the LINC complex. *J Cell Biol* **172**: 41–53.
- Dahl KN, Ribeiro AJ, Lammerding J. 2008. Nuclear shape, mechanics, and mechanotransduction. *Circ Res* **102**: 1307–1318.
- Dahl KN, Scaffidi P, Islam ME, Yodh AG, Wilson KL, Misteli T. 2006. Distinct structural and mechanical properties of the nuclear lamina in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci* **103**: 10271–10276.
- Davies BS, Fong LG, Yang SH, Coffinier C, Young SG. 2009. The posttranslational processing of prelamin A and disease. *Annu Rev Genomics Hum Genet* **10**: 153–174.
- Dechat T, Adam SA, Goldman RD. 2008a. Nuclear lamins and chromatin: When structure meets function. *Adv Enzyme Regul* **49**: 157–166.
- Dechat T, Gajewski A, Korbei B, Gerlich D, Daigle N, Hara-guchi T, Furukawa K, Ellenberg J, Foisner R. 2004. LAP2 α and BAF transiently localize to telomeres and specific regions on chromatin during nuclear assembly. *J Cell Sci* **117**: 6117–6128.
- Dechat T, Pfliegerhaer K, Sengupta K, Shimi T, Shumaker DK, Solimando L, Goldman RD. 2008b. Nuclear lamins: Major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev* **22**: 832–853.
- Dechat T, Shimi T, Adam SA, Rusinol AE, Andres DA, Spielmann HP, Sinensky MS, Goldman RD. 2007. Alterations in mitosis and cell cycle progression caused by a mutant lamin A known to accelerate human aging. *Proc Natl Acad Sci* **104**: 4955–4960.
- Delbarre E, Tramier M, Coppey-Moisand M, Gaillard C, Courvalin JC, Buendia B. 2006. The truncated prelamin A in Hutchinson-Gilford progeria syndrome alters segregation of A-type and B-type lamin homopolymers. *Hum Mol Genet* **15**: 1113–1122.

- Dessev G, Goldman R. 1988. Meiotic breakdown of nuclear envelope in oocytes of *Spisula solidissima* involves phosphorylation and release of nuclear lamin. *Dev Biol* **130**: 543–550.
- Dessev G, Iovcheva-Dessev C, Bischoff JR, Beach D, Goldman R. 1991. A complex containing p34cdc2 and cyclin B phosphorylates the nuclear lamin and disassembles nuclei of clam oocytes in vitro. *J Cell Biol* **112**: 523–533.
- Dessev G, Iovcheva C, Tasheva B, Goldman R. 1988. Protein kinase activity associated with the nuclear lamina. *Proc Natl Acad Sci* **85**: 2994–2998.
- Dessev G, Palazzo R, Rebhun L, Goldman R. 1989. Disassembly of the nuclear envelope of *spisula* oocytes in a cell-free system. *Dev Biol* **131**: 496–504.
- Dhe-Paganon S, Werner ED, Chi YI, Shoelson SE. 2002. Structure of the globular tail of nuclear lamin. *J Biol Chem* **277**: 17381–17384.
- Dreuillet C, Harper M, Tillit J, Kress M, Ernoult-Lange M. 2008. Mislocalization of human transcription factor MOK2 in the presence of pathogenic mutations of lamin A/C. *Biol Cell* **100**: 51–61.
- Dreuillet C, Tillit J, Kress M, Ernoult-Lange M. 2002. In vivo and in vitro interaction between human transcription factor MOK2 and nuclear lamin A/C. *Nucleic Acids Res* **30**: 4634–4642.
- Espada J, Varela I, Flores I, Ugalde AP, Cadinanos J, Pendas AM, Stewart CL, Tryggvason K, Blasco MA, Freije JM, et al. 2008. Nuclear envelope defects cause stem cell dysfunction in premature-aging mice. *J Cell Biol* **181**: 27–35.
- Farnsworth CC, Gelb MH, Glomset JA. 1990. Identification of geranylgeranyl-modified proteins in HeLa cells. *Science* **247**: 320–322.
- Favreau C, Dubosclard E, Ostlund C, Vigouroux C, Capeau J, Wehnert M, Higuert D, Worman HJ, Courvalin JC, Buendia B. 2003. Expression of lamin A mutated in the carboxyl-terminal tail generates an aberrant nuclear phenotype similar to that observed in cells from patients with Dunnigan-type partial lipodystrophy and Emery-Dreifuss muscular dystrophy. *Exp Cell Res* **282**: 14–23.
- Favreau C, Higuert D, Courvalin JC, Buendia B. 2004. Expression of a mutant lamin A that causes Emery-Dreifuss muscular dystrophy inhibits in vitro differentiation of C2C12 myoblasts. *Mol Cell Biol* **24**: 1481–1492.
- Fawcett DW. 1966. On the occurrence of a fibrous lamina on the inner aspect of the nuclear envelope in certain cells of vertebrates. *Am J Anat* **119**: 129–145.
- Ferraro A, Eufemi M, Cervoni L, Marinetti R, Turano C. 1989. Glycosylated forms of nuclear lamins. *FEBS Lett* **257**: 241–246.
- Finlan LE, Sproul D, Thomson I, Boyle S, Kerr E, Perry P, Ylstra B, Chubb JR, Bickmore WA. 2008. Recruitment to the nuclear periphery can alter expression of genes in human cells. *PLoS Genet* **4**: e1000039.
- Frasch M, Paddy M, Saumweber H. 1988. Developmental and mitotic behaviour of two novel groups of nuclear envelope antigens of *Drosophila melanogaster*. *J Cell Sci* **90**: 247–263.
- Frock RL, Kudlow BA, Evans AM, Jameson SA, Hauschka SD, Kennedy BK. 2006. Lamin A/C and emerin are critical for skeletal muscle satellite cell differentiation. *Genes Dev* **20**: 486–500.
- Furukawa K, Hotta Y. 1993. cDNA cloning of a germ cell specific lamin B3 from mouse spermatocytes and analysis of its function by ectopic expression in somatic cells. *Embo J* **12**: 97–106.
- Galiouva G, Bartova E, Raska I, Krejci J, Kozubek S. 2008. Chromatin changes induced by lamin A/C deficiency and the histone deacetylase inhibitor trichostatin A. *Eur J Cell Biol* **87**: 291–303.
- Georgatos SD, Pyrpasopoulou A, Theodoropoulos PA. 1997. Nuclear envelope breakdown in mammalian cells involves stepwise lamina disassembly and microtubule-drive deformation of the nuclear membrane. *J Cell Sci* **110**: 2129–2140.
- Gerace L, Blobel G. 1980. The nuclear envelope lamina is reversibly depolymerized during mitosis. *Cell* **19**: 277–287.
- Glass JR, Gerace L. 1990. Lamins A and C bind and assemble at the surface of mitotic chromosomes. *J Cell Biol* **111**: 1047–1057.
- Goldberg M, Harel A, Brandeis M, Rechsteiner T, Richmond TJ, Weiss AM, Gruenbaum Y. 1999. The tail domain of lamin Dm0 binds histones H2A and H2B. *Proc Natl Acad Sci* **96**: 2852–2857.
- Goldberg MW, Fiserova J, Huttenlauch I, Stick R. 2008a. A new model for nuclear lamina organization. *Biochem Soc Trans* **36**: 1339–1343.
- Goldberg MW, Huttenlauch I, Hutchison CJ, Stick R. 2008b. Filaments made from A- and B-type lamins differ in structure and organization. *J Cell Sci* **121**: 215–225.
- Goldman RD, Grin B, Mendez MG, Kuczmarski ER. 2008. Intermediate filaments: versatile building blocks of cell structure. *Curr Opin Cell Biol* **20**: 28–34.
- Goldman AE, Maul G, Steinert PM, Yang HY, Goldman RD. 1986. Keratin-like proteins that coisolate with intermediate filaments of BHK-21 cells are nuclear lamins. *Proc Natl Acad Sci* **83**: 3839–3843.
- Goldman AE, Moir RD, Montag-Lowy M, Stewart M, Goldman RD. 1992. Pathway of incorporation of microinjected lamin A into the nuclear envelope. *J Cell Biol* **119**: 725–735.
- Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, et al. 2004. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci* **101**: 8963–8968.
- Gonzalez JM, Navarro-Puche A, Casar B, Crespo P, Andres V. 2008. Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the nuclear envelope. *J Cell Biol* **183**: 653–666.
- Gonzalez-Suarez I, Redwood AB, Gonzalo S. 2009a. Loss of A-type lamins and genomic instability. *Cell Cycle* **8**: 3860–3865.
- Gonzalez-Suarez I, Redwood AB, Perkins SM, Vermolen B, Lichtensztejn D, Grotzky DA, Morgado-Palacin L, Gapud EJ, Sleckman BP, Sullivan T, et al. 2009b. Novel roles for A-type lamins in telomere biology and the DNA damage response pathway. *Embo J* **28**: 2414–2427.
- Goss VL, Hocevar BA, Thompson LJ, Stratton CA, Burns DJ, Fields AP. 1994. Identification of nuclear β II protein

T. Dechat et al.

- kinase C as a mitotic lamin kinase. *J Biol Chem* **269**: 19074–19080.
- Guelen L, Pagie L, Brasset E, Meuleman W, Faza MB, Talhout W, Eussen BH, de Klein A, Wessels L, de Laat W, et al. 2008. Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. *Nature* **453**: 948–951.
- Guilly MN, Kolb JP, Gosti F, Godeau F, Courvalin JC. 1990. Lamins A and C are not expressed at early stages of human lymphocyte differentiation. *Exp Cell Res* **189**: 145–147.
- Haithcock E, Dayani Y, Neufeld E, Zahand AJ, Feinstein N, Mattout A, Gruenbaum Y, Liu J. 2005. Age-related changes of nuclear architecture in *Caenorhabditis elegans*. *Proc Natl Acad Sci USA* **102**: 16690–16695.
- Han X, Feng X, Rattner JB, Smith H, Bose P, Suzuki K, Solomon MA, Scott MS, Burke BE, Riabowol K. 2008. Tethering by lamin A stabilizes and targets the ING1 tumour suppressor. *Nat Cell Biol* **10**: 1333–1340.
- Haraguchi T, Kojidani T, Koujin T, Shimi T, Osakada H, Mori C, Yamamoto A, Hiraoka Y. 2008. Live cell imaging and electron microscopy reveal dynamic processes of BAF-directed nuclear envelope assembly. *J Cell Sci* **121**: 2540–2554.
- Harper M, Tillit J, Kress M, Ernoult-Lange M. 2009. Phosphorylation-dependent binding of human transcription factor MOK2 to lamin A/C. *FEBS J* **276**: 3137–3147.
- Heald R, McKeon F. 1990. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. *Cell* **61**: 579–589.
- Heessen S, Fornerod M. 2007. The inner nuclear envelope as a transcription factor resting place. *EMBO Rep* **8**: 914–919.
- Heitlinger E, Peter M, Haner M, Lustig A, Aebi U, Nigg EA. 1991. Expression of chicken lamin B2 in *Escherichia coli*: Characterization of its structure, assembly, and molecular interactions. *J Cell Biol* **113**: 485–495.
- Hennekes H, Peter M, Weber K, Nigg EA. 1993. Phosphorylation on protein kinase C sites inhibits nuclear import of lamin B2. *J Cell Biol* **120**: 1293–1304.
- Houben F, Ramaekers FC, Snoeckx LH, Broers JL. 2007. Role of nuclear lamina-cytoskeleton interactions in the maintenance of cellular strength. *Biochim Biophys Acta* **1773**: 675–686.
- Houben F, Willems CH, Declercq IL, Hochstenbach K, Kamps MA, Snoeckx LH, Ramaekers FC, Broers JL. 2009. Disturbed nuclear orientation and cellular migration in A-type lamin deficient cells. *Biochim Biophys Acta* **1793**: 312–324.
- Huang S, Risques RA, Martin GM, Rabinovitch PS, Oshima J. 2008. Accelerated telomere shortening and replicative senescence in human fibroblasts overexpressing mutant and wild-type lamin A. *Exp Cell Res* **314**: 82–91.
- Ito H, Koyama Y, Takano M, Ishii K, Maeno M, Furukawa K, Horigome T. 2007. Nuclear envelope precursor vesicle targeting to chromatin is stimulated by protein phosphatase 1 in *Xenopus* egg extracts. *Exp Cell Res* **313**: 1897–1910.
- Ivorra C, Kubicek M, Gonzalez JM, Sanz-Gonzalez SM, Alvarez-Barrientos A, O'Connor JE, Burke B, Andres V. 2006. A mechanism of AP-1 suppression through interaction of c-Fos with lamin A/C. *Genes Dev* **20**: 307–320.
- Ji JY, Lee RT, Vergnes L, Fong LG, Stewart CL, Reue K, Young SG, Zhang Q, Shanahan CM, Lammending J. 2007. Cell nuclei spin in the absence of lamin b1. *J Biol Chem* **282**: 20015–20026.
- Johnson BR, Nitta RT, Frock RL, Mounkes L, Barbie DA, Stewart CL, Harlow E, Kennedy BK. 2004. A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. *Proc Natl Acad Sci* **101**: 9677–9682.
- Kandert S, Wehnert M, Muller CR, Buendia B, Dabauvalle MC. 2009. Impaired nuclear functions lead to increased senescence and inefficient differentiation in human myoblasts with a dominant p.R545C mutation in the LMNA gene. *Eur J Cell Biol* **88**: 593–608.
- Kennedy BK, Barbie DA, Classon M, Dyson N, Harlow E. 2000. Nuclear organization of DNA replication in primary mammalian cells. *Genes Dev* **14**: 2855–2868.
- Ketema M, Wilhelmsen K, Kuikman I, Janssen H, Hodzic D, Sonnenberg A. 2007. Requirements for the localization of nesprin-3 at the nuclear envelope and its interaction with plectin. *J Cell Sci* **120**: 3384–3394.
- Kilic F, Dalton MB, Burrell SK, Mayer JP, Patterson SD, Sinensky M. 1997. In vitro assay and characterization of the farnesylation-dependent prelamin A endoprotease. *J Biol Chem* **272**: 5298–5304.
- Kosak ST, Skok JA, Medina KL, Riblet R, Le Beau MM, Fisher AG, Singh H. 2002. Subnuclear compartmentalization of immunoglobulin loci during lymphocyte development. *Science* **296**: 158–162.
- Krimm I, Ostlund C, Gilquin B, Couprie J, Hossenlopp P, Mornon JP, Bonne G, Courvalin JC, Worman HJ, Zinn-Justin S. 2002. The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy. *Structure* **10**: 811–823.
- Kudlow BA, Stanfel MN, Burtner CR, Johnston ED, Kennedy BK. 2008. Suppression of proliferative defects associated with processing-defective lamin A mutants by hTERT or inactivation of p53. *Mol Biol Cell* **19**: 5238–5248.
- Kumaran RI, Spector DL. 2008. A genetic locus targeted to the nuclear periphery in living cells maintains its transcriptional competence. *J Cell Biol* **180**: 51–65.
- Lee JS, Hale CM, Panorchan P, Khatau SB, George JB, Tseng Y, Stewart CL, Hodzic D, Wirtz D. 2007. Nuclear lamin A/C deficiency induces defects in cell mechanics, polarization, and migration. *Biophys J* **93**: 2542–2552.
- Lee DC, Welton KL, Smith ED, Kennedy BK. 2009. A-type nuclear lamins act as transcriptional repressors when targeted to promoters. *Exp Cell Res* **315**: 996–1007.
- Lehner CF, Furstenberger G, Eppenberger HM, Nigg EA. 1986. Biogenesis of the nuclear lamina: in vivo synthesis and processing of nuclear protein precursors. *Proc Natl Acad Sci* **83**: 2096–2099.
- Lehner CF, Stick R, Eppenberger HM, Nigg EA. 1987. Differential expression of nuclear lamin proteins during chicken development. *J Cell Biol* **105**: 577–587.
- Lenz-Bohme B, Wismar J, Fuchs S, Reifegerste R, Buchner E, Betz H, Schmitt B. 1997. Insertional mutation of the

- Drosophila* nuclear lamin Dm0 gene results in defective nuclear envelopes, clustering of nuclear pore complexes, and accumulation of annulate lamellae. *J Cell Biol* **137**: 1001–1016.
- Leukel M, Jost E. 1995. Two conserved serines in the nuclear localization signal flanking region are involved in the nuclear targeting of human lamin A. *Eur J Cell Biol* **68**: 133–142.
- Leung GK, Schmidt WK, Bergo MO, Gavino B, Wong DH, Tam A, Ashby MN, Michaelis S, Young SG. 2001. Biochemical studies of Zmpste24-deficient mice. *J Biol Chem* **276**: 29051–29058.
- Lin F, Worman HJ. 1993. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J Biol Chem* **268**: 16321–16326.
- Liu J, Rolef Ben-Shahar T, Riemer D, Treinin M, Spann P, Weber K, Fire A, Gruenbaum Y. 2000. Essential roles for *Caenorhabditis elegans* lamin gene in nuclear organization, cell cycle progression, and spatial organization of nuclear pore complexes. *Mol Biol Cell* **11**: 3937–3947.
- Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang JD, Li KM, Chau PY, Chen DJ, et al. 2005. Genomic instability in laminopathy-based premature aging. *Nat Med* **11**: 780–785.
- Lloyd DJ, Trembath RC, Shackleton S. 2002. A novel interaction between lamin A and SREBP1: Implications for partial lipodystrophy and other laminopathies. *Hum Mol Genet* **11**: 769–777.
- Loewinger L, McKeon F. 1988. Mutations in the nuclear lamin proteins resulting in their aberrant assembly in the cytoplasm. *Embo J* **7**: 2301–2309.
- Lopez-Soler RI, Moir RD, Spann TP, Stick R, Goldman RD. 2001. A role for nuclear lamins in nuclear envelope assembly. *J Cell Biol* **154**: 61–70.
- Lourim D, Lin JJ. 1989. Expression of nuclear lamin A and muscle-specific proteins in differentiating muscle cells in ovo and in vitro. *J Cell Biol* **109**: 495–504.
- Luderus ME, de Graaf A, Mattia E, den Blaauwen JL, Grande MA, de Jong L, van Driel R. 1992. Binding of matrix attachment regions to lamin B1. *Cell* **70**: 949–959.
- Luderus ME, den Blaauwen JL, de Smit OJ, Compton DA, van Driel R. 1994. Binding of matrix attachment regions to lamin polymers involves single-stranded regions and the minor groove. *Mol Cell Biol* **14**: 6297–6305.
- Lutz RJ, Trujillo MA, Denham KS, Wenger L, Sinensky M. 1992. Nucleoplasmic localization of prelamin A: Implications for prenylation-dependent lamin A assembly into the nuclear lamina. *Proc Natl Acad Sci* **89**: 3000–3004.
- Ma L, Tsai MY, Wang S, Lu B, Chen R, Iii JR, Zhu X, Zheng Y. 2009. Requirement for Nudel and dynein for assembly of the lamin B spindle matrix. *Nat Cell Biol* **11**: 247–256.
- Machiels BM, Broers JL, Raymond Y, de Ley L, Kuipers HJ, Caberg NE, Ramaekers FC. 1995. Abnormal A-type lamin organization in a human lung carcinoma cell line. *Eur J Cell Biol* **67**: 328–335.
- Machiels BM, Henfling ME, Schutte B, van Engeland M, Broers JL, Ramaekers FC. 1996. Subcellular localization of proteasomes in apoptotic lung tumor cells and persistence as compared to intermediate filaments. *Eur J Cell Biol* **70**: 250–259.
- Maison C, Pyrpasopoulou A, Theodoropoulos PA, Georgatos SD. 1997. The inner nuclear membrane protein LAP1 forms a native complex with B-type lamins and partitions with spindle-associated mitotic vesicles. *Embo J* **16**: 4839–4850.
- Malhas AN, Lee CE, Vaux DJ. 2009. Lamin B1 controls oxidative stress responses via Oct-1. *J Cell Biol* **184**: 45–55.
- Malhas A, Lee CE, Sanders R, Saunders NJ, Vaux DJ. 2007. Defects in lamin B1 expression or processing affect interphase chromosome position and gene expression. *J Cell Biol* **176**: 593–603.
- Manju K, Muralikrishna B, Parnaik VK. 2006. Expression of disease-causing lamin A mutants impairs the formation of DNA repair foci. *J Cell Sci* **119**: 2704–2714.
- Mariappan I, Parnaik VK. 2005. Sequestration of pRb by cyclin D3 causes intranuclear reorganization of lamin A/C during muscle cell differentiation. *Mol Biol Cell* **16**: 1948–1960.
- Mariappan I, Gurung R, Thanumalayan S, Parnaik VK. 2007. Identification of cyclin D3 as a new interaction partner of lamin A/C. *Biochem Biophys Res Commun* **355**: 981–985.
- Markiewicz E, Ledran M, Hutchison CJ. 2005. Remodelling of the nuclear lamina and nucleoskeleton is required for skeletal muscle differentiation in vitro. *J Cell Sci* **118**: 409–420.
- Markiewicz E, Dechat T, Foisner R, Quinlan RA, Hutchison CJ. 2002. Lamin A/C binding protein LAP2alpha is required for nuclear anchorage of retinoblastoma protein. *Mol Biol Cell* **13**: 4401–4413.
- Mattout A, Goldberg M, Tzur Y, Margalit A, Gruenbaum Y. 2007. Specific and conserved sequences in *D melanogaster* and *C elegans* lamins and histone H2A mediate the attachment of lamins to chromosomes. *J Cell Sci* **120**: 77–85.
- McClintock D, Gordon LB, Djabali K. 2006. Hutchinson-Gilford progeria mutant lamin A primarily targets human vascular cells as detected by an anti-Lamin A G608G antibody. *Proc Natl Acad Sci* **103**: 2154–2159.
- McKeon FD, Kirschner MW, Caput D. 1986. Homologies in both primary and secondary structure between nuclear envelope and intermediate filament proteins. *Nature* **319**: 463–468.
- Meaburn KJ, Cabuy E, Bonne G, Levy N, Morris GE, Novelli G, Kill IR, Bridger JM. 2007. Primary laminopathy fibroblasts display altered genome organization and apoptosis. *Aging Cell* **6**: 139–153.
- Melcer S, Gruenbaum Y, Krohne G. 2007. Invertebrate lamins. *Exp Cell Res* **313**: 2157–2166.
- Moir RD, Montag-Low M, Goldman RD. 1994. Dynamic properties of nuclear lamins: lamin B is associated with sites of DNA replication. *J Cell Biol* **125**: 1201–1212.
- Moir RD, Yoon M, Khuon S, Goldman RD. 2000. Nuclear lamins A and B1: Different pathways of assembly during nuclear envelope formation in living cells. *J Cell Biol* **151**: 1155–1168.
- Molloy S, Little M. 1992. p34cdc2 kinase-mediated release of lamins from nuclear ghosts is inhibited by cAMP-dependent protein kinase. *Exp Cell Res* **201**: 494–499.
- Muchir A, van Engelen BG, Lammens M, Mislow JM, McNally E, Schwartz K, Bonne G. 2003. Nuclear envelope

T. Dechat et al.

- alterations in fibroblasts from LGMD1B patients carrying nonsense Y259X heterozygous or homozygous mutation in lamin A/C gene. *Exp Cell Res* **291**: 352–362.
- Muralikrishna B, Dhawan J, Rangaraj N, Parnaik VK. 2001. Distinct changes in intranuclear lamin A/C organization during myoblast differentiation. *J Cell Sci* **114**: 4001–4011.
- Nakajima N, Abe K. 1995. Genomic structure of the mouse A-type lamin gene locus encoding somatic and germ cell-specific lamins. *FEBS Lett* **365**: 108–114.
- Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalick J, Otway R, Verheyen E, et al. 2004. Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C-deficient mice. *J Clin Invest* **113**: 357–369.
- Ostlund C, Bonne G, Schwartz K, Worman HJ. 2001. Properties of lamin A mutants found in Emery-Dreifuss muscular dystrophy, cardiomyopathy and Dunnigan-type partial lipodystrophy. *J Cell Sci* **114**: 4435–4445.
- Ottaviani A, Rival-Gervier S, Boussouar A, Foerster AM, Rondier D, Sacconi S, Desnuelle C, Gilson E, Magdini F. 2009a. The D4Z4 macrosatellite repeat acts as a CTCF and A-type lamins-dependent insulator in facio-scapulo-humeral dystrophy. *PLoS Genet* **5**: e1000394.
- Ottaviani A, Schluth-Bolard C, Rival-Gervier S, Boussouar A, Rondier D, Foerster AM, Morere J, Bauwens S, Gazzo S, Callet-Bauchu E, et al. 2009b. Identification of a perinuclear positioning element in human subtelomeres that requires A-type lamins and CTCF. *Embo J* **28**: 2428–2436.
- Ottaviano Y, Gerace L. 1985. Phosphorylation of the nuclear lamins during interphase and mitosis. *J Biol Chem* **260**: 624–632.
- Ozaki T, Saijo M, Murakami K, Enomoto H, Taya Y, Sakiyama S. 1994. Complex formation between lamin A and the retinoblastoma gene product: Identification of the domain on lamin A required for its interaction. *Oncogene* **9**: 2649–2653.
- Paddy MR, Belmont AS, Saumweber H, Agard DA, Sedat JW. 1990. Interphase nuclear envelope lamins form a discontinuous network that interacts with only a fraction of the chromatin in the nuclear periphery. *Cell* **62**: 89–106.
- Pajerowski JD, Dahl KN, Zhong FL, Sammak PJ, Discher DE. 2007. Physical plasticity of the nucleus in stem cell differentiation. *Proc Natl Acad Sci* **104**: 15619–15624.
- Panorchan P, Wirtz D, Tseng Y. 2004b. Structure-function relationship of biological gels revealed by multiple-particle tracking and differential interference contrast microscopy: The case of human lamin networks. *Phys Rev E Stat Nonlin Soft Matter Phys* **70**: 041906.
- Panorchan P, Schafer BW, Wirtz D, Tseng Y. 2004a. Nuclear envelope breakdown requires overcoming the mechanical integrity of the nuclear lamina. *J Biol Chem* **279**: 43462–43467.
- Parry DA, Conway JF, Steinert PM. 1986. Structural studies on lamin. Similarities and differences between lamin and intermediate-filament proteins. *Biochem J* **238**: 305–308.
- Pegoraro G, Kubben N, Wickert U, Gohler H, Hoffmann K, Misteli T. 2009. Ageing-related chromatin defects through loss of the NURD complex. *Nat Cell Biol* **11**: 1261–1267.
- Peter M, Kitten GT, Lehner CF, Vorburger K, Bailer SM, Maridor G, Nigg EA. 1989. Cloning and sequencing of cDNA clones encoding chicken lamins A and B1 and comparison of the primary structures of vertebrate A- and B-type lamins. *J Mol Biol* **208**: 393–404.
- Peter M, Nakagawa J, Doree M, Labbe JC, Nigg EA. 1990. In vitro disassembly of the nuclear lamina and M phase-specific phosphorylation of lamins by cdc2 kinase. *Cell* **61**: 591–602.
- Pickersgill H, Kalverda B, de Wit E, Talhout W, Fornerod M, van Steensel B. 2006. Characterization of the *Drosophila melanogaster* genome at the nuclear lamina. *Nat Genet* **38**: 1005–1014.
- Prather RS, Sims MM, Maul GG, First NL, Schatten G. 1989. Nuclear lamin antigens are developmentally regulated during porcine and bovine embryogenesis. *Biol Reprod* **41**: 123–132.
- Rauner M, Sipos W, Goettsch C, Wutzl A, Foisner R, Pietschmann P, Hofbauer LC. 2009. Inhibition of lamin A/C attenuates osteoblast differentiation and enhances RANKL-dependent osteoclastogenesis. *J Bone Miner Res* **24**: 78–86.
- Reddy KL, Zullo JM, Bertolino E, Singh H. 2008. Transcriptional repression mediated by repositioning of genes to the nuclear lamina. *Nature* **452**: 243–247.
- Riemer D, Stuurman N, Berrios M, Hunter C, Fisher PA, Weber K. 1995. Expression of *Drosophila* lamin C is developmentally regulated: Analogies with vertebrate A-type lamins. *J Cell Sci* **108**: 3189–3198.
- Rober RA, Weber K, Osborn M. 1989. Differential timing of nuclear lamin A/C expression in the various organs of the mouse embryo and the young animal: A developmental study. *Development* **105**: 365–378.
- Rober RA, Sauter H, Weber K, Osborn M. 1990. Cells of the cellular immune and hemopoietic system of the mouse lack lamins A/C: distinction versus other somatic cells. *J Cell Sci* **95**: 587–598.
- Rodriguez S, Coppede F, Sagelius H, Eriksson M. 2009. Increased expression of the Hutchinson-Gilford progeria syndrome truncated lamin A transcript during cell aging. *Eur J Hum Genet* **17**: 928–937.
- Rusinol AE, Sinensky MS. 2006. Farnesylated lamins, progeroid syndromes and farnesyl transferase inhibitors. *J Cell Sci* **119**: 3265–3272.
- Scaffidi P, Misteli T. 2006. Lamin A-dependent nuclear defects in human aging. *Science* **312**: 1059–1063.
- Scaffidi P, Misteli T. 2008. Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. *Nat Cell Biol* **10**: 452–459.
- Schape J, Prausse S, Radmacher M, Stick R. 2009. Influence of lamin A on the mechanical properties of amphibian oocyte nuclei measured by atomic force microscopy. *Biophys J* **96**: 4319–4325.
- Schatten G, Maul GG, Schatten H, Chaly N, Simerly C, Balczon R, Brown DL. 1985. Nuclear lamins and peripheral nuclear antigens during fertilization and embryogenesis in mice and sea urchins. *Proc Natl Acad Sci* **82**: 4727–4731.
- Schermelleh L, Carlton PM, Haase S, Shao L, Winoto L, Kner P, Burke B, Cardoso MC, Agard DA, Gustafsson MG, et al. 2008. Subdiffraction multicolor imaging of

- the nuclear periphery with 3D structured illumination microscopy. *Science* **320**: 1332–1336.
- Shevelyov YY, Lavrov SA, Mikhaylova LM, Nurminsky ID, Kulathinal RJ, Egorova KS, Rozovsky YM, Nurminsky DI. 2009. The B-type lamin is required for somatic repression of testis-specific gene clusters. *Proc Natl Acad Sci* **106**: 3282–3287.
- Shimi T, Pflieger K, Kojima S, Pack CG, Solovei I, Goldman AE, Adam SA, Shumaker DK, Kinjo M, Cremer T, et al. 2008. The A- and B-type nuclear lamin networks: microdomains involved in chromatin organization and transcription. *Genes Dev* **22**: 3409–3421.
- Shumaker DK, Dechat T, Kohlmaier A, Adam SA, Bozovsky MR, Erdos MR, Eriksson M, Goldman AE, Khun S, Collins FS, et al. 2006. Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. *Proc Natl Acad Sci* **103**: 8703–8708.
- Shumaker DK, Lopez-Soler RI, Adam SA, Herrmann H, Moir RD, Spann TP, Goldman RD. 2005. Functions and dysfunctions of the nuclear lamin Ig-fold domain in nuclear assembly, growth, and Emery-Dreifuss muscular dystrophy. *Proc Natl Acad Sci USA* **102**: 15494–15499.
- Shumaker DK, Solimando L, Sengupta K, Shimi T, Adam SA, Grunwald A, Strelkov SV, Aebi U, Cardoso MC, Goldman RD. 2008. The highly conserved nuclear lamin Ig-fold binds to PCNA: Its role in DNA replication. *J Cell Biol* **181**: 269–280.
- Solovei I, Schermelleh L, During K, Engelhardt A, Stein S, Cremer C, Cremer T. 2004. Differences in centromere positioning of cycling and postmitotic human cell types. *Chromosoma* **112**: 410–423.
- Spann TP, Goldman AE, Wang C, Huang S, Goldman RD. 2002. Alteration of nuclear lamin organization inhibits RNA polymerase II-dependent transcription. *J Cell Biol* **156**: 603–608.
- Stewart-Hutchinson PJ, Hale CM, Wirtz D, Hodzic D. 2008. Structural requirements for the assembly of LINC complexes and their function in cellular mechanical stiffness. *Exp Cell Res* **314**: 1892–1905.
- Stewart C, Burke B. 1987. Teratocarcinoma stem cells and early mouse embryos contain only a single major lamin polypeptide closely resembling lamin B. *Cell* **51**: 383–392.
- Stick R, Angres B, Lehner CF, Nigg EA. 1988. The fates of chicken nuclear lamin proteins during mitosis: Evidence for a reversible redistribution of lamin B2 between inner nuclear membrane and elements of the endoplasmic reticulum. *J Cell Biol* **107**: 397–406.
- Strelkov SV, Schumacher J, Burkhard P, Aebi U, Herrmann H. 2004. Crystal structure of the human lamin A coil 2B dimer: Implications for the head-to-tail association of nuclear lamins. *J Mol Biol* **343**: 1067–1080.
- Stuurman N, Heins S, Aebi U. 1998. Nuclear lamins: Their structure, assembly, and interactions. *J Struct Biol* **122**: 42–66.
- Stuurman N, Sasse B, Fisher PA. 1996. Intermediate filament protein polymerization: Molecular analysis of *Drosophila* nuclear lamin head-to-tail binding. *J Struct Biol* **117**: 1–15.
- Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Nagashima K, Stewart CL, Burke B. 1999. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol* **147**: 913–920.
- Taimen P, Pflieger K, Shimi T, Moller D, Ben-Harush K, Erdos MR, Adam SA, Herrmann H, Medalia O, Collins FS, et al. 2009a. A progeria mutation reveals functions for lamin A in nuclear assembly, architecture, and chromosome organization. *Proc Natl Acad Sci* **106**: 20788–20793.
- Taimen P, Pflieger K, Shimi T, Moller D, Ben-Harush K, Erdos MR, Adam SA, Herrmann H, Medalia O, Collins FS, et al. 2009b. A progeria mutation reveals functions for lamin A in nuclear assembly, architecture, and chromosome organization. *Proc Natl Acad Sci* **106**: 20788–20793.
- Tang CW, Maya-Mendoza A, Martin C, Zeng K, Chen S, Feret D, Wilson SA, Jackson DA. 2008. The integrity of a lamin-B1-dependent nucleoskeleton is a fundamental determinant of RNA synthesis in human cells. *J Cell Sci* **121**: 1014–1024.
- Taniura H, Glass C, Gerace L. 1995. A chromatin binding site in the tail domain of nuclear lamins that interacts with core histones. *J Cell Biol* **131**: 33–44.
- Thompson LJ, Bollen M, Fields AP. 1997. Identification of protein phosphatase 1 as a mitotic lamin phosphatase. *J Biol Chem* **272**: 29693–29697.
- Tilgner K, Wojciechowski K, Jahoda C, Hutchison C, Markiewicz E. 2009. Dynamic complexes of A-type lamins and emerin influence adipogenic capacity of the cell via nucleocytoplasmic distribution of beta-catenin. *J Cell Sci* **122**: 401–413.
- Tsai MY, Zheng Y. 2005. Aurora A kinase-coated beads function as microtubule-organizing centers and enhance RanGTP-induced spindle assembly. *Curr Biol* **15**: 2156–2163.
- Tsai MY, Wang S, Heidinger JM, Shumaker DK, Adam SA, Goldman RD, Zheng Y. 2006. A mitotic lamin B matrix induced by RanGTP required for spindle assembly. *Science* **311**: 1887–1893.
- Tzur YB, Wilson KL, Gruenbaum Y. 2006. SUN-domain proteins: ‘Velcro’ that links the nucleoskeleton to the cytoskeleton. *Nat Rev Mol Cell Biol* **7**: 782–788.
- Vaughan A, Alvarez-Reyes M, Bridger JM, Broers JL, Ramaekers FC, Wehnert M, Morris GE, Whitfield WGF, Hutchison CJ. 2001. Both emerin and lamin C depend on lamin A for localization at the nuclear envelope. *J Cell Sci* **114**: 2577–2590.
- Vergnes L, Peterfy M, Bergo MO, Young SG, Reue K. 2004. Lamin B1 is required for mouse development and nuclear integrity. *Proc Natl Acad Sci* **101**: 10428–10433.
- Verstraeten VL, Broers JL, Ramaekers FC, van Steensel MA. 2007. The nuclear envelope, a key structure in cellular integrity and gene expression. *Curr Med Chem* **14**: 1231–1248.
- Vigouroux C, Auclair M, Dubosclard E, Pouchelet M, Capeau J, Courvalin JC, Buendia B. 2001. Nuclear envelope disorganization in fibroblasts from lipodystrophic patients with heterozygous R482Q/W mutations in the lamin A/C gene. *J Cell Sci* **114**: 4459–4468.
- Vorburger K, Kitten GT, Nigg EA. 1989. Modification of nuclear lamin proteins by a mevalonic acid derivative

T. Dechat et al.

- occurs in reticulocyte lysates and requires the cysteine residue of the C-terminal CXXM motif. *Embo J* **8**: 4007–4013.
- Ward GE, Kirschner MW. 1990. Identification of cell cycle-regulated phosphorylation sites on nuclear lamin C. *Cell* **61**: 561–577.
- Wheeler MA, Davies JD, Zhang Q, Emerson LJ, Hunt J, Shanahan CM, Ellis JA. 2007. Distinct functional domains in nesprin-1 α and nesprin-2 β bind directly to emerin and both interactions are disrupted in X-linked Emery-Dreifuss muscular dystrophy. *Exp Cell Res* **313**: 2845–2857.
- Williams RR, Azuara V, Perry P, Sauer S, Dvorkina M, Jorgensen H, Roix J, McQueen P, Misteli T, Merckenschlager M, et al. 2006. Neural induction promotes large-scale chromatin reorganisation of the Mash1 locus. *J Cell Sci* **119**: 132–140.
- Winter-Vann AM, Casey PJ. 2005. Post-prenylation-processing enzymes as new targets in oncogenesis. *Nat Rev Cancer* **5**: 405–412.
- Yuan J, Simos G, Blobel G, Georgatos SD. 1991. Binding of lamin A to polynucleosomes. *J Biol Chem* **266**: 9211–9215.
- Zackroff RV, Goldman RD. 1979. In vitro assembly of intermediate filaments from baby hamster kidney (BHK-21) cells. *Proc Natl Acad Sci* **76**: 6226–6230.
- Zhang FL, Casey PJ. 1996. Protein prenylation: Molecular mechanisms and functional consequences. *Annu Rev Biochem* **65**: 241–269.
- Zhang YQ, Sarge KD. 2008. Sumoylation regulates lamin A function and is lost in lamin A mutants associated with familial cardiomyopathies. *J Cell Biol* **182**: 35–39.
- Zhang Q, Bethmann C, Worth NE, Davies JD, Wasner C, Feuer A, Ragnauth CD, Yi Q, Mellad JA, Warren DT, et al. 2007. Nesprin-1 and -2 are involved in the pathogenesis of Emery Dreifuss muscular dystrophy and are critical for nuclear envelope integrity. *Hum Mol Genet* **16**: 2816–2833.
- Zhao K, Harel A, Stuurman N, Guedalia D, Gruenbaum Y. 1996. Binding of matrix attachment regions to nuclear lamin is mediated by the rod domain and depends on the lamin polymerization state. *FEBS Lett* **380**: 161–164.
- Zink D, Amaral MD, Englmann A, Lang S, Clarke LA, Rudolph C, Alt F, Luther K, Braz C, Sadoni N, et al. 2004. Transcription-dependent spatial arrangements of CFTR and adjacent genes in human cell nuclei. *J Cell Biol* **166**: 815–825.

Cold Spring Harbor Perspectives in Biology

Nuclear Lamins

Thomas Dechat, Stephen A. Adam, Pekka Taimen, Takeshi Shimi and Robert D. Goldman

Cold Spring Harb Perspect Biol 2010; doi: 10.1101/cshperspect.a000547 originally published online September 8, 2010

Subject Collection [The Nucleus](#)

Nuclear Compartments: An Incomplete Primer to Nuclear Compartments, Bodies, and Genome Organization Relative to Nuclear Architecture

Andrew S. Belmont

Uncovering the Principles of Genome Folding by 3D Chromatin Modeling

Asli Yildirim, Lorenzo Boninsegna, Yuxiang Zhan, et al.

3D or Not 3D: Shaping the Genome during Development

Juliane Glaser and Stefan Mundlos

The Impact of Space and Time on the Functional Output of the Genome

Marcelo Nollmann, Isma Bennabi, Markus Götz, et al.

Chromatin Mechanisms Driving Cancer

Berkley Gryder, Peter C. Scacheri, Thomas Ried, et al.

Liquid–Liquid Phase Separation in Chromatin

Karsten Rippe

Mechanical Forces in Nuclear Organization

Yekaterina A. Miroshnikova and Sara A. Wickström

Imaging Organization of RNA Processing within the Nucleus

Jeetayu Biswas, Weihai Li, Robert H. Singer, et al.

Mechanisms of Chromosome Folding and Nuclear Organization: Their Interplay and Open Questions

Leonid Mirny and Job Dekker

Epigenetic Reprogramming in Early Animal Development

Zhenhai Du, Ke Zhang and Wei Xie

Essential Roles for RNA in Shaping Nuclear Organization

Sofia A. Quinodoz and Mitchell Guttman

The Molecular and Nuclear Dynamics of X-Chromosome Inactivation

François Dossin and Edith Heard

Structure, Maintenance, and Regulation of Nuclear Pore Complexes: The Gatekeepers of the Eukaryotic Genome

Marcela Raices and Maximiliano A. D'Angelo

The Nuclear Lamina

Xianrong Wong, Ashley J. Melendez-Perez and Karen L. Reddy

The Nuclear Pore Complex as a Transcription Regulator

Michael Chas Sumner and Jason Brickner

Physical Nature of Chromatin in the Nucleus

Kazuhiro Maeshima, Shiori Iida and Sachiko Tamura

For additional articles in this collection, see <http://cshperspectives.cshlp.org/cgi/collection/>

**All Modifications and
Oligo Types Synthesized**
Long Oligos • Fluorescent • Chimeric • DNA • RNA • Antisense

Oligo Modifications?
Your wish is our command.

For additional articles in this collection, see <http://cshperspectives.cshlp.org/cgi/collection/>

**All Modifications and
Oligo Types Synthesized**

Oligo Modifications?
Your wish is our command.

Long Oligos • Fluorescent • Chimeric • DNA • RNA • Antisense