REVIEW

Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin

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Over the past few years it has become evident that the intermediate filament proteins, the types A and B nuclear lamins, not only provide a structural framework for the nucleus, but are also essential for many aspects of normal nuclear function. Insights into lamin-related functions have been derived from studies of the remarkably large number of disease-causing mutations in the human lamin A gene. This review provides an up-to-date overview of the functions of nuclear lamins, emphasizing their roles in epigenetics, chromatin organization, DNA replication, transcription, and DNA repair. In addition, we discuss recent evidence supporting the importance of lamins in viral infections.

In eukaryotic cells, chromatin is tightly packed in a highly organized fashion within a nucleus that is composed of two main compartments: the nucleoplasm and the nuclear envelope (NE). There are also subcompartments in the nucleus containing factors involved in essential nuclear functions such as DNA replication, transcription, and RNA splicing (Prasanth and Spector 2006; Spector 2006). The NE separates nuclear functions from cytoplasmic functions and at its inner surface it provides a docking site for chromatin. The major structural elements of the NE are the inner nuclear membrane (INM), the outer nuclear membrane (ONM), the nuclear pore complexes (NPCs), and the nuclear lamina. The lamina is comprised of a complex meshwork of proteins closely associated with the INM and attached to the periphery of NPCs and to chromatin (Fawcett 1966; Patrizi and Poger 1967; Aaronson and Blobel 1975). The main constituents of the lamina are the type V intermediate filament (IF) proteins, the nuclear lamins. Lamins are also found, in lower concentrations, distributed throughout the nucleoplasm. The organization of lamins at the nuclear periphery as well as within the nucleoplasm is influenced

by numerous lamin-binding proteins (Dorner et al. 2007; Schirmer and Foisner 2007; Wagner and Krohne 2007).

This review focuses on the role of nuclear lamins in the organization and regulation of chromatin in the interphase nucleus—specifically, the involvement of lamins in essential processes such as transcription, DNA replication, DNA repair, and various epigenetic phenomena involved in the regulation of euchromatin–heterochromatin transitions. Emphasis is also placed on the remarkable array of disease-causing mutations in the human lamin A gene, from which many of the most recent insights into lamin functions have been derived. In addition, we also discuss emerging ideas regarding the roles of lamins in viral infections.

General properties of the nuclear lamins

Nuclear lamins were initially described as the major protein components of detergent-high salt resistant “lamina” fractions of rat liver and chicken erythrocyte nuclei (Aaronson and Blobel 1975; Gerace et al. 1978). Subsequently it was shown that they are members of the IF protein family (Aebi et al. 1986; Goldman et al. 1986; McKeon et al. 1986). Lamin genes are found in all metazoa examined to date, but are absent in plants and unicellular organisms (Meier 2001; Melcer et al. 2007). Lamins are divided into A and B types based on sequence homologies. In mammals, two major A-type lamins (lamin A and C) and two major B-type lamins (lamin B1 and B2) have been characterized, in addition to the minor isoforms lamin AΔ10 (Machiels et al. 1996) and germ cell-specific lamins C2 (Furukawa et al. 1994) and B3 (Furukawa and Hotta 1993). While lamins B1 and B2–B3 are encoded by different genes (*LMNB1* and *LMNB2*, respectively), A-type lamins are derived from one gene (*LMNA*) by alternative splicing (Broers et al. 2006; Schumacher et al. 2006; Verstraeten et al. 2007).

Lamins as structural components of the nucleus

The lamins are composed of a long central α -helical rod domain, flanked by globular N-terminal (head) and C-terminal (tail) domains (Fig. 1A). Like most IF pro-

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Figure 1. Structure of nuclear lamins. (A) Schematic drawing of a pre-lamin polypeptide chain. The central α -helical rod domain (red), the NLS (gray), the Ig-fold (blue; its simplified structure indicating the nine β -sheets is depicted), and the C-terminal -CAAX box (green) are shown. (B) Post-translational processing of pre-lamin A, B1, and B2: A farnesyl group is attached to the cysteine residue of the -CAAX box by a farnesyltransferase; the last three residues (-AAX) are proteolytically cleaved off by an AAX endopeptidase; the carboxylic acid group (-COOH) of the C-terminal cysteine residue is methylated by a carboxyl methyltransferase. These steps lead to mature lamin B1 and B2. In the case of farnesylated/carboxymethylated pre-lamin A, an additional 15 C-terminal residues, including the farnesylated/carboxymethylated cysteine, are cleaved off by Zmpste24/FACE1. Inhibition of this step either due to mutations or deficiency in Zmpste24/FACE1 (indicated by the red X) or by protease inhibitors (PIs) can lead to severe phenotypes in mice and humans (for details, see the text). Note that inhibition of farnesylation by farnesyltransferase inhibitors (FTIs) results in a complete loss of processing. (C) Schematic drawings of the C-terminal tail domains of mature lamins A, C, B1, and B2. The following amino acid positions are indicated: start of the tail domain, first residue of the NLS, start and end of the Ig-fold, and C-terminal residue of the respective mature lamin. Note that lamins B1 and B2 are farnesylated and carboxymethylated, while lamins A and C are not.

teins, lamins self-assemble into higher-order structures whose basic subunit is a coiled-coil dimer formed by in parallel and in register interactions (Stuurman et al. 1998; Herrmann and Foisner 2003). Unlike cytoplasmic IFs, lamin dimers tend to form paracrystals in vitro rather than 10-nm filaments (Stuurman et al. 1998; Herrmann and Foisner 2003; Melcer et al. 2007). In addition to the central rod domain (Schirmer et al. 2001; Strelkov et al. 2004), it has been shown that the head and tail domains are also involved in lamin assembly (Sasse et al. 1998; Stuurman et al. 1998; Herrmann and Foisner 2003; Shumaker et al. 2005; Isobe et al. 2007). Although A- and B-type lamins appear to interact with each other in vitro (Georgatos et al. 1988; Ye and Worman 1995; Schirmer and Gerace 2004), little is known about the composition and structure of lamin polymers within the lamina, and even less is known about their nucleoplasmic structures. The structures that have been described within the lamina range from an orthogonal meshwork of 10- to 15-nm fibers seen in *Xenopus* oocyte germinal vesicles (Aebi et al. 1986; Stewart and Whytock 1988) to irregular filamentous meshworks reported in mammalian cells (Capco et al. 1982; de Graaf et al. 1991; Belmont et al. 1993). Within the lamina of interphase cells, both A- and B-type lamin structures are relatively stable,

as revealed by their long recovery time in fluorescence recovery after photobleaching (FRAP) experiments (Broers et al. 1999; Moir et al. 2000c).

Lamins contain a structural motif similar to a type s immunoglobulin fold (Ig-fold) within their C-terminal tail domain (Dhe-Paganon et al. 2002; Krimm et al. 2002) and a nuclear localization signal (NLS) between the central rod and the Ig-fold (Fig. 1A) that is required for the transport of lamins into the nucleus (Loewinger and McKeon 1988). Additionally, a -CAAX box is located at the C terminus of lamins B1 and B2 and lamin A, which leads to extensive post-translational processing of these proteins (Fig. 1; Young et al. 2005; Rusinol and Sinensky 2006). Initially expressed as pre-lamins, they undergo several modifications to become mature lamins (Fig. 1B). In the first step, a farnesyltransferase farnesylates the cysteine residue of the -CAAX box and subsequently the -AAX is removed by an endopeptidase, most likely Rce1 (Ras-converting enzyme 1) and/or Zmpste24 (Zinc metalloprotease related to Ste24p)/FACE1 (Rusinol and Sinensky 2006). In a third step the cysteine residue is carboxymethylated, a process catalyzed by the enzyme isoprenylcysteine carboxyl methyltransferase (Icmt). While the maturation of B-type lamins is terminated at this step resulting in their permanent farnesylation and car-

boxymethylation (Fig. 1C), lamin A is further processed by Zmpste24/FACE1 to form mature lamin A (Fig. 1B). This latter step results in the removal of an additional 15 amino acids from the C terminus of lamin A, including the farnesylated/carboxymethylated cysteine residue (Fig. 2B; Corrigan et al. 2005). It is noteworthy that the temporal sequence of these processing steps is critical; i.e., if farnesylation is blocked, the post-translational processing of lamins is inhibited (Fig. 1B; Rusinol and Sinensky 2006). The modifications of the –CAAX box are thought to play a role in targeting the lamins to the INM and also in establishing protein–protein interac-

tions (Rusinol and Sinensky 2006). Interestingly, the inhibition of lamin farnesylation, either by replacing the cysteine residue of the –CAAX box or by farnesyltransferase inhibitors (FTIs) (Fig. 1B) does not inhibit their incorporation into the nuclear lamina (Sasseville and Raymond 1995; Broers et al. 1999; Pendas et al. 2002; Gruber et al. 2005). Lamin C, which lacks the 98 C-terminal amino acids present in pre-lamin A and contains a unique C terminus comprised of six amino acids lacking a –CAAX box (Figs. 1C, 2A; Fisher et al. 1986; McKeon et al. 1986), also becomes incorporated into the nuclear lamina (Fong et al. 2006b). It is noteworthy that

Figure 2. Comparison of lamin A, lamin C, and LAΔ50 structures. (A) The 12 exons encoding lamin A and the residues 1–566 of lamin C (exons 1–10) are indicated along with their corresponding amino acid residues. In addition, the positions of 18 mutations associated with Hutchinson-Gilford progeria syndrome (HGPS) are shown (the number of incidents reported for each mutation is shown in parentheses) (<http://www.umd.be:2000>; <http://www.dmd.nl>): (blue diamond) 29 C > T (1); (dark-blue diamond) 412 G > A (1); (yellow diamond) 428 C > T (1); (green diamond) 433 G > A (1); (purple diamond) 899 G > A (1); (orange diamond) 1411 C > T + 1579 C > T (1); (dark-blue diamond) 1454 C > G (1); (light-blue diamond) 1583 C > T + 1619 C > T (1); (light-green diamond) 1626 G > C (4); (dark-purple diamond) 1733 A > T (1); (blue star) 1821 G > A (1); (red star) 1822 G > A (1); (purple star) 1824 C > T (37); (pink diamond) 1868 C > G (2); (dark-green diamond) 1930 C > T (1); (brown star) 1968 + 1 G > A (1). Mutations marked with a star lead to abnormal splicing of the last 150 nucleotides of exon 11, resulting in the expression of a mutant lamin A protein (pre-LAΔ50) lacking 50 amino acids from the C terminus of pre-lamin A (residues 607–656). These residues contain the second proteolytic cleavage site (magenta; residue 646) involved in pre-lamin A processing. For a description of the schematic drawing of pre-lamin A, pre-LAΔ50, and lamin C, see Figure 1, A and C. The six lamin C-specific residues (567–572) are indicated (light blue). Note that while most mutations affect both lamin A and C, some are specific for lamin A. (B) Differences in the post-translational processing between pre-lamin A and pre-LAΔ50. The amino acid sequences of pre-lamin A (residues 603–664) and pre-LAΔ50 (residues 603–614) are shown. Residues 607–656 in pre-lamin A, which are absent in pre-LAΔ50, are labeled blue, and the Zmpste24/FACE1 cleavage site (YL) within this region is labeled magenta. The first three steps, including farnesylation and carboxymethylation of the cysteine residue of the –CAAX box (–CSIM), are identical for both proteins (for details, see Fig. 1B). In the last step, the 15 C-terminal residues—including the farnesylated/carboxymethylated cysteine residue—are cleaved off from pre-lamin A by Zmpste24/FACE1, resulting in mature lamin A (residues 1–646) and a 15-amino-acid-long farnesylated/carboxymethylated peptide. As the Zmpste24/FACE1 cleavage site is missing in the mutant protein, LAΔ50 remains farnesylated and carboxymethylated.

the most variable region of the lamins, the C-terminal tail domain (Fig. 1C), contains the binding sites for most of the lamin-binding proteins (Goldman et al. 2002; Zastrow et al. 2004; Dorner et al. 2007; Schirmer and Foisner 2007; Wagner and Krohne 2007).

Both A- and B-type lamins are disassembled in a phosphorylation-dependent manner at the onset of mitosis (Fields and Thompson 1995) and upon dephosphorylation become incorporated into newly forming daughter cell nuclei during telophase/G1 (Fields and Thompson 1995; Thompson et al. 1997; Moir et al. 2000b). While B-type lamins relocate exclusively to the periphery of reassembling daughter nuclei, A-type lamins accumulate in the nucleoplasm at the end of mitosis and in early G1 (Bridger et al. 1993; Moir et al. 2000c; Dechat et al. 2004). Although most prevalent in early G1, nucleoplasmic lamins A/C are present throughout interphase (Goldman et al. 1992; Broers et al. 1999; Moir et al. 2000c) and are thought to play a role in retinoblastoma-mediated cell proliferation (Johnson et al. 2004; Pekovic et al. 2007), initiation of DNA replication (Kennedy et al. 2000), and RNA splicing (Jagatheesan et al. 1999; Kumaran et al. 2002), although the latter function is controversial (Vecerova et al. 2004). Lamin A/C structures present in the nucleoplasm appear to be more dynamic and less tightly bound to the nucleoskeleton than those associated with the lamina, based on detergent extractability and FRAP analyses (Broers et al. 1999; Moir et al. 2000c; Muralikrishna et al. 2004). Lamin B is also present in the nucleoplasm but as a more stable structure compared with A-type lamins (Moir et al. 2000c), and intranuclear lamin B foci are associated with sites of mid-late-S-phase replication (Moir et al. 1994). In addition, there is ultrastructural evidence suggesting that lamins are part of a nucleoskeleton distributed in the nucleoplasm (Hozak et al. 1995; Barboro et al. 2002).

As IF structural proteins, it is now well established that the lamins provide shape and mechanical stability to the nucleus (Houben et al. 2007). There is also evidence supporting a role for the lamins in maintaining the mechanical properties of the entire cell. For example, lamin A/C-deficient cells display impaired mechanotransduction, decreased mechanical stiffness, and defective cell migration (Houben et al. 2007; Lee et al. 2007). These changes in the micromechanical properties of cells may ultimately be explained by alterations in the linkages between the nucleoskeleton with the cytoskeleton. Important elements in such linkages include the integral proteins of the INM, Sun1 and Sun2, and of the ONM, nesprin-1, nesprin-2, and nesprin-3 α . Specifically, it is thought that the connection between the cytoplasm and nucleoplasm is mediated by nesprins interacting with Sun proteins in the luminal space between the INM and the ONM (Padmakumar et al. 2005; Crisp et al. 2006; Ketema et al. 2007). Sun1 in turn interacts with lamin A, but not with lamin C, B1, or B2 in the lamina region (Haque et al. 2006). While in the cytoplasm, nesprin-1 and nesprin-2 are thought to bind to actin (Warren et al. 2005) and nesprin-3 α binds to the cytoskeletal IF-binding protein, plectin (Wilhelmsen et al. 2005;

Ketema et al. 2007), which also binds to actin and possibly microtubules (Wiche 1998).

Nuclear lamin expression during development and differentiation

Studies of the early development of *Xenopus* have shown that oocytes contain mainly one B-type lamin, lamin B3 (XLB3) (Benavente et al. 1985; Stick and Hausen 1985) and minor amounts of XLB1 and XLB2 (Lourim et al. 1996). During development XLB3 persists only to the tail bud stage (stage 24) and reappears later in some adult cells (Benavente et al. 1985; Stick and Hausen 1985). While XLB1 and XLB2 are up-regulated during the mid-blastula transition and gastrulation (stages 8–12) (Benavente et al. 1985; Stick and Hausen 1985), XLA is not found in early tailbud embryos (stage 24), but is present in tadpoles (stage 45) (Wolin et al. 1987). Similar changes in lamin expression have been reported in early developing *Drosophila* (Riemer et al. 1995) and chicken embryos (Lehner et al. 1987). In mice, B-type lamins are expressed throughout early development, while lamins A/C are first detected in the trophoblast on embryonic day 9, in the embryoblast on day 10, and in myoblasts and other mesenchymal tissues by day 11 (Stewart and Burke 1987; Rober et al. 1989). These data suggest that lamin A/C expression is closely correlated with cell differentiation. This has been confirmed in several studies using cultured cells (for example, see Guilly et al. 1990; Rober et al. 1990; Mattia et al. 1992; Lin and Worman 1997). More recently it has been shown that lamins B1 and B2, but not lamins A/C, are expressed in undifferentiated mouse and human embryonic stem (ES) cells (Constantinescu et al. 2006). Upon differentiation, human ES cells appear to express lamins A/C prior to the down-regulation of the pluripotency marker Oct-3/4, but after the down-regulation of Tra-1-60, Tra-1-81, and the stage-specific embryonic antigen-4 (SSEA-4). The absence of lamins A/C in undifferentiated human ES cells has been suggested to be responsible for the high deformability of the nuclei in these cells (Pajerowski et al. 2007). Differential expression of A- and B-type lamins has also been shown in adult human tissues (Broers et al. 1997; Lin and Worman 1997; Tilli et al. 2003) and during neurogenesis in the adult rat brain (Takamori et al. 2007).

Insights into the role of lamins during development come from mutations in the B-type *Drosophila* lamin Dm0 that cause lethality at different embryonic or late pupal stages, depending on the site of the mutation (Gruenbaum et al. 2003; Osouda et al. 2005). In addition, when the only *Caenorhabditis elegans* lamin, LMN-1, is knocked down, embryonic arrest occurs at the 100- to 300-cell stage (Liu et al. 2000). Further insights into the requirement for a specific lamin isoform during development have been obtained from knocking out either *LMNA* or *LMNB1* in mice. The lamin A/C-deficient animals develop normally until birth, but have severe postnatal growth retardation and develop muscular dystrophy (Sullivan et al. 1999). The nuclei in *LMNA*-null mouse embryonic fibroblasts (MEFs) often display ir-

regular shapes, a localized loss of B-type lamins, and the redistribution of emerin, a lamin A-associated integral protein of the INM (Clements et al. 2000), to the endoplasmic reticulum (ER) (Sullivan et al. 1999). In contrast, mice that are null for lamin A but express lamin C and the B-type lamins appear to be healthy. The nuclei in cells derived from these mice exhibit minimal shape changes and emerin localizes normally in the INM (Fong et al. 2006b). On the other hand, lamin B1-deficient mice die at birth and have defective lungs and bones (Vergnes et al. 2004). A high percentage of MEFs derived from these mice have misshapen nuclei and an abnormal distribution of lamin A/C. They are also polyploid and senesce prematurely. In humans, a recent case study described a lamin A/C deficiency in which the fetus survived early development, was born prematurely at 30 wk, and died immediately (Muchir et al. 2003; van Engelen et al. 2005). The patient was homozygous for a nonsense mutation in *LMNA* and displayed severe growth retardation, multiple bone fractures and poorly developed striated muscles. Cells derived from this patient had abnormally shaped nuclei with lobules lacking lamins B1, B2, and Nup153 (a NPC protein), and emerin was distributed to the ER (Muchir et al. 2003).

There is little information available on the regulation of lamin gene expression. Lamin A/C expression can be induced by retinoic acid in mouse embryonic carcinoma cells (Lebel et al. 1987) and there is a retinoic acid-responsive element in the *LMNA* promoter that is regulated by the transcription factors c-Jun and Sp1/Sp3 (Okumura et al. 2004). There are also other regulatory motifs in the *LMNA* promoter binding the transcription factors Sp1/3, c-Jun, and c-Fos, and the transcriptional coactivator CREB-binding protein (Muralikrishna and Parnaik 2001; Janaki Ramaiah and Parnaik 2006). Within the first intron of *LMNA* there are binding sites for the transcription factors, hepatocyte nuclear factor-3 β and retinoic X receptor β (Arora et al. 2004). Recently, lamins A/C have been identified as p53 targets in mitomycin C-treated HCT116 colon carcinoma cells (Rahman-Roblick et al. 2007). Obviously more extensive studies are required in order to understand the regulation and function of the A- and B-type lamins during development and differentiation. Approaches to understanding the significance of the differential expression of lamins have involved silencing with RNAi in cultured cells. These studies have shown that down-regulation of either lamin B1 or B2 induces apoptosis in HeLa cells (Harborth et al. 2001). In contrast, HeLa cells in which lamins A/C have been silenced appeared to grow normally. Although this provides some useful information regarding the general requirements for A- and B-type lamins in cell growth, much more work is required to determine the specific functions of the A-type lamins in differentiation.

Nuclear lamins in disease and aging

Interest in nuclear lamins increased dramatically following the discovery that mutations in *LMNA* cause autosomal-dominant Emery-Dreifuss muscular dystrophy

(AD-EDMD) (Bonne et al. 1999). Since this discovery, an enormous number of *LMNA* mutations, the vast majority of which are heterozygous, have been linked to many diseases including X-linked EDMD, familial partial lipodystrophy (FPLD), dilated cardiomyopathy, limb girdle muscular dystrophy 1B, congenital muscular dystrophy, and premature aging or progeroid syndromes. The latter include Hutchinson-Gilford progeria syndrome (HGPS), atypical Werner's syndrome (WS), restricted dermopathy (RD), and mandibuloacral dysplasia (MAD) (Broers et al. 2006; Kudlow et al. 2007; Worman and Bonne 2007). Collectively, these diseases are known as the laminopathies. There are at least 11 distinct diseases (Worman and Bonne 2007) associated with >300 different mutations in *LMNA* producing ~200 mutant lamin A/C proteins (for details, see <http://www.umd.be:2000>; <http://www.dmd.nl>; <http://www.interfil.org>). Remarkably, both the number of *LMNA* mutations and of their associated diseases continues to grow.

In stark contrast to *LMNA*, there are very few diseases associated with mutations in the *LMNB1/B2* genes. These include autosomal-dominant leukodystrophy caused by a duplication of *LMNB1* and acquired partial lipodystrophy caused by *LMNB2* mutations (Hegele et al. 2006; Padiath et al. 2006). Mutations in several lamin-binding proteins have also been linked to diseases. For example, mutations in the lamin B receptor (LBR) cause Pelger-Huet anomaly and HEM/Greenberg skeletal dysplasia (Worman and Bonne 2007). Mutations in the lamina-associated polypeptide (LAP) 2 α cause a form of dilated cardiomyopathy, and mutations in emerin cause a form of X-linked EDMD (Vlcek and Foisner 2007a; Worman and Bonne 2007). Interestingly, the LAP2 α and emerin mutations are associated with diseases that can also be caused by *LMNA* mutations. Since both of these lamin-associated proteins specifically bind to lamin A (Zastrow et al. 2004), it is possible that these mutations inhibit the association of LAP2 α or emerin with lamins A/C, causing at least some of the phenotypes observed in the respective diseases.

Because of its potential role as a model for human aging, the most intensively studied laminopathy to date has been the premature aging disease, HGPS. Investigations into the cellular and molecular basis of this rare disorder have provided numerous important insights into the structure and function of lamins A/C and into the mechanisms causing this devastating childhood disease. The most prevalent (65% of 57 HGPS cases analyzed) of the 18 *LMNA* mutations associated with HGPS (Fig. 2A) is the single nucleotide substitution, 1824 C > T (<http://www.umd.be:2000>; <http://www.dmd.nl>). This mutation activates a cryptic splice site resulting in the expression of a mutant lamin A lacking 50 amino acids within its C terminus (LAA50/progerin) (Fig. 2; De Sandre-Giovannoli et al. 2003; Eriksson et al. 2003). Besides the 1824 C > T mutation, three other HGPS mutations, 1822 G > A, 1821 G > A, and 1968 + 1 G > A, result in the same abnormal splicing event (Fig. 2A; Eriksson et al. 2003; Moulson et al. 2007). Since the deleted amino acids are just upstream of the -CAAX box and

contain the second Zmpste24/FACE1 cleavage site, LA Δ 50/progerin is permanently farnesylated and carboxymethylated (Fig. 2B; Glynn and Glover 2005; Dechat et al. 2007). This leads to an abnormal membrane association of the mutant protein throughout the cell cycle (Cao et al. 2007; Dechat et al. 2007). It has also been shown that LA Δ 50/progerin is abnormally associated with the nuclear lamina (Goldman et al. 2004; Scaffidi and Misteli 2005; Dahl et al. 2006). These abnormalities contribute to several other phenotypes associated with HGPS, including lobulation of nuclei, thickening of the lamina, loss of peripheral heterochromatin, and alterations in specific heterochromatin marks (Figs. 3, 4; De Sandre-Giovannoli et al. 2003; Eriksson et al. 2003; Goldman et al. 2004; Scaffidi and Misteli 2005; Shumaker et al. 2006). In addition, expression of LA Δ 50/progerin leads to mitotic defects comprising delays in cytokinesis and nuclear reassembly, abnormal chromosome segregation, and binucleation (Cao et al. 2007; Dechat et al. 2007). Many, but not all, of these phenotypes observed in cultured fibroblasts from HGPS patients become most obvious at late passage numbers. The latter

Figure 3. Electron microscopic observation of normal and HGPS fibroblasts. Low-magnification views show peripheral heterochromatin and nucleoplasmic heterochromatic foci in the normal nucleus (A), which are both absent in the highly lobulated HGPS nucleus (B). A high-magnification view of the nuclear envelope of a HGPS nucleus (D) shows a loss of peripheral heterochromatin and a thickening of the nuclear lamina compared with a normal nucleus (C). (C) Cytoplasm; (N) nucleus. Bars: A,B, 5 μ M; C,D, 300 nm.

Figure 4. Alterations in histone methylation patterns in HGPS fibroblasts. Normal and HGPS fibroblasts from female donors were double-labeled with antibodies against lamins A/C (red) and against trimethylation of either Lys 9 in histone H3 (H3K9me3; A,B), Lys 27 in histone H3 (H3K27me3; C,D), or Lys 20 in histone H4 (H4K20me3; E,F) (all green). Note the decrease of H3K9me3 (B) and H3K27me3 (D) and the increase of H4K20me3 (F) in the lobulated HGPS nuclei compared with normal nuclei (A,C,E). The decrease in H3K27me3 is best observed at the inactive X chromosome, which is normally enriched in this histone modification (see arrowhead in C). Bars, 10 μ M.

finding is most likely attributable to the higher concentration of LA Δ 50/progerin that has been reported in older cell cultures (Goldman et al. 2004; McClintock et al. 2006).

Evidence that LA Δ 50/progerin may contribute directly to vascular disease comes from the finding that it appears to accumulate in vascular smooth muscle and endothelial cell nuclei in skin biopsies from an HGPS patient (McClintock et al. 2006). In addition, a progressive loss of vascular smooth muscle cells was found in an HGPS mouse model (Varga et al. 2006). In an effort to mimic HGPS in mice, additional models have been developed that display progeroid phenotypes to varying degrees (Stewart et al. 2007). Two of these animal models have provided new insights into disease mechanisms (Yang et al. 2006, 2008). In mice expressing lamin C and LA Δ 50/progerin only (*LMNA*^{HG/LCO}), the steady-state level of the mutant protein appears to be lower compared with mice also expressing lamin A (*LMNA*^{HG/+}). While the latter animals display severe progeria-like disease

phenotypes, the elimination of wild-type lamin A leads to improvements in the overall health of the animals. Mutations in *Zmpste24*/*FACE1*, leading to the accumulation of farnesylated and carboxymethylated pre-lamin A (Fig. 1B), have also been linked to HGPS, RD, and MAD (Young et al. 2005; Worman and Bonne 2007), and mice deficient in *Zmpste24* resemble progeroid phenotypes (Stewart et al. 2007). Because permanent farnesylation of either LA Δ 50/progerin or farnesylated pre-lamin A is thought to be responsible for the pathophysiological changes seen in these diseases, several attempts have been undertaken to rescue the cellular phenotypes by inhibiting farnesylation with FTIs (Glynn and Glover 2005; Toth et al. 2005; Cao et al. 2007; Dechat et al. 2007). In addition, specific silencing of LA Δ 50/progerin has been used in attempts to "rescue cells" expressing this mutant protein (Huang et al. 2005; Scaffidi and Misteli 2005). Although these approaches appeared to restore nuclear shape and some heterochromatin marks to a normal appearance in cells derived from HGPS patients, it is not clear if there is a complete reversal of disease phenotypes. When *LMNA*^{HG/+} mice or *ZMPSTE24*^{-/-} mice were treated with an FTI, they showed an improvement in their overall health compared with untreated littermates (Fong et al. 2006a; Yang et al. 2006). Since there are no other possible treatments in sight, FTIs are now being tested in HGPS patients (for details, see <http://www.progeriaresearch.org>). However, the impact of these drugs on the processing and functions of wild-type lamins (including lamins B1 and B2 and lamin A expressed from the unaffected *LMNA* allele) must also be taken into consideration (Fig. 1B). Recent support for this comes from the finding that the distribution of B-type lamins is altered in the G1 phase of the cell cycle in cells treated with FTIs (Dechat et al. 2007).

Of great interest is the possibility that the altered lamins expressed in progeria patients may be involved not only in premature aging, but also in normal aging, as LA Δ 50/progerin has been found in a small number of cells in cultures obtained from healthy individuals, especially in those from older donors (Scaffidi and Misteli 2006; Cao et al. 2007). Recently, it has also been shown that LA Δ 50/progerin is expressed at low levels in skin biopsies from healthy individuals ranging in age from newborn to 97 yr and that the mutant protein seems to accumulate with age (McClintock et al. 2007). In addition, alterations in nuclear shape and structure, similar to those found in premature aging, have been described in dermal fibroblasts from old individuals (Scaffidi and Misteli 2006), in normal human fibroblasts with increasing passage number (Cao et al. 2007), and in aged *C. elegans* (Haithcock et al. 2005).

The role of nuclear lamins in chromatin organization and related functions

Heterochromatin is highly organized and in mammalian cells mainly associated with nucleoli and with regions of the lamina (Fig. 3A,C). Although these lamina regions are thought to provide a transcriptionally repressive en-

vironment, other regions of the lamina, which are not associated with heterochromatin (Fig. 3A,C), could conceivably be involved in gene expression. In support of this, it has previously been shown that a genetic locus, which has been targeted to the nuclear periphery by lamin B1, maintains its ability to be transcriptionally induced (Kumaran and Spector 2008). Beside heterochromatin, entire chromosomes are also organized into well-defined regions or territories within mammalian nuclei (Cremer et al. 2006). These territories are arranged in a nonrandom fashion, with gene-rich chromosomes, like human chromosome 19, residing preferentially deep inside the nucleus and gene-poor chromosomes, like human chromosome 18, more likely to be positioned in the region of the lamina (Croft et al. 1999). This is not only true for whole chromosome territories, but also for smaller domains of chromosomes (Kupper et al. 2007). Positions within these territories appear to be related to the control of gene expression and other nuclear activities (Fraser and Bickmore 2007; Lanctot et al. 2007). Recent models of nuclear architecture depict lamins and their associated proteins as determinants of chromosome positioning throughout the nucleus (Goldman et al. 2002; Dorner et al. 2007; Vlcek and Foisner 2007b). Thus the lamins would be either directly or indirectly involved in anchoring chromatin to the nuclear lamina and would also act as a nucleoplasmic scaffold for organizing chromatin elsewhere in the nucleus. In addition, lamins appear to play a role in several nuclear functions that require remodeling of chromatin, including DNA replication, DNA repair, and transcription.

Interactions between nuclear lamins and chromatin

Early biochemical evidence supporting lamin/chromatin interactions came from the biochemical analysis of HeLa nuclear lamina preparations (Bouvier et al. 1985) and from UV cross-linking experiments using calf thymus or Ehrlich ascites tumor cell nuclear "matrices" (Boulikas 1986; Galcheva-Gargova and Dessev 1987). Furthermore, lamins A/C bind to mitotic chromosomes (Burke 1990; Glass and Gerace 1990), and polynucleosomal particles in vitro (Yuan et al. 1991). Furthermore, A-type lamins have been identified as conserved peripheral proteins of human metaphase chromosomes (Takata et al. 2007). The interaction between the lamins and chromatin appears to involve their non- α -helical C-terminal tail domain and the N- and C-terminal tail domains of core histones (Hoger et al. 1991; Yuan et al. 1991; Schmidt and Krohne 1995; Taniura et al. 1995; Goldberg et al. 1999; Mattout et al. 2007). Interestingly, this interaction may also involve the NLS of the lamins (Mattout et al. 2007). There are also reports that lamins can bind directly to DNA (Shoeman and Traub 1990; Baricheva et al. 1996; Rzepecki et al. 1998; Stierle et al. 2003) and that this may involve specific sequences in the matrix attachment/scaffold-associated regions (MARs/SARs) (Luderus et al. 1994; Zhao et al. 1996). This possibility is further supported by the finding that lamin Dm0 interacts with

transcriptionally inactive DNA sequences in *Drosophila* (Pickersgill et al. 2006).

There is additional evidence that lamins interact with chromatin and DNA through lamin-binding proteins (Mattout-Drubezki and Gruenbaum 2003; Dorner et al. 2007; Schirmer and Foisner 2007). One example for such a cross-bridging protein is LBR, an integral protein of the INM, which interacts with lamin B, DNA, and the human heterochromatin protein 1 (HP1) (Worman et al. 1990; Ye and Worman 1994, 1996). Other proteins that interact with both lamins and chromatin are LAP2 α and LAP2 β (Foisner and Gerace 1993; Furukawa et al. 1997; Dechat et al. 1998, 2000). While LAP2 α binds specifically to lamins A/C (Dechat et al. 2000), LAP2 β interacts exclusively with B-type lamins (Foisner and Gerace 1993). Another proposed linker between the nuclear lamins and chromatin is the DNA-bridging protein, barrier-to-autointegration factor (BAF) (Segura-Totten and Wilson 2004; Margalit et al. 2007), which has been reported to bind to dsDNA (Zheng et al. 2000), to histones (Montes de Oca et al. 2005), to lamin-binding proteins containing a LEM (LAP2s, emerin, and MAN1) domain (Shumaker et al. 2001), and to A-type lamins (Holaska et al. 2003). The number of interactions between lamins, lamin-binding proteins, and DNA/chromatin is growing at an extremely rapid pace. However, the functional significance and further biochemical verification of these complex interactions remains to be determined.

The role of lamins in the organization of interphase chromatin and epigenetics

The importance of lamins in chromatin organization is most evident in cells derived from patients suffering from various laminopathies and in the *LMNA*-null mouse (Table 1). In fibroblasts and cardiomyocytes derived from *LMNA*-null mice there is a dissociation of heterochromatin from some regions of the nuclear periphery (Sullivan et al. 1999; Nikolova et al. 2004). Similar changes in peripheral heterochromatin or a more general loss of heterochromatin have been reported in cells from patients with *LMNA* mutations causing AD-EDMD (Sabatelli et al. 2001), FPLD (Capanni et al. 2003), MAD (Filesi et al. 2005; Lombardi et al. 2007), and HGPS (Fig. 3B,D; Goldman et al. 2004; Columbaro et al. 2005). In cells from HGPS patients, it has been shown that these abnormalities in chromatin organization are related to epigenetic changes, specifically to changes of specific histone methylations known to define heterochromatin. These histone methylations include the trimethylation of histone H3 at Lys 9 (H3K9me3) and of histone H4 at Lys 20 (H4K20me3), which define constitutive heterochromatin, and H3K27me3, which defines facultative heterochromatin (Martin and Zhang 2005; Sarma and Reinberg 2005). With respect to these epigenetic marks, a down-regulation of H3K9me3 and H3K27me3 and an up-regulation of H4K20me3 have been observed in HGPS fibroblasts (Fig. 4; Columbaro et al. 2005; Scaffidi and Misteli 2005; Shumaker et al. 2006). Changes in H3K9me3 patterns have also been observed in MAD fi-

broblasts (Filesi et al. 2005) and in cells derived from old healthy individuals expressing LA Δ 50/progerin (Scaffidi and Misteli 2006). In addition to the changes in histone methylation, HP1 α , which is normally associated with H3K9me3, was found to be down-regulated and partially dissociated from H3K9me3 sites in HGPS fibroblasts (Scaffidi and Misteli 2005; Shumaker et al. 2006). Taken together, these findings clearly demonstrate that the expression of mutant lamins leads to global changes in the epigenetic organization of chromatin, which undoubtedly contributes to the phenotypes observed in different laminopathies, including defects in DNA repair and alterations in gene expression (see below).

The positioning of chromosome territories may also involve lamins. For example, there is some evidence that chromosome territories 13 and 18, normally positioned at the nuclear periphery, are displaced into the nuclear interior in the cells from some types of laminopathy patients (Meaburn et al. 2007). Furthermore, MEFs deficient in either lamin B1 or the lamin B1 processing enzyme Rce1 display global changes in gene expression and a movement of the gene-poor chromosome 18 away from the lamina region (Malhas et al. 2007). The latter was accompanied by the up-regulation of a gene cluster on that chromosome. Further evidence supporting a role for lamins in chromosome positioning comes from the finding that the normal localization at the nuclear periphery of a genetic locus on human chromosome 4 associated with facioscapulohumeral muscular dystrophy (FSHD) is altered in human lamin A/C-null cells (Masny et al. 2004).

Studies of lamin degradation during apoptosis also support a role for lamins in chromatin organization. Following the induction of apoptosis, cell death and DNA condensation are greatly delayed in cells expressing mutants of lamins A or B that render them uncleavable by caspases (Rao et al. 1996). In addition, inhibition of caspase-6-mediated lamin A/C cleavage blocks chromatin condensation and apoptotic body formation (Ruchaud et al. 2002). Furthermore, expression of caspase-8 in mesenchymal stem cells alters lamin organization, causing deformation of the NE. These changes are accompanied by telomere aggregation and the translocation of centromeres to more peripheral locations (Raz et al. 2006).

Lamins in the epigenetic regulation of chromatin: consequences and potential mechanisms

Although little is known about the detailed mechanisms underlying the specific interactions between lamins and the organization of chromatin, some insights have been revealed in studies of the human laminopathies. For example, the decrease of the heterochromatin mark H3K9me3 in pericentric regions observed in HGPS cells carrying the 1824C > T mutation is accompanied by an up-regulation of pericentric chromosome 9 sat III transcripts (Shumaker et al. 2006). This suggests that there is a link between changes in histone methylation caused by LA Δ 50/progerin and transcriptional activation of nor-

Table 1. *Changes in heterochromatin organization caused by lamin A/C mutations or deficiencies*

Mutation ^a	Species	Clinical phenotype ^b	Cell type/tissue ^c	Chromatin phenotype ^d	Detection method ^e	Reference
Knockout	Mouse	Retarded growth rate, muscular dystrophy	MEFs and hepatocytes	Local loss of peripheral heterochromatin	Electron microscopy	Sullivan et al. 1999
			Cardiomyocytes	Fragmentation and displacement of heterochromatin	FISH with pancentromeric probe	Nikolova et al. 2004
				Peripheral and central heterochromatin clumping	Electron microscopy	
1580 G > C (R527P)	Human	AD-EDMD	Skeletal muscle	Reduced peripheral heterochromatin, heterochromatin clumps	Electron microscopy	Sabatelli et al. 2001
1444 C > T (R482W)	Human	FPLD	Dermal fibroblasts	Loss of peripheral heterochromatin	Electron microscopy	Capanni et al. 2003
1318 G > A, 1580 G > A (V440M, R527H)	Human	MAD	Dermal fibroblasts	Detachment of heterochromatin from the periphery	Electron microscopy	Lombardi et al. 2007
1580 G > A (R527H)	Human	MAD	Dermal fibroblast	Loss of peripheral heterochromatin	Electron microscopy	Fiesi et al. 2005
				Delocalization and solubilization of H3K9me3 and HP1 β	Immunofluorescence	
1824 C > T (alternative splicing; G608G) ^f	Human	HGPS	Dermal fibroblasts	Loss of peripheral heterochromatin, general loss of heterochromatin	Electron microscopy	Goldman et al. 2004; Columbaro et al. 2005
				Decrease in H3K9me1	Immunofluorescence	Columbaro et al. 2005
				Decrease in H3K9me3		Columbaro et al. 2005;
					Immunofluorescence, immunoblotting	Scaffidi and Misteli 2005; Shumaker et al. 2006
				Decrease in H3K27me3		Shumaker et al. 2006
				Increase in H4K20me3 Down-regulation of HP1 α and dissociation from H3K9me3 sites	Immunofluorescence	Scaffidi and Misteli 2005; Shumaker et al. 2006

^aThe DNA base pair changes and the amino acid changes (in parentheses) are shown.^bThe phenotypes are as follows: autosomal-dominant Emery-Dreifuss muscular dystrophy (AD-EDMD), familial partial lipodystrophy (FPLD), mandibuloacral dysplasia (MAD), and Hutchinson-Gilford progeria syndrome (HGPS).^cThe cell types or tissue examined are listed.^dAlterations in chromatin organization described. (H3K9me3) Histone H3 trimethylated at Lys 9; (HP1) heterochromatin-associated protein 1; (H3K9me1) histone H3 monomethylated at Lys 9; (H3K27me3) histone H3 trimethylated at Lys 27; (H4K20me3) histone H4 trimethylated at Lys 20.^eMicroscopic methods used.^fThis mutation does not cause an amino acid change, but results in alternative splicing (for details, see the text).

mally heterochromatic regions. Furthermore, the expression of LAD50/progerin also results in the loss of H3K27me3 on the inactive X chromosome (Xi), which leads to some decondensation of the Xi (Shumaker et al. 2006). These changes frequently occur prior to alterations in nuclear shape and do not result in a dissociation of *XIST* RNA from the Xi. However, it remains un-

known whether there is transcriptional activation of the Xi in HGPS. The reduction in H3K27me3 is probably the direct result of the significant decrease in the expression of the histone methyltransferase (HMT), enhancer of zeste homolog (EZH2), that has been reported in HGPS fibroblasts (Shumaker et al. 2006). Changes in histone methylation caused by the expression of mutant lamins

could also account for telomere shortening reported in cells from HGPS and WS patients (Hofer et al. 2005), and in normal cells overexpressing HGPS lamin A mutants (Huang et al. 2008). Telomeres are normally enriched in the heterochromatic marks H3K9me3 and H4K20me3 (Blasco 2007). Furthermore, a decrease in H4K20me3 has been related to telomere elongation (Benetti et al. 2007). Therefore the increase in H4K20me3 and decrease in H3K9me3 (Shumaker et al. 2006) may be the cause of telomere shortening observed in HGPS.

A potential mediator of the changes observed in histone methylation in the various laminopathies is the retinoblastoma gene product (pRb) (Fig. 5), which binds to A-type lamins and is altered in cells either expressing mutant lamins A/C or deficient in lamins A/C (for details, see below). For example, pRb regulates the expression of Ezh2 and is required for H3K27 trimethylation (Bracken et al. 2003; Kotake et al. 2007). Furthermore, pRb associates with and regulates the HMTs SUV39H1 and Suv4-20h responsible for H3K9 methylation and H4K20me3, respectively (Nielsen et al. 2001; Gonzalo et al. 2005; Isaac et al. 2006). In addition, lamins may also interact directly with HMTs and histone demethylases and/or regulate the state of histone methylation by direct interaction with histones. These interactions may be impaired due to the expression of mutant lamins, leading to alterations in histone methylation patterns.

Lamins in DNA replication

Metazoan cells contain ~30,000 replicons (Keller et al. 2002), which are spatially and temporally regulated during DNA replication in S phase. There is a significant amount of data indicating that lamins play an important role in the regulation of this complex process. For example, lamin B1 colocalizes with the replication factor proliferating cell nuclear antigen (PCNA) in replication factories during late S phase in 3T3 cells (Moir et al. 1994), and lamin A is associated with sites of early replication in primary fibroblasts (Kennedy et al. 2000). The role of lamins in DNA replication has been most extensively studied in nuclei assembled in vitro in *Xenopus* egg interphase extracts. If the major lamin in *Xenopus*

eggs, XLB3, is immunodepleted from these extracts prior to nuclear assembly or its assembly state is disrupted by introducing a dominant-negative N-terminally deleted mutant lamin, DNA replication is inhibited (Newport et al. 1990; Meier et al. 1991; Ellis et al. 1997; Spann et al. 1997; Moir et al. 2000a). The addition of this dominant-negative mutant causes the redistribution of endogenous lamins into intranuclear foci along with the DNA replication elongation factors PCNA and replication factor C (RFC). Under these conditions, the DNA replication initiation factors, DNA polymerase α , minichromosome maintenance protein 3 (MCM3), and the origin recognition complex (ORC) protein Orc2 appear to function normally, as supported by the synthesis of short pieces of DNA that correspond to Okazaki fragments (Spann et al. 1997; Moir et al. 2000a). When these lamin-disrupted nuclei are transferred to fresh untreated extracts, the chain elongation phase of replication is rapidly reinitiated as the abnormal lamin foci disappear and normal lamin organization is re-established (Moir et al. 2000a). An association between lamins and PCNA during replication is further supported by the finding that PCNA is more readily extracted from nuclei assembled in lamin-depleted extracts (Jenkins et al. 1993). These data suggest that nuclear lamins play a role in organizing a nucleoplasmic scaffold that is necessary for the elongation phase of replication. Support for this hypothesis comes from nuclei assembled in *Xenopus* extracts containing $\text{Zn}^{2+}/\text{Fe}^{2+}$ chelators. These nuclei have assembled NEs and NPCs but are deficient in lamins and are unable to replicate their DNA (Shumaker et al. 1998).

Lamins in transcription

Evidence for a role of lamins in transcription comes from studies using N-terminally deleted lamins, which disrupt the head-to-tail assemblies of lamin dimers and higher-order lamin structures. When these mutant lamins are introduced into nuclei of either BHK 21 cells or of *Xenopus* embryos, they drive the disassembly of the endogenous lamin network, leading to an impairment of transcription as monitored by a reduction in BrUTP incorporation (Spann et al. 2002). Specifically, the activity of RNA polymerase II (pol II), but not of pol I or pol III, was found to be inhibited. These mutants also induce the formation of lamin aggregates, which recruit the TATA-binding protein (TBP), a factor known to play an important role in the initiation of transcription (Spann et al. 2002). However, the specific inhibition of pol II activity by the mutant lamin cannot be attributed to the recruitment of TBP to lamin aggregates, as TBP associates with all three RNA polymerases (Gill and Tjian 1992). Therefore, the possibility that pol II itself or pol II-specific binding partners are also recruited to these aggregates has to be investigated in the future. In agreement with the above findings overexpression of either lamin A or C leads to a dramatic reduction in pol II transcription in HeLa cells (Kumaran et al. 2002). Further evidence for a role of lamins in transcription comes from the finding that lamins A/C interact with the zinc finger transcrip-

Figure 5. Schematic diagram depicting potential pathways in the epigenetic regulation of chromatin by lamins A/C. Red arrows indicate a direct regulation and/or interaction, whereas black arrows indicate indirect evidences for a role of lamins A/C in the regulation of the respective factors. The retinoblastoma protein may be an important link in these processes (for details, see the text).

tion factor MOK2 (Dreuillet et al. 2002) and that MOK2 mislocalizes into abnormal nuclear aggregates upon the expression of pathogenic lamin A/C mutants (Dreuillet et al. 2008).

Lamins in cell proliferation

There is also evidence that lamins A/C are involved in gene expression related to the regulation of the cell cycle. Most notably the A-type lamins appear to interact in vitro with pRb (Ozaki et al. 1994; Markiewicz et al. 2005). pRb is a tumor suppressor and major cell cycle regulator that in its hypophosphorylated state binds and inhibits the E2 factor (E2F) family of transcription factors required for cell cycle progression (Giacinti and Giordano 2006). Upon hyperphosphorylation of pRb by cyclin/cyclin-dependent kinase (CDK) complexes, E2F is released to initiate S phase. A role for lamins in this process is further suggested by the finding that hypophosphorylated pRb is tightly associated with lamin A/C-enriched nucleoskeletal preparations of early G1 cells (Mancini et al. 1994). Furthermore, primary cultures of fibroblasts contain intranuclear foci associated with both lamins A/C and pRb from early G1 until early S phase (Kennedy et al. 2000). In addition, overexpression of lamin mutants that form nuclear aggregates also recruit pRb (Markiewicz et al. 2002; Hubner et al. 2006).

Lamins also seem to be involved in regulating the state of pRb phosphorylation. This is supported by the decrease in pRb dephosphorylation found in lamin A/C-deficient cells in response to the growth factor- β 1 (TGF- β 1) and by the evidence that PP2A phosphatase forms a complex with lamins A/C and pRb (Van Berlo et al. 2005). In addition, there is evidence for a significant reduction in hyperphosphorylated pRb in HGPS fibroblasts, although total pRb levels appear unaltered (Dechat et al. 2007).

Immunoprecipitation, in vitro binding, and differential extraction assays suggest that pRb is retained in the nucleus in a complex containing lamins A/C and LAP2 α (Markiewicz et al. 2002; Johnson et al. 2004). In addition, there is a dramatic reduction in pRb levels in *LMNA*^{-/-} fibroblasts, suggesting that lamins are involved in regulating the turnover and proteasomal degradation of pRb (Johnson et al. 2004). Similar decreases in pRb levels are also found in the liver of *ZMPSTE24*^{-/-} mice, most likely related to the accumulation of abnormally farnesylated and carboxymethylated lamin A (Varela et al. 2005). Based on these findings, it has been suggested that the increased rate of cell proliferation and the decreased capacity to undergo cell cycle arrest reported for lamin A/C-deficient cells is attributable to the destabilization of pRb (Johnson et al. 2004; Van Berlo et al. 2005). This destabilization is independent of gankyrin and MDM2, two oncoproteins involved in pRb degradation (Nitta et al. 2007). In further support of a role for lamin A/C/LAP2 α /pRb complexes in cell cycle control, it has been shown that down-regulation of LAP2 α is accompanied by an acceleration of cell growth and impairment of cell cycle exit upon serum starvation (Dorner et al. 2006). In

contrast to these results, it has also been shown that the down-regulation of either lamins A/C or LAP2 α can cause G1 cell cycle arrest in human dermal fibroblasts (Pekovic et al. 2007). These latter results conflict with the other studies showing accelerated proliferation in lamin A- or Lap2 α -deficient cells. This conflict may be attributable to the different cell types used in the individual studies. Obviously the resolution of these differences is an important topic for future investigations.

Based on these findings, it is interesting to speculate that *LMNA* mutations could impair the interactions between lamins A/C and pRb. Such mutations could alter the tumor-suppressing functions of pRb, leading to tumorigenesis. Indeed, lamins appear to play a role in cancer (Prokocimer et al. 2006), although it is not clear yet if they are directly involved in the development and progression of cancer or if the changes found in lamin expression levels in various cancers (for example, see Gaetke et al. 2007; Hudson et al. 2007) are an indirect consequence of cellular transformation.

Lamins in differentiation

The developmental regulation of lamin expression has led various laboratories to suggest that these IF proteins play a role in differentiation. As indicated above, B-type lamins are constitutively expressed, while lamins A/C are first expressed when differentiation is initiated during early development. More specifically, in the case of muscle, there are pRb- and cyclin D3-dependent changes in lamin A/C organization and solubility during myoblast differentiation (Muralikrishna et al. 2001; Mariappan and Parnaik 2005; Markiewicz et al. 2005). Cyclin D3—which is a regulatory subunit of CDK4, CDK6, and CDK2 and is critical for G1 progression—has also been reported to interact directly with lamins A/C (Mariappan et al. 2007). Furthermore, expression of an EDMD lamin A mutant in C2C12 myoblasts, which induces elevated levels of hyperphosphorylated pRb, leads to an inhibition of the differentiation of myoblasts into myotubes (Favreau et al. 2003). Lamin A also appears to form a complex with the muscle-specific transcription factor MyoD (Bakay et al. 2006) and muscular dystrophy mutations in lamin A and emerin that inhibit skeletal muscle regeneration have been related to a disruption in the pRb–MyoD pathway (Bakay et al. 2006; Frock et al. 2006; Melcon et al. 2006). In mice engineered to express a homozygous mutation in *LMNA* linked to human AD-EDMD or deficient in emerin, the mitogen-activated protein kinase (MAPK) signaling pathway appears to be abnormally activated (Muchir et al. 2007a,b). These findings, as well as those derived from studies of other laminopathies (e.g., HGPS, MAD, FPLD) (Capanni et al. 2003; Robinson et al. 2003; Amati et al. 2004; Csoka et al. 2004; Scaffidi and Misteli 2005) suggest that global changes in gene expression that can lead to inhibition of cell differentiation are a common feature of the laminopathies. With respect to this, two similar models for the development of laminopathies have been proposed recently based on an impairment of adult stem cell dif-

ferentiation involved in tissue regeneration (Gotzmann and Foisner 2006; Halaschek-Wiener and Brooks-Wilson 2007).

The association of some *LMNA* mutations with the development of lipodystrophies has led to the suggestion that lamins play a role in adipocyte differentiation. Further evidence for this comes from the finding that the adipocyte differentiation factor, sterol response element-binding protein 1 (SREBP1), interacts with the C terminus of lamins A/C and that this interaction is impaired to various degrees by FPLD mutations in lamin A (Lloyd et al. 2002; Hubner et al. 2006). Another study shows impaired adipocyte differentiation in 3T3 cells overexpressing either wild-type lamin A or an FPLD mutant lamin A, while lamins A/C-deficient MEFs differentiated more readily into fat-containing cells than control cells (Boguslavsky et al. 2006). Taken together, these findings suggest that the ratio between lamin A and SREBP1 as well as their proper interaction are required for normal adipocyte differentiation and that alterations in this interaction contribute to the development of lipodystrophies.

Lamins in DNA repair

Evidence for a role for the nuclear lamins in DNA repair comes mainly from studies of premature aging diseases, as it has been shown that the HGPS mutant protein, LAΔ50/progerin, or farnesylated pre-lamin A lead to defects in DNA repair. For example, the recruitment of the repair factor p53-binding protein (53BP1) to sites of DNA damage is impaired and the presence of fragmented DNA after irradiation is prolonged in HGPS fibroblasts and in *ZMPSTE24*^{-/-} MEFs (Liu et al. 2005). In addition, sensitivity to various DNA-damaging agents causing double-strand breaks (DSBs), to UV radiation, and to γ-irradiation is increased in *ZMPSTE24*^{-/-} mice (Liu et al. 2005). These mice also show an activation of the p53 stress signaling pathway under normal conditions, most likely due to damaged DNA (Vergnes et al. 2004). Furthermore, phosphorylated histone H2AX (γ-H2AX), a hallmark of DSBs, is increased in HGPS patient fibroblasts, in RD patient fibroblasts carrying a mutation in *ZMPSTE24*, and in *ZMPSTE24*^{-/-} mice (Liu et al. 2005, 2006; Varela et al. 2005). All these findings suggest that there is an accumulation of damaged DNA in premature aging disorders due to defects in the repair machinery.

Intriguingly, the nuclei of a subpopulation of skin fibroblasts from normal elderly donors, which express an increase in LAΔ50/progerin, display also a higher percentage of γ-H2AX foci compared with fibroblasts from young individuals (Scaffidi and Misteli 2006). Furthermore, the expression of HGPS mutant lamin A in HeLa cells increases the levels of γ-H2AX (Liu et al. 2006), and this is correlated with defects in DNA repair foci (Manju et al. 2006). These mutants also effect the localization and expression levels of ATR (for ataxia-telangiectasia-mutated [ATM] and Rad3-related) kinase, a key regulator in the DNA damage signaling pathway (Manju et al. 2006). Changes in the normal localization of ATM and

ATR kinases, reflecting an activation of these enzymes, were also observed in HGPS and RD fibroblasts (Liu et al. 2006). Interestingly, knockdown of the ATR and ATM kinases by siRNA rescued the early replication arrest phenotype seen in HGPS and RD fibroblasts (Liu et al. 2006). On the other hand, treatment of these cells with an FTI, which restores normal nuclear shape, does not appear to reverse the abnormalities seen in the DNA repair system (Liu et al. 2006).

Other insights into the mechanisms underlying the accumulation of DNA damage in HGPS and RD fibroblasts come from the finding that the DSB repair factors, Rad50 and Rad51, do not colocalize with the increased number of γH2AX foci present in these cells (Liu et al. 2007). This suggests that the targeting of these essential factors to the DSB repair machinery is inhibited when mutant lamin A is present. Interestingly, the nucleotide excision repair factor, xeroderma pigmentosum group A (XPA), which is not involved in DSB repair, is found at these abnormal γH2AX foci, which appears to inhibit normal DNA repair (Liu et al. 2007).

Taken together, these findings support defects in the DNA repair machinery in patients suffering from progeroid syndromes due to expression of LAΔ50/progerin or abnormal levels of farnesylated pre-lamin A. Similar defects in DNA repair have been reported in normal aging. Although all these studies clearly imply that nuclear lamins are involved in DNA repair, their precise role in this process remains to be elucidated.

The emerging roles of lamins in viral infections

There is increasing evidence that lamins play a role in the infection cycles of viruses. Most information in support for this comes from studies of the replication cycle of cytomegalovirus (CMV) and herpes simplex virus type-1 (HSV-1), both members of the *Herpesviridae* family. These viruses assemble their capsids and encapsidate their replicated viral DNA in the nucleus, while the final steps in the maturation of virions takes place in the cytoplasm (Mettenleiter et al. 2006). The nucleocapsids exit the nucleus in a two-step process involving primary envelopment at the INM and fusion of their primary membrane with the ONM to facilitate their movement into the cytoplasm. In order to gain access to the INM, the nuclear lamina has to be destabilized. There is evidence that this destabilization involves the phosphorylation and disassembly of the lamins specifically in locations where viruses are accessing the INM (Radsak et al. 1991).

Viruses and the disassembly of lamins

In the search for candidate viral proteins playing a role in the lamin disassembly process two murine CMV proteins, M50/p35 and M53/p38, have been identified (Muranyi et al. 2002). When M50/p35, a type II transmembrane protein, is expressed in CV-1 cells, it localizes to the NE. Lamins A, B, and C appear to be excluded from

areas where M50/p35 accumulates. Coexpression of M50/p35 and M53/p38 as well as CMV infection leads to the recruitment of Ca-dependent protein kinases C (PKCs) from the cytoplasm to the NE, resulting in increased phosphorylation of lamins A, B, and C as determined by ^{32}P -incorporation (Muranyi et al. 2002). In agreement with these findings, there is evidence that pUL50, the human CMV counterpart of murine M50/p35, interacts directly with PKC ϵ and PKC ζ and can recruit PKC α to the NE (Milbradt et al. 2007). These findings suggest that the recruitment of PKCs by M50/p35 leads to the localized phosphorylation and disassembly of the lamins within the lamina. Besides PKCs, the human CMV kinase pUL97 has been shown to phosphorylate lamins A, C, and B1 in vitro and to lead to the redistribution of lamins A/C from the NE to intranuclear foci when overexpressed in cells (Marschall et al. 2005). Localization of pUL97 to the NE is mediated by direct interaction with the LBR-binding protein p32 (Marschall et al. 2005).

A local loss of lamins A/C from the nuclear lamina has also been observed in HSV-1 infected cells (Scott and O'Hare 2001). The HSV-1 proteins pUL31 and pUL34, homologs of M50/p35 and M53/p38, have been shown to be involved in the redistribution of lamins from the NE in infected cells (Reynolds et al. 2004; Simpson-Holley et al. 2005). In these studies, both proteins have been shown to localize to the nuclear lamina and to bind directly to lamins A/C in vitro. Furthermore, pUL31 and pUL32 recruit PKC δ , a proapoptotic kinase, and PKC α to the NE (Park and Baines 2006). This leads to the phosphorylation of lamin B as determined by ^{32}P -incorporation. Uniform distribution of the PKCs along the NE appears to be dependent on the HSV-1 kinase U $_S$ 3. The U $_S$ 3 can also phosphorylate lamins A/C in vitro, and its overexpression leads to changes in nuclear shape and disruptions in lamins A, B, and C in the lamina region (Bjerke and Roller 2006; Mou et al. 2007). In addition, two Epstein-Barr virus (EBV) proteins, BFRF1 and BFLF2 (homologs of pUL31 and pUL34), required for envelopment and egress from the nucleus, are located in the NE region, where they are suggested to form a complex with lamin B (Gonnella et al. 2005). Taken together, it appears that the recruitment of either host cells or viral kinases to the NE, where they phosphorylate and disassemble lamin structures, represent major steps in the process of the primary envelopment and migration of *Herpesviridae* viruses from the nucleus to the cytoplasm. It will be of great interest in the future to determine the specific sites of phosphorylation and their impact on lamin structure and assembly states.

Lamins are also involved in human immunodeficiency virus 1 (HIV1) infections. The expression of HIV1 Vpr, a virion-associated protein, induces herniations of the NE lacking the A- and B-type lamins and NPCs (de Noronha et al. 2001). These herniations frequently rupture, permitting the movement of the Wee1 kinase from the nucleus to the cytoplasm and of the Cdc25C phosphatase and cyclin B1 in the reverse direction. All three proteins are regulators of the mitotic kinase CDK1, and

changes in their subcellular distribution appear to be required for the G2/M-phase transition (Ferrari 2006; Trinkle-Mulcahy and Lamond 2006). Therefore it has been proposed that these disruptions in the nuclear lamins are related to mechanisms responsible for the G2 cell cycle arrest in HIV1-infected cells (de Noronha et al. 2001).

Lamin-binding partners and virus infectivity

The lamin A-binding proteins BAF, LAP2 α , and emerin have also been implicated in viral infections. BAF was originally described as a facilitator of the preintegration complexes (PICs) involved in the incorporation of retroviral cDNA into the genome of host mammalian cells (Segura-Totten and Wilson 2004). Recently, it has been shown that LAP2 α stabilizes the association of BAF with the PIC of the Moloney murine leukemia virus (MMLV) and that knockdown of LAP2 α impairs viral replication in NIH3T3 cells (Suzuki et al. 2004). Emerin appears to be required for the efficient integration of viral cDNA into the host genome in HIV1 infections in primary macrophages (Jacque and Stevenson 2006). However, in HeLa cells silenced for emerin, BAF, or LAP2 α or in emerin-deficient MEFs, both HIV1 and MMLV infectivity appears to be normal (Shun et al. 2007). The discrepancy in the various observations could be explained by different compensatory systems or factors associated with the nuclear envelope present in the various types of cells used. It is obvious, however, that lamins and several of their binding partners are involved in distinct processes of the infection cycles of various viruses.

Viral therapeutics and lamins

It is also interesting to consider changes in lamin function that may be attributable to therapeutic protocols used in virus infections. For example, HIV-infected patients treated with highly active anti-retroviral therapy (HAART) often develop lipodystrophies resembling those caused by mutations in *LMNA* (for example, see Behrens et al. 2000). In HAART, HIV patients are treated with a combination of several drugs, including specific HIV protease inhibitors (PIs) (Hoffmann and Mulcahy 2006). Recent findings suggest that defective pre-lamin A processing caused by some of the PIs used in the HAART treatment (Fig. 1B) contribute to the lipodystrophy phenotype (Clarke 2007). Altered distributions of lamins A/C and B, accumulation of pre-lamin A, nuclear deformations, and a down-regulation and abnormal accumulation at the NE of the adipocyte differentiation factor SREBP1 have all been reported in 3T3 preadipocytes treated with HAART PIs (Caron et al. 2003). These alterations accompany defects in the process of the differentiation of these cells into adipocytes.

Two recent studies have provided evidence in support of a more direct involvement of the PI-induced defects in pre-lamin A processing in the development of lipodystrophies in HIV patients. First, fibroblasts from lipodys-

trophy patients and control fibroblasts treated with PIs display similar phenotypes (Caron et al. 2007). These phenotypes include pre-lamin A accumulation, alterations in the NE, and premature replicative senescence, all of which can be reversed with FTIs. Secondly, inhibition of Zmpste24 by PIs used in the HAART treatment (Fig. 1B) leads to an accumulation of pre-lamin A in human and mouse fibroblasts similar to that observed in *ZMPSTE24*^{-/-} fibroblasts (Coffinier et al. 2007). A recent report shows a reduction in lamin A but not lamin C mRNA levels in abdominal subcutaneous adipose tissues from HAART-treated HIV-positive patients whether these patients had clinical indications of lipodystrophy (Miranda et al. 2007). These findings suggest that HAART treatment affects lamin A processing both at the transcriptional and post-translational levels and raises the possibility that feedback control mechanisms connecting these two levels of lamin A regulation may be involved. Although these data are very interesting, there is no direct proof that defects in lamin A processing are responsible for the development of lipodystrophies in HIV patients treated with HAART. In fact, a recent study shows that the down-regulation of lamins A/C does not appear to alter the inhibitory effect on adipocyte differentiation by PIs (Kudlow et al. 2005).

Summary and conclusions

In summary, there has been an explosion in interest in the nuclear lamins over the past few years. Studies of normal cells and cells from the multitude of laminopathy patients demonstrate that these type V IF proteins play important and in some cases essential roles in a wide range of nuclear functions, including transcription, DNA replication, DNA repair, and cell proliferation and differentiation. However, the detailed mechanisms remain unknown and have to be determined in future studies. In addition, lamins are suggested to take part in the structural organization and epigenetic regulation of chromatin. Although it is clear that chromatin organization and histone methylation are altered in diseases caused by mutant lamins, virtually nothing is known about the specific functions of lamins in these processes under normal physiological conditions. Since lamins are expressed in a developmentally regulated manner, they may be involved in the regulation of the epigenetic changes responsible for cell differentiation (Surani et al. 2007), specifically in the differentiation steps of embryonic (which are devoid of lamins A/C) and adult stem cells.

The majority of the data available led us to propose a model in which lamins act as a dynamic molecular scaffold for chromatin and chromatin interacting/modifying proteins throughout the nucleus (Goldman et al. 2002; Shumaker et al. 2003). This scaffold may vary from cell type to cell type, dependent on the expression levels of the various lamin isoforms. In this way it may contribute to the determination of the specific functions of the respective cell. In addition, different disease-causing mutations appear to differ in their structural properties in

vitro and in situ (Wiesel et al. 2008), suggesting that they affect the various lamin structures present in the nucleus in different ways. Taken together, cell-type- and mutant-dependent alterations in the lamin scaffold may be attributable to the variations in phenotypes and affected tissues observed in the various diseases caused by the enormous number of mutations in *LMNA* described so far.

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