Lamins, laminopathies and disease mechanisms: Possible role for proteasomal degradation of key regulatory proteins

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Lamins are major structural proteins of the nucleus and are essential for nuclear integrity and organization of nuclear functions. Mutations in the human lamin genes lead to highly degenerative genetic diseases that affect a number of different tissues such as muscle, adipose or neuronal tissues, or cause premature ageing syndromes. New findings on the role of lamins in cellular signalling pathways, as well as in ubiquitin-mediated proteasomal degradation, have given important insights into possible mechanisms of pathogenesis.

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1. Nuclear lamins

The nuclear lamina is the main architectural component of the metazoan nucleus and encompasses a filamentous protein network that is associated with the inner nuclear membrane and also extends into the interior of the nucleus. The major components of the lamina are a group of nuclear proteins termed the lamins, which belong to the type V intermediate filament superfamily of proteins. The lamina plays an essential role in maintaining the integrity of the nuclear envelope and provides anchoring sites for chromatin. Lamins are involved in the organization of nuclear functions such as DNA replication and transcription, and have been proposed to play important roles in diverse cellular pathways. Two major kinds of lamins are present in higher eukaryotes. The B-type lamins are constitutively expressed in all somatic cell types, whereas the expression of A-type lamins is restricted to differentiated cells of most lineages. More than 250 mutations in the human lamin A gene (*LMNA*) have been associated with at least 15 debilitating inherited diseases, collectively termed laminopathies, that affect specific tissues such as skeletal muscle, cardiac muscle, adipose tissue and bone, and also cause premature ageing or progeria syndromes. Mutations in lamin B1 and lamin B2 genes as well as genes coding for various nuclear membrane proteins have also been associated with heritable diseases. Current research in this area has given valuable insights into possible mechanisms of pathogenesis and additional functional roles of lamins, especially in specific signalling pathways. This review summarizes recent findings on the deleterious effects of lamin mutations on nuclear organization and function, and explores the possibility that nuclear dysfunction is due to proteasomal degradation of essential proteins. More detailed information on various aspects of lamin biology has been covered in excellent reviews on the subject (Worman and Courvalin 2005; Broers *et al.* 2006; Capell and Collins 2006; Dechat *et al.* 2008; Parnaik 2008).

The A- and B-type lamins differ in their solubility properties, expression patterns and localization during mitosis (Goldman *et al.* 2002; Herrmann *et al.* 2007).

Keywords. DNA repair; heterochromatin; lamin; nuclear envelope; proteasome; ubiquitin ligases

Abbreviations used: ATR, ATM-and-Rad3-related; BAF, barrier-to-autointegration factor; Cdk1, cyclin-dependent kinase 1; CMT, Charcot-Marie-Tooth disorder; DCM, dilated cardiomyopathy; EMD, Emery-Dreifuss muscular dystrophy; FPLD, familial partial lipodystrophy; HGPS, Hutchinson-Gilford progeria syndrome; HP1α, heterochromatin protein 1α; Ig, immunoglobulin; LAP, lamin-associated-polypeptide; LEM, LAP, emerin, MAN1; LGMD, limb girdle muscular dystrophy; MAD, mandibuloacral dysplasia; MAPK, mitogen-activated protein kinase; PCNA, proliferating cell nuclear antigen; pRb, retinoblastoma protein; SREBP1, sterol response element binding protein 1; SUN, Sad1/UNC-84 homology

Lamins A and C (henceforth called lamin A/C) are alternatively spliced products of the lamin A gene, *LMNA*, whereas lamins B1 and B2 are coded by two separate genes, *LMNB1* and *LMNB2*. Additional splice variants of the lamins are germ-cell-specific lamins C2 and B3, which are encoded by *LMNA* and *LMNB2*, respectively, and a minor somatic cell isoform of lamin A termed lamin AΔ10. *LMNA* has been mapped to the locus 1q21.2-q21.3 in the human genome, whereas *LMNB1* and *LMNB2* have been mapped to the loci 5q23.3-q31.1 and 19p13.3, respectively. *Drosophila melanogaster* has two lamin genes, the B-type lamin Dm_0 gene (*lam*Dm_0), which is expressed in most cells and the A-type lamin C gene (*lamC*), whose expression is developmentally regulated. *Caenorhabditis elegans* has only one lamin gene, *lmn-1*, which is expressed in all cells except the mature sperm. Genome sequence analysis of yeast and *Arabidopsis* indicates that these species do not have lamins. Thus, lamins appear to have evolved in animal cells.

Lamins are characterized by a tripartite structure consisting of a central α-helical rod domain flanked by non-helical N-terminal 'head' and C-terminal 'tail' domains that is typical of intermediate filament proteins (Herrmann *et al.* 2007). The central rod domain drives the interaction between two lamin proteins to form a coiled-coil dimer, the basic structural unit of lamin assembly. The head-to-tail associations between two lamin dimers lead to the formation of protofilaments that have the propensity to associate laterally in different configurations such as parallel, staggered or half-staggered to give rise to the 10 nm lamin filament. The three-dimensional crystal structure of the lamin A/C globular tail domain has revealed a compact, well-defined structure termed the immunoglobulin (Ig) domain or fold; Ig domains serve as structural scaffolds or may mediate specific intermolecular interactions with other proteins. Most of the disease-causing mutations in the rod domain affect lamin assembly and cause increased mobility of lamins in live cells (Gilchrist *et al.* 2004; Broers *et al.* 2005; Tripathi *et al.* 2009).

The C-terminii of lamins A, B1 and B2 bear a CaaX motif (C, cysteine; a, aliphatic; X, any amino acid), which is post-translationally modified by cysteine farnesylation followed by proteolytic cleavage of the last three amino acids (aaX) and methyl esterification of the carboxyl group of the farnesylated cysteine residue. Farnesylation appears to be required for increasing the hydrophobicity of the C-terminus to allow targeting of lamins to the inner surface of the nuclear envelope. After nuclear envelope localization, the 18 C-terminal residues of pre-lamin A, including the farnesylated cysteine, are cleaved off by the ZMPSTE24 protease to form mature lamin A.

In addition to their typical localization at the nuclear periphery, lamins have also been detected in the interior of the nucleus in the form of foci or a diffuse network. Some of these intranuclear lamin structures have been implicated in establishing patterns of DNA replication sites (Moir *et al.* 1994; Kennedy *et al.* 2000) and in organizing transcription (Jagatheesan *et al.* 1999; Kumaran *et al.* 2002). Lamins are dispersed at the onset of mitosis, as a consequence of phosphorylation of essential serine residues on either end of the rod domain of lamin by cyclin-dependent kinase 1 (Cdk1), which results in depolymerization of the lamina into dimers and tetramers. The lamina is reassembled towards late telophase and in early G1 phase of the cell cycle (Gant and Wilson 1997).

Lamins can bind to two broad categories of proteins, nuclear membrane proteins and gene regulatory proteins (Worman and Courvalin 2005; Wilson and Foisner 2010). Several inner nuclear membrane proteins interact directly with lamins, which helps to anchor lamin filaments to the nuclear envelope. Prominent lamin-binding proteins are emerin, lamin B receptor and lamin-associated-polypeptides (LAPs) 1 and 2. Emerin, LAP2 and another envelope protein MAN1 possess a 40-residue folded motif called the LEM domain (derived from LAP, emerin, MAN1) that binds directly to barrier-to-autointegration factor (BAF), a conserved DNA-binding protein that is involved in higher-order chromatin structure and in nuclear assembly. Emerin has been reported to stabilize β-catenin and thereby influence the onset of adipogenesis (Tilgner *et al.* 2009). LAP2α forms functional complexes with lamin A and retinoblastoma protein (pRb) in the interior of the nucleus (Dechat *et al.* 2000; Markiewicz *et al.* 2002).

The nuclear envelope comprises approximately 80 transmembrane proteins (Schirmer and Gerace 2005). Two important families of nuclear membrane-bound proteins are the nesprins and the SUNs (Starr 2009). The nesprins (also called Syne/ANC-1 proteins) are large, actin-binding proteins that span the outer nuclear membrane, and exist in many forms with tissue-specific expression patterns due to alternate splicing. Most SUN (Sad1/UNC-84 homology) domain proteins contain multiple transmembrane domains and localize to the inner nuclear membrane. The N-terminal domains of SUN-1 and SUN-2 are located in the nucleoplasm and bind directly to A-type lamins; the C-terminal domains are localized in the lumen of the nuclear envelope, where they interact with nesprins. The nesprins and SUN domain proteins have been proposed to bridge the nuclear envelope and provide connectivity between the nucleus and cytoskeleton during processes such as nuclear positioning and migration.

There is substantial evidence that lamin A/C associates with specific gene regulatory factors as well as signalling molecules and thereby modulates their activities (Wilson and Foisner 2010). A few examples are described here. The active hypophosphorylated form of pRb, a tumour suppressor protein involved in regulation of the cell cycle and

apoptosis as well as in muscle and adipocyte differentiation, can bind to A-type lamins and also interact with LAP2α, and LAP2α–lamin A/C complexes are able to anchor pRb to the nuclear envelope (Markiewicz *et al.* 2002). Cyclin D3 interacts directly with lamin A/C in muscle cells, and binding interactions between lamin A/C, pRb and cyclin D3 are likely to play an important role in muscle differentiation (Mariappan and Parnaik 2005; Mariappan *et al.* 2007). Lamin A has been reported to bind to c-Fos and sequester it at the nuclear periphery, leading to repression of AP-1 transcriptional activity (Ivorra *et al.* 2006). An adipocyte differentiation factor, sterol response element binding protein 1 (SREBP1) has been shown to interact directly with lamin A by binding to the Ig-fold of the lamin A/C tail domain (Lloyd *et al.* 2002). The Ig-fold domain also binds directly to the DNA replication factor, proliferating cell nuclear antigen (PCNA), and this association has been proposed to be important for the spatial organization of DNA replication (Shumaker *et al.* 2008). Heat shock proteins like Hsp70 as well as small heat shock proteins associate with nuclear lamins and might be required to stabilise intranuclear lamin A/C under heat stress conditions (Willsie and Clegg 2002; Adhikari *et al.* 2004).

2. Laminopathies

Mutations in *LMNA* are associated with tissue-specific laminopathies that affect striated muscles, adipose tissue and peripheral nerves, and also cause premature ageing syndromes that afflict several tissues (figure 1). Certain cases of overlapping symptoms have also been described. The clinical condition termed Emery-Dreifuss muscular dystrophy (EMD) can be caused by mutations in the gene coding for emerin or lamin A/C (Bione *et al.* 1994; Bonne *et al.* 1999), and has also been linked to mutations in genes coding for other nuclear membrane proteins. The disease is marked by contractures of the elbows, Achilles tendons and posterior neck, slow progressive muscle wasting and dilated cardiomyopathy with atrioventricular conduction block. The majority of EMD mutations in *LMNA* are missense mutations and a few are small deletions or nonsense mutations; mutations are found in all exons of the gene. Most mutations are autosomal dominant, and both familial and sporadic mutations have been identified. Autosomal dominant mutations in *LMNA* are the most common cause of dilated cardiomyopathy (DCM) (Fatkin *et al.* 1999) and lead to a particularly severe form of the disease. DCM is a progressive disease that is characterized by ventricular dilatation and systolic dysfunction. In patients with *LMNA* mutations, DCM is usually accompanied by conduction defects and may include skeletal muscle involvement. Missense mutations and splicing defects in *LMNA* have also been linked to autosomal dominant limb girdle muscular dystrophy type 1B (LGMD1B) (Muchir *et al.* 2000). LGMD1B is a slowly progressing disease characterized by weakness and wasting of shoulder and pelvic muscles due to necrosis, and is accompanied by cardiac conduction defects in some patients.

Mutations in *LMNA* have been linked to Dunnigan-type familial partial lipodystrophy (FPLD) by several groups (Cao and Hegele 2000; Shackleton *et al.* 2000; Speckman *et al.* 2000). FPLD is an autosomal dominant disorder characterized by loss of fat tissue from the extremities and excess fat accumulation on the face and neck, beginning at puberty, and is accompanied by insulin-resistant diabetes, hyperlipidemia and atherosclerotic vascular disease. Approximately 90% of the mutations in FPLD are located in exon 8, with substitutions at arginine at 482 amino acid position being found in 75% of cases; mutation of this residue has been shown to block binding of the adipocyte differentiation factor SREBP1 (Lloyd *et al.* 2002).

An autosomal recessive mutation at R298C of *LMNA* gives rise to Charcot-Marie-Tooth disorder (CMT) type 2B, which is an axonal neuropathy characterized by peripheral loss of large myelinated fibres and axonal degeneration that results in sensory impairment with some reduction in motor nerve conduction velocity (De Sandre-Giovannoli *et al.* 2002).

The most deleterious effects of mutations in *LMNA* have been observed in the premature ageing disorder Hutchinson-Gilford progeria syndrome (HGPS) (De Sandre-Giovannoli *et al.* 2003; Eriksson *et al.* 2003). HGPS is an autosomal dominant condition that is characterized by short stature, early thinning of skin, loss of subcutaneous fat, premature atherosclerosis and cardiac failure leading to death. HGPS is a very rare disorder that affects about one in a million and leads to early mortality, usually in the second decade of life. The majority of cases are due to a *de novo* missense mutation (GGC to GGT) in exon 11 that does not cause an amino acid change (G608G) but leads to creation of an abnormal splice donor site which results in expression of a truncated pre-lamin A protein (also termed progerin or lamin AΔ50) with loss of 50 amino acids from the C-terminus including the second ZMPSTE24 cleavage site, resulting in a permanently farnesylated C-terminus. Mandibuloacral dysplasia (MAD) is a rare, autosomal recessive disorder characterized by postnatal growth retardation, skull and facial anomalies, skeletal abnormalities, mottled skin pigmentation, partial or generalized lipodystrophy and signs of premature ageing. Most patients with MAD type A, who exhibit partial lipodystrophy, have a R527H homozygous mutation in *LMNA* (Novelli *et al.* 2002). On the other hand, MAD type B, characterized by generalized loss of fat involving face, trunk and extremities, is caused by mutations in ZMPSTE24 protease, which is involved in the processing of pre-lamin A to lamin A (Agarwal *et al.* 2003).

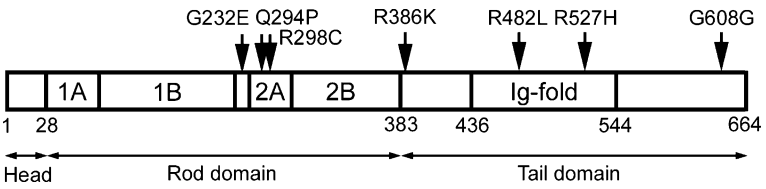

Figure 1. Schematic of lamin A protein structure and disease mutations identified in various laminopathies. Lamin A comprises a rod domain containing the α-helical segments 1A, 1B, 2A and 2B, which are flanked by a short head domain and a tail domain that harbours an Ig-fold motif. Mutations leading to EMD, LGMD1B and DCM occur throughout the protein (approximately 200 mutations have been identified), and a few EMD mutations are indicated (G232E, Q294P, R386K). Most cases of FPLD bear a mutation at R482, whereas those with MAD harbour the mutation R527H. An R298C mutation leads to CMT2B. Majority of HGPS patients bear a mutation at G608, which results in abnormal splicing of pre-lamin A and production of a mutant lamin A protein with a deletion of amino acid residues 607–656 (lamin AΔ50; *see* text for details).

Mutations in *LMNA* as well as *ZMPSTE24* are associated with restrictive dermopathy, which is a rare disorder characterized by intra-uterine growth retardation, tight and rigid skin with erosions, facial malformation, bone mineralization defects and early neonatal mortality (Navarro *et al.* 2004, 2005; Shackleton *et al.* 2005).

A few disease-causing mutations have been identified in the B-type lamin genes. Missense mutations in the lamin B2 gene have been associated with acquired partial lipodystrophy, which is a rare disease that results in a gradual loss of subcutaneous fat from the head, neck, upper extremities and thorax but not from the lower extremities (Hegele *et al.* 2006). Duplications of the lamin B1 gene have been identified in patients with adult onset leukodystrophy, a progressive neurological disorder characterized by loss of myelin in the central nervous system (Padiath *et al.* 2006). In general, mutations in the B-type lamins are likely to be highly deleterious, based on findings in mouse models. The knock-out of the mouse lamin B1 gene causes defects in embryonic development (Vergnes *et al.* 2004) and lamin B2-null mice show severe brain abnormalities (Coffinier *et al.* 2010). Genetic diseases due to mutations in genes encoding proteins that associate with lamins have also been reported (Worman and Courvalin 2005; Dechat *et al.* 2008; Parnaik 2008).

3. Deleterious effects of lamin mutations on nuclear organization and functions

Lamins play a crucial role in maintenance of nuclear shape and integrity, organization of chromatin and distribution of nuclear pore complexes. Lamins are also involved in the spatial organization of DNA replication, transcription and mitotic events, and are specifically cleaved during apoptosis. Binding of lamins to specific gene regulatory factors influences cellular signalling pathways involved in muscle differentiation, adipocyte differentiation, DNA repair, cellular proliferation and transforming growth-factor-β-mediated signalling (Broers *et al.* 2006; Capell and Collins 2006; Melcer *et al.* 2007; Dechat *et al.* 2008; Parnaik 2008). The functional role of lamins is strongly supported by data with disease-causing lamin mutants as well as earlier findings with loss-of-function lamin mutants in *C. elegans* and *D. melanogaster*, and dominant-negative mutants in cultured cells. Recent studies suggest that the lamina might play an active role in genome organization through specific binding to large genomic segments (Kind and van Steensel 2010).

HGPS cells exhibit severe nuclear abnormalities such as lobulation, blebbing and loss of heterochromatin (Eriksson *et al.* 2003; De Sandre-Giovannoli *et al.* 2003; Goldman *et al.* 2004; Taimen *et al.* 2009). The accumulation of farnesylated pre-lamin A in HGPS cells has been proposed to cause aberrant nuclear morphology and pathogenesis (Fong *et al.* 2004). This is supported by evidence for improvement of nuclear morphology by blocking farnesyl transferase activity in HGPS cells (Capell *et al.* 2005; Columbaro *et al.* 2005; Yang *et al.* 2005) or knocking out the *Zmpste24* gene in a mouse model (Fong *et al.* 2006). Importantly, administration of a farnesyl transferase inhibitor to *Zmpste24*-deficient mice can decrease progeria-like disease symptoms and improve survival (Fong *et al.* 2006), raising the possibility of beneficial effects of these drugs in humans. However, a caveat to the long-term use of farnesyl transferase inhibitors is a recent report that non-farnesylated pre-lamin A causes cardiomyopathy in mice (Davies *et al.* 2010).

Cells from patients with other laminopathies also display abnormal nuclear morphology. Fibroblasts from patients with EMD, LGMD, DCM and FPLD due to *LMNA* mutations show abnormal nuclear phenotypes with nuclear blebbing and aberrant lamin foci in up to 20% of the cells (Vigouroux *et al.* 2001; Capanni *et al.* 2003; Favreau *et al.* 2003; Muchir *et al.* 2004). Exogenous expression of several lamin A/C disease mutants in mouse or human cells causes aberrant nuclear morphology, altered lamina assembly, mislocalization of emerin and disruption of the endogenous nuclear lamina (Östlund *et al.* 2001; Raharjo *et al.* 2001; Vigouroux *et al.* 2001; Favreau *et al.* 2003; Manju *et al.* 2006). Aberrant nuclear morphology results in cellular

senescence, downregulation of transcription, impaired DNA repair and apoptosis (Capanni *et al.* 2003; Goldman *et al.* 2004; Lammerding *et al.* 2004; Manju *et al.* 2006; Gurudatta *et al.* 2010). An interesting observation is that nuclei from old individuals acquire defects that are similar to those seen in cells from HGPS patients, and this has been attributed to accumulation of progerin (Scaffidi and Misteli 2006).

4. Molecular and cellular basis of pathogenesis

The reported molecular and cellular defects in laminopathic cells range from susceptibility to physical stress due to weakening of the nuclear lamina-envelope network to alterations in tissue-specific gene expression patterns and altered protein–protein interactions. Interestingly, in certain cases, lamin misexpression can trigger degradation of key regulatory proteins in the cell, some of which have tissue-specific functions. These are described in greater detail below.

As the majority of mutations in *LMNA* affect muscle tissue, there is considerable interest in understanding the role played by A-type lamins in muscle development and the effects of mutations on this process. Valuable insights into cellular defects associated with lamin A deficiency, in particular, those leading to muscular dystrophy and cardiomyopathy, have been obtained from the mouse lamin A gene knock-out model (Sullivan *et al.* 1999). *Lmna*$^{-/-}$ mice show symptoms of EMD and DCM and die by 6–8 weeks of age. Fibroblasts from *Lmna*$^{-/-}$ mice show aberrant nuclear morphology and herniations of the envelope, and in response to mechanical strain, these fibroblasts exhibit increased nuclear deformations and defective mechanotransduction, together with reduced expression of genes activated by NF-κB (Lammerding *et al.* 2004). Cardiomyocytes from these mice show abnormal nuclear architecture, relocalization of heterochromatin to the nuclear interior and changes in localization of the cytoskeletal filament protein desmin, leading to contractile dysfunction (Nikolova *et al.* 2004). Activation of the mitogen-activated protein kinase (MAPK) signalling pathway has been observed in the H222P-knock-in mouse model of EMD (Muchir *et al.* 2007).

Certain markers of muscle differentiation such as MyoD and pRb, as well as desmin are decreased in *Lmna*$^{-/-}$ myoblasts (Frock *et al.* 2006). Both MyoD and desmin transcripts are reduced in proliferating *Lmna*$^{-/-}$ myoblasts but pRb transcript levels are normal. The degradation of pRb protein in *Lmna*$^{-/-}$ fibroblasts can be reversed by treatment with proteasomal inhibitors or ectopic expression of lamin A/C, suggesting that a normal lamina is required for pRb stability (Johnson *et al.* 2004). In addition to dysfunction of pRb in terminal differentiation, the pRb-mediated G1-S phase transition is hindered in HGPS cells,

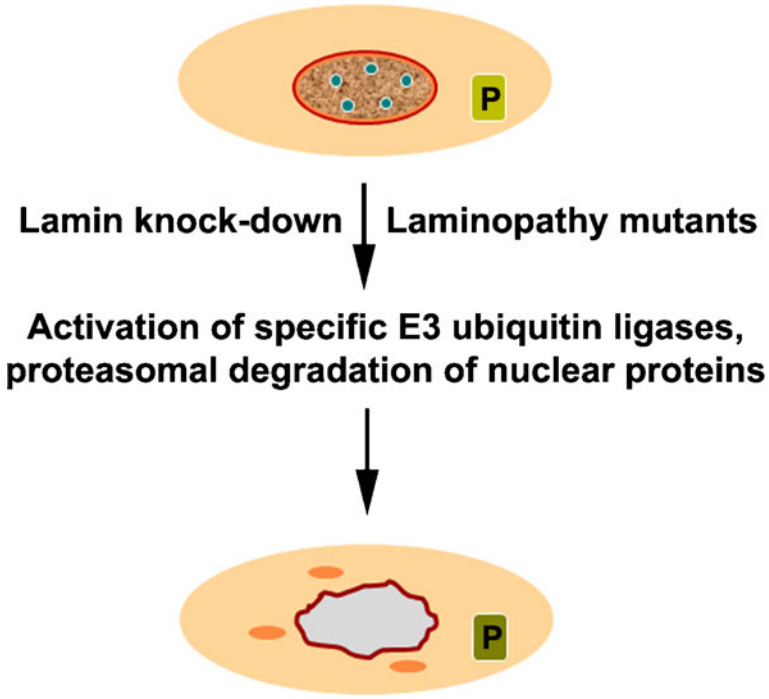

Figure 2. Model for effects of lamin misexpression on protein stability and nuclear structure. Expression of laminopathy mutants or lamin A/C shRNA leads to activation of specific E3 ubiquitin ligases such as RNF123 and HECW2, as well as the F-box protein FBXW10, resulting in increased proteasomal degradation (P) of HP1α and β (blue) and other regulatory factors (brown), as well as dispersal of emerin (orange) and aberrant nuclear lamina morphology (maroon).

probably due to inhibition of phosphorylation of pRb by Cdk4 kinase (Dechat *et al.* 2007); these cells also display abnormal localization of progerin during mitosis and mitotic defects (Cao *et al.* 2007; Dechat *et al.* 2007). C2C12 myoblasts stably expressing a common EMD-causing lamin A mutation, R453W, are deficient in expression of myogenic markers like myogenin, do not exit the cell cycle properly and are eventually targeted for apoptosis (Favreau *et al.* 2004). Differentiation is also impaired in myoblasts expressing the EMD mutants G232E, Q294P or R386K (Parnaik and Manju 2006).

In fibroblasts from an LGMD1B patient with a homozygous *LMNA* nonsense mutation (Y259X), which leads to absence of lamin A, the integral membrane proteins emerin and nesprin-1α are mislocalized to the ER and subsequently degraded; this degradation is mediated by the proteasomal machinery (Muchir *et al.* 2006). Proteomics analysis has demonstrated that reduction of lamin A/C to ~10% of normal values by an shRNA approach in HeLa cells leads to depletion of 34 proteins, most of which are involved in cytoskeletal organization, cell cycle regulation and proliferation (Chen *et al.* 2009).

Fibroblasts from the *Zmpste24*-null mouse, which is a model for progeria, show genomic instability, higher sensitivity to DNA damaging agents, and impairment in recruitment of repair proteins such as p53 binding protein 1 (53BP1) and Rad51 to sites of DNA lesions (Liu *et al.* 2005), as well as upregulation of p53 targets (Varela *et al.* 2005). In $Lmna^{-/-}$ fibroblasts, 53BP1 is degraded by the proteasomal machinery, and this may contribute to telomere dysfunction in these cells (Gonzalez-Suarez *et al.* 2009). In cell culture models, lamin mutants impair the formation of DNA repair foci and hinder the recruitment of 53BP1 to repair sites after short-term DNA damage; these mutants cause degradation of ATM-and-Rad3-related (ATR) kinase in untreated cells (Manju *et al.* 2006).

Loss of heterochromatin in HGPS cells is accompanied by downregulation of trimethylation at lysine 9 of histone H3 (H3K9), which normally marks pericentric constitutive heterochromatin (Columbaro *et al.* 2005; Shumaker *et al.* 2006). Furthermore, the inactive X chromosome from a female HGPS patient shows loss of trimethylation at lysine 27 of histone H3 (H3K27), a mark for facultative heterochromatin, which results in reduced association with heterochromatin protein 1α (HP1α) (Shumaker *et al.* 2006). Cells from patients with MAD type A due to a R527H mutation in *LMNA* also exhibit accumulation of pre-lamin A and loss of peripheral heterochromatin, together with mislocalization of HP1β, trimethylated H3K9 and LBR (Filesi *et al.* 2005). A recent study has reported another progeria mutation, E145K that is highly disruptive of nuclear structure but does not respond to treatment with a farnesyl transferase inhibitor (Taimen *et al.* 2009).

Expression of the lamin A EMD mutants G232E, Q294P and R386K in HeLa cells results in depletion of HP1α and β isoforms; treatment with proteasomal inhibitors leads to restoration of levels of HP1 isoforms, stable association of lamin mutants with the nuclear periphery, rim localization of the inner nuclear membrane lamin-binding protein emerin and partial improvement of nuclear morphology. FBXW10, a member of the F-box family of substrate-binding proteins that are components of RING ubiquitin ligases such as SCF-ligase, is induced several-fold in cells expressing lamin mutants, and expression of FBXW10 directly leads to depletion of HP1α and β and dispersal of emerin (Chaturvedi and Parnaik 2010). This is the first report on the identification of specific components of the ubiquitination pathway that are activated by lamin misexpression (*see* schematic in figure 2). Two other ubiquitin ligases that are upregulated upon expression of lamin mutants or in lamin A knock-down cells, RNF123 and HECW2, are also involved in degradation of HP1 isoforms and other regulatory proteins (Parnaik, Chaturvedi and Muralikrishna, unpublished work). Thus ubiquitin-mediated proteasomal degradation of essential nuclear proteins may afford a distinct mechanism for the deleterious effects of disease-causing lamin mutants.

5. Concluding remarks

Lamins are essential for nuclear integrity and spatial organization of nuclear functions, and they also provide interconnections between the cytoplasm and the nucleus. Binding interactions between lamins and specific proteins lead to the formation of critical regulatory networks. Studies with laminopathic mutations in both cellular and animal models have given valuable information on the role of lamins in key signalling pathways. It is becoming increasingly evident that certain highly deleterious mutations in lamin A/C are able to affect multiple cellular processes, leading to general cellular toxicity and cell death. Both decreased levels of lamin A/C and lamin missense mutations trigger proteasomal degradation of essential proteins. Recent findings on the identification of specific components of the ubiquitination pathway that are activated by lamin misexpression have provided new insights into these processes. Further studies should yield a better understanding of the mechanism of activation of ubiquitin ligases in laminopathic cells.

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