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REVIEW ARTICLE

Partners and post-translational modifications of nuclear lamins

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Abstract Nuclear intermediate filament networks formed by A- and B-type lamins are major components of the nucleoskeleton that are required for nuclear structure and function, with many links to human physiology. Mutations in lamins cause diverse human diseases ('laminopathies'). At least 54 partners interact with human A-type lamins directly or indirectly. The less studied human lamins B1 and B2 have 23 and seven reported partners, respectively. These interactions are likely to be regulated at least in part by lamin post-translational modifications. This review summarizes the binding partners and post-translational modifications of human lamins and discusses their known or potential implications for lamin function.

Keywords Lamin · Phosphorylation · Acetylation · *O*-GlcNAcylation · Ubiquitylation · SUMOylation · Oxidation · Nucleoskeleton · Nuclear envelope · Laminopathy

Introduction

Lamins are major components of the nucleoskeleton in multicellular animals (metazoans), not found in plants or fungi (Dittmer and Misteli 2011). Lamins tether chromatin, bind signaling proteins and support epigenetic regulation, mechanotransduction, development, transcription, replication and DNA damage repair (Dechat et al. 2008; Dittmer and Misteli 2011; Simon and Wilson 2011). How lamins contribute to such a remarkable range of activities is for the most part unknown: a new saga in biology that begins with a seemingly simple structural polymer. Lamins form highly stable filament networks near the inner membrane of the nuclear envelope and are also distributed throughout the nucleoplasm except for the nucleolus (Gerace and Huber 2012; Dittmer and Misteli 2011; Simon and Wilson 2011). Mammals express two types of lamins, the B-type (lamins B1, B2 and B3) encoded by *LMNB1* and *LMNB2* (Dittmer and Misteli 2011; Schumacher et al. 2006), and A-type (lamins A, C, AΔ10, C2, and AΔ50, also known as 'progerin') generated by alternative splicing of *LMNA* (Dittmer and Misteli 2011; Bokenkamp et al. 2011).

Mutations in lamins cause a variety of diseases, collectively termed laminopathies (Worman 2012; Butin-Israeli et al. 2012). So far nearly 400 different disease-causing mutations in A-type lamins have been identified, underscoring their significance to cell and tissue biology and human physiology. Diseases are now also being mapped to B-type lamins. Duplication of the *LMNB1* gene can cause leukodystrophy (Padiath et al. 2006; Schuster et al. 2011; Brussino et al. 2010; Molloy et al. 2012) or leukoencephalopathy (Brussino et al. 2009), and certain mutations in *LMNB2* correlate with increased susceptibility to acquired partial lipodystrophy (Hegele et al. 2006).

Both A- and B-type lamins are synthesized as precursors that are post-translationally processed prior to filament assembly. All lamins except lamin C are first farnesylated at the cysteine of the C-terminal CaaX motif (Beck et al. 1990; Farnsworth et al. 1989), then proteolytically cleaved by either Rce1 or Zmpste24, and finally carboxymethylated by Icmt1 (Nigg et al. 1992; Young et al. 2005; Maske et al. 2003; Varela et al. 2005). The lamin A precursor (prelamin A) is further processed by Zmpste24-dependent cleavage after Tyr-646 to generate mature lamin A (Pendas et al. 2002; Bergo et al. 2002; Barrowman et al. 2012).

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Lamin proteins have a small N-terminal 'head' domain, a long coiled-coil 'rod' domain and a large C-terminal 'tail' that includes a globular Ig-fold domain (Dechat et al. 2008; Dittmer and Misteli 2011). Lamin assembly was successfully reconstituted in vitro only recently (Ben-Harush et al. 2009). Studies of purified lamins show that they first dimerize via their rod domain; dimers then associate head-to-tail to form linear polymers, which in turn associate laterally in groups of three or four in a staggered anti-parallel manner to form ~10-nm-diameter filaments (Ben-Harush et al. 2009; Herrmann et al. 2004; Gerace and Huber 2012). The actual organization of lamina networks in somatic cells is unknown.

A- and B-type lamins can interact directly in vitro (Ye and Worman 1995; Schirmer and Gerace 2004), but in living cells appear to preferentially form independent filament networks. High-resolution microscopy of endogenous lamins A/C and B1 (Shimi et al. 2008) as well as FRET analysis of exogenous lamins A and B1 (Delbarre et al. 2006) support the existence of separate lamin A/C or B1 homopolymers in close contact with each other. The spatial separation of lamin A and B1 homopolymers was lost in cells that also expressed lamin A bearing the Hutchinson–Gilford progeria syndrome (HGPS)-causing Δ50 deletion ('progerin') (Delbarre et al. 2006). Remarkably, biochemical analysis suggests lamins A and C (the first 566 residues of which are identical) also form homodimers and homopolymers preferentially in vivo, via unknown mechanisms (Kolb et al. 2011).

In the nucleus lamins reportedly bind partners (Wilson and Foisner 2010; Zastrow et al. 2004). Lamin A is the most extensively studied with at least 29 reported direct binding partners (Fig. 1, Table 1), and at least 24 proteins identified by co-immunoprecipitation from cells or other indirect methods (Table 2). Many new potential partners are being uncovered (Roux et al. 2012; Kubben et al. 2010). The B-type lamins are less studied, with 23 reported direct or indirect partners for lamin B1 (Table 3) and only seven for lamin B2 (Table 4). Lamin partners in other animals, including *Drosophila* JIL-1 kinase (Bao et al. 2005) and *Xenopus* α-importin (Adam et al. 2008), are conserved in humans and may therefore also associate with human lamins.

The functional association of many certain partners including LEM-domain proteins, BAF, Rb and LINC complex components has been confirmed genetically or in cells as discussed in recent reviews (Wilson and Foisner 2010; Simon and Wilson 2011; Dechat et al. 2010; Dittmer and Misteli 2011). Biochemical and biological validation will be crucial to move this field forward, since many partners identified in vitro lack proven biological relevance, and 'associated' proteins (e.g., those identified by co-immunoprecipitation from cells in Table 2) lack evidence that binding is direct. Nuclear lamina networks are largely insoluble under typical co-immunoprecipitation conditions, and some methods (e.g., sonication) can create small 'chunks' of lamina that appear soluble (e.g., not pelleted by 12,000 × *g* centrifugation) but might contain dozens or hundreds of different proteins that co-immunoprecipitate together. Another confounding issue is that lamins can bind DNA (Stierle et al. 2003). Hence one must rule out the possibility that 'direct' binding of certain partners to lamins is actually mediated by DNA in the reaction. For example, this artifact caused two proteins (Cone-rod homeobox [Crx]; HIV-1 matrix [MA]) and one polypeptide (C-terminal domain of MAN1) to be misidentified as direct partners for the dsDNA-binding protein BAF, and was corrected by NMR analysis of protein-protein binding and by re-testing under DNA-free conditions (Huang et al. 2011). A related artifact can be solved by using the DNA intercalator, ethidium bromide, to 'bump off' proteins (e.g., PARP1; Ku70/80) that bind DNA ends nonspecifically (Lai and Herr 1992).

A major unanswered question is how lamin associations with specific partners are regulated. To facilitate further studies, this review focuses on post-translational modifications of human lamins, including the few cases where the functional consequences of specific modifications are known.

Phosphorylation

Following the discovery that lamins are reversibly disassembled during mitosis (Gerace and Blobel 1980), early studies focused on lamin phosphorylation during mitosis. The head domain of all lamins includes an evolutionarily conserved site phosphorylated by the mitotic cyclin-dependent kinase CDK1 (Peter and Stick 2012). Peptide sequencing identified this site as Ser-22 in human lamins A/C, Ser-23 in lamin B1 and Ser-37 in lamin B2 (Fig. 2a). The first mammalian lamin B2 cDNA to be studied, thought to be the physiological form, was actually missing 20 N-terminal residues and hence dominantly disrupted nuclear lamina organization in transfected cells (Schumacher et al. 2006); please note that these 20 'new' residues are included when numbering lamin B2 residues in this review. Lamin phosphorylation by CDK1 impedes assembly of head-to-tail polymers but does not disrupt lamin dimer formation (Heitlinger et al. 1991; Peter et al. 1991). CDK1 targets two regions important for head-to-tail association of lamin A dimers (Strelkov et al. 2004); phosphorylation at Ser-22, and at Ser-392, Ser-404 and Ser-406 at the opposite end of the coiled-coil domain, are required to depolymerize lamin filaments during mitosis (Heald and McKeon 1990; Peter et al. 1990; Ward and Kirschner 1990; Eggert et al. 1991; Enoch et al. 1991; Thompson and Fields 1996; Schneider et al. 1999; Fig. 2b). Phosphorylation of the A-type lamin in

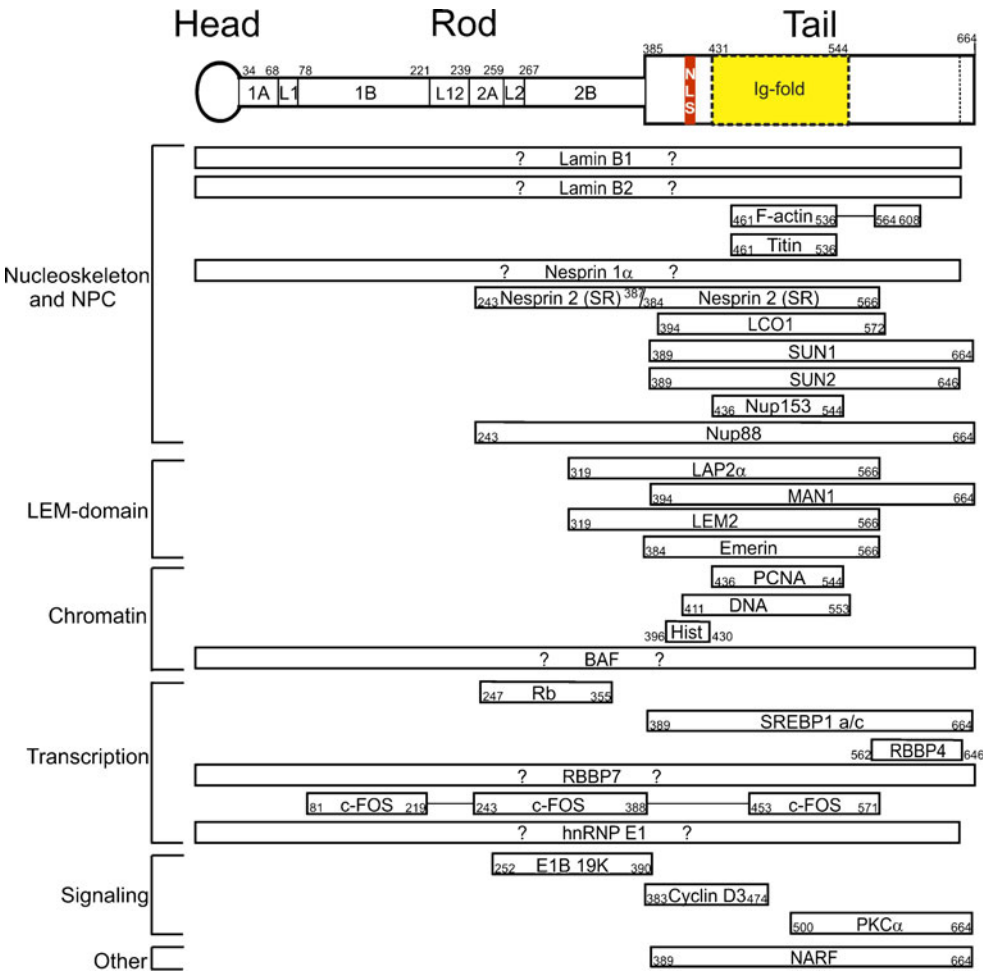

Fig. 1 Lamin A molecule and direct binding partners. Diagram of major domains of human lamin A and mapped regions involved in binding to specific partners. The rod domain is subdivided into four coiled-coil regions (1A, 1B, 2A, 2B), which are separated by linker regions L1, L12 and L2. NLS, nuclear localization signal. *Question marks* indicate partners whose binding region on lamin A is unmapped

Drosophila, named lamin C, at Ser-37 (homologous to human lamins A/C Ser-22) increases the solubility of the lamin protein and eliminates its ability to interact with chromatin in vitro (Zaremba-Czogalla et al. 2012).

The protein kinase C (PKC) family also regulates lamins during mitosis (Peter et al. 1990; Hocevar et al. 1993). In zebrafish, lamins are phosphorylated by PKC first (Collas 1999), suggesting PKC phosphorylation might 'unmask' sites for CDK1 phosphorylation (Buendia et al. 2001). Supporting this idea, mitotic PKC- and CDK1-mediated disassembly of lamin B1 is triggered by diacylglycerol (DAG) generated by either lipin in HeLa cells (Mall et al. 2012) or by PLCβ1 in mouse erythroleukemia cells (Fiume et al. 2009). Conversely, lamin filament assembly in HeLa cells during early G1 requires dephosphorylation of B-type lamins by AKAP149-PP1 (Steen et al. 2003). However, mitosis also involves dephosphorylation: in Xenopus oocytes, unidentified PKA site(s) must be dephosphorylated for lamin filaments to disassemble (Molloy and Little 1992).

Recent high-throughput proteomic studies revealed further, extensive human lamin phosphorylation during mitosis (Olsen et al. 2010; Daub et al. 2008; Malik et al. 2009; Wang et al. 2008, 2010; Fig. 2, Table 5). Many mitotic phosphorylation sites are clustered in the head domain and near the Nuclear Localization Signal (NLS) (Fig. 3). However, it is important to note that some mitotic sites are also targeted during interphase (Table 5) as discussed below. With 61 known phosphorylation sites (Fig. 3, Table 5) lamins A/C have more than twice as many known sites as lamin B1 (32 sites; Fig. 3, Table 6) or lamin B2 (28 sites; Fig. 3, Table 7). Two sites are unique to the lamin C isoform (Table 5). In general, the head and tail domains account for most phosphorylation sites, with the highest density between the rod domain and NLS (Fig. 3).

PKC family members also regulate non-mitotic functions of lamins. PKC phosphorylation of B-type lamins in sea urchin sperm triggers lamina disassembly prior to fertilization (Collas et al. 1997). Lamin A/C Ser-525, in the Ig-fold domain, is reportedly phosphorylated only during interphase (Table 5; Eggert et al. 1993). In human dermal fibroblasts, PKC specifically modifies at least one site in lamin B2 during S-phase (Kill and Hutchison 1995). In leukemia cells, increased lamin B2 phosphorylation is proposed to extend G1 phase (Meier et al. 1997). PKC phosphorylation of chicken lamin B2 inhibits lamin B2 import into the nucleus during interphase (Hennekes et al. 1993). Finally,

Table 1 Reported direct binding partners of lamin A

Protein	Lamin A residues	Method	Reference
Lamin B1	ND	Recombinant Affi-bead pulldown	Schirmer and Gerace 2004
Lamin B2	ND	Recombinant Affi-bead pulldown	Schirmer and Gerace 2004
F-actin	461–536 and 564–608	Recombinant high-speed pelleting	Simon et al. 2010
Titin	461–536	Recombinant pulldown	Zastrow et al. 2006
Nesprin1α	ND	Blot overlay	Mislow et al. 2002
Nesprin2	243–387 and 384–566	Recombinant pulldown	Libotte et al. 2005
LCO1	394–572	TnT pulldown	Vlcek et al. 2004
SUN1	389-664	TnT pulldown	Haque et al. 2006
SUN2	389–646	TnT pulldown	Crisp et al. 2006
Nup153	436–544	TnT pulldown	Al-Haboubi et al. 2011
Nup88	243–664	Recombinant pulldown	Lussi et al. 2011
LAP2α	319–566	Blot overlay	Dechat et al. 2000
MAN1	394–664	Blot overlay/Microtiter assay	Mansharamani and Wilson 2005
LEM2	319–566	Blot overlay	Brachner et al. 2005
Emerin	384–566	Yeast-2-Hybrid/Blot overlay	Sakaki et al. 2001 Lee et al. 2001
PCNA	436–544	Recombinant pulldown	Shumaker et al. 2008
DNA	411–553	Blot overlay/cosedimentation	Stierle et al. 2003
Histones	396–430	Microtiter assay	Taniura et al. 1995
BAF	ND	Microtiter assay	Holaska et al. 2003
Rb	247–355	TnT pulldown	Ozaki et al. 1994 Mancini et al. 1994
SREBP1	389–664	Recombinant pulldown	Lloyd et al. 2002
RBBP4	562–646	Recombinant pulldown	Pegoraro et al. 2009
RBBP7	ND	TnT pulldown	Pegoraro et al. 2009
c-FOS	81–219, 243–388 and 453–571	Recombinant pulldown	Ivorra et al. 2006
hnRNP E1	ND	TnT gel shift	Zhong et al. 2005
E1B 19 K	252–390	TnT pulldown	Rao et al. 1997
Cyclin D3	383–474	Recombinant pulldown	Mariappan et al. 2007
PKCα	500–664	Blot overlay	Martelli et al. 2002
NARF	389–664	TnT pulldown	Barton and Worman 1999

ND not determined

both PKCα (Shimizu et al. 1998) and PKCδ (Cross et al. 2000) phosphorylate B-type lamins at unknown sites during apoptosis.

Other kinases that target lamins include PKA, S6-kinase II and Akt (Tables 5 and 6). Ser-50 phosphorylation of the B-type lamin in *Drosophila*, named lamin Dm0, by PKA inhibits head-to-tail dimerization (Stuurman 1997); interestingly, among human lamins this modification appears to be detectably conserved only in lamin B1, on Ser-28 (Table 6; Olsen et al. 2010; Rigbolt et al. 2011). Human lamins A/C are phosphorylated by S6-kinase II at Ser-404; the functional significance of this modification is unknown (Ward and Kirschner 1990), but it has since been detected under a variety of cellular conditions (Table 5). For example, following insulin treatment, the Akt kinase phosphorylates lamins A/C at Ser-404 in HEK 293 T cells (Cenni et al. 2008). Cells that express lamin A bearing either the S404A mutation or a nearby R401C Emery–Dreifuss muscular dystrophy (EDMD)-causing mutation have disorganized lamina networks and nuclear blebbing (Cenni et al. 2008).

Phosphorylation of lamins A/C is generally reduced in myoblasts from EDMD and limb girdle muscular dystrophy (LGMD) patients (Cenni et al. 2005). The N terminus of lamins A/C is phosphorylated in cycling C2C12 myoblasts, and insulin treatment specifically increases phosphorylation of lamin A, but not lamin C (Cenni et al. 2005). Insulin stimulation also increases phosphorylation of lamins A/C in quiescent baby hamster kidney fibroblasts (Friedman and Ken 1988). Neither the kinase(s) responsible for phosphorylating lamins A/C in response to insulin signaling in myoblasts or kidney fibroblasts, nor their target sites, have been identified.

A study of lamin B2 in DLD-1 colorectal cancer cell lines using phospho-site specific antibodies revealed differential

Table 2 Examples of proteins that associate with lamin A (direct binding untested)

Protein	Lamin A residues	Method	Reference
LAP1	ND	Cosedimentation from membrane fraction	Foisner and Gerace 1993
UBC9	ND	In vitro SUMOylation, Yeast-2-Hybrid and CO-IP	Zhang and Sarge 2008 Zhong et al. 2005
MRPS26	ND	Yeast-2-Hybrid	Zhong et al. 2005
Filamin A	ND	Yeast-2-Hybrid	Zhong et al. 2005
Unc13D	ND	Yeast-2-Hybrid	Zhong et al. 2005
EGF1	ND	Yeast-2-Hybrid and CO-IP	Zhong et al. 2005
Mel18	ND	Yeast-2-Hybrid and CO-IP	Zhong et al. 2005
SREBP2	379-664	Yeast-2-Hybrid	Lloyd et al. 2002
12-(*R*)Lipoxygenase	463–664	Yeast-2-Hybrid	Tang et al. 2000
Supervillin	221–448	Yeast-2-Hybrid	Smith et al. 2010
MOK2	243–387	GST pulldown from cells	Dreuillet et al. 2002
TonEBP	ND	CO-IP from cells	Favale et al. 2007
PP2A	ND	CO-IP from cells	Van Berlo et al. 2005
LUMA	ND	CO-IP from cells	Bengtsson and Otto 2008
ERK1/2	247–355	CO-IP from cells	Gonzalez et al. 2008
Pro-amphiregulin	247–355	CO-IP from cells	Isokane et al. 2008
Ing1	ND	CO-IP from cells	Han et al. 2008
αII spectrin	ND	CO-IP from cells	Sridharan et al. 2006
βIV spectrin	ND	CO-IP from cells	Sridharan et al. 2006
Protein 4.1	ND	CO-IP from cells	Sridharan et al. 2006
nMyo1c	ND	CO-IP from cells	Holaska and Wilson 2007
PP1	ND	CO-IP from cells	Steen and Collas 2001
AKAP149	ND	CO-IP from cells	Steen and Collas 2001
Smad3	ND	CO-IP from cells	Grimsby et al. 2004
Prx1	ND	CO-IP from cells	Kubben et al. 2010

CO-IP co-immunoprecipitation, *ND* not determined

phosphorylation of five sites during the cell cycle (Kuga et al. 2010). Thr-34 and Ser-37 are phosphorylated during prophase until late anaphase. Ser-405 phosphorylation levels increase during prophase and are maintained until late G1, whereas Ser-407 is phosphorylated only during G1 and prophase, and Ser-421 is phosphorylated during the S-to-G2 transition (Kuga et al. 2010). Of these five lamin B2 phosphorylation sites, four are conserved in both lamins A/C and B1 (corresponding to lamin B2 residues Thr-34, Ser-37, Ser-405, and Ser407), and the fifth site (lamin B2 Ser-421) is conserved in lamins A/C (Fig. 2). High-throughput proteomic studies showed lamins are also phosphorylated in cells treated with EGF (Olsen et al. 2006) or MAPK inhibitors (Pan et al. 2009), and in human colon adenocarcinoma cells (Kim et al. 2005), human epithelial cancer cells (Moritz et al. 2010), and differentiating human embryonic stem cells (ESCs) (Rigbolt et al. 2011; Van Hoof et al. 2009) (Fig. 2, Tables 5–7). The criterion for including modifications in this review was access to supporting (published) evidence. Updated information about modifications and sites, both published and unpublished, can be found online (e.g., Phosphosite database at www.phosphosite.org).

Twelve phosphorylation sites are conserved in all three human lamins (Fig. 2); all but one are located in head or tail regions important for mitotic lamin depolymerization (lamins A/C residues Thr-19, Ser-22, Thr-24, Ser-390, Ser-392, Thr-394, Ser-395, Ser-398, Ser-403, Ser-404, Ser-407; Fig. 2). The other conserved phosphorylation site is lamin A/C residue Ser-303 in the coil 2B region (Fig. 2). Four additional phospho-sites are conserved between lamins A/C and B1 (lamin A residues Thr-3, Ser-18, Ser-277, Ser-652); lamins A/C and B2 share six additional sites (lamin A residues Thr-64, Ser-71, Ser-301, Ser-406, Thr-409, Ser-458), and lamins B1 and B2 share four (lamin B1 residues Ser-232, Tyr-359, Ser-401, Ser-406) (Fig. 2), potentially reflecting phospho-dependent regulation of other conserved functions. By contrast, unique phosphorylation sites are likely to reflect the differential regulation of lamins in diverse tissues (Vergnes et al. 2004; Coffinier et al. 2010; Takamori et al. 2007; Coffinier et al. 2011; Kim et al. 2011b).

Several other differences in the patterns of phosphorylation of human lamins stand out. Lamins A/C have many phosphorylation sites in coils 1A and 1B, the L1 linker in the rod domain, and the Ig-fold, whereas homologous regions in lamins B1 and B2 have few or no known sites (Fig. 3). On the

Table 3 Examples of proteins that interact directly or indirectly with lamin B1

Protein	Lamin B1 residues	Method	Reference
Lamin A	ND	Recombinant Affi-bead pulldown	Schirmer and Gerace 2004
Lamin C	ND	Recombinant Affi-bead pulldown	Schirmer and Gerace 2004
F-actin	463–537	Recombinant high-speed pelleting	Simon et al. 2010
CDK1	ND	In vivo kinase	Goss et al. 1994
PKC	1–588	Recombinant pulldown	Tabellini et al. 2002
LAP2	78–258	Yeast-2-Hybrid	Furukawa and Kondo 1998
LBR	ND	Pulldown of native	Ye and Worman 1994
Plectin	ND	Blot overlay	Foisner et al. 1991
LAP1β	ND	CO-IP from cells	Maison et al. 1997
LCO1	395–586	TnT pulldown	Vlcek et al. 2004
MELK	ND	In vivo kinase	Beullens et al. 2005
Emerin	1–188	TnT pulldown	Vaughan et al. 2001
Nudel	ND	CO-IP from cells	Ma et al. 2009
DNA	412–554	Blot overlay/cosedimentation	Stierle et al. 2003
Histones	397–432	Microtiter assay	Taniura et al. 1995
Nup153	244–586	TnT pulldown	Al-Haboubi et al. 2011
Titin	463–538	Recombinant pulldown	Zastrow et al. 2006
PCNA	244–586	Recombinant pulldown	Shumaker et al. 2008
MAN1	394–586	Blot overlay/Microtiter assay	Mansharamani and Wilson 2005
PP1	ND	CO-IP from cells	Steen and Collas 2001
AKAP149	ND	CO-IP from cells	Steen and Collas 2001
PLCβ1	ND	CO-IP from cells	Fiume et al. 2009
Oct-1	ND	CO-IP from cells and FRET	Malhas et al. 2009

CO-IP co-immunoprecipitation

other hand, lamin B1 has eight phosphorylation sites in coil 2B, whereas lamins A/C have only four and lamin B2 three (Fig. 2). Only five phosphorylated Tyr residues have been identified (lamin A Tyr-81, lamin B1 Tyr-359 and Tyr-377, lamin B2 Tyr-374 and Tyr-515); we assume more sites exist, since Tyr phosphorylation tends to be labile under the experimental conditions used in many previous studies.

Table 4 Examples of proteins that interact directly or indirectly with lamin B2

Protein	Lamin B2 residues	Method	Reference
Lamin A	ND	Recombinant Affi-bead pulldown	Schirmer and Gerace 2004
Lamin C	ND	Recombinant Affi-bead pulldown	Schirmer and Gerace 2004
PKC	ND	In vivo kinase	Kasahara et al. 1991
Supervillin	161–342	Yeast-2-Hybrid	Smith et al. 2010
PP1	ND	CO-IP from cells	Steen and Collas 2001
AKAP149	ND	CO-IP from cells	Steen and Collas 2001
Nup153	258–620	TnT pulldown	Al-Haboubi et al. 2011

CO-IP co-immunoprecipitation

Lamin A residues 560–649, which have no counterpart in B-type lamins, are extensively phosphorylated and all 11 known phospho-sites in this region are eliminated by the HGPS-causing Δ50 deletion (loss of residues 608–658), pointing to lamin A misregulation as another likely consequence of this 'accelerated aging' mutation (Fig. 2). Among the nearly 400 disease-causing mutations in lamin A (Dittmer and Misteli 2011), remarkably only four disrupt known phosphorylation sites (Thr-10, Ser-303, Ser-395, Thr-505). However, many known phosphorylation sites are located near disease-causing mutations and might be affected indirectly. For example, lamin A Ser-458 is phosphorylated only in muscle cells from EDMD and LGMD patients who have mutations specifically in the Ig-fold domain, which can be up to seventy residues away from Ser-458 (Mitsuhashi et al. 2010).

The CDK1 phosphorylation sites on lamins are exploited by both herpes simplex virus and Epstein–Barr virus to disassemble lamins and thereby enable nascent virus particles to bud through the nuclear envelope (Lee and Chen 2010). The Epstein–Barr virus encodes its own kinase, BGLF4, which targets CDK1 sites on lamins A/C. The nuclear exit of Epstein–Barr virus is inhibited in cells that overexpress lamin

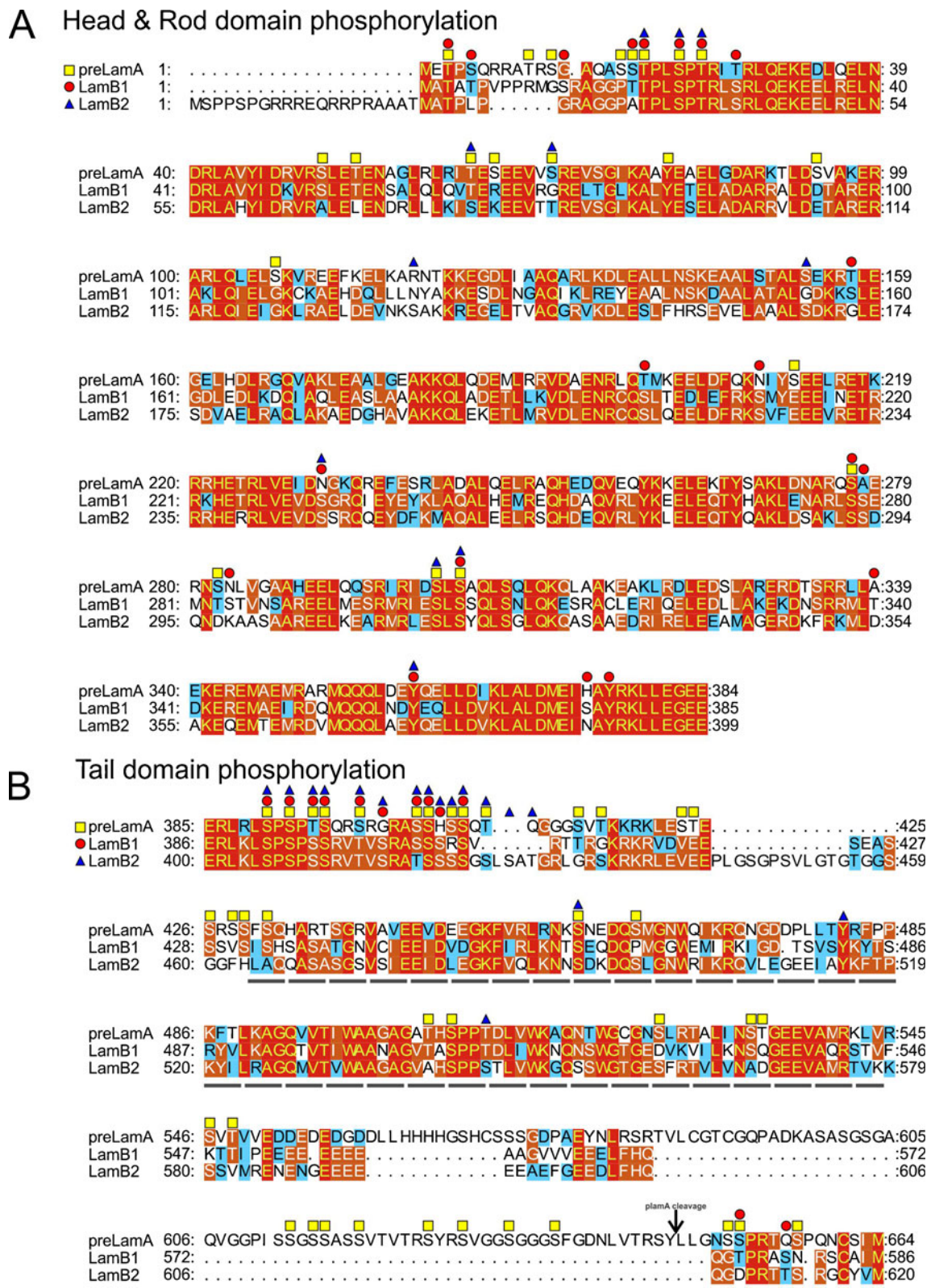

Fig. 2 Conservation of known phosphorylation sites in human lamins. Sequence alignment of the rod and head domains (**a**) or tail domains (**b**) of human lamins A (including precursor-specific C-terminal residues), B1 and B2 based on accession numbers NP_733821.1, NP_005564 and NP_116126, respectively. The locations of all known phosphorylation sites are indicated above; *squares*, *circles* and *triangles* indicate residues phosphorylated in lamins A, B1 and B2, respectively. *Arrow* indicates the Zmpste24 cleavage site in pre-lamin A (plamA cleavage). Underlined residues in **b** comprise the lamin Ig-fold domain (Dhe-Paganon et al. 2002; Krimm et al. 2002; Ruan et al. 2012)

Table 5 Phosphorylation sites in human lamins A and C

Cells	HeLa							K562	hESCs		HT-29	Epithelial cancer	HEK293	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	MAPK inhibit	MAPK inhibit	Differentiation		WCL	WCL	EB virus	In vitro	
P-aa	Olsen 2010	Daub 2008	Wang 2010	Malik 2009	Wang 2008	Olsen 2006	Pan 2009	Pan 2009	Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Lee 2008	Haas and Jost 1993	
T3	×														
T10						×						×			PKCα
S12	×			×			×					×			
S17		×		×					×						
S18	×	×		×											
T19	×		×	×		×	×		×	×				×	CDK1, PKCα
S22	×	×	×	×	×	×	×	×	×	×			×	×	CDK1, BGLF4
T24	×					×		×	×						
S51				×											
T54									×						
T64	×														
S66	×			×											
S71				×											
Y81									×						
S94						×									
S107	×								×						
S212	×														
S277	×														
S282	×														
S301	×											×			
S303												×			
S390	×	×	×	×	×		×	×	×	×	×	×	×		CDK1, BGLF4
S392	×	×	×	×	×		×	×	×	×	×		×	×	CDK1, BGLF4
T394	×		×					×	×						
S395	×				×		×	×	×						PKCα
S398	×											×			
S403	×	×					×		×			×		×	PKCα
S404	×	×					×	×	×	×		×		×	PKCα, Akt
S406	×						×		×		×	×			
S407	×						×	×	×		×	×			S6-kinase II
T409	×						×				×	×			
S414	×						×	×	×			×			
T416	×						×		×			×			PKCα
S423	×										×				

Table 5 (continued)

Cells	HeLa							K562	hESCs		HT-29	Epithelial cancer	HEK293	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	MAPK inhibit	MAPK inhibit	Differentiation		WCL	WCL	EB virus	In vitro	
P-aa	Olsen 2010	Daub 2008	Wang 2010	Malik 2009	Wang 2008	Olsen 2006	Pan 2009	Pan 2009	Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Lee 2008	Haas and Jost 1993	
T424	×														
S426	×														
S428	×								×						
S429	×														
S431	×								×						
S458	×						×		×						
S463	×														
T505	×														
S507	×														
S525														×	PKCα
S533				×											
T534				×											
Lamin A only															
S613	×														
S615	×														
S616	×			×											
S619	×														
S625	×														
S628	×			×			×								
S632	×			×											
S636	×			×			×		×						
S546												×			
T548												×			
S651		×													
S652	×												×		PKCα, BGLF4
S657													×		BGLF4
Lamin C only															
S568	×														
S570	×														

S & M S- and M-phase arrested cells

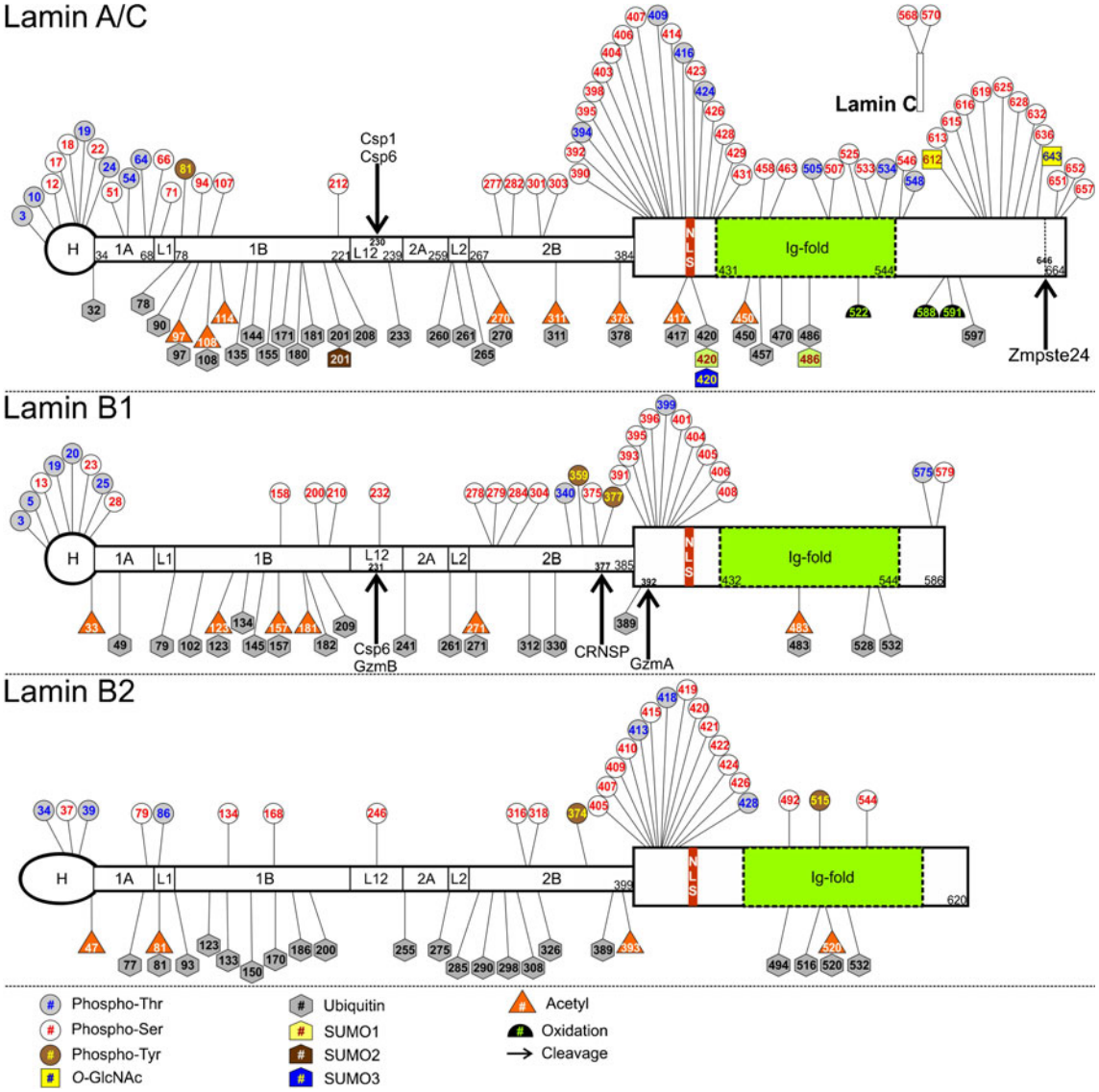

Fig. 3 Post-translational modifications of human lamins. Lamin schematics indicating specific residues that are post-translationally modified by phosphorylation, acetylation, *O*-GlcNAcylation, SUMOylation, ubiquitylation, or oxidation. *Arrows* indicate sites cleaved by the pre-lamin A processing protease Zmpste24, or apoptotic proteases Caspase 1 (*Csp1*), Caspase 6 (*Csp6*), Granzyme A (*GzmA*), Granzyme B (*GzmB*), or CRNSP

A bearing five Ser-to-Ala substitutions at Ser-22, Ser-390, Ser-392, Ser-652, and Ser-657 (Lee et al. 2008). Four of these sites (all but Ser-657) can also be phosphorylated in uninfected cells (Table 5). Intriguingly, the nuclear export of large ribonucleoprotein complexes in response to Wnt signaling in *Drosophila* muscle cells also involves direct 'budding' through the nuclear envelope (Speese et al. 2012).

O-GlcNAcylation

O-GlcNAc (β-*O*-linked *N*-acetylglucosamine) is a reversible single sugar modification of Ser or Thr residues that can compete or cooperate with phosphorylation to regulate signaling, transcription and mitosis (Hart and Copeland 2010). This modification is found on both nuclear and cytoplasmic proteins (Hart and Copeland 2010). In mitotic spindles isolated from HeLa cells, lamin A was *O*-GlcNAcylated at Ser-612 and Thr-643 (Wang et al. 2010). Both residues are located in the unique C-terminal region of lamin A (Fig. 3). In mouse brain tissue, lamin A is *O*-GlcNAcylated at Ser-611 and Ser-613 (Alfaro et al. 2012); mouse Ser-613 is homologous to human lamin Ser-612. The functional consequences of lamin A *O*-GlcNAcylation are unknown. Lamins were first reported to be glycosylated over 20 years ago (Ferraro et al. 1989), but whether this represents *O*-GlcNAcylation or a different modification(s) is unknown.

Table 6 Phosphorylation sites in human lamin B1

Cells	HeLa								K562	hESCs		HT-29	Epithelial cancer	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	WCL	MAPK inhibit	MAPK inhibit	Differentiation		WCL	WCL	In vitro	
P-aa	Olsen 2010	Daub 2008	Wang 2010	Malik 2009	Wang 2008	Olsen 2006	Imami et al. 2008	Pan 2009	Pan 2009	Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Goss 1994	
T3	×			×							×				
T5	×										×				
S13							×								
T19	×	×		×		×				×	×				
T20	×	×		×		×		×	×	×	×				
S23	×	×	×	×	×	×		×	×	×	×			×	CDK1
T25	×					×			×	×					
S28						×				×					
S158	×														
S200						×									
S210	×									×					
S232				×											
S278	×			×	×										
S279					×										
S284	×			×	×										
S304			×												
T340										×					
Y359													×		
S375	×			×											
Y377	×														
S391									×	×		×			
S393			×						×	×		×			
S395										×				×	PKCβ1
S396										×					
T399										×					
S401										×					
S404	×					×				×					
S405										×			×	×	PKCβ1
S406										×			×		
S408										×			×		
T575	×					×		×		×	×				
S579					×										

S & M S- and M-phase arrested cells

Table 7 Phosphorylation sites in human lamin B2

Cells	HeLa					K562	hESCs		Epithelial cancer
	Mitosis	S & M	Spindle	EGF	MAPK inhibit	MAPK inhibit	Differentiation		WCL
P-aa	Olsen 2010	Daub 2008	Malik 2009	Olsen 2006	Pan 2009	Pan 2009	Rigbolt 2011	Van Hoof 2009	Moritz 2010
T34	×	×	×	×	×	×	×	×	
S37	×	×	×		×		×	×	
T39					×	×	×		
T79							×		
T86							×		
S134			×						
S168	×								
S246			×						
S316									×
S318									×
Y374								×	
S405	×	×	×	×	×	×	×		
S407	×	×		×	×	×	×		
S409	×			×			×		
S410	×			×			×		
T413							×		
T415							×		
T418							×		
S419			×				×	×	
S420	×						×	×	
S421	×						×		
S422	×						×	×	
S424	×	×					×	×	
S426	×						×	×	
T428	×								
S492	×								
Y515	×								
S544	×								

S & M S- and M-phase arrested cells

Oxidation

Reactive oxygen species (ROS) are produced during oxygen metabolism and can regulate many pathways including cell senescence (Bartz and Piantadosi 2010). In primary human dermal fibroblasts, lamin A tail domain residues Cys-522, Cys-588 and Cys-591 can be oxidized, yielding both intra- and inter-molecular disulfide bridges (Pekovic et al. 2011). In cells that overexpress lamin A bearing the triple C522A/C588A/C591A mutation, nuclei are misshapen and cells enter senescence prematurely in response to oxidative stress (Pekovic et al. 2011; Sieprath et al. 2012). Premature senescence was also reported in lamin A null fibroblasts (Pekovic et al. 2011), suggesting A-type lamins are an important 'sink' for ROS that helps protect cells.

SUMOylation

SUMO (small ubiquitin-like modifier) proteins are covalently and reversibly attached to Lys residues on target proteins (Gareau and Lima 2010). SUMO modifications can regulate the localization, function and interactions of target proteins, and influence many pathways including nuclear import/export, transcription, apoptosis, cell cycle regulation, and protein stability (Geiss-Friedlander and Melchior 2007).

The enzymes that add or remove SUMO localize mostly at the nuclear envelope or in the nucleus (Wilkinson and Henley 2010; Zhang et al. 2002; Mingot et al. 2001). However, at least one, the SUMO-specific isopeptidase SENP2, associates dynamically with nuclear pore complexes (Goeres et al. 2011) and is regulated by shuttling between the nucleus and cytoplasm (Itahana et al. 2006). Many cytosolic proteins are controlled by SUMOylation including mitochondrial proteins, plasma membrane proteins and (in yeast) septins, all of which are unlikely to shuttle into the nucleus.

Human lamins A/C are modified by SUMO2 at Lys-201, both in vitro and in vivo. This modification is important for lamin A localization and filament assembly; both activities are disrupted by K201R or by nearby cardiomyopathy-causing E203G or E203K mutations, which also decrease cell viability (Zhang and Sarge 2008). A-type lamins can also be modified by a different SUMO, SUMO1 at two positions, Lys-420 (in the NLS) and Lys-486 (in the Ig-fold) both in vitro and in vivo (Simon et al. 2013). SUMOylation of the Ig-fold residue Lys-486 is disrupted by the familial partial lipodystrophy-causing G465D and K486N mutations (Simon et al. 2013). Lys-420 is alternatively modified by SUMO3 in HEK293 cells (Galisson et al. 2011).

In contrast to lamin A/C residues Lys-201 and Lys-420, which are located at canonical SUMOylation consensus sites, Lys-486 is not. Instead, Lys-486 represents a proposed 'conformational' consensus SUMOylation site, recognition of which is proposed to require Gly-465 and negatively charged residues Glu-460 and Asp-461, located directly beneath Lys-486 in the Ig-fold domain structure (Krimm et al. 2002; Simon et al. 2013). Lamins A/C and lamin B1 were also identified as potential targets of SUMO4 in serum-starved HEK293 cells (Guo et al. 2005).

At any given time only a few percent, at most, of lamins are SUMOylated (Zhang and Sarge 2008; Simon et al. 2013), similar to other characterized SUMO substrates (Johnson 2004; Hay 2005). This scarcity suggests the enzymes that add and remove SUMO either have limited access to lamin A, or are tightly controlled by other regulators in the nuclei of specific cell types. The timing and extent to which lamin A is SUMOylated in human tissues affected by FPLD disease (Simon et al. 2013) or cardiomyopathy (Zhang and Sarge 2008), and the downstream consequences of modification by SUMO1, SUMO2 or SUMO3 are open questions.

Acetylation

First discovered as a modification of histones, many other proteins are now known to be acetylated, including some (e.g., tubulin) that reside in the cytoplasm (Glozak et al. 2005). Both A- and B-type lamins were reportedly acetylated in high-throughput studies of HeLa cells (Kim et al. 2006) and a human acute myeloid leukemia cell line (MV4-11 cells; Choudhary et al. 2009). Eight acetylation sites were identified in A-type lamins: six in the rod domain (Lys-97, Lys-108, Lys-114, Lys-270, Lys-311, Lys-378), one in the NLS (Lys-417) and one in the Ig-fold (Lys-450) (Fig. 3). Lamin B1 has six acetylation sites (Lys-33, Lys-123, Lys-157, Lys-181, Lys-271, Lys-483) and lamin B2 has four (Lys-47, Lys-81, Lys-393, Lys-520) (Fig. 3). All three human lamins have one known acetylation site in the Ig-fold domain. Both B-type lamins have a known acetylation site at the border between the head domain and coiled-coil rod (Fig. 3; Choudhary et al. 2009). Nothing is known about the timing or functional consequences of lamin acetylation. However, since lamins associate with LEM-domain proteins (emerin and LAP2β) and HDAC3 to tether silent chromatin (Somech et al. 2005; Guelen et al. 2008; Zullo et al. 2012; Reddy et al. 2008; Demmerle et al. 2012), we speculate lamin acetylation might influence chromatin tethering.

Ubiquitylation

Ubiquitin was the first discovered small protein modification of other proteins. Like SUMO, it is covalently attached to Lys residues on target proteins; two enzymes (E1, E2) first prepare ubiquitin for transfer, with target specificity dictated by a variety of ubiquitin ligase (E3) enzymes (Neutzner and Neutzner 2012). Ubiquitin can be attached to another ubiquitin, creating a 'chain' that marks the target for proteolytic degradation. By contrast, attachment of a single ubiquitin is known to influence target proteins in diverse ways and regulates many specific cellular pathways and nuclear functions (Strieter and Korasick 2012). The impact of poly- and mono-ubiquitinylation, which can have major roles in the regulation of protein function and the spatial and temporal coordination of pathways, on the functions of lamins A/C, B1 and B2 are essentially unknown.

High-throughput mass spectrometry analysis of ubiquitylated proteins in HEK293T cells (Wagner et al. 2011) and HCT-116 cells, a colon adenocarcinoma cell line (Kim et al. 2011a), revealed widespread ubiquitylation of human lamins A/C, B1 and B2. Most ubiquitylation sites are located in the rod domain (Fig. 3) and might therefore influence lamin dimerization or filament assembly. Whereas poly-ubiquitylation is assumed to influence lamin turnover, the functional consequences of lamin mono-ubiquitylation are unknown.

Several residues can be either ubiquitylated or acetylated as reported for seven lamin A residues (Lys-97, Lys-108, Lys-270, Lys-311, Lys-378, Lys-417, Lys-450), four lamin B1 residues (Lys-123, Lys-157, Lys-271, Lys-483), and two lamin B2 residues (Lys-81, Lys-520). Lamin A/C Lys-201

can be either ubiquitylated or SUMO2-modified and Lys-486 can be either ubiquitylated or SUMO1-modified (Simon et al. 2013). Lamin A/C Lys-420, located in the NLS, can be either ubiquitylated, SUMO1-modified or SUMO3-modified. These competing modifications may differentially regulate lamin interactions and functions in specific tissues.

Lamins, as major structural proteins of the cell, are targeted for destruction early in apoptosis. They are directly cleaved by caspases 1 and 6 (Takahashi et al. 1996), granzymes A and B (Zhang et al. 2001), and CRNSP (Ca^{+2}-regulated nuclear scaffold protease; Clawson et al. 1992) at sites located near many ubiquitylation sites (Fig. 3).

Conclusion and perspectives

In humans, 92 residues in lamins A/C, 52 in lamin B1, and 51 in lamin B2 are reportedly post-translationally modified, yet the only well-defined functional consequence (mitotic disassembly) was discovered more than 20 years ago. Lamins are probably also regulated by other modifications not discussed here, including ADP ribosylation (Adolph 1987). Furthermore, lamin modifications in other organisms might differ from those in human lamins both in detail (e.g., due to amino acid sequence differences; e.g., mouse lamin A/C phosphosites Ser-5, Thr-199, Thr-480, Ser-572; Eggert et al. 1993) and in substance, as diverging metazoan lineages evolved. Indeed, species-specific posttranslational modifications might explain why some lamin A mutations that cause a specific human disease, yield a different phenotype in mice (Stewart et al. 2007).

Modifications have the potential to regulate all aspects of lamin function, from filament assembly to the nuanced binding of tissue-specific partners. However, one must keep these modifications in perspective — even rare modification sites can be detected by modern mass spectrometry, giving the erroneous impression that lamins are always modified. Lamin modifications in living cells are likely to be relatively rare and transient due to the constant interplay between different modifying and de-modifying enzymes, with one known exception: mitosis, when many specific residues are phosphorylated at >80 % stoichiometry (Olsen et al. 2010; Ward and Kirschner 1990; Peter et al. 1990; Kill and Hutchison 1995). Huge gaps in knowledge about the nature, regulation and consequences of these modifications must be filled to understand how lamins function, and how specific mutations lead to disease.

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