Published in final edited form as:
Chromosoma. 2013 March ; 122(0): 13–31. doi:10.1007/s00412-013-0399-8.

Partners and post-translational modifications of nuclear lamins

Dan N. Simon and **Katherine L. Wilson***
Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore MD 21205 USA

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 fifty-four partners interact with human A-type lamins directly or indirectly. The less studied human lamins B1 and B2 have twenty-three 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

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 leucoencephalopathy (Brussino et al. 2009), and certain mutations in *LMNB2* correlate with increased susceptibility to acquired partial lipodystrophy (Hegele et al. 2006).

*Corresponding author klwilson@jhmi.edu Phone: 410-955-1801 Fax: 410-502-7826.

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 (pre-lamin 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).

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 (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 many partners (Wilson and Foisner 2010; Zastrow et al. 2004). Lamin A is the most extensively studied with at least 29 reported direct binding partners (Figure 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 7 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 12,000g 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 (Figure 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; Figure 2B). Phosphorylation of the A-type lamin in *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, PKC- and CDK1-mediated disassembly of lamin B1 in HeLa cells is triggered by the diacylglycerol (DAG) generating enzyme lipin (Mall et al. 2012). In mouse erythroleukemia cells lamin B1 phosphorylation by PLCβ1 promotes mitotic lamin filament disassembly (Fiume et al. 2009; Guo et al. 2005). 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; Wang et al. 2010; Figure 2, Table 5). Many mitotic phosphorylation sites are clustered in the head domain and near the Nuclear Localization Signal (NLS) (Figure 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 (Figure 3, Table 5) lamins A/C have more than twice as many known sites as lamin B1 (32 sites; Figure 3, Table 6) or lamin B2 (28 sites; Figure 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 (Figure 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, 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, 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 293T 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 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 (Figure 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) (Figure 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 (Figure 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; Figure 2). The other conserved phosphorylation site is lamin A/C residue Ser-303 in the coil 2B region (Figure 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) (Figure 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 (Figure 3). On the other hand, lamin B1 has eight phosphorylation sites in coil 2B, whereas lamins A/C have only four and lamin B2 three (Figure 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.

Lamin A residues 560-649, which have no counterpart in B-type lamins, are extensively phosphorylated and all eleven 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 (Figure 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 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 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 (Figure 3). In

mouse brain tissue, lamin A is *O*-GlcNAcylated at Ser611 and Ser613 (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.

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. 2012). SUMOylation of the Ig-fold residue Lys-486 is disrupted by the familial partial lipodystrophy-causing G465D and K486N mutations (Simon et al. 2012). 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. 2012). 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. 2012), 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. 2012) 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) (Figure 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) (Figure 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 (Figure 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 (Figure 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. 2012). 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 (Figure 3).

Conclusion and perspectives

In humans, ninety-two residues in lamins A/C, fifty-two in lamin B1, and fifty-one 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.

Acknowledgments

We thank Michael J. Matunis, Gerald W. Hart and Jason M. Berk for insightful discussions and comments on the manuscript. We apologize to authors whose work could not be cited due to space limitations. We gratefully acknowledge support from the NIH (RO1 048646 to K.L.W.).

REFERENCES

Adam SA, Sengupta K, Goldman RD. Regulation of nuclear lamin polymerization by importin alpha. J Biol Chem. 2008; 283(13):8462–8468. [PubMed: 18227062]

Adolph KW. ADPribosylation of nuclear proteins labeled with [3H]adenosine: changes during the HeLa cycle. Biochim Biophys Acta. 1987; 909(3):222–230. [PubMed: 3040104]

Al-Haboubi T, Shumaker DK, Koser J, Wehnert M, Fahrenkrog B. Distinct association of the nuclear pore protein Nup153 with A- and B-type lamins. Nucleus. 2011; 2(5):500–509. [PubMed: 21983083]

Alfaro JF, Gong CX, Monroe ME, Aldrich JT, Clauss TR, Purvine SO, Wang Z, Camp DG 2nd, Shabanowitz J, Stanley P, Hart GW, Hunt DF, Yang F, Smith RD. Tandem mass spectrometry identifies many mouse brain O-GlcNAcylated proteins including EGF domain-specific O-GlcNAc transferase targets. Proc Natl Acad Sci U S A. 2012; 109(19):7280–7285. [PubMed: 22517741]

Bao X, Zhang W, Krencik R, Deng H, Wang Y, Girton J, Johansen J, Johansen KM. The JIL-1 kinase interacts with lamin Dm0 and regulates nuclear lamina morphology of Drosophila nurse cells. J Cell Sci. 2005; 118(Pt 21):5079–5087. [PubMed: 16254246]

Barrowman J, Hamblet C, Kane MS, Michaelis S. Requirements for efficient proteolytic cleavage of prelamin A by ZMPSTE24. PLoS One. 2012; 7(2):e32120. [PubMed: 22355414]

Barton RM, Worman HJ. Prenylated prelamin A interacts with Narf, a novel nuclear protein. J Biol Chem. 1999; 274(42):30008–30018. [PubMed: 10514485]

Bartz RR, Piantadosi CA. Clinical review: oxygen as a signaling molecule. Crit Care. 2010; 14(5):234. [PubMed: 21062512]

Beck LA, Hosick TJ, Sinensky M. Isoprenylation is required for the processing of the lamin A precursor. J Cell Biol. 1990; 110(5):1489–1499. [PubMed: 2335559]

Ben-Harush K, Wiesel N, Frenkiel-Krispin D, Moeller D, Soreq E, Aebi U, Herrmann H, Gruenbaum Y, Medalia O. The supramolecular organization of the C. elegans nuclear lamin filament. J Mol Biol. 2009; 386(5):1392–1402. [PubMed: 19109977]

Bengtsson L, Otto H. LUMA interacts with emerin and influences its distribution at the inner nuclear membrane. J Cell Sci. 2008; 121(4):536–548. [PubMed: 18230648]

Bergo MO, Gavino B, Ross J, Schmidt WK, Hong C, Kendall LV, Mohr A, Meta M, Genant H, Jiang Y, Wisner ER, Van Bruggen N, Carano RA, Michaelis S, Griffey SM, Young SG. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. Proc Natl Acad Sci U S A. 2002; 99(20):13049–13054. [PubMed: 12235369]

Beullens M, Vancauwenbergh S, Morrice N, Derua R, Ceulemans H, Waelkens E, Bollen M. Substrate specificity and activity regulation of protein kinase MELK. J Biol Chem. 2005; 280(48):40003–40011. [PubMed: 16216881]

Bokenkamp R, Raz V, Venema A, DeRuiter MC, van Munsteren C, Olive M, Nabel EG, Gittenberger-de Groot AC. Differential temporal and spatial progerin expression during closure of the ductus arteriosus in neonates. PLoS One. 2011; 6(9):e23975. [PubMed: 21915271]

Brachner A, Reipert S, Foisner R, Gotzmann J. LEM2 is a novel MAN1-related inner nuclear membrane protein associated with A-type lamins. J Cell Sci. 2005; 118(24):5797–5810. [PubMed: 16339967]

Brussino A, Vaula G, Cagnoli C, Mauro A, Pradotto L, Daniele D, Di Gregorio E, Barberis M, Arduino C, Squadrone S, Abete MC, Migone N, Calabrese O, Brusco A. A novel family with Lamin B1 duplication associated with adult-onset leucoencephalopathy. J Neurol Neurosurg Psychiatry. 2009; 80(2):237–240. [PubMed: 19151023]

Brussino A, Vaula G, Cagnoli C, Panza E, Seri M, Di Gregorio E, Scappaticci S, Camanini S, Daniele D, Bradac GB, Pinessi L, Cavalieri S, Grosso E, Migone N, Brusco A. A family with autosomal dominant leukodystrophy linked to 5q23.2-q23.3 without lamin B1 mutations. Eur J Neurol. 2010; 17(4):541–549. [PubMed: 19961535]

Buendia B, Courvalin JC, Collas P. Dynamics of the nuclear envelope at mitosis and during apoptosis. Cell Mol Life Sci. 2001; 58(12-13):1781–1789. [PubMed: 11766879]

Butin-Israeli V, Adam SA, Goldman AE, Goldman RD. Nuclear lamin functions and disease. Trends Genet. 2012; 28(9):464–471. [PubMed: 22795640]

Cenni V, Bertacchini J, Beretti F, Lattanzi G, Bavelloni A, Riccio M, Ruzzene M, Marin O, Arrigoni G, Parnaik V, Wehnert M, Maraldi NM, de Pol A, Cocco L, Marmiroli S. Lamin A Ser404 is a nuclear target of Akt phosphorylation in C2C12 cells. J Proteome Res. 2008; 7(11):4727–4735. [PubMed: 18808171]

Cenni V, Sabatelli P, Mattioli E, Marmiroli S, Capanni C, Ognibene A, Squarzoni S, Maraldi NM, Bonne G, Columbaro M, Merlini L, Lattanzi G. Lamin A N-terminal phosphorylation is associated with myoblast activation: impairment in Emery-Dreifuss muscular dystrophy. J Med Genet. 2005; 42(3):214–220. [PubMed: 15744034]

Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, Walther TC, Olsen JV, Mann M. Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science. 2009; 325(5942):834–840. [PubMed: 19608861]

Clawson GA, Norbeck LL, Hatem CL, Rhodes C, Amiri P, McKerrow JH, Patierno SR, Fiskum G. Ca(2+)-regulated serine protease associated with the nuclear scaffold. Cell Growth Differ. 1992; 3(11):827–838. [PubMed: 1467310]

Coffinier C, Chang SY, Nobumori C, Tu Y, Farber EA, Toth JI, Fong LG, Young SG. Abnormal development of the cerebral cortex and cerebellum in the setting of lamin B2 deficiency. Proc Natl Acad Sci U S A. 2010; 107(11):5076–5081. [PubMed: 20145110]

Coffinier C, Jung HJ, Nobumori C, Chang S, Tu Y, Barnes RH 2nd, Yoshinaga Y, de Jong PJ, Vergnes L, Reue K, Fong LG, Young SG. Deficiencies in lamin B1 and lamin B2 cause neurodevelopmental defects and distinct nuclear shape abnormalities in neurons. Mol Biol Cell. 2011; 22(23):4683–4693. [PubMed: 21976703]

Collas P. Sequential PKC- and Cdc2-mediated phosphorylation events elicit zebrafish nuclear envelope disassembly. J Cell Sci. 1999; 112(6):977–987. [PubMed: 10036247]

Collas P, Thompson L, Fields AP, Poccia DL, Courvalin JC. Protein kinase C-mediated interphase lamin B phosphorylation and solubilization. J Biol Chem. 1997; 272(34):21274–21280. [PubMed: 9261138]

Crisp M, Liu Q, Roux K, Rattner JB, Shanahan C, Burke B, Stahl PD, Hodzic D. Coupling of the nucleus and cytoplasm: role of the LINC complex. J Cell Biol. 2006; 172(1):41–53. [PubMed: 16380439]

Cross T, Griffiths G, Deacon E, Sallis R, Gough M, Watters D, Lord JM. PKC-delta is an apoptotic lamin kinase. Oncogene. 2000; 19(19):2331–2337. [PubMed: 10822384]

Daub H, Olsen JV, Bairlein M, Gnad F, Oppermann FS, Korner R, Greff Z, Keri G, Stemmann O, Mann M. Kinase-selective enrichment enables quantitative phosphoproteomics of the kinome across the cell cycle. Mol Cell. 2008; 31(3):438–448. [PubMed: 18691976]

Dechat T, Adam SA, Taimen P, Shimi T, Goldman RD. Nuclear lamins. Cold Spring Harb Perspect Biol. 2010; 2(11):a000547. [PubMed: 20826548]

Dechat T, Korbei B, Vaughan OA, Vlcek S, Hutchison CJ, Foisner R. Lamina-associated polypeptide 2alpha binds intranuclear A-type lamins. J Cell Sci. 2000; 113(19):3473–3484. [PubMed: 10984438]

Dechat T, Pfleghaar K, Sengupta K, Shimi T, Shumaker DK, Solimando L, Goldman RD. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. Genes Dev. 2008; 22(7):832–853. [PubMed: 18381888]

Delbarre E, Tramier M, Coppey-Moisan M, Gaillard C, Courvalin JC, Buendia B. The truncated prelamin A in Hutchinson-Gilford progeria syndrome alters segregation of A-type and B-type lamin homopolymers. Hum Mol Genet. 2006; 15(7):1113–1122. [PubMed: 16481358]

Demmerle J, Koch AJ, Holaska JM. The nuclear envelope protein emerin binds directly to histone deacetylase 3 (HDAC3) and activates HDAC3 activity. J Biol Chem. 2012; 287(26):22080–22088. [PubMed: 22570481]

Dhe-Paganon S, Werner ED, Chi YI, Shoelson SE. Structure of the globular tail of nuclear lamin. J Biol Chem. 2002; 277(20):17381–17384. [PubMed: 11901143]

Dittmer TA, Misteli T. The lamin protein family. Genome Biol. 2011; 12(5):222. [PubMed: 21639948]

Dreuillet C, Tillit J, Kress M, Ernoult-Lange M. In vivo and in vitro interaction between human transcription factor MOK2 and nuclear lamin A/C. Nucleic Acids Res. 2002; 30(21):4634–4642. [PubMed: 12409453]

Eggert M, Radomski N, Linder D, Tripier D, Traub P, Jost E. Identification of novel phosphorylation sites in murine A-type lamins. Eur J Biochem. 1993; 213(2):659–671. [PubMed: 8477740]

Eggert M, Radomski N, Tripier D, Traub P, Jost E. Identification of phosphorylation sites on murine nuclear lamin C by RP-HPLC and microsequencing. FEBS Lett. 1991; 292(1-2):205–209. [PubMed: 1959608]

Enoch T, Peter M, Nurse P, Nigg EA. p34cdc2 acts as a lamin kinase in fission yeast. J Cell Biol. 1991; 112(5):797–807. [PubMed: 1999458]

Farnsworth CC, Wolda SL, Gelb MH, Glomset JA. Human lamin B contains a farnesylated cysteine residue. J Biol Chem. 1989; 264(34):20422–20429. [PubMed: 2684976]

Favale NO, Sterin Speziale NB, Fernandez Tome MC. Hypertonic-induced lamin A/C synthesis and distribution to nucleoplasmic speckles is mediated by TonEBP/NFAT5 transcriptional activator. Biochem Biophys Res Commun. 2007; 364(3):443–449. [PubMed: 18028879]

Ferraro A, Eufemi M, Cervoni L, Marinetti R, Turano C. Glycosylated forms of nuclear lamins. FEBS Lett. 1989; 257(2):241–246. [PubMed: 2583268]

Fiume R, Ramazzotti G, Teti G, Chiarini F, Faenza I, Mazzotti G, Billi AM, Cocco L. Involvement of nuclear PLCbeta1 in lamin B1 phosphorylation and G2/M cell cycle progression. FASEB J. 2009; 23(3):957–966. [PubMed: 19028838]

Foisner R, Gerace L. Integral membrane proteins of the nuclear envelope interact with lamins and chromosomes, and binding is modulated by mitotic phosphorylation. Cell. 1993; 73(7):1267–1279. [PubMed: 8324822]

Foisner R, Traub P, Wiche G. Protein kinase A- and protein kinase C-regulated interaction of plectin with lamin B and vimentin. Proc Natl Acad Sci U S A. 1991; 88(9):3812–3816. [PubMed: 2023931]

Friedman DL, Ken R. Insulin stimulates incorporation of 32Pi into nuclear lamins A and C in quiescent BHK-21 cells. J Biol Chem. 1988; 263(3):1103–1106. [PubMed: 3275664]

Furukawa K, Kondo T. Identification of the lamina-associated-polypeptide-2-binding domain of B-type lamin. Eur J Biochem. 1998; 251(3):729–733. [PubMed: 9490046]

Galisson F, Mahrouche L, Courcelles M, Bonneil E, Meloche S, Chelbi-Alix MK, Thibault P. A novel proteomics approach to identify SUMOylated proteins and their modification sites in human cells. Mol Cell Proteomics. 2011; 10(2):M110 004796. [PubMed: 21098080]

Gareau JR, Lima CD. The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. Nat Rev Mol Cell Biol. 2010; 11(12):861–871. [PubMed: 21102611]

Geiss-Friedlander R, Melchior F. Concepts in sumoylation: a decade on. Nat Rev Mol Cell Biol. 2007; 8(12):947–956. [PubMed: 18000527]

Gerace L, Blobel G. The nuclear envelope lamina is reversibly depolymerized during mitosis. Cell. 1980; 19(1):277–287. [PubMed: 7357605]

Gerace L, Huber MD. Nuclear lamina at the crossroads of the cytoplasm and nucleus. J Struct Biol. 2012; 177(1):24–31. [PubMed: 22126840]

Glozak MA, Sengupta N, Zhang X, Seto E. Acetylation and deacetylation of non-histone proteins. Gene. 2005; 363:15–23. [PubMed: 16289629]

Goeres J, Chan PK, Mukhopadhyay D, Zhang H, Raught B, Matunis MJ. The SUMO-specific isopeptidase SENP2 associates dynamically with nuclear pore complexes through interactions with karyopherins and the Nup107-160 nucleoporin subcomplex. Mol Biol Cell. 2011; 22(24):4868–4882. [PubMed: 22031293]

Gonzalez JM, Navarro-Puche A, Casar B, Crespo P, Andres V. Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the nuclear envelope. J Cell Biol. 2008; 183(4):653–666. [PubMed: 19015316]

Goss VL, Hocevar BA, Thompson LJ, Stratton CA, Burns DJ, Fields AP. Identification of nuclear beta II protein kinase C as a mitotic lamin kinase. J Biol Chem. 1994; 269(29):19074–19080. [PubMed: 8034666]

Grimsby S, Jaensson H, Dubrovska A, Lomnytska M, Hellman U, Souchelnytskyi S. Proteomics-based identification of proteins interacting with Smad3: SREBP-2 forms a complex with Smad3 and inhibits its transcriptional activity. FEBS Lett. 2004; 577(1-2):93–100. [PubMed: 15527767]

Guelen L, Pagie L, Brasset E, Meuleman W, Faza MB, Talhout W, Eussen BH, de Klein A, Wessels L, de Laat W, van Steensel B. Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. Nature. 2008; 453(7197):948–951. [PubMed: 18463634]

Guo D, Han J, Adam BL, Colburn NH, Wang MH, Dong Z, Eizirik DL, She JX, Wang CY. Proteomic analysis of SUMO4 substrates in HEK293 cells under serum starvation-induced stress. Biochem Biophys Res Commun. 2005; 337(4):1308–1318. [PubMed: 16236267]

Haas M, Jost E. Functional analysis of phosphorylation sites in human lamin A controlling lamin disassembly, nuclear transport and assembly. Eur J Cell Biol. 1993; 62(2):237–247. [PubMed: 7925482]

Han X, Feng X, Rattner JB, Smith H, Bose P, Suzuki K, Soliman MA, Scott MS, Burke BE, Riabowol K. Tethering by lamin A stabilizes and targets the ING1 tumour suppressor. Nat Cell Biol. 2008; 10(11):1333–1340. [PubMed: 18836436]

Haque F, Lloyd DJ, Smallwood DT, Dent CL, Shanahan CM, Fry AM, Trembath RC, Shackleton S. SUN1 interacts with nuclear lamin A and cytoplasmic nesprins to provide a physical connection between the nuclear lamina and the cytoskeleton. Mol Cell Biol. 2006; 26(10):3738–3751. [PubMed: 16648470]

Hart GW, Copeland RJ. Glycomics hits the big time. Cell. 2010; 143(5):672–676. [PubMed: 21111227]

Hay RT. SUMO: a history of modification. Mol Cell. 2005; 18(1):1–12. [PubMed: 15808504]

Heald R, McKeon F. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. Cell. 1990; 61(4):579–589. [PubMed: 2344612]

Hegele RA, Cao H, Liu DM, Costain GA, Charlton-Menys V, Rodger NW, Durrington PN. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. Am J Hum Genet. 2006; 79(2):383–389. [PubMed: 16826530]

Heitlinger E, Peter M, Haner M, Lustig A, Aebi U, Nigg EA. Expression of chicken lamin B2 in Escherichia coli: characterization of its structure, assembly, and molecular interactions. J Cell Biol. 1991; 113(3):485–495. [PubMed: 2016332]

Hennekes H, Peter M, Weber K, Nigg EA. Phosphorylation on protein kinase C sites inhibits nuclear import of lamin B2. J Cell Biol. 1993; 120(6):1293–1304. [PubMed: 8449977]

Herrmann H, Kreplak L, Aebi U. Isolation, characterization, and in vitro assembly of intermediate filaments. Methods Cell Biol. 2004; 78:3–24. [PubMed: 15646613]

Hocevar BA, Burns DJ, Fields AP. Identification of protein kinase C (PKC) phosphorylation sites on human lamin B. Potential role of PKC in nuclear lamina structural dynamics. J Biol Chem. 1993; 268(10):7545–7552. [PubMed: 8463284]

Holaska JM, Lee KK, Kowalski AK, Wilson KL. Transcriptional repressor germ cell-less (GCL) and barrier to autointegration factor (BAF) compete for binding to emerin in vitro. J Biol Chem. 2003; 278(9):6969–6975. [PubMed: 12493765]

Holaska JM, Wilson KL. An emerin “proteome”: purification of distinct emerin-containing complexes from HeLa cells suggests molecular basis for diverse roles including gene regulation, mRNA splicing, signaling, mechanosensing, and nuclear architecture. Biochemistry. 2007; 46(30):8897–8908. [PubMed: 17620012]

Huang Y, Cai M, Clore GM, Craigie R. No interaction of barrier-to-autointegration factor (BAF) with HIV-1 MA, cone-rod homeobox (Crx) or MAN1-C in absence of DNA. PLoS One. 2011; 6(9):e25123. [PubMed: 21966431]

Imami K, Sugiyama N, Kyono Y, Tomita M, Ishihama Y. Automated phosphoproteome analysis for cultured cancer cells by two-dimensional nanoLC-MS using a calcined titania/C18 biphasic column. Anal Sci. 2008; 24(1):161–166. [PubMed: 18187866]

Isokane M, Hieda M, Hirakawa S, Shudou M, Nakashiro K, Hashimoto K, Hamakawa H, Higashiyama S. Plasma-membrane-anchored growth factor pro-amphiregulin binds A-type lamin and regulates global transcription. J Cell Sci. 2008; 121(21):3608–3618. [PubMed: 18946024]

Itahana Y, Yeh ET, Zhang Y. Nucleocytoplasmic shuttling modulates activity and ubiquitination-dependent turnover of SUMO-specific protease 2. Mol Cell Biol. 2006; 26(12):4675–4689. [PubMed: 16738331]

Ivorra C, Kubicek M, Gonzalez JM, Sanz-Gonzalez SM, Alvarez-Barrientos A, O'Connor JE, Burke B, Andres V. A mechanism of AP-1 suppression through interaction of c-Fos with lamin A/C. Genes Dev. 2006; 20(3):307–320. [PubMed: 16452503]

Johnson ES. Protein modification by SUMO. Annu Rev Biochem. 2004; 73:355–382. [PubMed: 15189146]

Kasahara K, Chida K, Tsunenaga M, Kohno Y, Ikuta T, Kuroki T. Identification of lamin B2 as a substrate of protein kinase C in BALB/MK-2 mouse keratinocytes. J Biol Chem. 1991; 266(30): 20018–20023. [PubMed: 1939065]

Kill IR, Hutchison CJ. S-phase phosphorylation of lamin B2. FEBS Lett. 1995; 377(1):26–30. [PubMed: 8543011]

Kim JE, Tannenbaum SR, White FM. Global phosphoproteome of HT-29 human colon adenocarcinoma cells. J Proteome Res. 2005; 4(4):1339–1346. [PubMed: 16083285]

Kim SC, Sprung R, Chen Y, Xu Y, Ball H, Pei J, Cheng T, Kho Y, Xiao H, Xiao L, Grishin NV, White M, Yang XJ, Zhao Y. Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. Mol Cell. 2006; 23(4):607–618. [PubMed: 16916647]

Kim W, Bennett EJ, Huttlin EL, Guo A, Li J, Possemato A, Sowa ME, Rad R, Rush J, Comb MJ, Harper JW, Gygi SP. Systematic and quantitative assessment of the ubiquitin-modified proteome. Mol Cell. 2011a; 44(2):325–340. [PubMed: 21906983]

Kim Y, Sharov AA, McDole K, Cheng M, Hao H, Fan CM, Gaiano N, Ko MS, Zheng Y. Mouse B-type lamins are required for proper organogenesis but not by embryonic stem cells. Science. 2011b; 334(6063):1706–1710. [PubMed: 22116031]

Kolb T, Maass K, Hergt M, Aebi U, Herrmann H. Lamin A and lamin C form homodimers and coexist in higher complex forms both in the nucleoplasmic fraction and in the lamina of cultured human cells. Nucleus. 2011; 2(5):425–433. [PubMed: 22033280]

Krimm I, Ostlund C, Gilquin B, Couprie J, Hossenlopp P, Mornon JP, Bonne G, Courvalin JC, Worman HJ, Zinn-Justin S. The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy. Structure. 2002; 10(6):811–823. [PubMed: 12057196]

Kubben N, Voncken JW, Demmers J, Calis C, van Almen G, Pinto Y, Misteli T. Identification of differential protein interactors of lamin A and progerin. Nucleus. 2010; 1(6):513–525. [PubMed: 21327095]

Kuga T, Nozaki N, Matsushita K, Nomura F, Tomonaga T. Phosphorylation statuses at different residues of lamin B2, B1, and A/C dynamically and independently change throughout the cell cycle. Exp Cell Res. 2010; 316(14):2301–2312. [PubMed: 20580708]

Lai JS, Herr W. Ethidium bromide provides a simple tool for identifying genuine DNA-independent protein associations. Proc Natl Acad Sci U S A. 1992; 89(15):6958–6962. [PubMed: 1495986]

Lee CP, Chen MR. Escape of herpesviruses from the nucleus. Rev Med Virol. 2010; 20(4):214–230. [PubMed: 20069615]

Lee CP, Huang YH, Lin SF, Chang Y, Chang YH, Takada K, Chen MR. Epstein-Barr virus BGLF4 kinase induces disassembly of the nuclear lamina to facilitate virion production. J Virol. 2008; 82(23):11913–11926. [PubMed: 18815303]

Lee KK, Haraguchi T, Lee RS, Koujin T, Hiraoka Y, Wilson KL. Distinct functional domains in emerin bind lamin A and DNA-bridging protein BAF. J Cell Sci. 2001; 114(Pt 24):4567–4573. [PubMed: 11792821]

Libotte T, Zaim H, Abraham S, Padmakumar VC, Schneider M, Lu W, Munck M, Hutchison C, Wehnert M, Fahrenkrog B, Sauder U, Aebi U, Noegel AA, Karakesisoglou I. Lamin A/C-dependent localization of Nesprin-2, a giant scaffolder at the nuclear envelope. Mol Biol Cell. 2005; 16(7):3411–3424. [PubMed: 15843432]

Lloyd DJ, Trembath RC, Shackleton S. A novel interaction between lamin A and SREBP1: implications for partial lipodystrophy and other laminopathies. Hum Mol Genet. 2002; 11(7):769–777. [PubMed: 11929849]

Lussi YC, Hugi I, Laurell E, Kutay U, Fahrenkrog B. The nucleoporin Nup88 is interacting with nuclear lamin A. Mol Biol Cell. 2011; 22(7):1080–1090. [PubMed: 21289091]

Ma L, Tsai MY, Wang S, Lu B, Chen R, Iii JR, Zhu X, Zheng Y. Requirement for Nudel and dynein for assembly of the lamin B spindle matrix. Nat Cell Biol. 2009; 11(3):247–256. [PubMed: 19198602]

Maison C, Pyrpasopoulou A, Theodoropoulos PA, Georgatos SD. The inner nuclear membrane protein LAP1 forms a native complex with B-type lamins and partitions with spindle-associated mitotic vesicles. EMBO J. 1997; 16(16):4839–4850. [PubMed: 9305626]

Malhas AN, Lee CF, Vaux DJ. Lamin B1 controls oxidative stress responses via Oct-1. J Cell Biol. 2009; 184(1):45–55. [PubMed: 19139261]

Malik R, Lenobel R, Santamaria A, Ries A, Nigg EA, Korner R. Quantitative analysis of the human spindle phosphoproteome at distinct mitotic stages. J Proteome Res. 2009; 8(10):4553–4563. [PubMed: 19691289]

Mall M, Walter T, Gorjanacz M, Davidson IF, Nga Ly-Hartig TB, Ellenberg J, Mattaj IW. Mitotic lamin disassembly is triggered by lipid-mediated signaling. J Cell Biol. 2012; 198(6):981–990. [PubMed: 22986494]

Mancini MA, Shan B, Nickerson JA, Penman S, Lee WH. The retinoblastoma gene product is a cell cycle-dependent, nuclear matrix-associated protein. Proc Natl Acad Sci U S A. 1994; 91(1):418–422. [PubMed: 8278403]

Mansharamani M, Wilson KL. Direct binding of nuclear membrane protein MAN1 to emerin in vitro and two modes of binding to barrier-to-autointegration factor. J Biol Chem. 2005; 280(14): 13863–13870. [PubMed: 15681850]

Mariappan I, Gurung R, Thanumalayan S, Parnaik VK. Identification of cyclin D3 as a new interaction partner of lamin A/C. Biochem Biophys Res Commun. 2007; 355(4):981–985. [PubMed: 17321498]

Martelli AM, Bortul R, Tabellini G, Faenza I, Cappellini A, Bareggi R, Manzoli L, Cocco L. Molecular characterization of protein kinase C-alpha binding to lamin A. J Cell Biochem. 2002; 86(2):320–330. [PubMed: 12112001]

Maske CP, Hollinshead MS, Higbee NC, Bergo MO, Young SG, Vaux DJ. A carboxyl-terminal interaction of lamin B1 is dependent on the CAAX endoprotease Rce1 and carboxymethylation. J Cell Biol. 2003; 162(7):1223–1232. [PubMed: 14504265]

Meier R, Muller PR, Hirt A, Leibundgut K, Ridolfi-Luthy A, Wagner HP. Differential phosphorylation of lamin B2 in normal and leukemic cells. Leuk Res. 1997; 21(9):841–847. [PubMed: 9393599]

Mingot JM, Kostka S, Kraft R, Hartmann E, Gorlich D. Importin 13: a novel mediator of nuclear import and export. EMBO J. 2001; 20(14):3685–3694. [PubMed: 11447110]

Mislow JM, Holaska JM, Kim MS, Lee KK, Segura-Totten M, Wilson KL, McNally EM. Nesprin-1alpha self-associates and binds directly to emerin and lamin A in vitro. FEBS Lett. 2002; 525(1-3):135–140. [PubMed: 12163176]

Mitsuhashi H, Hayashi YK, Matsuda C, Noguchi S, Wakatsuki S, Araki T, Nishino I. Specific phosphorylation of Ser458 of A-type lamins in LMNA-associated myopathy patients. J Cell Sci. 2010; 123(Pt 22):3893–3900. [PubMed: 20980393]

Molloy A, Cotter O, van Spaendonk R, Sistermans E, Sweeney B. A patient with a rare leukodystrophy related to lamin B1 duplication. Ir Med J. 2012; 105(6):186–187. [PubMed: 22973660]

Molloy S, Little M. p34cdc2 kinase-mediated release of lamins from nuclear ghosts is inhibited by cAMP-dependent protein kinase. Exp Cell Res. 1992; 201(2):494–499. [PubMed: 1322319]

Moritz A, Li Y, Guo A, Villen J, Wang Y, MacNeill J, Kornhauser J, Sprott K, Zhou J, Possemato A, Ren JM, Hornbeck P, Cantley LC, Gygi SP, Rush J, Comb MJ. Akt-RSK-S6 kinase signaling networks activated by oncogenic receptor tyrosine kinases. Sci Signal. 2010; 3(136):ra64. [PubMed: 20736484]

Neutzner M, Neutzner A. Enzymes of ubiquitination and deubiquitination. Essays Biochem. 2012; 52:37–50. [PubMed: 22708562]

Nigg EA, Kitten GT, Vorburger K. Targeting lamin proteins to the nuclear envelope: the role of CaaX box modifications. Biochem Soc Trans. 1992; 20(2):500–504. [PubMed: 1397650]

Olsen JV, Blagoev B, Gnad F, Macek B, Kumar C, Mortensen P, Mann M. Global, in vivo, and site-specific phosphorylation dynamics in signaling networks. Cell. 2006; 127(3):635–648. [PubMed: 17081983]

Olsen JV, Vermeulen M, Santamaria A, Kumar C, Miller ML, Jensen LJ, Gnad F, Cox J, Jensen TS, Nigg EA, Brunak S, Mann M. Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis. Sci Signal. 2010; 3(104):ra3. [PubMed: 20068231]

Ozaki T, Saijo M, Murakami K, Enomoto H, Taya Y, Sakiyama S. Complex formation between lamin A and the retinoblastoma gene product: identification of the domain on lamin A required for its interaction. Oncogene. 1994; 9(9):2649–2653. [PubMed: 8058329]

Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, Koeppen A, Hogan K, Ptacek LJ, Fu YH. Lamin B1 duplications cause autosomal dominant leukodystrophy. Nat Genet. 2006; 38(10): 1114–1123. [PubMed: 16951681]

Pan C, Olsen JV, Daub H, Mann M. Global effects of kinase inhibitors on signaling networks revealed by quantitative phosphoproteomics. Mol Cell Proteomics. 2009; 8(12):2796–2808. [PubMed: 19651622]

Pegoraro G, Kubben N, Wickert U, Gohler H, Hoffmann K, Misteli T. Ageing-related chromatin defects through loss of the NURD complex. Nat Cell Biol. 2009; 11(10):1261–1267. [PubMed: 19734887]

Pekovic V, Gibbs-Seymour I, Markiewicz E, Alzoghaibi F, Benham AM, Edwards R, Wenhert M, von Zglinicki T, Hutchison CJ. Conserved cysteine residues in the mammalian lamin A tail are essential for cellular responses to ROS generation. Aging Cell. 2011; 10(6):1067–1079. [PubMed: 21951640]

Pendas AM, Zhou Z, Cadinanos J, Freije JM, Wang J, Hultenby K, Astudillo A, Wernerson A, Rodriguez F, Tryggvason K, Lopez-Otin C. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. Nat Genet. 2002; 31(1):94–99. [PubMed: 11923874]

Peter A, Stick R. Evolution of the lamin protein family: What introns can tell. Nucleus. 2012; 3(1)

Peter M, Heitlinger E, Haner M, Aebi U, Nigg EA. Disassembly of in vitro formed lamin head-to-tail polymers by CDC2 kinase. EMBO J. 1991; 10(6):1535–1544. [PubMed: 1851086]

Peter M, Nakagawa J, Doree M, Labbe JC, Nigg EA. In vitro disassembly of the nuclear lamina and M phase-specific phosphorylation of lamins by cdc2 kinase. Cell. 1990; 61(4):591–602. [PubMed: 2188731]

Rao L, Modha D, White E. The E1B 19K protein associates with lamins in vivo and its proper localization is required for inhibition of apoptosis. Oncogene. 1997; 15(13):1587–1597. [PubMed: 9380411]

Reddy KL, Zullo JM, Bertolino E, Singh H. Transcriptional repression mediated by repositioning of genes to the nuclear lamina. Nature. 2008; 452(7184):243–247. [PubMed: 18272965]

Rigbolt KT, Prokhorova TA, Akimov V, Henningsen J, Johansen PT, Kratchmarova I, Kassem M, Mann M, Olsen JV, Blagoev B. System-wide temporal characterization of the proteome and phosphoproteome of human embryonic stem cell differentiation. Sci Signal. 2011; 4(164):rs3. [PubMed: 21406692]

Roux KJ, Kim DI, Raida M, Burke B. A promiscuous biotin ligase fusion protein identifies proximal and interacting proteins in mammalian cells. J Cell Biol. 2012; 196(6):801–810. [PubMed: 22412018]

Ruan J, Xu C, Bian C, Lam R, Wang JP, Kania J, Min J, Zang J. Crystal structures of the coil 2B fragment and the globular tail domain of human lamin B1. FEBS Lett. 2012; 586(4):314–318. [PubMed: 22265972]

Sakaki M, Koike H, Takahashi N, Sasagawa N, Tomioka S, Arahata K, Ishiura S. Interaction between emerin and nuclear lamins. J Biochem. 2001; 129(2):321–327. [PubMed: 11173535]

Schirmer EC, Gerace L. The stability of the nuclear lamina polymer changes with the composition of lamin subtypes according to their individual binding strengths. J Biol Chem. 2004; 279(41): 42811–42817. [PubMed: 15284226]

Schneider U, Mini T, Jeno P, Fisher PA, Stuurman N. Phosphorylation of the major Drosophila lamin in vivo: site identification during both M-phase (meiosis) and interphase by electrospray ionization tandem mass spectrometry. Biochemistry. 1999; 38(14):4620–4632. [PubMed: 10194384]

Schumacher J, Reichenzeller M, Kempf T, Schnolzer M, Herrmann H. Identification of a novel, highly variable amino-terminal amino acid sequence element in the nuclear intermediate filament protein lamin B(2) from higher vertebrates. FEBS Lett. 2006; 580(26):6211–6216. [PubMed: 17070523]

Schuster J, Sundblom J, Thuresson AC, Hassin-Baer S, Klopstock T, Dichgans M, Cohen OS, Raininko R, Melberg A, Dahl N. Genomic duplications mediate overexpression of lamin B1 in adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms. Neurogenetics. 2011; 12(1):65–72. [PubMed: 21225301]

Shimi T, Pfleghaar K, Kojima S, Pack CG, Solovei I, Goldman AE, Adam SA, Shumaker DK, Kinjo M, Cremer T, Goldman RD. The A- and B-type nuclear lamin networks: microdomains involved in chromatin organization and transcription. Genes Dev. 2008; 22(24):3409–3421. [PubMed: 19141474]

Shimizu T, Cao CX, Shao RG, Pommier Y. Lamin B phosphorylation by protein kinase calpha and proteolysis during apoptosis in human leukemia HL60 cells. J Biol Chem. 1998; 273(15):8669–8674. [PubMed: 9535842]

Shumaker DK, Solimando L, Sengupta K, Shimi T, Adam SA, Grunwald A, Strelkov SV, Aebi U, Cardoso MC, Goldman RD. The highly conserved nuclear lamin Ig-fold binds to PCNA: its role in DNA replication. J Cell Biol. 2008; 181(2):269–280. [PubMed: 18426975]

Sieprath T, Darwiche R, De Vos WH. Lamins as mediators of oxidative stress. Biochem Biophys Res Commun. 2012; 421(4):635–639. [PubMed: 22538370]

Simon DN, Domaradzki T, Hofmann WA, Wilson KL. Lamin A tail modification by SUMO1 is disrupted by familial partial lipodystrophy-causing mutations. Mol Biol Cell. 2012; 24(3):342–50. [PubMed: 23243001]

Simon DN, Wilson KL. The nucleoskeleton as a genome-associated dynamic 'network of networks'. Nat Rev Mol Cell Biol. 2011; 12(11):695–708. [PubMed: 21971041]

Simon DN, Zastrow MS, Wilson KL. Direct actin binding to A- and B-type lamin tails and actin filament bundling by the lamin A tail. Nucleus. 2010; 1(3):264–272. [PubMed: 21327074]

Smith TC, Fang Z, Luna EJ. Novel interactors and a role for supervillin in early cytokinesis. Cytoskeleton (Hoboken). 2010; 67(6):346–364. [PubMed: 20309963]

Somech R, Shaklai S, Geller O, Amariglio N, Simon AJ, Rechavi G, Gal-Yam EN. The nuclear-envelope protein and transcriptional repressor LAP2beta interacts with HDAC3 at the nuclear periphery, and induces histone H4 deacetylation. J Cell Sci. 2005; 118(Pt 17):4017–4025. [PubMed: 16129885]

Speese SD, Ashley J, Jokhi V, Nunnari J, Barria R, Li Y, Ataman B, Koon A, Chang YT, Li Q, Moore MJ, Budnik V. Nuclear envelope budding enables large ribonucleoprotein particle export during synaptic Wnt signaling. Cell. 2012; 149(4):832–846. [PubMed: 22579286]

Sridharan DM, McMahon LW, Lambert MW. alphaII-Spectrin interacts with five groups of functionally important proteins in the nucleus. Cell Biol Int. 2006; 30(11):866–878. [PubMed: 16889989]

Steen RL, Beullens M, Landsverk HB, Bollen M, Collas P. AKAP149 is a novel PP1 specifier required to maintain nuclear envelope integrity in G1 phase. J Cell Sci. 2003; 116(11):2237–2246. [PubMed: 12697839]

Steen RL, Collas P. Mistargeting of B-type lamins at the end of mitosis: implications on cell survival and regulation of lamins A/C expression. J Cell Biol. 2001; 153(3):621–626. [PubMed: 11331311]

Stewart CL, Kozlov S, Fong LG, Young SG. Mouse models of the laminopathies. Exp Cell Res. 2007; 313(10):2144–2156. [PubMed: 17493612]

Stierle V, Couprie J, Ostlund C, Krimm I, Zinn-Justin S, Hossenlopp P, Worman HJ, Courvalin JC, Duband-Goulet I. The carboxyl-terminal region common to lamins A and C contains a DNA binding domain. Biochemistry. 2003; 42(17):4819–4828. [PubMed: 12718522]

Strelkov SV, Schumacher J, Burkhard P, Aebi U, Herrmann H. Crystal structure of the human lamin A coil 2B dimer: implications for the head-to-tail association of nuclear lamins. J Mol Biol. 2004; 343(4):1067–1080. [PubMed: 15476822]

Strieter ER, Korasick DA. Unraveling the complexity of ubiquitin signaling. ACS Chem Biol. 2012; 7(1):52–63. [PubMed: 22196026]

Stuurman N. Identification of a conserved phosphorylation site modulating nuclear lamin polymerization. FEBS Lett. 1997; 401(2-3):171–174. [PubMed: 9013881]

Tabellini G, Bortul R, Aluigi M, Billi AM, Bareggi R, Grill V, Narducci P, Martelli AM. Binding of elements of protein kinase C-alpha regulatory domain to lamin B1. Cell Signal. 2002; 14(10): 819–827. [PubMed: 12135703]

Takahashi A, Alnemri ES, Lazebnik YA, Fernandes-Alnemri T, Litwack G, Moir RD, Goldman RD, Poirier GG, Kaufmann SH, Earnshaw WC. Cleavage of lamin A by Mch2 alpha but not CPP32: multiple interleukin 1 beta-converting enzyme-related proteases with distinct substrate recognition properties are active in apoptosis. Proc Natl Acad Sci U S A. 1996; 93(16):8395–8400. [PubMed: 8710882]

Takamori Y, Tamura Y, Kataoka Y, Cui Y, Seo S, Kanazawa T, Kurokawa K, Yamada H. Differential expression of nuclear lamin, the major component of nuclear lamina, during neurogenesis in two germinal regions of adult rat brain. Eur J Neurosci. 2007; 25(6):1653–1662. [PubMed: 17432957]

Tang K, Finley RL Jr. Nie D, Honn KV. Identification of 12-lipoxygenase interaction with cellular proteins by yeast two-hybrid screening. Biochemistry. 2000; 39(12):3185–3191. [PubMed: 10727209]

Taniura H, Glass C, Gerace L. A chromatin binding site in the tail domain of nuclear lamins that interacts with core histones. J Cell Biol. 1995; 131(1):33–44. [PubMed: 7559784]

Thompson LJ, Fields AP. betaII protein kinase C is required for the G2/M phase transition of cell cycle. J Biol Chem. 1996; 271(25):15045–15053. [PubMed: 8663071]

Van Berlo JH, Voncken JW, Kubben N, Broers JL, Duisters R, van Leeuwen RE, Crijns HJ, Ramaekers FC, Hutchison CJ, Pinto YM. A-type lamins are essential for TGF-beta1 induced PP2A to dephosphorylate transcription factors. Hum Mol Genet. 2005; 14(19):2839–2849. [PubMed: 16115815]

Van Hoof D, Munoz J, Braam SR, Pinkse MW, Linding R, Heck AJ, Mummery CL, Krijgsveld J. Phosphorylation dynamics during early differentiation of human embryonic stem cells. Cell Stem Cell. 2009; 5(2):214–226. [PubMed: 19664995]

Varela I, Cadinanos J, Pendas AM, Gutierrez-Fernandez A, Folgueras AR, Sanchez LM, Zhou Z, Rodriguez FJ, Stewart CL, Vega JA, Tryggvason K, Freije JM, Lopez-Otin C. Accelerated ageing in mice deficient in Zmpste24 protease is linked to p53 signalling activation. Nature. 2005; 437(7058):564–568. [PubMed: 16079796]

Vaughan A, Alvarez-Reyes M, Bridger JM, Broers JL, Ramaekers FC, Wehnert M, Morris GE, Whitfield WGF, Hutchison CJ. Both emerin and lamin C depend on lamin A for localization at the nuclear envelope. J Cell Sci. 2001; 114(14):2577–2590. [PubMed: 11683386]

Vergnes L, Peterfy M, Bergo MO, Young SG, Reue K. Lamin B1 is required for mouse development and nuclear integrity. Proc Natl Acad Sci U S A. 2004; 101(28):10428–10433. [PubMed: 15232008]

Vlcek S, Foisner R, Wilson KL. Lco1 is a novel widely expressed lamin-binding protein in the nuclear interior. Exp Cell Res. 2004; 298(2):499–511. [PubMed: 15265697]

Wagner SA, Beli P, Weinert BT, Nielsen ML, Cox J, Mann M, Choudhary C. A proteome-wide, quantitative survey of in vivo ubiquitylation sites reveals widespread regulatory roles. Mol Cell Proteomics. 2011; 10(10):M111 013284.

Wang B, Malik R, Nigg EA, Korner R. Evaluation of the low-specificity protease elastase for large-scale phosphoproteome analysis. Anal Chem. 2008; 80(24):9526–9533. [PubMed: 19007248]

Wang Z, Udeshi ND, Slawson C, Compton PD, Sakabe K, Cheung WD, Shabanowitz J, Hunt DF, Hart GW. Extensive crosstalk between O-GlcNAcylation and phosphorylation regulates cytokinesis. Sci Signal. 2010; 3(104):ra2. [PubMed: 20068230]

Ward GE, Kirschner MW. Identification of cell cycle-regulated phosphorylation sites on nuclear lamin C. Cell. 1990; 61(4):561–577. [PubMed: 2188730]

Wilkinson KA, Henley JM. Mechanisms, regulation and consequences of protein SUMOylation. Biochem J. 2010; 428(2):133–145. [PubMed: 20462400]

Wilson KL, Foisner R. Lamin-binding Proteins. Cold Spring Harb Perspect Biol. 2010; 2(4):a000554. [PubMed: 20452940]

Worman HJ. Nuclear lamins and laminopathies. J Pathol. 2012; 226(2):316–325. [PubMed: 21953297]

Ye Q, Worman HJ. Primary structure analysis and lamin B and DNA binding of human LBR, an integral protein of the nuclear envelope inner membrane. J Biol Chem. 1994; 269(15):11306–11311. [PubMed: 8157662]

Ye Q, Worman HJ. Protein-protein interactions between human nuclear lamins expressed in yeast. Exp Cell Res. 1995; 219(1):292–298. [PubMed: 7628545]

Young SG, Fong LG, Michaelis S. Prelamin A, Zmpste24, misshapen cell nuclei, and progeria--new evidence suggesting that protein farnesylation could be important for disease pathogenesis. J Lipid Res. 2005; 46(12):2531–2558. [PubMed: 16207929]

Zaremba-Czogalla M, Piekarowicz K, Wachowicz K, Koziol K, Dubinska-Magiera M, Rzepecki R. The different function of single phosphorylation sites of Drosophila melanogaster lamin Dm and lamin C. PLoS One. 2012; 7(2):e32649. [PubMed: 22393432]

Zastrow MS, Flaherty DB, Benian GM, Wilson KL. Nuclear titin interacts with A- and B-type lamins in vitro and in vivo. J Cell Sci. 2006; 119(2):239–249. [PubMed: 16410549]

Zastrow MS, Vlcek S, Wilson KL. Proteins that bind A-type lamins: integrating isolated clues. J Cell Sci. 2004; 117(Pt 7):979–987. [PubMed: 14996929]

Zhang D, Beresford PJ, Greenberg AH, Lieberman J. Granzymes A and B directly cleave lamins and disrupt the nuclear lamina during granule-mediated cytolysis. Proc Natl Acad Sci U S A. 2001; 98(10):5746–5751. [PubMed: 11331782]

Zhang H, Saitoh H, Matunis MJ. Enzymes of the SUMO modification pathway localize to filaments of the nuclear pore complex. Mol Cell Biol. 2002; 22(18):6498–6508. [PubMed: 12192048]

Zhang YQ, Sarge KD. Sumoylation regulates lamin A function and is lost in lamin A mutants associated with familial cardiomyopathies. J Cell Biol. 2008; 182(1):35–39. [PubMed: 18606848]

Zhong N, Radu G, Ju W, Brown WT. Novel progerin-interactive partner proteins hnRNP E1, EGF, Mel 18, and UBC9 interact with lamin A/C. Biochem Biophys Res Commun. 2005; 338(2):855–861. [PubMed: 16248985]

Zullo JM, Demarco IA, Pique-Regi R, Gaffney DJ, Epstein CB, Spooner CJ, Luperchio TR, Bernstein BE, Pritchard JK, Reddy KL, Singh H. DNA sequence-dependent compartmentalization and silencing of chromatin at the nuclear lamina. Cell. 2012; 149(7):1474–1487. [PubMed: 22726435]

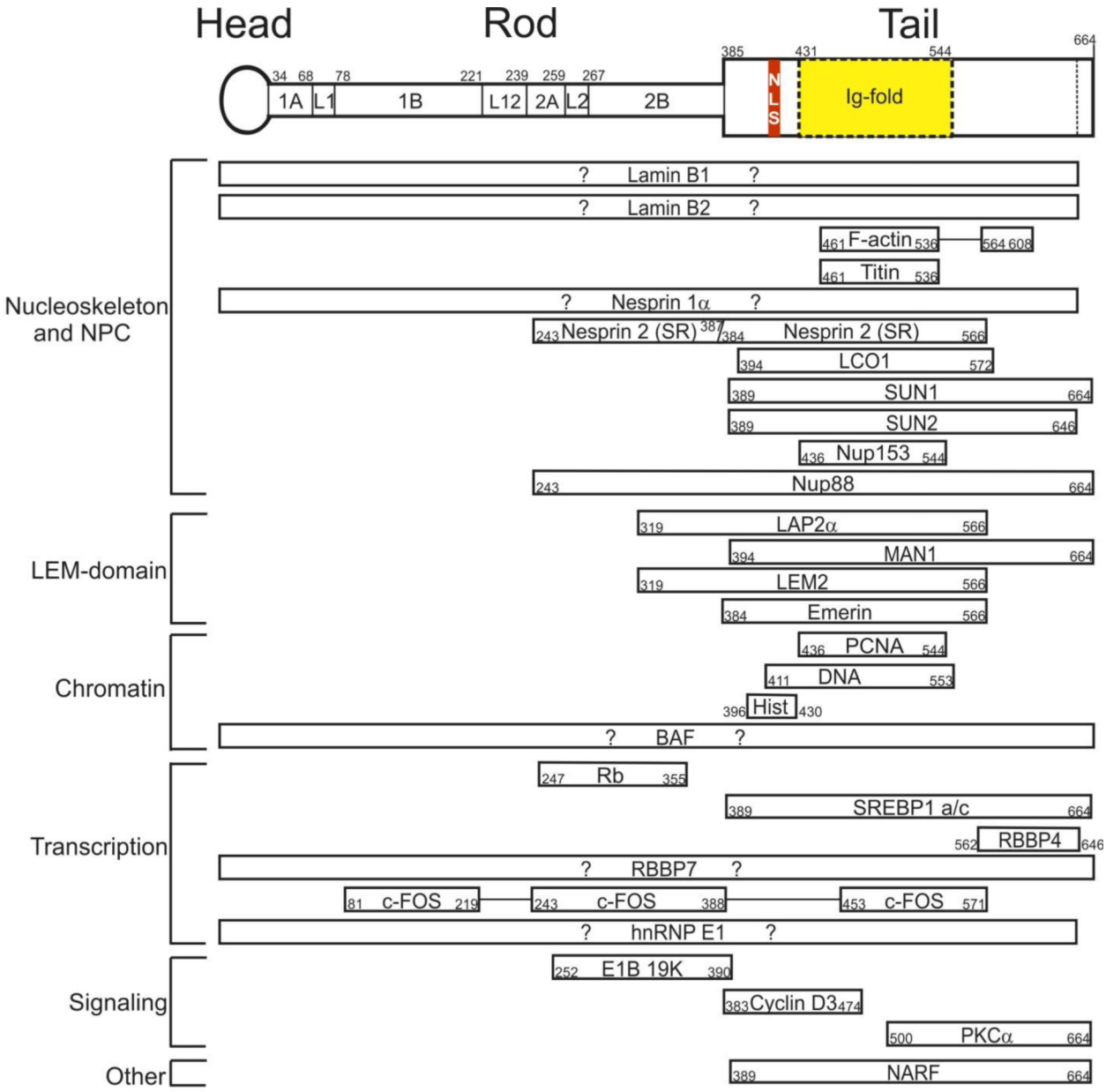

Figure 1. Lamin A molecule and direct binding partners

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.

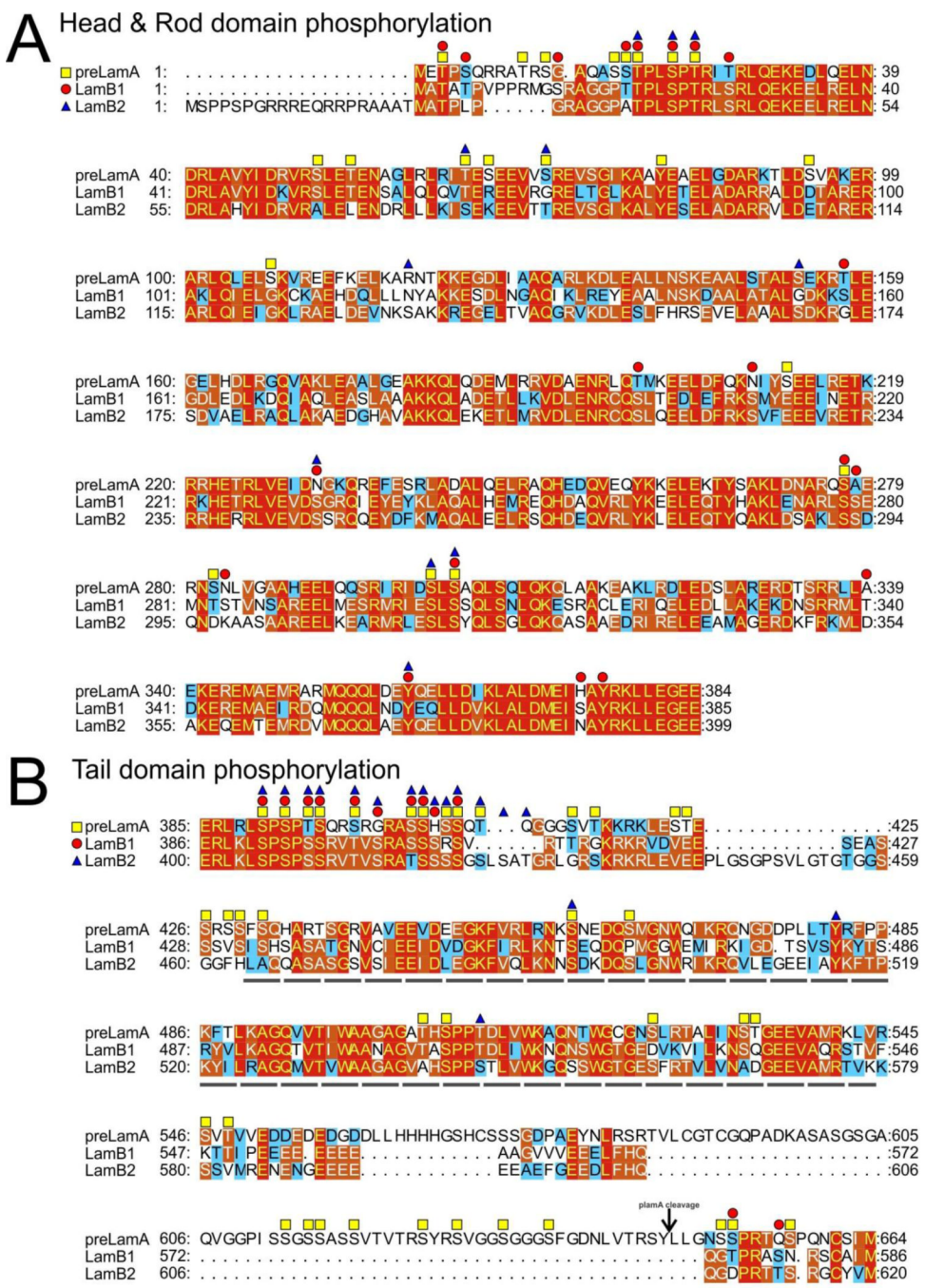

Figure 2. Conservation of known phosphorylation sites in human lamins

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 or 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).

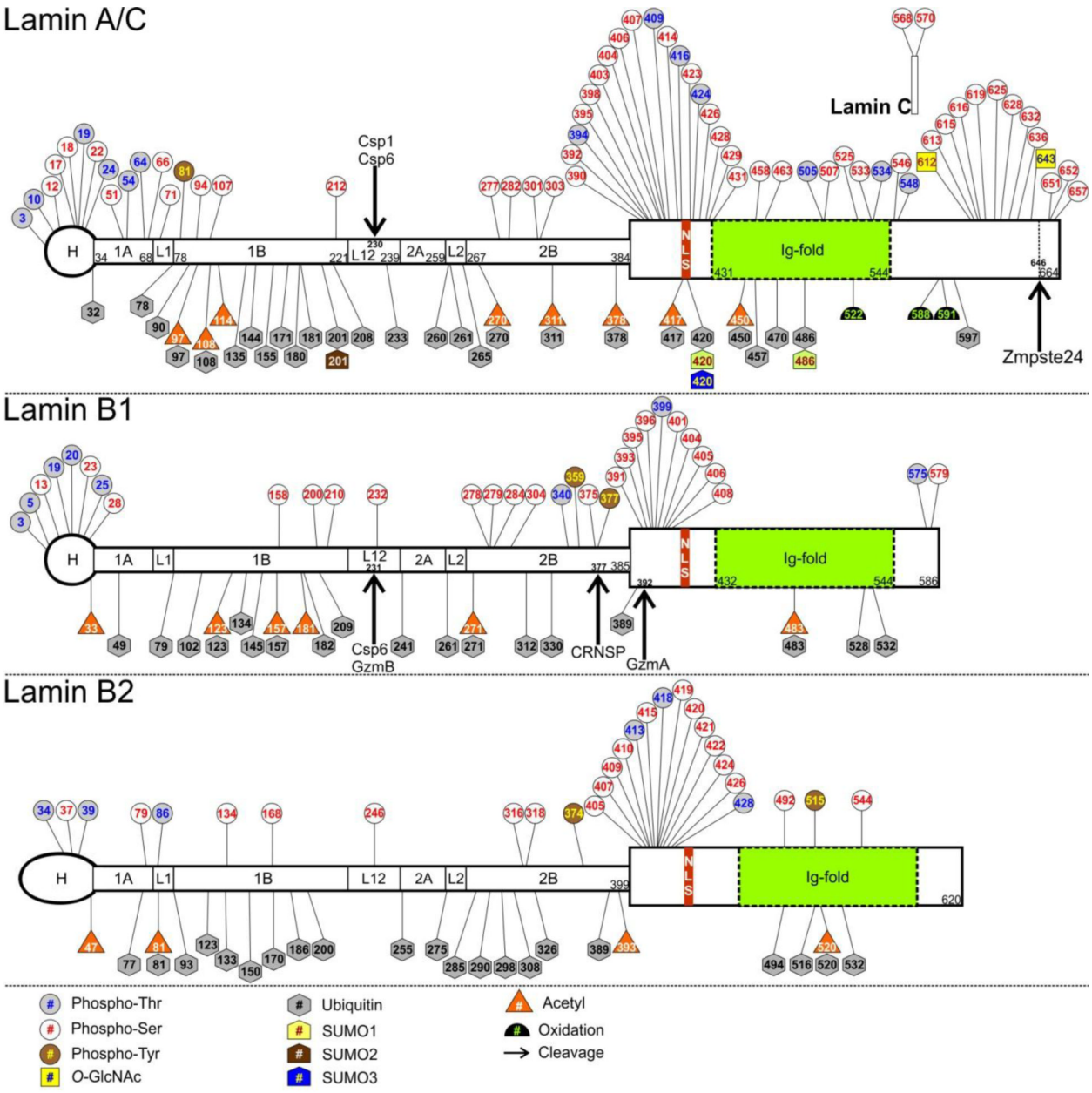

Figure 3. Post-translational modifications of human lamins

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.

Table 1

Reported direct binding partners of lamin A.

Protein	Lamin A residues	Method	Reference
Lamin B1	ND*	Recombinant Affi-bead pulldown	Schirmer & Gerace 2004
Lamin B2	ND		
F-actin	461-536 & 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 & 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 & 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	
c-FOS	81-219 & 243-388 & 453-571	Recombinant pulldown	Ivorra et al. 2006
hnRNP E1	ND	TnT gel shift	Zhong et al. 2005
E1B 19K	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 & Worman 1999

*ND, not determined.

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 & Gerace 1993
UBC9	ND	In vitro SUMOylation, Yeast-2-Hybrid & CO-IP	Zhang and Sarge 2008 Zhong et al. 2005
MRPS26	ND	Yeast-2-Hybrid	Zhong et al. 2005
Filamin A	ND		
Unc13D	ND		
EGF	ND	Yeast-2-Hybrid & CO-IP	
Mel18	ND		
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 & 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		
Protein 4.1	ND		
nMyo1c	ND	CO-IP from cells	Holaska & Wilson 2007
PP1	ND	CO-IP from cells	Steen & Collas 2001
AKAP149	ND		
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.

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 & Gerace 2004
Lamin C	ND		
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 & Kondo 1998
LBR	ND	Pulldown of native	Ye & 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 & Wilson 2005
PP1	ND	CO-IP from cells	Steen & Collas 2001
AKAP149	ND		
PLCβ1	ND	CO-IP from cells	Fiume et al. 2009
Oct-1	ND	CO-IP from cells & FRET	Malhas et al. 2009

CO-IP, Co-immunoprecipitation.

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 & Gerace 2004
Lamin C	ND		
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 & Collas 2001
AKAP149	ND		
Nup153	258-620	TnT pulldown	Al-Haboubi et al. 2011

CO-IP, Co-immunoprecipitation.

Table 5

Phosphorylation sites in human lamins A and C

Cells	HeLa							K562	hESCs		HT-29	Epith cancer	HEK293	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	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		Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Lee 2008	Haas & Jost 1993	
T3	X														
T10						X						X			PKCα
S12	X			X			X					X			
S17		X		X					X						
S18	X	X		X											
T19	X		X	X		X	X		X	X				X	CDK1, PKCα
S22	X	X	X	X	X	X	X	X	X	X			X	X	CDK1, BGLF4
T24	X					X		X	X						
S51				X											
T54									X						
T64	X														
S66	X			X											
S71				X											
Y81									X						
S94						X									
S107	X								X						
S212	X														
S277	X														
S282	X														
S301	X											X			
S303												X			
S390	X	X	X	X	X		X	X	X	X	X	X	X		CDK1, BGLF4
S392	X	X	X	X	X		X	X	X	X	X		X	X	CDK1, BGLF4
T394	X		X					X	X						
S395	X				X		X	X	X						PKCα

Cells	HeLa							K562	hESCs		HT-29	Epith cancer	HEK293	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	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		Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Lee 2008	Haas & Jost 1993	
S398	X											X			
S403	X	X					X		X			X		X	PKCα
S404	X	X					X	X	X	X		X		X	PKCα, Akt
S406	X						X		X		X	X			
S407	X						X	X	X		X	X			S6-kinase II
T409	X						X				X	X			
S414	X						X	X	X			X			
T416	X						X		X			X			PKCα
S423	X										X				
T424	X														
S426	X														
S428	X								X						
S429	X														
S431	X								X						
S458	X						X		X						
S463	X														
T505	X														
S507	X														
S525														X	PKCα
S533				X											
T534				X											
Lamin A only															
S613	X														
S615	X														
S616	X			X											
S619	X														
S625	X														

Cells	HeLa							K562	hESCs		HT-29	Epith cancer	HEK293	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	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		Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Lee 2008	Haas & Jost 1993	
S628	X			X			X								
S632	X			X											
S636	X			X			X		X						
S546												X			
T548												X			
S651		X													
S652	X												X		PKCα, BGLF4
S657													X		BGLF4
Lamin C only															
S568	X														
S570	X														

Table 6

Phosphorylation sites in human lamin B1

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

Cells	HeLa								K562	hESCs		HT-29	Epith. cancer	Human	Kinase
	Mitosis	S & M	Mitotic spindle			EGF	WCL	MAPK inhibit		Differentiation		WCL	WCL	In vitro	
P-aa	Olsen 2010	Daub 2008	Wang 2010	Malik 2009	Wang 2008	Olsen 2006	Imami 2008	Pan 2009		Rigbolt 2011	Van Hoof 2009	Kim 2005	Moritz 2010	Goss 1994	
S401										X					
S404	X					X				X					
S405										X			X	X	PKCβ1
S406										X			X		
S408										X			X		
T575	X					X		X		X	X				
S579					X										

Table 7

Phosphorylation sites in human lamin B2

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

Cells	HeLa				K562	hESCs		Epith. cancer
	Mitosis	S & M	Spindle	EGF	MAPK inhibit	Differentiation		WCL
P-aa	Olsen 2010	Daub 2008	Malik 2009	Olsen 2006	Pan 2009	Rigbolt 2011	Van Hoof 2009	Moritz 2010
S492	X							
Y515	X							
S544	X							