Lamin-binding Proteins

Katherine L. Wilson[1] and Roland Foisner[2]

[1]Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

[2]Max F. Perutz Laboratories, Department of Medical Biochemistry, Medical University of Vienna, Vienna 1030

Correspondence: roland.foisner@meduniwien.ac.at

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A- and B-type lamins are the major intermediate filaments of the nucleus. Lamins engage in a plethora of stable and transient interactions, near the inner nuclear membrane and throughout the nucleus. Lamin-binding proteins serve an amazingly diverse range of functions. Numerous inner-membrane proteins help anchor lamin filaments to the nuclear envelope, serving as part of the nuclear "lamina" network that is essential for nuclear architecture and integrity. Certain lamin-binding proteins of the inner membrane bind partners in the outer membrane and mechanically link lamins to the cytoskeleton. Inside the nucleus, lamin-binding proteins appear to serve as the "adaptors" by which the lamina organizes chromatin, influences gene expression and epigenetic regulation, and modulates signaling pathways. Transient interactions of lamins with key components of the transcription and replication machinery may provide an additional level of regulation or support to these essential events.

The eukaryotic cell nucleus is a complex membrane-bounded organelle that houses, organizes, and regulates the genome. The nucleus is structurally organized into functional domains, one of which is the nuclear envelope (NE). The NE has two concentric membranes, named the "inner" and "outer" nuclear membranes (INM and ONM, respectively). These membranes are separated by a 30–50 nm lumen, and fuse to form holes (pores) occupied by nuclear pore complexes (NPCs), which mediate active and passive movement of molecules between the cytoplasm and nucleoplasm (Gruenbaum et al. 2005; Stewart et al. 2007). The NE and its lumen are continuous with the endoplasmic reticulum (ER) and share many ER functions. However, the INM and ONM are also each structurally and functionally unique, because of specific enrichments for distinct integral membrane proteins (Schirmer and Gerace 2005; Schirmer and Foisner 2007). In mammals, the INM in particular appears to be populated by over 50 different membrane proteins, most of which are uncharacterized. Among characterized INM proteins, most can bind directly to A- or B-type lamins, or both.

A- and B-type lamins polymerize to form separate networks of nuclear intermediate filaments that concentrate near the INM in metazoans (Dechat et al. 2008). Many INM proteins are localized by binding directly or indirectly to lamin filaments. This network of filaments and

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lamin-binding proteins at the INM is known as the "peripheral lamina." B-type lamins are essential for cell viability and development, whereas A-type lamins arose later in evolution and are nonessential. Lamins are important structurally and as "scaffolds" for many other proteins and complexes in the nucleus.

Lamin filaments are important for the assembly, structure, shape, and mechanical stability of metazoan nuclei. There is also growing evidence that lamins regulate chromatin organization and gene expression, and influence signaling (Gruenbaum et al. 2005; Dechat et al. 2008). These functions involve a full spectrum of biochemical interactions between lamins, chromatin, and a variety of partners, including regulatory proteins responsive to external and intrinsic signals (Fig. 1). The pace of discovering new lamin-binding proteins has nearly overwhelmed our capacity to characterize them. Each new partner has the potential to provide fresh insight into the structure and regulation of the nucleoskeleton and its relationships with the genome. Further motivation for research in this area comes with the discovery that an increasing number of human diseases are linked to defects in lamins or lamin-binding proteins.

THE CONCEPT OF LAMINA-ASSOCIATED POLYPEPTIDES

The term lamina-associated-polypeptide (LAP) was coined to define a novel group of nuclear proteins that cofractionated with lamins and required high concentrations of monovalent salts and nonionic detergents to extract them from nuclei (Senior and Gerace 1988; Foisner

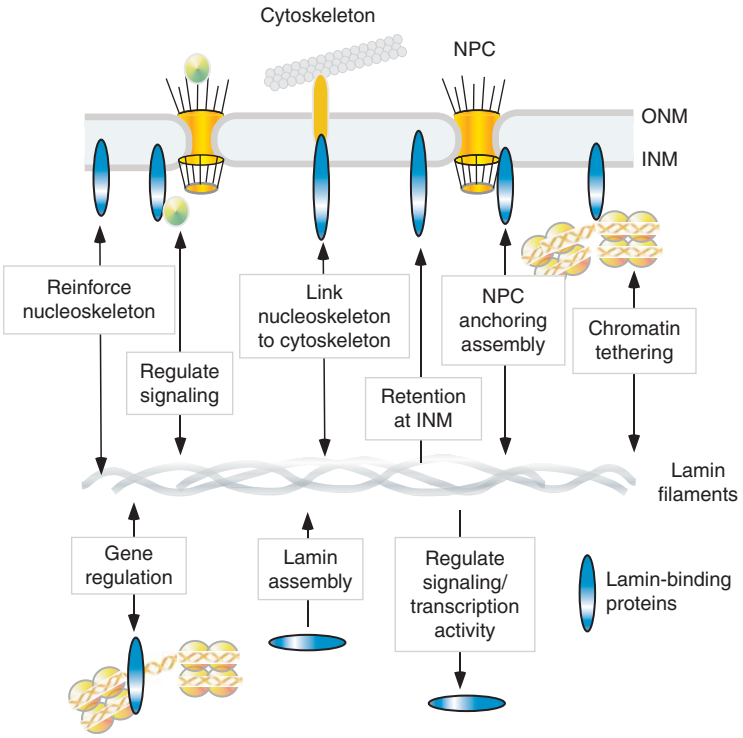

Figure 1. Overview of known roles for lamin-binding proteins. Many lamin-binding proteins located in the INM, on chromatin, and in the nucleoplasm are thought to have mechanical and structural roles, such as reinforcing the nucleoskeleton, interlinking the nucleoskeleton and cytoskeleton, anchoring NPCs, and tethering chromatin to the nuclear envelope. Others regulate signaling or transcription. Many lamin-binding proteins require lamins for their correct localization, whereas others regulate or facilitate lamin assembly.

and Gerace 1993). The first characterized LAPs were all integral INM proteins: LAP1 (Martin et al. 1995) and LAP2 (Harris et al. 1994; Furukawa et al. 1995; Berger et al. 1996) each has one transmembrane domain and is expressed as multiple isoforms, whereas the so-called lamin B receptor (LBR) has eight transmembrane domains (Worman et al. 1990). These proteins all bind lamins directly in vitro (Worman et al. 1988; Foisner and Gerace 1993; Furukawa et al. 1998). Since then, around 80 additional putative NE membrane proteins have been discovered (Schirmer et al. 2005; Schirmer and Foisner 2007). Most fit the original LAP criterion (resistance to biochemical extraction) and localize at the NE, but are untested for binding to lamins. The LAP concept expanded as lamins (Moir et al. 2000b; Naetar et al. 2008) and lamin-binding proteins including Narf (Barton and Worman 1999), LAP2α (Naetar et al. 2008), and Lco1 (Vlcek et al. 2004; Naetar et al. 2008) were discovered in the nuclear interior. Lamin-binding proteins can have widely differing, and differentially regulated, affinities for lamins that might influence their biochemical extraction. Some proteins are known to bind lamins directly and relatively stably at the NE or in the nuclear interior. By contrast, other proteins bind lamins more transiently, probably as a means of regulating their activities; these partners include PCNA (Shumaker et al. 2008), c-Fos (Gonzalez et al. 2008), retinoblastoma (Rb) (Johnson et al. 2004; Pekovic et al. 2007), and Oct-1 (Malhas et al. 2009).

LEM-DOMAIN PROTEINS AND BAF: TETHERING CHROMATIN TO THE NUCLEOSKELETON

One prominent family of lamin-binding proteins involved in nuclear architecture and chromatin organization share the LEM (LAP2, Emerin, MAN) domain, an ~45-residue motif that folds as two α-helices (Laguri et al. 2001). The LEM domain binds a conserved metazoan chromatin protein named Barrier to Autointegration Factor, BAF (Furukawa 1999; Cai et al. 2001; Lee et al. 2001; Shumaker et al. 2001; Shimi et al. 2004; Cai et al. 2007). BAF, a mobile lamin-binding protein, can "bridge" DNA and interacts with histones (Margalit et al. 2007). Most, but not all, LEM proteins are integral INM proteins with one or two transmembrane domains (Fig. 2). Mammals have four genes encoding characterized LEM proteins, LAP2 (α, β, and other isoforms), MAN1, emerin (Lin et al. 2000), and LEM2/NET25 (Schirmer et al. 2003; Brachner et al. 2005; Chen et al. 2006; Ulbert et al. 2006), and three uncharacterized genes encoding predicted nonmembrane proteins, LEM3, LEM4, and LEM5 (Lee and Wilson 2004), known respectively as ANKLE1, ANKLE2, and LEMD1. Three LEM proteins (emerin, LEM2, and LEM3) are conserved in *Caenorhabditis elegans* (Lee et al. 2000; Gruenbaum et al. 2002; Liu et al. 2003). Four are expressed in *Drosophila*: MAN1 (Wagner et al. 2006), otefin (Goldberg et al. 1998; Jiang et al. 2008), and Bocksbeutel α and β(Wagner et al. 2004). The functions and interactions of LEM proteins, lamins, and BAF are strongly conserved between mammals, nematodes, and flies, suggesting they have fundamental roles in the nucleus.

Some LEM-domain proteins have additional domains that bind DNA, or other chromatin proteins. For example, LAP2β can bind HA95, a chromatin protein involved in DNA replication (Martins et al. 2003). All isoforms of LAP2 have a second "LEM-like" domain that binds DNA, rather than BAF (Cai et al. 2001; Laguri et al. 2001). Similarly, MAN1 and probably LEM2 binds DNA directly via a carboxy-terminal "winged helix" domain (Caputo et al. 2006). Furthermore, all tested LEM proteins bind either A- or B-type lamins, or both, directly (Clements et al. 2000; Lee et al. 2001; Sakaki et al. 2001; Brachner et al. 2005; Mansharamani and Wilson 2005), and some require this interaction to localize at the NE (Sullivan et al. 1999; Vaughan et al. 2001; Brachner et al. 2005). Lamins, in turn, also directly bind DNA (Shoeman and Traub 1990; Luderus et al. 1992; Stierle et al. 2003) and histones (Taniura et al. 1995; Mattout et al. 2007). Thus, a complex network of interactions between lamins, LEM proteins, BAF, and, most likely, other INM proteins is involved in anchoring chromatin to the NE and lamins.

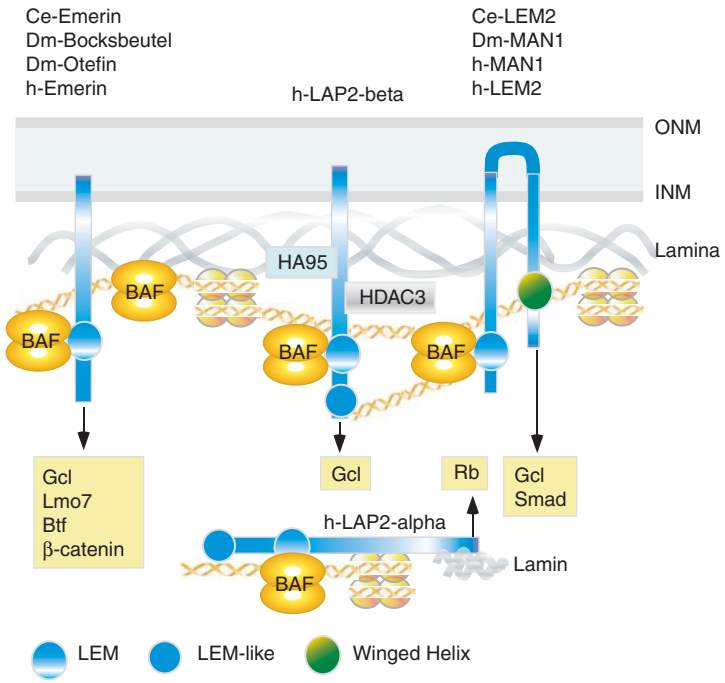

Figure 2. LEM-domain proteins organize chromatin and regulate signaling and transcription. Domain organizations of characterized LEM proteins; the LEM motif confers direct binding to barrier to autointegration factor (BAF). All LEM proteins can bind A- and/or B-type lamins. Some, including human (h-)emerin, *C. elegans* (Ce-) emerin, *D. melanogaster* (Dm-) bocksbeutel α, and Dm-Otefin, have one transmembrane (TM) domain. LAP2 proteins, expressed only in vertebrates, also have a DNA-binding "LEM-like" domain. Others (e.g., hLem2, Ce-Lem2, hMAN1, and Dm-MAN1) have two TM domains and a carboxy-terminal Winged Helix domain that binds DNA. Some, including hLAP2α (shown) and three uncharacterized LEM proteins (not shown), have no TM domain. LEM proteins have additional functional domains; e.g., LAP2β partners include replication protein HA95 and HDAC3; LAP2β recruits HDAC3 to the NE and contributes to epigenetic regulation. Emerin binds many transcription factors including GCL, Lmo7, Btf, and β-catenin. GCL also binds hLAP2β and hMAN1, suggesting functional overlap. MAN1 is unique in binding regulatory Smads, and inhibits BMP and TGF-β signaling.

LEM proteins might appear to function redundantly in chromatin organization because there are so many of them, and functional inactivation of any single tested LEM gene does not grossly disrupt chromatin organization. Functional overlap is supported by *C. elegans* studies, which showed that double-knockdown of two LEM proteins (Ce-emerin and Ce-lem2) caused embryonic lethality at the 100-cell stage, when embryonic gene expression normally begins, with phenotypes that included aneuploidy, grossly defective chromatin organization and nuclear structure, and failure to assemble nuclei after mitosis (Liu et al. 2003). Nearly identical phenotypes are caused by down-regulating either Ce-lamin or BAF alone (Gruenbaum et al. 2005; Margalit et al. 2005a), strongly suggesting that BAF and LEM-domain proteins are key components of nuclear architecture.

Nevertheless, despite potential redundancies, eliminating just one LEM protein, for example emerin in mice, can affect nuclear structure: Emerin-null skeletal muscle nuclei are fragile (Ozawa et al. 2006), and show significantly increased autophagic degradation of structurally aberrant regions of the nucleus (Park et al. 2009a). Lamin mutations also cause obvious defects in nuclear shape and chromatin organization (Sabatelli et al. 2001; Scaffidi and Misteli 2006; Shumaker et al. 2006; Wang

et al. 2006; Hakelien et al. 2008; Park et al. 2009b), as well as enhanced autophagic degradation of nuclei (Park et al. 2009a). Further evidence for the physiological relevance of both lamins and LEM proteins in chromatin organization comes from recent genome-wide studies to identify lamina-bound DNA. The analysis of methylated DNA in cultured *Drosophila* cells expressing lamin B1 fused to DNA methyltransferase (Dam), revealed ~500 genes in close contact with the lamina (Pickersgill et al. 2006). In human fibroblasts, this strategy revealed both lamin B1 and emerin in close contact with >1300 sharply defined domains in the genome, most of which were flanked either by binding sites for the insulator protein CTCF, or by E2F/DP-regulated promoters (Guelen et al. 2008). Interestingly, at least two INM LEM proteins, LAP2β and emerin, are implicated in the regulation of E2F/DP promoters (Nili et al. 2001; Holaska and Wilson 2006), and both CTCF and A-type lamins are required for the insulator function of a subtelomeric array of *D4Z4* repeats, shortening of which cause Facio-Scapulo-Humeral Dystrophy (FSHD) (Ottaviani et al. 2009). Future application of genome-wide "close contact" studies to other LEM proteins, and other types of lamin-binding proteins, may provide much-needed insight into their relationships with chromosomes. Interestingly, in proliferating cells, these "relationships" might be established actively while nuclei reassemble during mitotic anaphase and telophase. Nuclear assembly involves a complex series of interactions between chromatin, membranes, INM and ONM proteins, lamins, and other mitotically solubilized components, the mechanisms and regulation of which remain poorly understood (Margalit et al. 2005b; Anderson and Hetzer 2008; Guttinger et al. 2009). However, protein–protein interactions, for example between BAF, lamins, and LEM proteins, are required because nuclear assembly fails when one component is missing, as shown in *C. elegans* studies (Margalit et al. 2005b), and also fails in HeLa cells that express emerin and BAF mutants with impaired interactions (Haraguchi et al. 2001).

LINC COMPLEXES LINK THE NUCLEAR INTERIOR TO THE CYTOPLASM

Many independent studies in yeast, worms, flies, and mammals converged on a major discovery: Membrane proteins of the NE mechanically interlink the nucleoskeleton and cytoskeleton. These "LINC" complexes (Crisp et al. 2006) enable the regulated, cytoplasmic-motor-driven movement of the entire nucleus to new positions within the cell, and the movement of entire NE-tethered chromosomes to new positions along the NE (for reviews, see Tzur et al. 2006b; Wilhelmsen et al. 2006; Starr 2009). In addition, gene-regulatory responses to external force must now be assumed to potentially involve not only indirect signaling from the cell surface, but also direct signaling via mechanotransducing complexes at the NE.

Considered at the simplest level, LINC complexes consist of lamin-binding SUN-domain proteins in the INM that interact in the NE lumen with KASH-domain proteins (Fig. 3) anchored in the ONM (Hodzic et al. 2004; Padmakumar et al. 2005; Crisp et al. 2006; Haque et al. 2006); KASH proteins also bind directly or indirectly to cytoplasmic actin, microtubules, centrosomes, or intermediate filaments (Zhang et al. 2001; Zhen et al. 2002; Padmakumar et al. 2004; Wilhelmsen et al. 2005; McGee et al. 2006; Roux et al. 2009). It is important to note that at least two of the many KASH-domain protein isoforms (nesprin-1α and nesprin-2β) are INM proteins that bind directly to lamins and emerin (Mislow et al. 2002a; Mislow et al. 2002b; Zhang et al. 2005).

SUN-domain proteins, conserved from yeast to humans, are defined by a 120-residue motif located in the lumenal space of the NE; the name SUN was based on *S. pombe* Sad1 and *D. melanogaster* UNC-84 (Malone et al. 1999). *C. elegans* and *D. melanogaster* each have two *SUN* genes: *UNC84* and germ-cell-specific *matefin/SUN1* in *C. elegans*, and *Klaroid* and *CG6589* in *Drosophila*. Mammals have four: *SUN1* and *SUN2*, and testis-specific genes *SUN3* and *Spag4* (reviewed in Starr 2009). Human SUN1 (hSUN1) and hSUN2 each have a coiled-coil domain near the SUN domain that

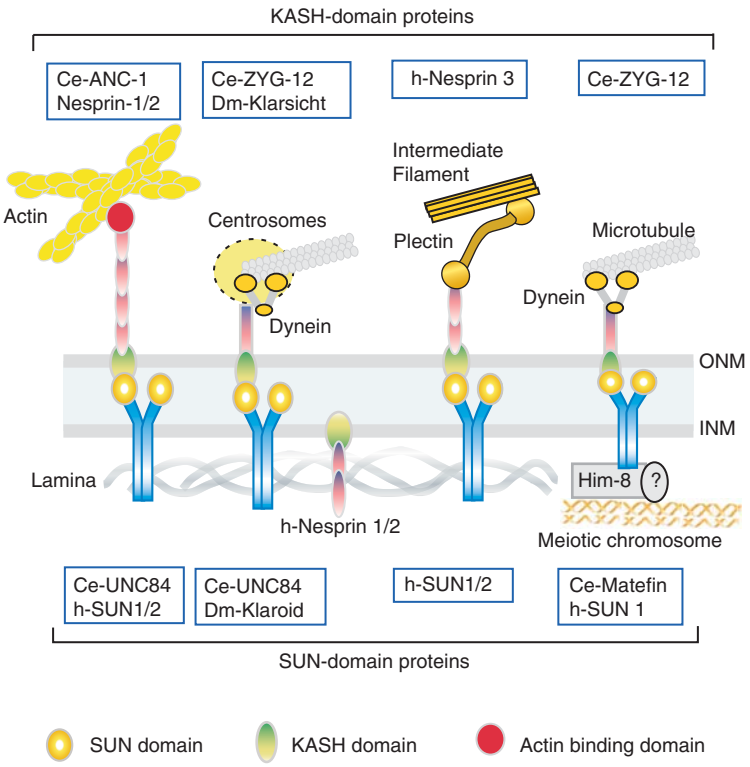

Figure 3. SUN- and KASH-domain proteins interact in the NE lumen to form LINC (Links Nucleoskeleton and Cytoskeleton) complexes. SUN-domain proteins span the INM and dimerize; each nucleoplasmic domain binds lamins and each SUN-domain in the NE lumen binds the KASH domain of an ONM-embedded KASH protein, which binds actin, centrosomes/microtubules, or plectin/intermediate filaments in the cytoplasm. Only one KASH domain partner of a SUN dimer is depicted. SUN proteins also bind, potentially via Him-8, the pairing centers of meiotic chromosomes. Many additional nesprin isoforms reside elsewhere, including the INM; e.g., human nesprins-1α and -2β in the INM bind lamins and emerin (not shown).

mediates dimerization and is also involved in binding the KASH domain; their exposed nucleoplasmic amino-terminal domain binds lamins (reviewed by Tzur et al. 2006b; Starr 2009).

KASH- (Klarsicht, ANC-1, Syne homology) domain nomenclature is confusing because these proteins were identified in diverse species before their conservation was recognized. Mammalian KASH proteins are now known as "nesprins." The KASH domain comprises a single carboxy-terminal transmembrane domain followed by a 35-residue lumenal domain. ONM-localized KASH proteins require the interaction with SUN-domain proteins for retention at the ONM. *C. elegans* encodes three known KASH-domain proteins (ANC-1, UNC-83, and ZYG-12) (Starr and Han 2002; Malone et al. 2003; McGee et al. 2006) and *D. melanogaster* encodes the two proteins Klarsicht and MSP 300 (Patterson et al. 2004; Xie and Fischer 2008). Nesprin isoform complexity is much higher in mammals, which have four known genes: *Nesprin-1 (SYNE1), nesprin-2 (SYNE2), nesprin-3, and nesprin-4*. The *Nesprin*-1 and -2 genes are alternatively transcribed and alternatively spliced to produce more than 12 protein isoforms each, from small to enormous (>1 MDa). Some isoforms lack the KASH domain and are not membrane-localized, whereas others localize at the INM or even the Golgi complex (Starr and Fischer 2005; Wilhelmsen et al.

2006). All nesprins have multiple "spectrin repeat" domains that confer an extended configuration, but can also mediate specific protein–protein interactions. For example, specific spectrin repeat domains in the small, INM-localized isoform nesprin-1α mediate direct binding to lamins, emerin, and other nesprin-1α molecules (Mislow et al. 2002a). The largest isoforms of nesprin-1 and -2 bind actin (Zhen et al. 2002; Padmakumar et al. 2004). Nesprin-3 binds plectin, a cytoskeletal protein that binds cytoplasmic intermediate filaments (Wilhelmsen et al. 2005), whereas nesprin-4 binds kinesin 1, a plus-end-directed microtubule-dependent motor, and may be involved in dislocalizing the centrosome and Golgi membranes away from the nucleus in epithelial cells (Roux et al. 2009).

LINC complexes formed by SUN- and KASH-domain proteins are known to determine the spacing between the INM and ONM (Crisp et al. 2006), position NPCs (Liu et al. 2007), and control nuclear size and NE architecture (Luke et al. 2008). Different combinations of SUN- and KASH-domain proteins mediate different functions (Fig. 3), including force-transfer across the NE, and the stiffness of the cytoskeleton (Stewart-Hutchinson et al. 2008). In *C. elegans*, the SUN protein UNC84 anchors nuclei to cytoplasmic actin filaments via the KASH-domain protein ANC-1 (Malone et al. 1999; Starr and Han 2002), mediates movement of nuclei via a different KASH partner (UNC-83) (Starr et al. 2001), and attaches centrosomes to the NE via a third KASH partner (ZYG-12) and the dynein subunit DLI-1 (Malone et al. 2003) (Fig. 3). The other *C. elegans* SUN-domain protein, matefin/SUN1, is also required to recruit the proapoptotic protein CED-4 to the NE (Tzur et al. 2006a), implying additional roles for LINC complexes in death signaling. In *Drosophila*, LINC complexes mediate centrosome attachment to the NE, and nuclear migration in developing photoreceptor cells (Patterson et al. 2004; Kracklauer et al. 2007). In mice, deletions in the nesprin-1 or nesprin-2 genes, or overexpression of the KASH-domain, which destroys endogenous LINC complexes, disrupts nuclear organization, results in failure of nuclei to cluster at neuromuscular junctions (Grady et al. 2005; Zhang et al. 2007), and can cause muscular dystrophy (Puckelwartz et al. 2009).

Amazingly, LINC complexes can also transmit mechanical force from the cytoskeleton through the NE to move chromosomes, for example during meiotic prophase, when telomeres attach to the NE and cluster to form bouquet-like structures that facilitate chromosome pairing (Chikashige et al. 2007). In a *C. elegans matefin/SUN1* mutant strain, chromosome reorganization is disrupted in early meiosis, and ZYG-12 "patches" do not form on the NE (Penkner et al. 2007). This suggests meiotic chromosome clustering and homolog recognition requires both matefin/SUN1 and ZYG-12 (a KASH-domain protein), potentially via HIM-8-mediated attachment of pairing centers to matefin/SUN1 (Penkner et al. 2007). Similarly, mammalian SUN1 and SUN2 (Ding et al. 2007; Schmitt et al. 2007) are telomere-associated between the leptotene and diplotene stages of meiosis, and SUN1-knockout mice have both impaired NE-telomere association and impaired homolog pairing (Ding et al. 2007). The meiotic functions of mammalian SUN proteins do not require A-type lamins (Schmitt et al. 2007). Potential roles for B-type lamin(s) remain to be tested in mammals, and seem likely because in *C. elegans* the nuclear migration and nuclear anchoring functions of LINC complexes require the one (B-type) lamin expressed in this organism (Lee et al. 2002). However, similar SUN- and KASH-dependent pathways exist in *S. pombe* and *S. cerevisiae*, which do not have lamins (Starr 2009).

It is unknown how the functions and interactions of SUN and KASH proteins are regulated (Starr 2009). One interesting possibility is that LINC complexes might be regulated by proteins located in the NE lumen. This possibility is suggested by Torsin A, a so-called "AAA+ ATPase" enzyme located in the NE/ER lumen that is required to localize nesprin (Nery et al. 2008).

REGULATION OF SIGNALING AND DIFFERENTIATION BY LAMIN-BINDING PROTEINS

The plasma membrane contains many structural complexes (e.g., focal adhesions and dystroglycan

complex) that can be dynamically regulated and generate signals to which cells respond in a tissue-specific manner, in many cases at the level of gene regulation. There is increasing evidence that this paradigm might also apply to lamin-associated protein complexes at the NE, and in the nucleoplasm. The concept of "lamin-linked dynamic signaling" is supported by studies on several LEM-domain proteins. For example, LAP2β, the largest INM-localized LAP2 isoform, binds lamin B specifically, and also directly interacts with transcription regulators (e.g., GCL) and epigenetic modifiers including HDAC3, and contributes to transcriptional repression (Nili et al. 2001; Somech et al. 2005). Interestingly, another INM-localized LEM protein, MAN1, directly binds and inhibits R-Smads and functions as a major regulator of BMP- and TGF-β-signaling in early vertebrate development (Osada et al. 2003; Raju et al. 2003; Lin et al. 2005; Mansharamani and Wilson 2005; Pan et al. 2005; Cohen et al. 2007). Roles for lamin-binding proteins in TGF-β-signaling are also reported in *Drosophila*: The INM-localized LEM protein Otefin binds directly to Medea (Smad-4) and they physically tether their repressed target locus, *bam* ("bag of marbles"), at the NE (Jiang et al. 2008).

The INM protein emerin also supports the paradigm of complex regulation of protein–protein interactions and signaling at the NE. Emerin directly binds more than ten known partners, suggesting a degree of biochemical complexity at the NE that rivals many cell surface structures. Among these partners are structural proteins (nesprin-1α, nesprin-2β, actin, nuclear myosin 1c, lamins, and tubulin), other INM proteins (MAN1 and LUMA), proteins involved in signaling, transcription, mRNA splicing (β-catenin, GCL, Lmo7, Btf, and YT521-B), and of course, BAF (Lee et al. 2001; Mislow et al. 2002a; Holaska et al. 2003; Haraguchi et al. 2004; Holaska et al. 2004; Mansharamani and Wilson 2005; Holaska et al. 2006; Markiewicz et al. 2006; Wheeler et al. 2007; Bengtsson and Otto 2008) (for reviews, see Bengtsson and Wilson 2004; Wagner and Krohne 2007). The biochemical purification of emerin-associated protein complexes from HeLa cell nuclei suggests emerin can form at least six distinct multiprotein complexes (Holaska and Wilson 2007). Some putative complexes included primarily architectural components (e.g., lamins, actin, nuclear myosin 1c, and nuclear αII-spectrin), whereas others included chromatin and gene regulators (e.g., histones, Lmo7, Rb, and components of the Nuclear Co-Repressor [NCoR] complex). Emerin may also be involved in sensing and responding to mechanical tension at the NE (Lammerding et al. 2005). The interaction of Lmo7 (Holaska et al. 2006) and β-catenin (Markiewicz et al. 2006) with emerin regulates their nuclear export and represses their activity. These regulatory functions may be important for muscle and adipocyte differentiation, respectively (Holaska et al. 2006; Tilgner et al. 2009). It is still unclear how emerin regulates the nuclear export of these factors. Emerin was also reported to localize in the ONM and mediate centrosome-NE attachment (Salpingidou et al. 2007).

How emerin "knows" when to assemble or disassemble particular complexes, and how its localization in the INM versus ONM is regulated, are important open questions. Growing evidence that emerin is phosphorylated suggests mechanisms by which different kinases and signaling pathways might directly control its binding to specific partners, including BAF (Hirano et al. 2005; Roberts et al. 2006; Schlosser et al. 2006; Luo et al. 2009).

REGULATION OF SIGNALING AND PROLIFERATION CONTROL BY LAMIN-BINDING PROTEINS IN THE NUCLEAR INTERIOR

The largest LAP2 isoform, LAP2α, lacks a transmembrane domain, localizes to the nuclear interior, and specifically binds A-type lamins (Dechat et al. 2000; Vlcek et al. 2002; Dechat et al. 2004). In proliferating cells, LAP2α is essential and sufficient to target and retain a subset of lamins within the nuclear interior (Naetar et al. 2007; Naetar et al. 2008). Nucleoplasmic lamins are stable, but more mobile than peripheral lamins, suggesting interior lamins assemble

differently or bind to chromatin (Moir et al. 2000b). LAP2α and lamin A also bind directly to tumor suppressor Rb (Ozaki et al. 1994; Markiewicz et al. 2002; Pekovic et al. 2007), and LAP2α is involved in Rb-mediated repression of E2F/Rb target genes (Dorner et al. 2006) and Rb-dependent proliferation control in tissue progenitor stem cells (Naetar et al. 2008). The physiological relevance of intranuclear LAP2α-lamin complexes in Rb regulation is supported by studies showing destabilization and proteolytic degradation (Johnson et al. 2004; Nitta et al. 2006; Nitta et al. 2007) and impaired phosphorylation-dependent repressor activity control (Van Berlo et al. 2005) of Rb in cells lacking A-type lamins.

"FAMILIAR" REGULATORY PROTEINS AND ENZYMES DISCOVERED TO BIND LAMINS

In addition to Rb, other known transcription factors and regulators have been discovered to bind A- and/or B-type lamins directly. This binding, whether transient or stable in vivo, suggests these proteins—and pathways they represent—either require or are influenced by lamins. These lamin-binding proteins include cyclin D3 (Mariappan et al. 2007), transcription factors cFos, Oct-1, SREBP1, MOK2, and tumor suppressor ING1 (Han et al. 2008), an enzyme named 12(S)-lipoxygenase (12[S] LOX) (Tang et al. 2000), and at least two kinases: protein kinase C α (PKCα) and JIL-1 kinase (Bao et al. 2005) (reviewed in Zastrow et al. 2004; Vlcek and Foisner 2007). Binding to lamin B1 sequesters transcription factor Oct-1 at the NE, away from promoters; in lamin B1-deficient cells, Oct-1-dependent genes that respond to oxidative stress and reactive oxygen species are misregulated (Malhas et al. 2009). Similarly, c-Fos, an early response transcription factor, is sequestered at the NE by A-type lamins (Ivorra et al. 2006) and during mitogen activated protein (MAP) kinase signaling, activated ERK1/2 interacts with lamin A and c-Fos at the NE to rapidly release c-Fos and facilitate cell proliferation (Gonzalez et al. 2008). Deregulation of this pathway in emerin and lamin A-deficient cells might up-regulate ERK-mediated signaling, a known phenotype of certain lamin- or emerin-deficient cells (Muchir et al. 2007; Muchir et al. 2009). Lamin A is also reported to affect Notch signaling, required to differentiate mesenchymal stem cells, by tethering SKIP, a coactivator of Notch-dependent target genes (Scaffidi and Misteli 2008). A better understanding of these interactions is sorely needed because it might begin to illuminate how and why nuclear architecture defects, for example in accelerated aging or other diseases linked to mutations in lamins and lamin-binding proteins, might disrupt signaling and gene regulation pathways.

The nuclear import receptor, importin α, is also a lamin-binding protein (Adam et al. 2008). Importin α inhibits lamin assembly in vitro, suggesting it prevents newly synthesized lamins from assembling in the cytoplasm; this interaction is disrupted by Ran-GTP, found at high levels only within nuclei, releasing the assembly block once lamins are in the nucleus.

PCNA, the Sliding Clamp "Ring" for DNA Replication, Binds Lamins

Lamins are also involved in DNA replication. Replication is a structural challenge, because replication complexes must traverse each huge chromosome, including regions tethered as heterochromatin to the NE. DNA replication complexes are anchored to nucleoskeletal structures (Hozak et al. 1993). During replication, the NE-anchored heterochromatin becomes disconnected, moves to replication complexes, and is then retethered at the NE (Li et al. 1998). DNA replication arrests at the elongation phase in nuclei subjected to lamina network disruption by "dominant–negative" lamin fragments (Spann et al. 1997; Moir et al. 2000a). In a breakthrough for this understudied area, PCNA (proliferating cell nuclear antigen), which forms a sliding clamp "ring" ahead of the replication fork, was found to bind lamins directly (Shumaker et al. 2008). Further study of PCNA, the first but perhaps not the only lamin-binding component of DNA replication machinery, might shed light on how and why this fundamental process came to depend on the nucleoskeleton and lamins in metazoans.

LAMIN-BINDING PROTEINS AND HUMAN DISEASE

The diversity and physiological relevance of lamin-binding proteins is reflected in the growing number of human diseases linked to genes encoding lamins or lamin-binding proteins (Broers et al. 2006; Capell and Collins 2006; Worman and Bonne 2007). These diseases are known collectively as "laminopathies" or "envelopathies." More than 12 overlapping or distinct syndromes including autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) are caused by mutations in the gene encoding A-type lamins (*LMNA*). In several cases, the same or clinically indistinguishable diseases can also be caused by mutations in one or more lamin-binding proteins. For example, EDMD is also caused by X-linked recessive loss of emerin (Bione et al. 1994), or dominant missense mutations in *SYNE1* or *SYNE2*, encoding nesprin-1 and nesprin-2, respectively (Zhang et al. 2007; Puckelwartz et al. 2009). These similar pathologies suggest the disruption of a functional complex(es) that requires products of all four genes (Gotzmann and Foisner 2006). On the other hand, mutations in emerin can also cause other syndromes including Limb-Girdle muscular dystrophy, cardiomyopathy with conduction defects, or familial atrial fibrillation (Ben Yaou et al. 2007; Ura et al. 2007; Karst et al. 2008). "Classical" EDMD is characterized by progressive muscle wasting, contractures of tendons, and cardiomyopathy with ventricular conduction system defects (Bione et al. 1994; Manilal et al. 1996). Most X-linked EDMD patients are functionally null for emerin because of instability of the mutated protein or, more rarely, failed INM retention of mutant emerin proteins. In many AD-EDMD patients with *LMNA* mutations, emerin drifts into the ER and is functionally lost from the NE (Broers et al. 2006; Worman and Bonne 2007); however, with *LMNA* mutations, one must assume many additional INM or ONM proteins similarly mislocalize, if their retention at the NE requires A-type lamins. Gene-expression profiling of muscle biopsies from EDMD patients (Bakay et al. 2006) and emerin-down-regulated mouse cells (Melcon et al. 2006) suggested shared defects in the expression of genes regulated by *Rb1* and *MyoD*, which are required for muscle stem cell regulation and muscle differentiation (Gotzmann and Foisner 2006). A mutation in LAP2α that disrupts binding to lamin A is known to cause dilated cardiomyopathy (Taylor et al. 2005). Whether this mutation might also impair Rb activity, or reflect a novel role of LAP2α, is unknown. Additional disease mechanisms are suggested by the impaired organization and function of the neuromuscular junction in lamin-null mice and AD-EDMD patients (Mejat et al. 2009), and evidence that emerin is regulated by Her2 signaling (Tifft et al. 2009).

"Signaling" Laminopathies Linked to MAN1 and LBR

Heterozygous loss-of-function mutations in MAN1 (*LEMD3)* cause osteopoikilosis, Buschke-Ollendorff syndrome, and melorheostosis, characterized by increased bone density (Hellemans et al. 2004). This pathology may result from impaired MAN1 regulation of TGF-β (Smad) signaling (discussed above), which is important for bone development.

LBR, the INM-localized sterol reductase that also binds lamin B, is required for nuclei to change shape and reorganize chromatin in differentiating neutrophils (Hoffmann et al. 2002). LBR is proposed to associate with heterochromatic under-acetylated chromatin (Polioudaki et al. 2001; Makatsori et al. 2004) through binding to heterochromatin protein 1 (HP1) (Ye and Worman 1996). Heterozygous LBR mutations cause Pelger-Huet anomaly, a benign autosomal dominant syndrome characterized by abnormal nuclear shape and chromatin organization in blood granulocytes (Hoffmann et al. 2002). Greater loss of LBR protein correlates with more severe phenotypes, including developmental delay, epilepsy, and skeletal abnormalities (Hoffmann et al. 2007). Mutations that significantly reduce the sterol reductase activity of LBR are linked to autosomal recessive Greenberg's skeletal dysplasia, characterized by lethal skeletal and visceral anomalies (Waterham et al. 2003).

Central Nervous System (CNS) Laminopathies

Brain pathologies with genetic links to lamins or lamin-binding proteins were noticeably missing, until recently. Surprisingly, the duplication of *LMNB1*, encoding lamin B1, causes autosomal dominant leukodystrophy, a slowly progressive disorder characterized by widespread demyelination of the CNS (Padiath et al. 2006; Brussino et al. 2009). Proper regulation of lamin B1 expression is crucial for oligodendrocyte development and myelination (Lin and Fu 2009). The lamin B1-binding proteins and pathways that underlie these functions in the brain are open questions.

Primary dystonia is a CNS-based autosomal-dominant movement disorder caused by mutations in the AAA+ATPase torsin A. This brain pathology was traced to the aberrantly tight binding of the mutated torsin A protein to the lumenal domain of LAP1 (Naismith et al. 2004; Goodchild and Dauer 2005), an INM protein that binds A- and B-type lamins. Wild-type torsin A is recruited to the NE by LAP1 when ATP is bound, whereas torsin A distributes throughout the ER lumen in the absence of ATP; the immobilization of mutant torsin A in the NE lumen correlates with cytoskeletal protein accumulation near the NE and disrupted cytoskeletal dynamics, neurite extension, and cell adhesion (Hewett et al. 2006).

In addition to causing EDMD, other mutations in nesprin-1 (*SYNE1*) can cause autosomal-recessive cerebellar ataxia (Gros-Louis et al. 2007), characterized by impaired walking. Although this pathology might reflect impaired function of a brain-specific postsynaptic nesprin-1 isoform, parallel disruption of nuclear isoforms cannot be ruled out.

CONCLUDING REMARKS

Lamin-binding proteins are an emerging class of proteins that may explain how chromosomes are organized, how nuclei are assembled after mitosis or moved to new positions in the cell, and how transcription, replication, signaling, and many other activities are supported by lamin filaments and the nucleoskeleton. Further exploration of this understudied area of cell biology may lead to improved and potentially therapeutic understanding of many human diseases.

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