THE NUCLEAR LAMINA COMES OF AGE

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Abstract | Many nuclear proteins form lamin-dependent complexes, including LEM-domain proteins, nesprins and SUN-domain proteins. These complexes have roles in chromatin organization, gene regulation and signal transduction. Some link the nucleoskeleton to cytoskeletal structures, ensuring that the nucleus and centrosome assume appropriate intracellular positions. These complexes provide new insights into cell architecture, as well as a foundation for the understanding of the molecular mechanisms that underlie the human laminopathies — clinical disorders that range from Emery–Dreifuss muscular dystrophy to the accelerated ageing seen in Hutchinson–Gilford progeria syndrome.

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The nuclear and cytoplasmic compartments of eukaryotic cells are separated by the nuclear envelope (NE). The NE consists of two concentric membranes — the outer (ONM) and inner (INM) nuclear membranes — nuclear pore complexes (NPCs) and an underlying nuclear lamina network (FIG. 1). The ONM is continuous with the endoplasmic reticulum (ER) and is covered with ribosomes. The INM and ONM are separated by a lumenal space, but join at sites that are occupied by NPCs, which mediate bidirectional transport of macromolecules between the cytoplasm and the nucleus. The nuclear lamina is a network of lamin polymers and lamin-binding proteins that are embedded in the INM. In the nuclear interior, lamins also form stable complexes (internal lamina), the structure of which is unknown.

Lamin proteins are the main components of the lamina network and of nuclear architecture. Lamins are type-V INTERMEDIATE-FILAMENT PROTEINS, which have a short N-terminal 'head' domain, a long α-helical coiled-coil 'rod' domain, and a globular 'tail' domain. The rod domain mediates lamin dimerization, whereas the head and tail domains mediate head-to-tail polymer assembly and higher-order assembly[1].

It is increasingly clear that lamins support a broad range of functions through interactions with proteins that function in many cellular pathways. Also, the number of INM proteins that have been identified in mammalian cells is growing rapidly[2], and many of these proteins are also likely to bind lamins. The identification and analysis of lamin-binding proteins is essential to understand the diverse cellular roles that are attributed to the nuclear lamina. Mutations in lamins and lamin-binding proteins cause a wide range of heritable or sporadic human diseases, which are collectively known as the laminopathies (BOX 1). So far, most laminopathies are linked to mutations in A-type lamins. However, two integral membrane proteins are also disease-linked: emerin — which binds both A- and B-type lamins and lamin-B receptor (LBR) — which binds B-type lamins. In this review, we summarize the evidence for lamin-dependent protein complexes with proposed roles in chromatin organization, gene expression, nuclear architecture and signalling through transforming growth factor β (TGFβ). We also discuss complexes that traverse the nuclear envelope, which have roles in nuclear positioning and mechanical anchoring to the cytoskeleton.

Lamins

Lamins are grouped as A- and B-types on the basis of their biochemical properties and behaviour during mitosis[1]. B-type lamins are essential for cell viability, are expressed in all cells during development, have acidic

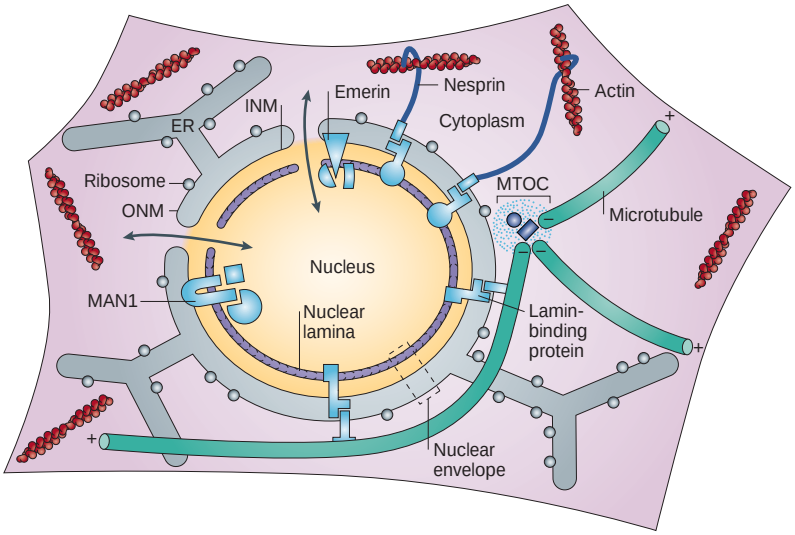

Figure 1 | **Schematic diagram of a human cell showing the nucleus and other selected structures (not to scale).** The nuclear envelope (NE) has two membranes (inner and outer; INM and ONM, respectively), which join to form 'pores' that are occupied by nuclear pore complexes (NPCs; not depicted). For clarity, only two nuclear pores are depicted. NPCs mediate traffic in and out of the nucleus, as indicated by the double-headed arrows. The NE is continuous with the endoplasmic reticulum (ER) network. Microtubules, which originate at the centrosome (or microtubule organizing center; MTOC), and microtubule-dependent motors (not shown) regulate the position of the nucleus by attaching to lamin-dependent protein complexes (shown as blue interlocking shapes) at the NE. Certain ONM-localized members of the nesprin protein family attach to actin filaments (red). The proposed nuclear actin network (to which emerin and A-type lamins bind) is depicted in FIG. 5. The lamin-filament network near the INM is shown in purple; internal lamins are not shown. Lamin-dependent complexes that are formed by integral INM proteins, such as emerin (blue triangle) and MAN1 (blue U-shape) are shown in FIGS 5,6, respectively. In normal cells, proteins that localize specifically to the INM (or ONM) give bright fluorescent signals at the NE when they are stained by indirect immunofluorescence (not depicted). In cells that lack A-type lamins (not depicted), many of these proteins are not retained at the NE but instead drift throughout the NE/ER network[12,13,21,36,79].

isoelectric points when separated on the basis of their electric charge, and are post-translationally modified by ISOPRENYLATION. This modification helps B-type lamins attach to the INM (and to INM proteins) during interphase, and to remain attached to membranes (specifically, ER membranes) when the NE disassembles during mitosis. A-type lamins (A, C, AΔ10 and C2) arise from a single gene (*LMNA*) by alternative mRNA splicing; they are distinguished from B-type lamins, both biochemically (A-type lamins have neutral isoelectric points) and functionally. A-type lamins are expressed in a tissue-specific manner, disperse as soluble proteins during mitosis, and are probably incorporated into the nuclear lamina later than B-type lamins during post-mitotic nuclear assembly. Some A-type lamins, including A and AΔ10, are initially isoprenylated, but the modified C-terminus is subsequently cleaved by a specific metalloproteinase[3,4] to form the mature protein. Lamins C and C2 are not isoprenylated or cleaved.

More than 25 years have passed since lamins were discovered, and it has been 20 years since lamins were first recognized as the most ancient intermediate-filament proteins[1], yet little is known about how lamins assemble in the nucleus of somatic cells[5]. It is unclear whether A- and B-type lamins co-polymerize *in vivo*, or how lamins are organized in the nuclear interior, although both A- and B-type lamins are stable components of the nucleus. During mitosis, lamins first depolymerize and subsequently reassemble. During telophase and early G1, when daughter nuclei reassemble their lamina infrastructure, lamins are relatively mobile, with FLUORESCENCE RECOVERY AFTER PHOTOBLEACHING (FRAP) halftimes of about 30 minutes, whereas, later in interphase, lamin polymers are nearly immobile, with FRAP halftimes of about 3 hours[6]. Several studies indicate that these dynamic properties are regulated by post-translational modifications (for example, phosphorylation and dephosphorylation) and by lamin-binding partners. Purified lamins have been notoriously difficult to assemble into the expected 10-nm-diameter filaments *in vitro*. For example, purified vertebrate and *Drosophila melanogaster* lamins form stable paracrystalline arrays that are not physiologically relevant, as they do not exist *in vivo*[1]. In an important recent breakthrough, conditions were found in which the only lamin of *Caenorhabditis elegans*, Ce-lamin (a B-type lamin), forms stable 10-nm intermediate filaments *in vitro*[7]. Natural (endogenous) 10-nm filaments have so far only been directly visualized in the *Xenopus laevis* oocyte NE[8].

Lamin-binding proteins

Lamins bind *in vitro* to many known INM proteins, including emerin, MAN1, LBR, lamina-associated polypeptides-1 and -2β (LAP1, LAP2β) and nesprin-1α. Lamins can also bind chromatin proteins (histone H2A or H2B dimers), as well as ostensibly soluble proteins including lamina-associated polypeptide-2α (LAP2α), Kruppel-like protein (MOK2), actin, retinoblastoma protein (RB), barrier-to-autointegration factor (BAF), sterol-response-element-binding protein (SREBP) and one or more components of RNA-polymerase-II-dependent transcription complexes and DNA-replication complexes[9,10]. Lamins and their associated proteins are proposed to have roles in large-scale chromatin organization[11–14], the spacing of NPCs[11,15], the positioning of the nucleus in cells[16,17] and the reassembly of the nucleus after mitosis[18]. Furthermore, essential nuclear functions depend on lamins, notably DNA replication[19] and RNA-polymerase-II-dependent gene expression[20]. Lamins are further proposed to anchor multiprotein complexes in which integral proteins of the ONM and INM 'hold hands' across the NE lumen, thereby 'bridging' the NE and mechanically coupling the nucleoskeleton and cytoskeleton. At present, proteins that are proposed to participate in NE 'bridging' include UNC-84 and UNC-83 (REFS 16,21), ZYG-12 (REF. 22) and nesprins[23].

Chromatin silencing and LBR

In most cells, a large proportion of transcriptionally silent HETEROCHROMATIN localizes near the nuclear periphery[24]. Lamins seem to be important for the attachment of chromatin to the NE, as heterochromatin is lost from the nuclear periphery in fibroblasts and myocytes from *LMNA*-knockout mice, and in fibroblasts from patients with Hutchinson–Gilford

INTERMEDIATE-FILAMENT PROTEINS
A large family of proteins with a central coiled-coil 'rod' domain that polymerize into stable ~10-nm-diameter filaments in cells. These filaments are thicker than actin ('thin') filaments but thinner than microtubules, hence 'intermediate'. Lamins (type-V intermediate-filament proteins) are found only in the nucleus.

ISOPRENYLATION
Enzyme-mediated post-translational covalent attachment of a hydrophobic isoprenyl moiety to proteins.

Box 1 | The laminopathies

Mutations in A-type lamins or lamin-binding proteins cause various diseases ('laminopathies'). Mutations in emerin, an X-linked gene, cause Emery–Dreifuss muscular dystrophy (EDMD), which is characterized by early contractures of major tendons, muscle wasting in the upper and lower limbs, CARDIOMYOPATHY and cardiac conduction defects[94]. Heterozygous mutations in lamin-B receptor (LBR) cause the Pelger–Huet anomaly (PHA) in blood granulocytes[29]. PHA nuclei have fewer lobules, indicating the incomplete differentiation of neutrophils. Homozygous mutations in LBR cause Greenberg skeletal dysplasia[27], an embryonic lethal CHONDRODYSTROPHY.

Over 180 disease-causing mutations have been mapped throughout *LMNA* (see the Leiden Muscular Dystrophy pages in the online links box) including both autosomal-dominant and -recessive forms of EDMD. Some dominant mutations cause limb-girdle muscular dystrophy or dilated cardiomyopathy, both of which include cardiac conduction defects. The only disease for which mutations seem to cluster (in the tail domain of A-type lamins) is the autosomal dominant Dunnigan-type familial partial lipodystrophy, which is characterized by loss of adipose tissue from the extremities, excess adipose tissue in the face and neck, insulin resistance and usually diabetes mellitus that begins at puberty or later in life. Recessive laminopathies that are caused by mutations in the tail domain of A-type lamins include axonal neuropathy (Charcot–Marie–Tooth disorder type-2) or skeletal malformations associated with postnatal growth retardation, mottled cutaneous pigmentation and partial lipodystrophy (mandibuloacral dysplasia).

Accelerated ageing (Hutchison–Gilford progeria syndrome; HGPS) is caused by the C_{1824}→T mutation (G608G), which creates an ectopic mRNA-splicing site that deletes 50 residues from the tail domain of A-type lamins. HGPS is characterized by growth retardation, loss of subcutaneous fat, atherosclerosis, bone deformations, delayed dentition, hair loss, sclerodermatous skin and cardiovascular disease. Atypical HGPS is caused by dominant mutations in the rod domain. Other dominant mutations in the rod domain can cause another form of progeria (atypical Werner syndrome)[95]. The phenotype of any given *LMNA* mutation can vary between individuals and between siblings[96]. Some patients with a single mutation suffer from several laminopathies[97]. A neonatally lethal syndrome, restrictive dermopathy, is caused by tail deletions in A-type lamins or mutations in the gene that encodes the lamin-A-processing metalloproteinase ZMPSTE24 (REF. 86).

progeria syndrome (HGPS)[13,25,26] — a clinical disorder that is caused by mutations in the *LMNA* gene (BOX 1). At the molecular level, this attachment is probably multipronged, mediated directly by chromatin binding to lamins, and mediated indirectly by chromatin binding to membrane proteins, which, in turn, bind lamins. The most well-characterized example of a chromatin-and lamin-binding membrane protein is LBR (FIG. 2).

LBR, an integral membrane protein, is essential during human development, as homozygous mutations that disrupt its enzyme activity are lethal[27]. As its name suggests, LBR binds B-type lamins, but, *in vitro*, it also binds directly to double stranded (ds)DNA, histone H3–H4 tetramers, chromatin-associated protein HA95 and HETEROCHROMATIN PROTEIN-1 (HP1)[28], which contains both a chromodomain and a chromo-shadow domain and which mediates gene silencing. Further support for LBR involvement in chromatin organization comes from mutations in LBR that cause the Pelger–Huet anomaly (PHA)[29], an autosomal dominant (but clinically silent) phenotype in which white-blood-cell nuclei have abnormal chromatin organization and decreased lobulation. The membrane-embedded domain of LBR has sterol-reductase activity (FIG. 2), but how this enzyme activity might relate to LBR regulation of chromatin structure and nuclear architecture is unknown. These findings collectively implicate lamin-dependent LBR complexes in both chromatin structure and sterol-dependent signalling in the nucleus.

FLUORESCENCE RECOVERY AFTER PHOTOBLEACHING (FRAP). A microscope technique used to measure the movement (for example, diffusion rates) of fluorescently tagged molecules over time *in vivo*. Specific regions in a cell are irreversibly photobleached using a laser; fluorescence is restored by diffusion of fluorescently tagged unbleached molecules into the bleached area.

HETEROCHROMATIN
Highly compacted chromatin that is transcriptionally inactive. Includes structural regions of the chromosome that lack genes (for example, centromeres; 'constitutive' heterochromatin) as well as genes that are silenced in a given cell type ('facultative' heterochromatin).

Lamins, LEM-domain proteins and BAF complexes

The LEM domain is a ~40 residue motif that is found in several INM and nucleoplasmic proteins[30,31]. All LEM-domain proteins that have been tested so far bind directly to A- or B-type lamins (or both) *in vitro*, as shown for emerin, LAP2α and LAP2β in vertebrates[32,33,34], Ce-emerin and Ce-MAN1 in *C. elegans*[12] and Otefin and Bocksbeutel in *D. melanogaster*[35,36]. All LEM-domain proteins that have been tested also bind BAF[37,38], an essential, small, dimeric protein that binds dsDNA nonspecifically *in vitro*[39] and that represses the transcriptional activator cone-rod homeobox protein (CRX) *in vivo*[40].

In the interphase nucleus, the LEM-domain proteins and BAF form an inter-dependent network that is based on the integrity of lamin filaments. In lamin-depleted cells, emerin, Ce-MAN1, and Bocksbeutel are not retained at the NE and instead mislocalize to ER membranes[12,13,36]. Furthermore, Ce-BAF enrichment near the nuclear periphery in *C. elegans* embryos requires the membrane-bound LEM-domain proteins Ce-MAN1 and Ce-emerin[12]. Therefore, lamin mutations that result in mislocalized lamin-binding proteins can secondarily mislocalize other proteins, which amplifies the biological effects of these mutations. BAF, lamins and certain LEM-domain proteins (notably LAP2α) are also present in the nuclear interior, where they support cell-cycle regulation[41,42,43], replication and transcription (discussed below), presumably also by functioning as a scaffold for multiprotein complexes. Therefore, mutations that severely disrupt lamina organization could have significant effects on cell function during interphase.

When lamin expression is downregulated in *C. elegans* embryos, interphase nuclei have abnormally condensed chromatin, and mitotic cells have gross defects in chromosome segregation including anaphase chromosome 'bridges' that lead to ANEUPLOIDY[11]. Similar phenotypes are observed in *C. elegans* when both Ce-emerin and Ce-MAN1 are downregulated, or when Ce-BAF is downregulated[12,39]. Therefore, interactions between lamins, LEM-domain proteins and Ce-BAF are proposed to influence chromatin organization during both interphase and mitosis. Ce-BAF does not localize at the nuclear periphery after mitosis in cells that are downregulated for either Ce-lamin, or both Ce-MAN1 plus Ce-emerin[12]. At first glance, these findings in *C. elegans* indicate that lamin filaments are the 'bedrock' for LEM-domain proteins, which in turn recruit BAF. However, in mammalian cells, a dominant-negative BAF mutant was found to disrupt post-mitotic nuclear assembly of emerin, LAP2β and A-type lamins, but not B-type lamins, which illustrates the mutual inter-dependence of this triad of proteins during nuclear assembly[44]. LEM-domain proteins and BAF might be important to

CARDIOMYOPATHY
Weakening of the heart muscle that results in a decreased cardiac pumping force.

CHONDRODYSTROPHY
Inherited skeletal disorders in which cartilage is prematurely or inappropriately converted to bone. Non-lethal forms can cause dwarfism.

HETEROCHROMATIN PROTEIN-1 (HP1). Originally identified in *D. melanogaster*, HP1 is a protein that silences chromatin by binding histone H3 when the H3 tail is methylated at amino-acid residue Lys9 (Me-H3K9).

ANEUPLOIDY
Having an abnormal number of chromosomes (too many or too few).

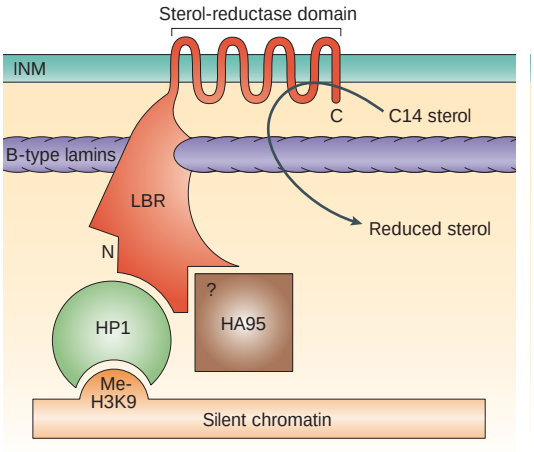

Figure 2 | **The lamin-B receptor is a membrane-embedded enzyme with an exposed domain that binds B-type lamins and other partners.** The exposed N-terminal domain (N) of the lamin-B receptor (LBR) binds several partners, including B-type lamins and heterochromatin protein HP1 (shown), as well as DNA and histones H3/H4 (not shown). HP1 binds 'silenced' forms of histone H3 that are methylated at Lys9 (Me-K9H3). Chromatin protein HA95 co-immunoprecipitates with LBR but might bind LBR indirectly. The eight transmembrane spans of LBR have sterol-reductase activity that is essential for human development. Because LBR is anchored through B-type lamins and chromatin, its enzyme activity is restricted to the inner nuclear membrane (INM) and presumably has nuclear functions. It is unknown whether the enzyme activity and chromatin-binding functions of LBR are related. C, C terminus.

assemble lamin filaments and therefore rebuild the nuclear lamina after mitosis, although these same proteins later depend on lamins for their own localization during interphase. Co-dependent roles in nuclear structure and function might make it difficult to dissect the mechanisms of laminopathy disease.

Lamins, LEM-domain proteins and gene regulation

Lamins are required to support RNA-polymerase-II-dependent gene expression *in vivo*[20]. There are now several examples of transcription factors, including RB, that bind lamins or lamin-associated proteins[45]. RB regulates entry into S-phase and terminal differentiation. Tethering to A-type lamins is required for RB stability, as RB is rapidly degraded by proteosomes in *Lmna*-null mouse cells[43]. The interactions between transcriptional regulators and LEM-domain proteins (such as LAP2β and emerin) that are discussed below, provide mechanistic insight into other roles for lamin-dependent complexes in gene regulation.

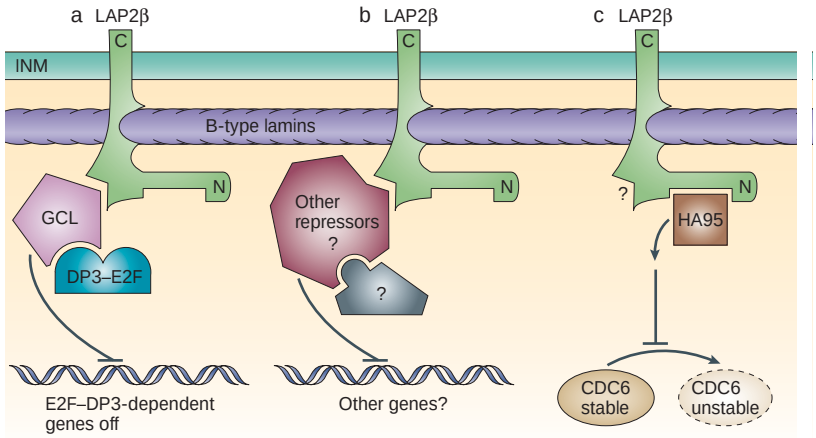

Figure 3 | **LAP2β mediates gene silencing and indirectly stabilizes pre-replication complexes. a** | Lamina-associated polypeptide (LAP)2β has many partners at the inner nuclear membrane (INM), including B-type lamins and germ cell-less (GCL), which binds the DP3 subunit of the E2F–DP3 transcription factor. When co-overexpressed, LAP2β and GCL synergistically repress an E2F–DP3-dependent reporter gene *in vivo*[46]. Other LAP2β partners that are not depicted include DNA and barrier-to-autointegration factor (BAF)[32,38]. **b** | In cells that overexpress LAP2β, but not GCL, the overexpressed LAP2β still represses the E2F–DP3-dependent reporter gene *in vivo*[46]. We therefore speculate that LAP2β can recruit other endogenous regulators ('other repressors') and their associated genes. **c** | Chromatin protein HA95 binds two regions in LAP2β. One region (shown) overlaps the LEM domain and is implicated in stabilizing cell-division-cycle protein-6 (CDC6), a key component of the pre-replication complex[49]. This 'replication-relevant' HA95-binding site is present in all LAP2 isoforms including LAP2α, an abundant protein that binds lamin A and retinoblastoma protein (RB) in the nuclear interior[105]. The second HA95-binding region (not shown) overlaps with the lamin-binding region in LAP2β, but HA95 does not seem to compete with B-type lamins. This second region in LAP2β is relevant for nuclear assembly, but not for DNA replication[49]. C, C terminus; N, N terminus.

LAP2β mediates gene repression. LAP2β binds B-type lamins and a ubiquitous transcriptional regulator that is known as germ cell-less (GCL). GCL localizes preferentially near the INM of the NE[46,47]. GCL binds and inhibits the DP3 subunit of the heterodimeric transcriptional activator E2F–DP3 (REFS 46,48). In transfection studies with an E2F–DP3-dependent reporter gene, cells that overexpressed both LAP2β and GCL repressed the reporter as effectively as RB, which is an alternative transcriptional regulator (FIG. 3a). Furthermore, overexpression of LAP2β alone was sufficient to repress the E2F–DP3-dependent reporter gene, which provided the first evidence for gene regulation by a LEM-domain protein[46] and indicated that LAP2β might similarly recruit other (endogenous) repressors (FIG. 3b). Interestingly, LAP2β also contributes to the initiation of DNA replication. HA95, which can also bind LBR (FIG. 2), interacts with LAP2β, and this complex somehow stabilizes cell-division-cycle protein-6 (CDC6), an important component of pre-replication complexes[49] (FIG. 3c).

Emerin binds GCL and other gene regulators. Emerin is another LEM-domain protein that overlaps functionally with LAP2β, as it also binds directly to lamins and GCL. Emerin is expressed in nearly all tissues, but its loss causes the X-linked recessive form of Emery–Dreifuss muscular dystrophy (EDMD), which affects only a subset of tissues (BOX 1). Emerin co-immunoprecipitates with GCL from HeLa cells and forms a stable trimeric complex with GCL and lamin A *in vitro*[50] (FIG. 4a). Interestingly, GCL is displaced by BAF *in vitro* (FIG. 4c), possibly due to partially overlapping binding sites on emerin[50,51]. The mutually exclusive binding of GCL and BAF to emerin indicates that emerin can form at least two

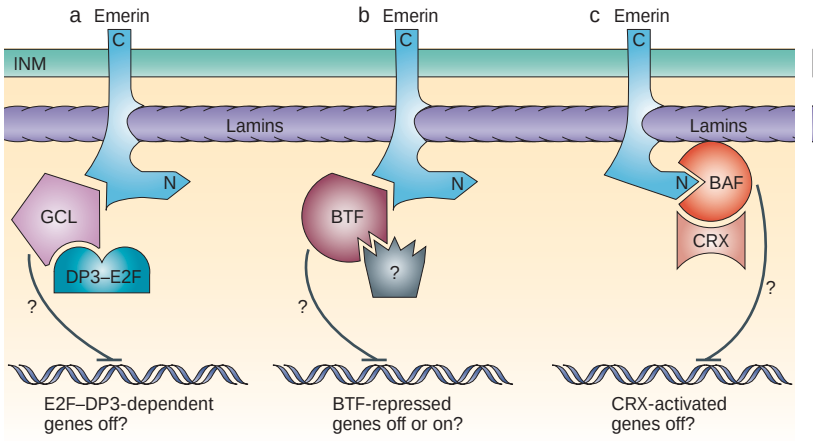

Figure 4 | **Emerin binds many transcriptional regulators *in vitro*; models for *in vivo* function.** Emerin binds A- and B-type lamins *in vitro*, as well as at least four gene regulators, including germ cell-less (GCL), BCL2-associated transcription factor (BTF) and barrier-to-autointegration factor (BAF). For simplicity, the regulator-binding region in emerin, to which all regulators (except BAF) bind, is depicted as a single site, although it involves residues on both sides of the lamin-binding site, and partially overlaps the BAF-binding region[50,52]. Two regulators are shown: GCL (**a**), which binds the DP3 subunit of E2F–DP3 heterodimers and represses E2F–DP3-dependent gene expression, and BTF (**b**), a cell-death-promoting transcription repressor, the DNA-specific partner of which, is unknown. Emerin-null cells have gene-expression defects that are rescued by exogenous emerin[106]. However the molecular roles of emerin in gene expression are untested, so the models shown in parts **a** and **b** are speculative. BAF binds directly to both lamin A and emerin *in vitro* (**c**), and blocks GCL binding to emerin[50]. BAF binds directly to dsDNA (not shown) and to the homeodomain transcription activator cone-rod homeobox protein (CRX), and represses CRX-dependent genes *in vivo*[40]. Part **c** speculatively suggests that BAF represses CRX when bound to emerin or other LEM-domain proteins. However, BAF is highly mobile in living cells[107], so other models are plausible. C, C terminus; INM, inner nuclear membrane; N, N terminus.

distinct lamin-anchored complexes. The GCL-binding region in emerin is recognized by at least three other gene regulators, including a death-promoting repressor that is known as BCL2-associated transcription factor (BTF; FIG. 4b)[52]. These data implicate emerin–lamin complexes in transcriptional regulation, but it is not yet known how emerin behaves *in vivo*.

Emerin binds and stabilizes actin filaments

Surprisingly, emerin, an integral INM protein of the NE, also binds actin. Actin is an abundant protein in muscle cells, where it is required for muscle contraction. Actin is also one of the main components of the cytoskeleton in all cell types and is required for cell division, motility, mechanical resilience and cell integrity. Notably, actin is also present in the nucleus[53]. Nuclear actin is involved in many activities including chromatin remodelling, the formation of heterogeneous nuclear RNA particles, stress responses, nuclear export and transcription[53]. For example, a nuclear-specific isoform of myosin I, an actin-dependent motor, interacts with the RNA-polymerase-II complex and is implicated in transcription activity[54]. Which, if any, of these roles might involve polymeric actin (F-actin) is not known. Indeed, understanding the nature and variety of actin polymers in the nucleus is a significant challenge in cell biology[53,55]. Nuclear actin is not recognized by most actin antibodies or by phalloidin, a compound that binds cytoplasmic F-actin. Nonetheless, there are at least two monoclonal antibodies that recognize nuclear-specific conformations of polymeric actin[55].

Both lamin A and emerin bind monomeric globular (G)-actin *in vitro*[51,56,57]. Nuclear emerin from mature muscle and differentiating myotube cells co-immunoprecipitates with lamins, α-ACTIN, β-ACTIN and protein kinase A (PKA)[58,59], which indicates that the composition or function of nuclear emerin–lamin–actin complexes might be regulated by phosphorylation by PKA. Recent work indicates that emerin has a special role with respect to nuclear actin. In biochemical studies, emerin binds and caps the pointed end of polymeric, filamentous (F)-actin with an affinity of 300–500 nM (REF. 60), and thereby stabilizes F-actin *in vitro*. Emerin also co-purifies with nuclear-specific isoforms of αII-SPECTRIN[60], a filamentous protein that binds F-actin. Other nuclear parallels to the cytoskeleton are emerging. For example, a protein that is known as protein 4.1 links spectrin to F-actin in the cytoplasm, and stabilizes the actin cortical network. Cells also express nuclear isoforms of protein 4.1 (REFS 61,62), which might carry out similar functions in the nucleus. The actin-binding region of nuclear protein 4.1 is essential for nuclear assembly in *X. laevis* egg extracts[63], which indicates that both actin and protein 4.1 have structural roles during nuclear assembly. Interestingly, loss of A-type lamins causes both mechanical weakness and defects in mechanical-stress-dependent gene expression *in vivo*[64]. In mechanical studies of the *X. laevis* oocyte NE, the lamina behaves like a reinforced network of stiff rods, which resist compression forces while maintaining their ability to expand elastically (leading the lamina to be described as functioning like a molecular shock absorber)[65]. It will be interesting to know if interactions between lamins and F-actin contribute to these mechanical properties of the lamina. LAP2β, a LEM-domain protein that is closely related to emerin, was 20-fold less active than emerin in actin-polymerization assays[60], which indicates that emerin might have unique roles that involve actin. Therefore, as well as possible roles in gene regulation, lamin-bound emerin is proposed to anchor an actin- and spectrin-containing structural network at the INM[60] (FIG. 5). As mechanical weakness contributes to the pathology that is found in at least some laminopathy-affected tissues, an important question for the future is which other INM and soluble proteins influence actin dynamics in the nucleus. If emerin is an important element of the proposed nuclear actin cortical network, its mislocalization in *Lmna*-null cells might disrupt the mechanical integrity of the nucleus.

MAN1 and signal transduction

Vertebrates express MAN1, a LEM-domain protein that crosses the INM twice[30]. The C-terminal domain of MAN1 binds directly to receptor-regulated SMAD (R-SMAD) proteins[66], which mediate signalling downstream of bone morphogenetic proteins (BMPs)

α-ACTIN, β-ACTIN AND γ-ACTIN
In higher eukaryotes there are three actin isoforms; α-actin is specific to muscle cells, whereas β-actin and γ-actin are present in all cells.

SPECTRIN
A family of tetrameric, actin-binding proteins. The functional molecule consists of two α/β heterodimers.

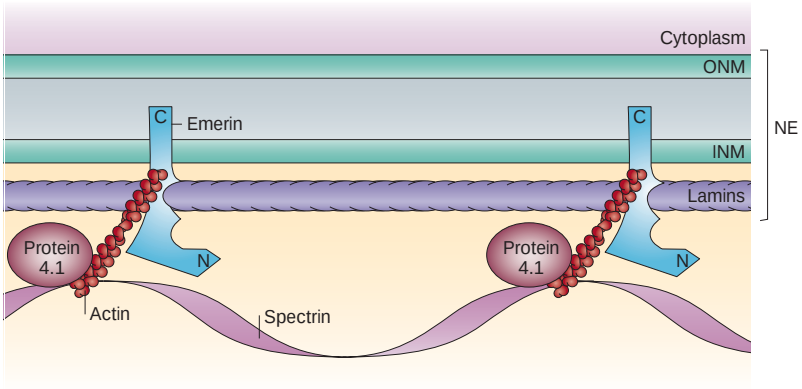

Figure 5 | **Proposed emerin-anchored actin cortical network at the nuclear envelope.** Emerin binds and caps the pointed end of F-actin *in vitro*, and affinity-purifies several actin-binding proteins including a nuclear-enriched isoform of spectrin, which is a filamentous actin-binding protein[60]. In the cytoplasm, protein 4.1 reinforces the cortical actin network at the cell membrane by linking spectrin to short actin filaments. A similar 'cortical' network is proposed to exist at the inner nuclear membrane (INM), and to mechanically reinforce the lamina network[60]. The actin-binding domain of nuclear-specific isoforms of protein 4.1 is essential to reconstruct nuclei after mitosis[63]. This indicates further roles for nuclear actin filaments, protein 4.1 and possibly spectrin during nuclear assembly (not shown). C, C terminus; N, N terminus; NE, nuclear envelope; ONM, outer nuclear membrane.

and other members of the TGFβ superfamily[67]. *X. laevis* Man1 inhibits signalling downstream of Bmp4, through direct binding to a subset of R-Smads (1, 5 or 8) and thereby blocks VENTRALIZATION during embryogenesis[67] (FIG. 6). Activated (phosphorylated) R-Smads normally multimerize with a 'co-Smad' (for example, Smad4), accumulate in the nucleus, bind specific transcription factors and regulate many genes, which include those encoding transcription factors such as *X. laevis* Vent1, Vent2 and Msx1 (REF. 68) (FIG. 6). Msx1 is potentially relevant to EDMD and other laminopathies because it represses muscle differentiation[69]. Smad signalling can be blocked in several ways. Upstream, Bmp4 itself is antagonized by factors that are secreted by the SPEMANN ORGANIZER, which block universal ventralization and allow neuroectoderm and dorsal mesoderm to develop[70]. However, once Bmp4 binds the cell surface, further signalling can be regulated by inhibitory Smads, which function at several levels and shuttle in and out of the nucleus[67]. In *X. laevis* embryos that have been injected with the C-terminal domain of Man1, cells fail to acquire a ventral fate[66], which indicates that activated Smads can be inhibited by binding to Man1 at the nuclear envelope. In support of this model, human MAN1 binds a different subset of R-SMADs (SMAD2 and 3), and inhibits signalling downstream of TGFβ *in vivo* (H. Worman, personal communication). It will be interesting to watch the MAN1 story unfold, since MAN1 is the first lamin-dependent INM protein with a direct role in signal transduction. SMAD-mediated signalling pathways have key roles in tissue differentiation and tissue homeostasis[67]. We therefore speculate that MAN1, as a SMAD-binding protein, has the potential to regulate vertebrate tissues at many levels.

VENTRALIZATION
Loss of dorsal-axis specification during early development, which produces embryos with ventral-only fates.

SPEMANN ORGANIZER
Specialized tissue at the dorsal lip of the blastopore in amphibian embryos, which directs formation of the embryonic body axis.

P CELLS
Ventral cord blast cells in *C. elegans*.

SYNCYTIAL HYPODERMAL CELLS
Many of the hypodermal cells that establish the basic body shape of *C. elegans* form multinucleate syncytia by cell fusion during development.

Lamin-dependent links to the cytoskeleton

The position of the nucleus within each cell is regulated. This positioning requires the activity of actin, microtubules and microtubule-dependent motors[16,17]. Remarkably, various studies reveal that nuclear positioning also depends on the nuclear lamina, and involves novel membrane proteins that localize uniquely to the ONM, but not to the ER.

Lamins, UNC-84, UNC-83 and nuclear positioning. Nuclear positioning has been studied extensively in *C. elegans*. Mutations in either *C. elegans* UNC-84 or UNC-83 affect the polarization of gut primordial cells and disrupt nuclear migration in P-CELL precursors, which leads to P-cell death and uncoordinated movement[71]. UNC-84, an integral protein of the NE, is also required for nuclear positioning (anchoring) in SYNCYTIAL HYPODERMAL CELLS in *C. elegans*[72]. UNC-84 and four human proteins share a C-terminal motif of ~120 residues, the SUN (Sad1/UNC-84 homology) domain[71]. The SUN domain of human SUN2 localizes to the NE lumen[73]. UNC-84 is detectable at the NE of essentially all *C. elegans* cells from the 26-cell-embryo stage onwards, although the precise membrane topology and exact location (INM versus ONM) are not known. UNC-84 colocalizes with Ce-lamin[21], and furthermore, the NE localization of UNC-84 depends on Ce-lamin. However it is not known whether UNC-84 binds Ce-lamin directly[21]. A second *C. elegans* SUN-domain protein, matefin, specifically localizes to the INM[74]. The topology of UNC-84 and its partners in the NE are important, because these proteins are proposed to mechanically link microtubule-dependent motors to the nuclear lamina, perhaps by forming protein–protein complexes that bridge the NE[16,21] (FIG. 7). Resistance to biochemical fractionation, a criterion that is often used to distinguish lamin-binding INM proteins from 'typical' ONM or ER proteins, must be interpreted cautiously because we are now aware that some ONM proteins (for example, UNC-83 and UNC-84) might resist extraction without binding directly to lamins.

UNC-84 binds directly to another integral membrane protein, UNC-83. This *in vitro* interaction requires the SUN domain of UNC-84 and possibly the membrane-anchoring Klarsicht domain of UNC-83 (REF. 16). UNC-83 localization also requires the SUN domain of UNC-84 (REF. 16), however, mutations in *unc-83* do not affect the localization of UNC-84 (REF. 21). Therefore, the NE localization of UNC-83 depends on UNC-84, which, in turn, depends on lamins. These findings are consistent with models in which UNC-83 faces the cytoplasm, but crosses the ONM and binds a domain of UNC-84 in the lumen of the NE[21] (FIG. 7, left). Alternatively, if both proteins localize to the ONM, the lumenal domain of UNC-84 might 'hold hands' with an unidentified INM protein that binds directly to lamins (not depicted in FIG. 7). Based on the phenotype of *unc-84* or *unc-83* mutants, the UNC-83–UNC-84 complex is proposed to facilitate nuclear migration and positioning by mechanically linking microtubule-dependent motors to the nuclear lamina.

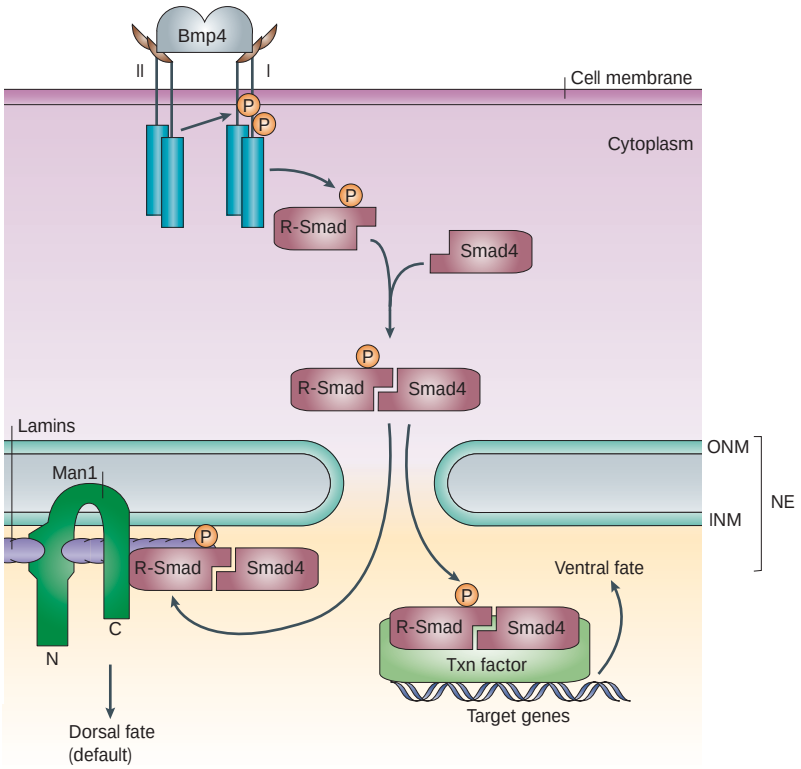

Figure 6 | **Man1 represses Smad signalling downstream of Bmp4 in *Xenopus laevis* embryos.** Bone morphogenetic protein (Bmp)4 and other members of the TGFβ superfamily are secreted proteins (dimers) that bind heterodimeric receptors. The type-II receptor ('II') phosphorylates the type-I receptor ('I'), which then phosphorylates the regulatory Smad (R-Smad)[67]. Different cell types express different R-Smads. R-Smad1, 5 and 8 mediate Bmp signals, whereas R-Smad2 and 3 mediate Tgfβ signals[67]. The phospho-R-Smad binds a co-Smad (for example, Smad4), accumulates in the nucleus, and oligomerizes with gene-specific transcription factors (Txn factors) to activate or repress various genes that collectively confer a ventral fate during development. Ventralization fails in *Xenopus laevis* embryos that express (or are injected with) the C-terminal domain of Man1 (REF. 66). This indicates that sequestration of R-Smad/co-Smad complexes by Man1 at the inner nuclear membrane (INM) inhibits signalling; by default, cells maintain a dorsal fate. The colocalization of Man1 and R-Smad at the INM that is predicted by this model remains to be tested *in vivo*. NE, nuclear envelope; ONM, outer nuclear membrane; P, phosphate.

Lamins, nesprins and nuclear 'outreach' to actin and microtubules. Nesprins, which have been identified in many laboratories and given many names (BOX 2) are also proposed to mechanically bridge the NE. In humans, nesprins are encoded by two genes: nesprin-1 and nesprin-2. Both genes give rise to a splendid array of alternatively-spliced transcripts, some of which rival titin, the largest known human transcript[75]. Many isoforms of nesprin-1 and nesprin-2 bind F-actin *in vitro* and colocalize with the actin cytoskeleton *in vivo* when visualized by indirect immunofluorescence. Many nesprin isoforms have a Klarsicht domain at their C-terminus, which anchors them to the NE, presumably at the ONM[23,76]. Other isoforms such as nesprin-1α localize inside the nucleus (see below). In *C. elegans*, ANC-1 encodes a giant (8,546-residue) nesprin protein, with typical features that include an N-terminal pair of actin-binding CALPONIN-HOMOLOGY DOMAINS followed by six 903-residue repeats and a C-terminal Klarsicht domain[77] (BOX 2). In the nucleus of muscle cells, immunolocalization studies show that the N-terminus of ANC-1 colocalizes with cytoplasmic actin, whereas the C-terminus embeds in the NE, presumably at the ONM[17]. *Anc-1* mutations do not affect the localization of UNC-84 (REF. 21) but the NE localization of ANC-1, like that of UNC-83, requires the SUN domain of UNC-84 (REF. 17) (FIG. 7, right). As both UNC-84 (a SUN-domain protein) and ANC-1 (a nesprin) are evolutionarily conserved in metazoans, complexes between SUN-domain and nesprin-family members might mechanically link the nucleoskeleton and the actin cytoskeleton (FIG. 7, right). We speculate that UNC-84 anchors ANC-1 (nesprin) and UNC-83 separately, as depicted in FIG. 7, as these partners connect to different cytoskeletal structures. Notably, ANC-1 interacts with cytoplasmic F-actin whereas UNC-83 associates with microtubules.

Purified emerin also binds nesprin-1α[78], and both emerin and nesprin-1α are displaced to the ER network in human *LMNA*-null fibroblasts[79]. This supports the lamin-dependent nature of nesprin-containing NE-bridging complexes. Bridging complexes are probably dynamic in living cells, since mammalian nuclei rotate slowly (minutes or hours) independent of the surrounding cytoplasm[80].

The nuclear lamina and centrosome position

The microtubule organizing center (or CENTROSOME) is tightly associated with the NE in metazoan cells. This positioning requires microtubules and microtubule-dependent motor components, including DYNEIN heavy, intermediate and light chains[81,82]. It is unknown if dynein and microtubules function only to initially bring centrosomes to the NE, or if they actively maintain centrosome position. In *C. elegans*, centrosome position also depends on the nuclear lamina, ONM proteins and centrosome proteins[22]. For example, ZYG-12 belongs to the Hook family of proteins, which are thought to link various organelle membranes to microtubules[83]. Endogenous ZYG-12 contains a putative transmembrane domain and localizes both to the centrosome and the NE (presumably at the ONM); its C-terminal region binds to itself and the dynein light chain. Since ZYG-12 has a dual localization (the NE and centrosomes), its self-association is proposed to link centrosomes to the ONM[22]. This proposed role is supported by the phenotype of ZYG-12-deficient embryos: centrosomes appear morphologically normal but fail to associate with the NE. These embryos have defects in chromosome segregation that lead to aneuploidy and death[22]. Whether ZYG-12 binds other NE-bridging components, or functions independently, is an intriguing question.

For its anchorage to the ONM, ZYG-12 somehow depends on a putative lamin-binding INM protein matefin/SUN-1 (REF. 22) Matefin/SUN-1 is a *C. elegans* SUN-domain-containing INM protein that has two putative transmembrane domains and that binds lamins *in vitro*[74]. Downregulating *mtf-1/sun-1* in early embryos causes centrosomes to detach from the NE, and displaces ZYG-12 from the NE, but not from the

CALPONIN-HOMOLOGY DOMAIN
A ~110-residue, actin-binding domain that is common to many actin-binding proteins, including cytoskeletal and signal-transduction proteins.

CENTROSOME
The microtubule-organizing center, an organelle that contains the centrioles and that anchors the 'minus' ends of microtubules.

DYNEIN
A microtubule-dependent motor protein that is powered by ATP hydrolysis.

Box 2 | Nesprins

The proteins that are encoded by the nesprin-1 and nesprin-2 genes are among the largest in the cell. The human nesprin-1 locus at chromosome position 6q25 has 147 exons that encode up to 8,797 residues[75,98]. The nesprin-2 locus (14q23) has 115 exons that encode 6,884 residues[75]. There are many splicing isoforms for both nesprin-1 and nesprin-2, which have acquired many names including cpg-2 (REF. 99), syne-1 and syne-2 (REF. 100), myne-1 and myne-2 (REF. 101), enaptin[76], ANC-1 (REF. 17), MSP-300 (REF. 102) and NUANCE[23]. A relatively small isoform, nesprin-1α, localizes at the nuclear inner membrane and binds both lamin A and emerin[78,101]. The longest isoforms contain an actin-binding domain at their N-terminus, which colocalizes with actin *in vivo*[17,23,76], and a membrane-localizing Klarsicht domain at their C-terminus[75]. The Klarsicht domain spans the membrane and, in longer nesprin isoforms, is anchored in the outer membrane of the nuclear envelope[17,103]. Nesprins have several spectrin repeat (SR) domains, each of which consists of ~106 residues that form a triple-helical bundle. SR domains mediate protein–protein interactions, crosslink actin and microtubules, and function as molecular scaffolds or stabilizers. SR domains are also found in many cytosolic proteins, including dystrophin, mutations in which cause Duchenne muscular dystrophy.

Other nesprin isoforms seem to anchor to the Golgi apparatus or mitochondria. In epithelial cells, overexpression of the Golgi-binding domain of nesprin-1 causes the Golgi to collapse into a condensed structure near the centrosome[104]. Further evidence that the nesprin family anchors other organelles comes from *Caenorhabditis elegans anc-1* mutants, which are defective in the positioning not only of nuclei (see text)[71], but also of mitochondria[71,72]. *Drosophila melanogaster* and *C. elegans* each encode one gene that is orthologous to nesprins, known as *MSP-300* and *ANC-1*, respectively[17,102]. Proposed roles for nesprins in the mechanical linking of the nuclear envelope to the cytoskeleton and nucleoskeleton are described in the text.

centrosome. So, ZYG-12 probably depends on an INM protein for its anchorage to the ONM[22]. Another protein is thought to replace matefin/SUN-1 after mid-embryogenesis, when maternally deposited matefin/SUN-1 is naturally depleted[74]. Matefin/SUN-1 continues to be expressed only in germline cells, where it is required for germline proliferation or survival after the third larval stage[74]. However, in contrast to early embryos, centrosomes seem to maintain their NE position in the germ cells of *mtf-1/sun-1*-null larvae (A. Fridkin and Y.G., unpublished observations). Because somatic cells lack matefin/SUN-1, it can be predicted that somatic cells express other INM proteins that bind ZYG-12 and help to localize centrosomes.

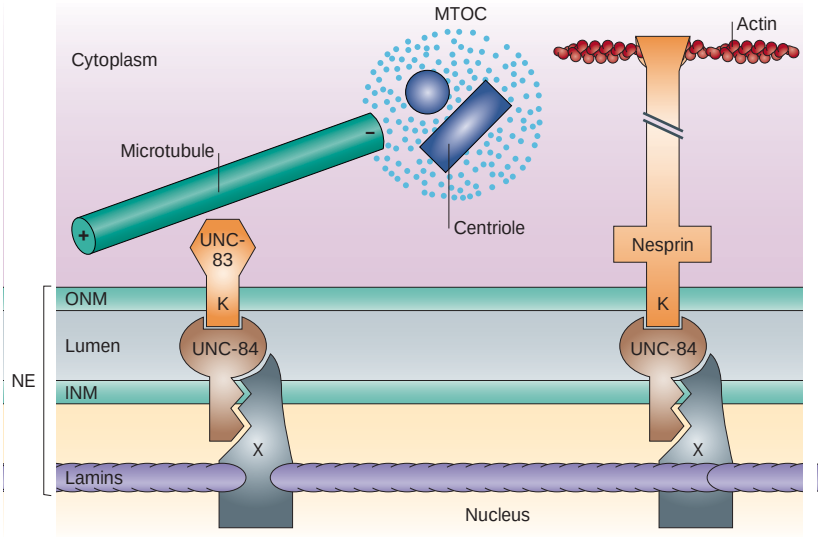

Figure 7 | **UNC-84-containing complexes are proposed to 'bridge' the nuclear envelope and link lamins to the cytoskeleton.** UNC-84 is a SUN (Sad1/UNC-84 homology)-domain protein. In *Caenorhabditis elegans*, the nuclear envelope (NE) localization of UNC-84 depends on lamins[21]. Whether UNC-84 localizes to the inner nuclear membrane (INM) or outer nuclear membrane (ONM) is unknown. For simplicity, only one location (INM) is depicted. The C-terminus of UNC-84 binds directly to UNC-83, an ONM protein that is required for microtubule-dependent nuclear migration *in vivo*[16]. The mechanism by which UNC-83 binds microtubules is unknown. The centrosome (or microtubule-organizing centre; MTOC) anchors microtubules and provides directionality for nuclear movement; minus-end-directed motors, such as dynein, that attach to the ONM, pull the nucleus toward the centrosome. Another protein named ZYG-12 (not depicted) connects the ONM directly to the centrosome. In *C. elegans*, the C-terminus of UNC-84 also binds directly to ANC-1, a nesprin protein. ANC-1 is very long (8,546 residues; depicted by the parallel lines), with its C-terminus in the ONM, and its N-terminus in the cytoplasm where it binds actin[17]. Both UNC-83 and ANC-1 have a so-called Klarsicht domain (K) at their C-terminus, which spans the membrane. (Despite the Klarsicht domain, UNC-83 is not a nesprin.) We speculate that UNC-84 binds these otherwise-distinct partners through their Klarsicht domain. There is no evidence that UNC-84 directly binds lamins, which indicates that UNC-84 might be anchored by an unknown lamin-binding protein (X) at the INM.

What do laminopathies reveal about lamins?

Human disease has been linked to mutations in the genes that encode A-type lamins, emerin and LBR, all of which are expressed in most human tissues. Many laminopathy syndromes disrupt only one or a few major tissues (adipocytes, bones, granulocytes or peripheral neurons), whereas others affect combinations of tissues. For example, EDMD, which is caused by mutations in the genes that encode either emerin or A-type lamins, affects certain skeletal muscles, tendons and the heart, whereas progeria (premature ageing) syndromes and restrictive dermopathy, which are linked to mutations in A-type lamins, affect skin, hair, fat, muscle, bone and the cardiovascular system[84–86] (BOX 1). Other laminopathies cause insulin resistance and phenotypes that might be secondary to changes in body-fat location. The range, diversity and tissue-specificity of laminopathy phenotypes are providing valuable clues about the functions that require lamins, and will ultimately allow researchers to focus on the specific roles of A-type lamins, and gene-expression pathways, that are relevant to each disease.

Fibroblasts that are derived from some laminopathy patients have a reduced resistance to mechanical stress[87,88] and, as discussed above, fibroblasts and myocytes from *Lmna*-null mice have impaired responses to mechanical stress[25,64,89]. At stress levels that

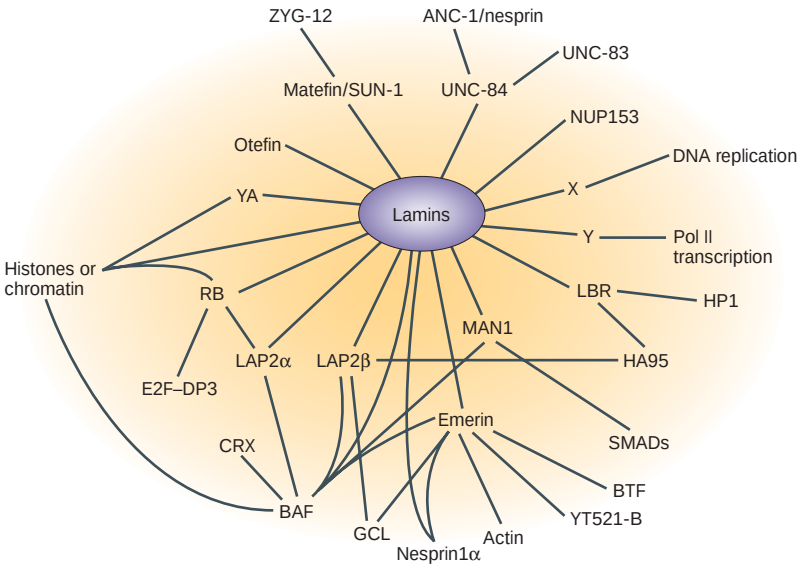

Figure 8 | **Summary of interactions between proteins of the nuclear lamina.** Lines connect pairs of proteins that interact directly *in vitro*, or indicate activities (for example, DNA replication) that depend on lamins. Some of these interactions are reviewed in detail elsewhere[9,10]. X and Y represent unknown proteins. BAF, barrier-to-autointegration factor; BTF, BCL2-associated transcription factor; CRX, cone-rod homeobox; GCL, Germ cell-less; HP1, heterochromatin protein-1; LAP1/2β, lamina-associated polypeptides-1 and -2β; LBR, lamin-B receptor; Pol II, RNA polymerase II; RB, retinoblastoma protein; YA, young arrest[35].

NFκB PATHWAY
A signal-transduction pathway with central roles in immune and stress responses, inflammation, cell adhesion and protection against apoptosis.

allow control fibroblasts to completely recover nuclear shape, *Lmna*-null nuclei remain misshapen, stretched and fragile. In normal cells, mechanical stress induces a survival response by activating the NF-κB PATHWAY. *Lmna*-null fibroblasts have reduced and attenuated activation of the NF-κB pathway[64]. Interestingly, late-passage HGPS fibroblast nuclei, despite their aberrantly thick lamina, have shapes that resemble mechanically stressed *Lmna*-null fibroblasts[26], which indicates a loss of mechanical integrity. HGPS fibroblasts also show classic lamin-null phenotypes, including the loss of peripheral heterochromatin and clustering of nuclear pores. Consistent with the dominance of HGPS mutations, overexpression of a progeria-causing form of lamin A in normal cells disrupts nuclear shape, DNA replication and the distribution of heterochromatin[26].

Because many nuclear proteins depend on lamins for their localization, lamin mutations have the potential to change the protein composition of the INM, nucleoplasm and cytoplasm. Precisely which proteins are displaced depends on whether their binding site on the lamin surface is disrupted by the mutation[10] and whether lamina organization *per se* is disrupted. In human cells that are homozygous for the Y259X mutation in *LMNA*, and which lack detectable A-type lamins, both emerin and nesprin-1 are displaced from the NE to the ER[79]. These findings are consistent with previous results for emerin and other nuclear-membrane proteins in lamin-deficient mouse cells, *D. melanogaster* and *C. elegans*[12,13,36]. The severe mutations (for example, a 50-residue deletion) that are seen in patients with progeria and restrictive dermopathy (BOX 1) are expected to directly and immediately disrupt associations with many lamin-binding partners and, consequently, to affect the corresponding downstream pathways, in addition to grossly disrupting lamina organization.

Consistent with pleiotropic effects, certain lamin mutations seem to disrupt cell-growth control and senescence. Fibroblasts from emerin-null patients divide faster than control fibroblasts[90]. By contrast, lamin-null Y259X homozygous fibroblasts grow slower than heterozygous or control fibroblasts[79]. Normal human fibroblasts undergo a limited number of divisions before entering senescence, a viable non-proliferating state. Fibroblasts from HGPS patients undergo fewer and much slower divisions, and enter senescence early[26]. HGPS cells also have short telomeres and little or no telomerase activity[91], which is consistent with reduced cell-division potential, as well as increased aneuploidy and reduced DNA-repair activity in response to treatment with ultraviolet light or γ-rays[92,93]. These phenotypes collectively indicate that lamins are required, either directly or indirectly, to avoid early senescence, maintain telomere length and repair DNA.

Future perspectives

The sum of knowledge about lamin-binding complexes and their nuclear functions is woefully low (FIG. 8) compared with our knowledge of protein complexes at the cell surface. This situation reminds us of the apocryphal three blind men, each studying a different part of the elephant — metaphorically speaking, we can now describe the tusk, foot and tail. However other vital parts and functions, and an integrated understanding of the whole, are important and interesting challenges for the future. A deeper understanding of the components, mechanisms and pathways that are regulated by lamin-dependent complexes will require diverse approaches that include detailed biochemical analysis and the discovery of new partners and complexes, as well as *in vivo* studies in relevant tissues and model organisms. Such *in vivo* approaches are particularly vital to understanding the pathological mechanisms and tissue-specificity of laminopathies, and to evaluate and design potential therapies.

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