REVIEWS

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Mechanisms and functions of nuclear envelope remodelling

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Abstract | As a compartment border, the nuclear envelope (NE) needs to serve as both a protective membrane shell for the genome and a versatile communication interface between the nucleus and the cytoplasm. Despite its important structural role in sheltering the genome, the NE is a dynamic and highly adaptable boundary that changes composition during differentiation, deforms in response to mechanical challenges, can be repaired upon rupture and even rapidly disassembles and reforms during open mitosis. NE remodelling is fundamentally involved in cell growth, division and differentiation, and if perturbed can lead to devastating diseases such as muscular dystrophies or premature ageing.

Ribonucleoprotein complexes
(RNP complexes). Large complexes composed of RNA and proteins, which are involved in a wide range of cellular processes such as translation, RNA processing and telomere function.

The boundary of the cell nucleus is formed by a specialized domain of the endoplasmic reticulum (ER) — the nuclear envelope (NE) — a double membrane sheet that comprises two closely juxtaposed lipid bilayers, which are termed the inner nuclear membrane (INM) and the outer nuclear membrane (ONM) (FIG. 1a). The INM and ONM are merged at numerous sites, thereby generating membrane pores for nucleocytoplasmic exchange. These pores are filled with nuclear pore complexes (NPCs), which constitute the major gateways for the selective bi-directional transport of macromolecules and the diffusion of small substances. Large protein complexes composed of nucleoporins (NUPs) serve as the building blocks for the membrane-attached, ring-shaped NPC framework[1] (FIG. 1a, inset). The functionality of NPCs as a diffusion barrier and as transport channels depends on a special class of NUPs that possess unstructured domains rich in Phe-Gly repeats (the so-called FG-NUPs). These NUPs provide binding sites for shuttling nuclear transport receptors and define the NPC diffusion limit[2]. However, nucleocytoplasmic communication is not limited to the exchange of material. Linker of the nucleoskeleton and cytoskeleton (LINC) complexes couple the NE to cytoskeletal structures and enable the transmission of forces across the nuclear boundary[3]. LINC complexes are built by the Sad1/UNC84 (SUN) domain-containing proteins at the INM that interact with ONM-localized nuclear envelope spectrin-repeat proteins (known as nesprins) and thereby form bridges across the NE[4] (FIG. 1a).

In metazoan cells and some other eukaryotes, the function of the NE as a physical barrier is supported by the nuclear lamina[5–7]. The lamina meshwork is formed by polymers of intermediate filament proteins, the A-type or B-type lamins[8], and proteins of the INM. B-Type lamins are farnesylated at their carboxy-terminal ends and are permanently embedded into the INM, whereas the lipid tail of the A-type lamins (encoded by *LMNA*) is cleaved off in the course of their biogenesis. The nuclear lamina provides a binding platform for heterochromatin domains, the so-called lamina-associated domains (LADs)[9–11] (FIG. 1a), and participates in genome organization and the regulation of gene expression. It also contributes to the mechanical resilience of the nucleus and fulfils important roles in development and differentiation. Overall, the NE is interconnected with cytoskeletal elements on its nuclear and cytoplasmic faces, thereby establishing an interwoven membrane–protein–chromatin network.

Although all the main structural elements of the NE interact tightly, the protein network is plastic and can be dynamically remodelled, which is important for various physiological processes. First, the NE needs to incorporate new components to meet the demands of cellular growth and to replace defective parts in response to malfunction and stress. Second, the NE adapts to mechanical challenges and changes its organization and shape upon force load. Third, dynamic remodelling of the NE is crucial for cell division. During open mitosis in higher eukaryotes, the NE even disassembles completely and then reforms. Fourth, recent studies have revealed an unexpected flexibility of the NE, allowing the export of large protein complexes such as virus particles and large ribonucleoprotein complexes (RNP complexes) by a vesicular transport process across the NE double membrane[12,13]. Finally, dynamic changes in NE composition and architecture accompany cell differentiation. In this Review, we summarize recent research on these multiple aspects of NE remodelling and discuss selected examples in more detail. We focus on mammalian cells and describe links between NE dysfunction and human diseases.

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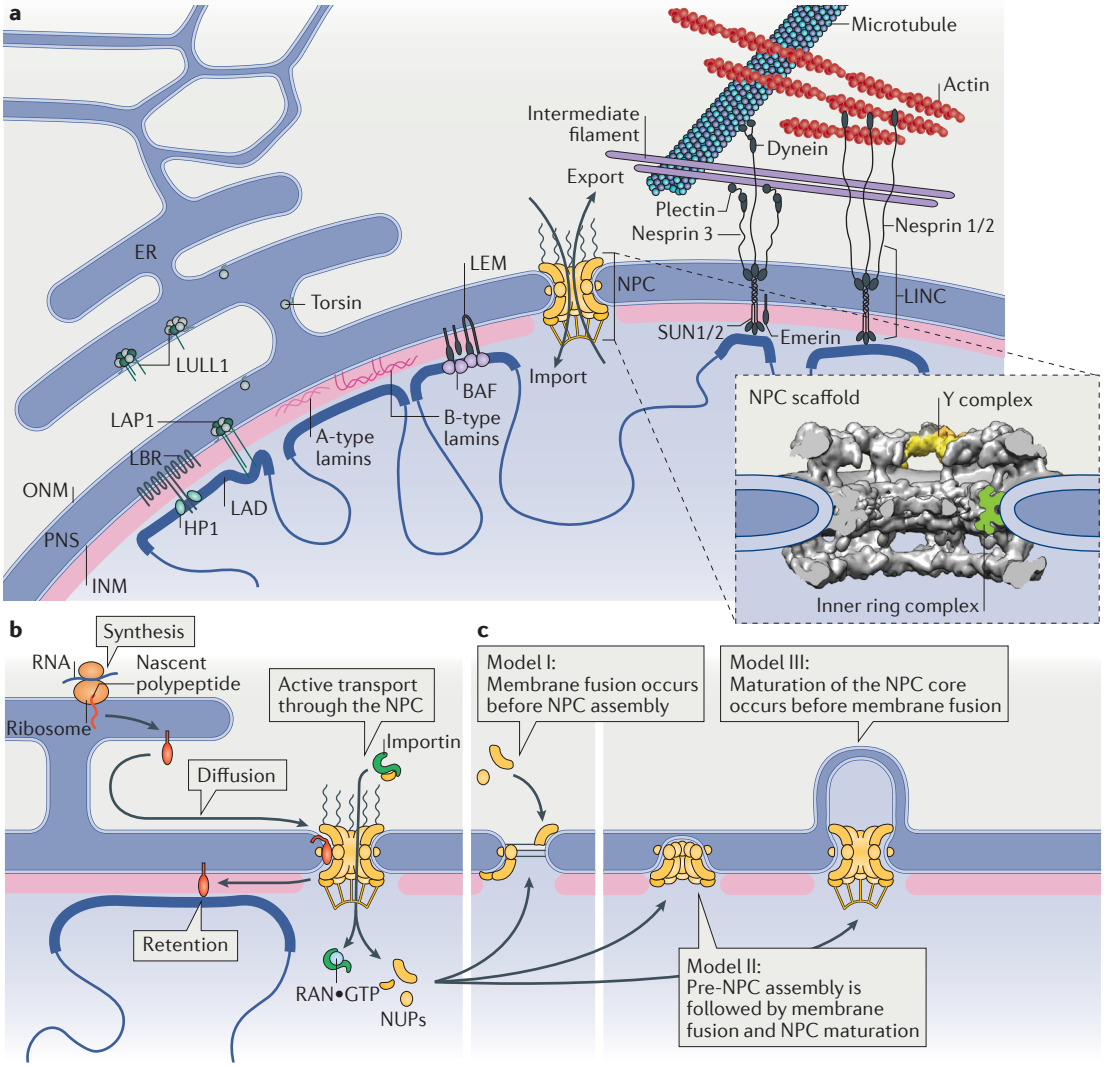


Figure 1 | **Nuclear envelope architecture and the integration of new components. a** | The nuclear envelope (NE) consists of the inner nuclear membrane (INM) and the outer nuclear membrane (ONM), which form a specialized membrane sheet of the endoplasmic reticulum (ER) that is attached to chromatin (dark blue). On the nuclear side, a network of nuclear lamins (pink) and integral membrane proteins provides mechanical support to the NE and contributes to chromatin organization by anchoring the so-called lamina-associated domains (LADs). The lamin B receptor (LBR), for example, tethers heterochromatin to the NE by binding to modified histones and heterochromatin protein 1 (HP1). LAP2, emerin, MAN1 (LEM)-domain proteins associate with nuclear lamins and the chromatin-associated barrier-to-autointegration factor (BAF). The nucleus is connected to the cytoskeleton by the linker of nucleoskeleton and cytoskeleton (LINC) complexes that span the NE. Sad1/UNC84 (SUN) domain-containing protein trimers of SUN1 or SUN2 (expressed in most cells) bind to the tails of nesprins in the perinuclear space (PNS). In the cytoplasm, nesprins interact with actin, intermediate filaments (via plectin) and microtubules (via molecular motors). Nuclear pore complexes (NPCs) allow for the selective, receptor-mediated import and export of macromolecules and the diffusion of metabolites and ions between the nucleus and the cytoplasm. These large proteinaceous channels are built by multiples of approximately 30 different nucleoporins (NUPs) that are organized into a macromolecular assembly of eightfold rotational symmetry. The NPC scaffold (see inset; Electron Microscopy Data Bank (EMDB) EMD-3103 (REF. 210)) is formed of eight spokes, each consisting of four Y complexes (NUP107–NUP160 subcomplex, two protomers coloured in yellow) and four inner ring subcomplexes (NUP53–NUP93 subcomplex, green). AAA-ATPases of the torsin family and their cofactors lamina-associated protein 1 (LAP1) or lumenal domain-like LAP1 (LULL1) form protein complexes in the PNS and ER lumen, respectively, and may support NE remodelling events. **b** | Newly synthesized INM-destined membrane proteins are inserted into the ER–ONM network, in which they distribute by diffusion. Passage through the NPC to the INM is only possible for transmembrane proteins that have extralumenal domains smaller than approximately 60 kDa. The accumulation of proteins at the INM is driven by their retention on chromatin or the lamina meshwork. INM-associated peripheral proteins and soluble nucleoporins reach the nuclear interior by receptor-mediated import that is dependent on importins and nuclear RAN•GTP. **c** | Assembly of new NPCs in the NE may either occur at a stabilized membrane pore that is formed after INM–ONM fusion (model I), or it can be initiated by the formation of immature pre-NPCs beneath the INM (model II). Subsequently, these pre-NPCs would be embedded into the NE and trigger INM–ONM fusion to complete maturation from the cytoplasmic side. Alternatively, pre-NPCs might mature further before INM–ONM fusion is elicited (model III).

Maintenance of NE homeostasis

During interphase in proliferating cells, the nuclear volume approximately doubles, and the NE surface area increases at a constant rate[14,15]. Concomitantly, new NPCs and other NE constituents are synthesized and incorporated into the expanding nuclear membrane. NE components are also degraded owing to their intrinsically limited lifespan or to them being damaged. Collectively, NE homeostasis is maintained by the balanced incorporation and disposal of material.

Integration of new NE components. Most newly synthesized, INM-destined integral membrane proteins are co-translationally inserted into the ER network and distribute to the ONM and INM by diffusion. Their accumulation at the INM is driven by retention on chromatin and/or the nuclear lamina[16–19] (FIG. 1b). Notably, at the junctions between the ONM and the INM, NPCs constitute a barrier that restricts free diffusion and prevents the passage of membrane proteins with extralumenal domains larger than approximately 60 kDa to the INM[16,17]. This NPC-based size restriction dictates which proteins can reach the INM. Thus, the INM can in principle be 'sampled' by ER membrane proteins that fulfil the NPC-based size criterion[16]. However, only proteins that bind efficiently to nuclear components will become enriched in the nuclear interior. Consistent with a diffusion–retention-based process, the targeting of proteins to the INM does not depend on active transport guided by a consensus sorting signal[18,19]. However, in both yeast and mammalian cells, some exceptional INM proteins involved in NPC assembly possess strong nuclear localization signals that confer INM localization, probably in conjunction with nuclear transport receptors[20–24].

The biosynthesis of new NPCs within the intact NE necessitates the assembly of huge protein complexes at sites where the INM and the ONM undergo fusion. This poses the intriguing problem of how membrane fusion and NPC formation are coordinated to limit or avoid an associated loss of nuclear integrity. Several models have been proposed to explain the mechanism of *de novo* NPC assembly during interphase (FIG. 1c). According to one possible scenario, the formation of immature pre-NPCs beneath the INM is an initial step, followed by their insertion into the NE, INM–ONM fusion and further maturation. Indeed, studies in budding yeast revealed that large structures — potentially NPC assembly intermediates — accumulate in cells that harbour defects in membrane fluidity or are depleted of specific NUPs such as Nup116 or Nup170 and its paralogue Nup157 (REFS 25–28). These large assemblies were associated with protrusions of the INM into the perinuclear space in the absence of INM-ONM fusion and contained NPC basket and scaffold NUPs. This supports the idea that a large NPC building block is inserted into the NE from the nuclear interior. Similar NUP-containing INM evaginations have also recently been described in mammalian cells[29]. Alternatively, however, membrane fusion could also be an initial event followed by the stabilization and expansion of the membrane pore synchronized with subsequent NPC assembly at the membrane pore. For both models, the mechanism that drives membrane fusion remains an enigma.

Although the process of NPC assembly is poorly defined, some insights into the order of events have been obtained from microscopy studies in mammalian cells. The recruitment of pore membrane protein of 121 kDa (POM121) to the INM is an important early step of interphase NPC biogenesis that precedes the incorporation of the NUP107–NUP160 scaffold subcomplex[15,22,24,30]. POM121 marks the sites of ONM–INM juxtaposition and has been suggested to cooperate with the LINC-complex component SUN1 in early steps of NPC biogenesis, potentially membrane fusion[30]. Targeting of the NUP107–NUP160 subcomplex to the INM-oriented face of the NPC assembly site depends on NUP153, which is delivered into the nucleus as a soluble protein by the import receptor transportin. After its release from transportin, NUP153 associates with the INM via an amino-terminal amphipathic helix and directs the NUP107–NUP160 subcomplex to the sites of NPC formation[31]. Another essential step in NPC assembly is the incorporation of the inner ring complex (FIG. 1a, inset), which is dependent on its constituents NUP53 and NUP155 and is presumably aided by the transmembrane NUPs nuclear division cycle protein 1 (NDC1) and POM121 (REFS 28,32); however, this is the least understood aspect of the assembly process.

NPC formation during interphase requires the deformation of the NE membrane in preparation for membrane fusion as well as the stabilization of the membrane pore after fusion. The amphipathic helix of NUP153 preferentially binds to highly curved membranes[31]. This preference may merely be used to enrich the protein at sites of membrane deformation, but it could also play a more active role by either stabilizing already deformed sites or bending the membrane at the prospective NPC assembly site. The yeast NUP153-related proteins Nup60 and Nup1 also contain amphipathic helices that have both membrane binding and bending capacities[33]. Similarly, other NUPs such as NUP133 (a component of the Y complex; FIG. 1a, inset) or NUP53 (a central scaffold NUP) possess amphipathic helices that have membrane curvature-sensing or deformation activity[24,34,35]. Collectively, these data highlight the importance of the membrane curvature-sensing and membrane-deforming motifs of scaffold NUPs for NPC assembly — a function that is further supported by the transient association of ER-shaping proteins with NPC assembly sites[36–38].

Degradation and quality control of NE components. The functionality of organelles depends on balancing the synthesis of new components with the elimination of damaged parts. In recent years, several quality control pathways were identified that ensure: first, the homeostasis of the NE proteome by the removal of membrane proteins at the INM; second, NE barrier function by surveillance for defective NPC assembly intermediates (for more details see BOX 1); and third, NE functionality by selective clearance of damaged parts by autophagy.

Perinuclear space
The lumen enclosed by the inner and outer nuclear membranes that is continuous with the lumen of the endoplasmic reticulum.

Amphipathic helix
An α-helix that contains hydrophobic and polar amino acid side chains on its opposing faces.

Autophagy
A lysosome-based degradation pathway for the destruction and recycling of cellular material.

As the NE is continuous with the ER, it is generally thought that INM proteins are subject to surveillance by ER protein quality control pathways. The first support for this hypothesis came from studies in budding yeast, in which a pool of the E3 ubiquitin ligase Doa10 (encoded by *SSM4*), which is a key component of the endoplasmic reticulum-associated degradation (ERAD) pathway, was shown to act at the INM[39,40]. A second pathway involves the INM-localized RING finger proteins amino acid sensor-independent protein 1 (Asi1) and Asi3, which together with Asi2 form the so-called Asi complex[41–43]. The endogenous, membrane-bound substrates of the Asi complex identified thus far comprise exclusively ER membrane proteins that are small enough to traverse NPCs. Thus, the Asi complex may contribute to the maintenance of INM 'identity' by removing mis-targeted ER proteins from the INM in yeast[41]. By contrast, molecular knowledge of NE quality control in metazoans is sparse. There are no reported homologues of Asi complex members outside fungi, and an involvement of conventional ERAD components such as the human orthologue of Doa10, membrane-associated ring-CH-type finger protein 6 (MARCH6; also known as TEB4)[44], in NE protein surveillance awaits experimental confirmation. Notably, the F-box proteins F-box/WD repeat-containing protein 1A (FBXW1A) and FBXW11, which are substrate adaptors for the soluble E3 ubiquitin ligase SKP1–CUL1–F-box (SCF) complex, influence the levels of the mammalian INM protein SUN2 (REF. 45). However, whether this is a direct consequence of SUN2 ubiquitylation by the SCF complex is unclear.

Remarkably, and in contrast to other NE constituents, mature NPCs are thought to be extremely long-lived[46–48]. In terminally differentiated cells such as rat neurons, parts of the central NPC scaffold indeed turn over very slowly with a half-life of up to 6 months, whereas peripheral NUPs are replaced more quickly. This difference indicates that certain NUPs or NUP subcomplexes can in fact be removed from intact NPCs for turnover, whereas extraction and replacement of central scaffold NUPs might be difficult. With increasing age, scaffold NUPs accumulate oxidative damage, which may lead to a deterioration of the barrier function of NPCs[48]. Whether cells are generally unable to eliminate damaged, mature NPCs, or whether the required surveillance pathways are inactive in terminally differentiated or aged cells, needs to be defined, but a lack of NPC turnover might have important implications for ageing[48].

In addition to these targeted quality control pathways, larger parts of the nucleus, including soluble nuclear material, NE components, lumenal ER proteins and potentially whole NPCs, can be degraded by autophagy. Recently, autophagy-related protein 39 (Atg39) was identified as a selective adaptor protein for this pathway in yeast[49]. In mammalian cells, genotoxic stress or oncogenic insults were shown to induce NE blebs, concomitant with autophagy-dependent degradation of lamin B1 (REFS 50,51). This selective autophagy pathway accompanies oncogene-induced senescence[50] and facilitates the removal of damaged genome fragments to target them for degradation — a mechanism that may protect cells from tumorigenesis[52].

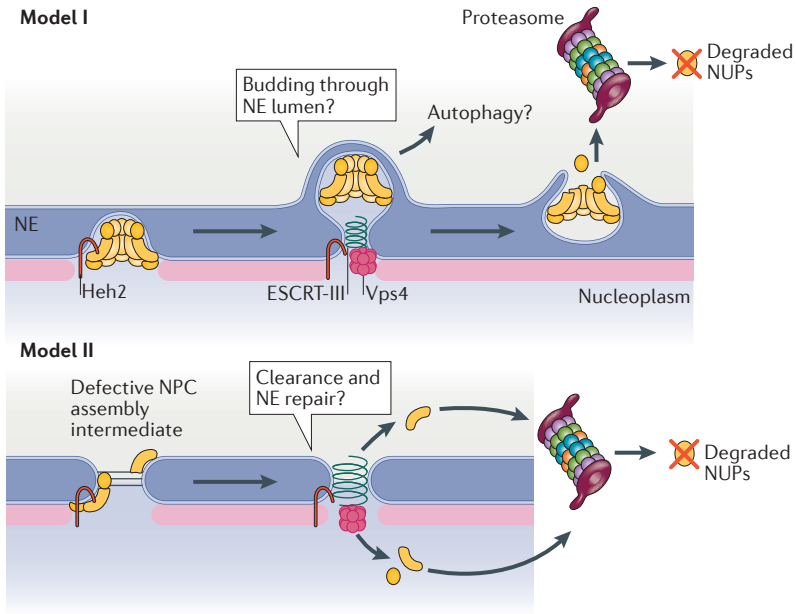
NE remodelling in response to force

Differences in overall tissue stiffness are reflected in the mechanical properties of the NE. Cells from stiff tissues contain more A-type than B-type lamins, a correlation

Box 1 | Surveillance of nuclear pore complex assembly

The assembly of very large protein complexes such as nuclear pore complexes (NPCs) might not be flawless and if defective, could jeopardize the functionality of the nuclear border. To eliminate defective, stalled NPC assembly intermediates, cells employ a surveillance mechanism that involves the inner nuclear membrane (INM) protein Heh2, which directs components of the endosomal sorting complex required for transport-III (ESCRT-III) machinery and the AAA-ATPase Vps4 to aborted NPC assembly intermediates, a process that was discovered in yeast[186]. ESCRT-III and Vps4 are known to cooperate in driving various membrane remodelling and repair events[187]. For some of these processes, ESCRT-III-based concentric spirals have been visualized at the necks of membrane constrictions, which has guided the formulation of topological models of the scission process. The mechanism by which ESCRT-III and Vps4 function in NPC surveillance is still elusive. The ESCRT-III machinery may, for instance, promote scission of vesicles containing misassembled NPCs from the INM into the perinuclear space. This may be followed by a second budding reaction through the outer nuclear membrane (ONM) and subsequent degradation of NPC-containing vesicles by autophagy or involve the fusion of INM-derived vesicles with the ONM to release the enclosed nucleoporins (NUPs) into the cytosol for degradation by the proteasome (see the figure, Model I). Consistent with this model, a few evaginations of the INM that contain potential NPC assembly intermediates are observed when Vps4 function is compromised[186]. Alternatively, ESCRT-III could mediate the clearance and closure (repair) of double-membrane pores that contain defective NPC structures, and thereby release NUPs into the nucleoplasm or cytoplasm for proteasomal degradation (see the figure, Model II).

In yeast cells that lack ESCRT-III or Vps4, defective NPC assembly intermediates are concentrated in a large cluster at the NE, and this cluster is retained in the mother cell during division[186]. The asymmetric inheritance of these NPC clusters resembles that of other organelle-associated inclusion bodies that form owing to a failure of cellular protein quality control mechanisms, such as the juxtanuclear quality control compartment (JUNQ) and insoluble protein deposits (IPODs)[188,189]. The clustering of non-functional proteins in aggregates for asymmetric partitioning during cell division might be a strategy to avoid the delivery of material that will eventually be harmful to daughter cells. Whether clustered NPC assembly intermediates contribute to the ageing of budding yeast mother cells, as proposed for protein aggregates[190,191], is an exciting open question.



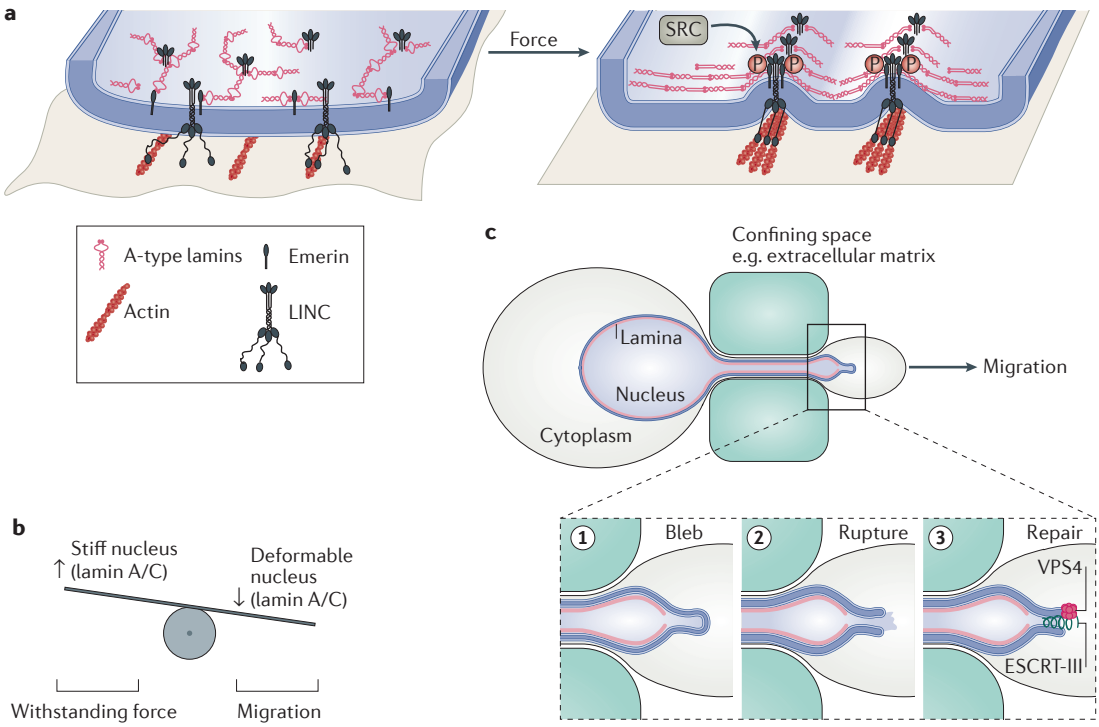


Figure 2 | **Nuclear envelope remodelling in response to mechanical cues and rupture. a** | The nuclear envelope (NE) responds to force by a stiffening of the nuclear lamina that involves phosphorylation (indicated by P) of emerin by SRC kinase, which strengthens the interaction between linker of nucleoskeleton and cytoskeleton (LINC) complexes and A-type lamins. At sites where strong tension is exerted by actin cables, nuclear indentations are formed, LINC complexes become enriched and lamin filaments are reorganized. **b** | The appropriate balance between nuclear rigidity (high A-type lamin levels) and deformability (low A-type lamin levels) is crucial for migrating cells. **c** | Cells must be able to drastically deform their nuclei to migrate through confined spaces in tissues, which is favoured by low levels of lamin A/C. When a nucleus traverses a constriction, a protrusion or 'bleb' can form at the leading tip (step 1) and in some cases, these blebs may rupture (step 2). This causes a transient loss in NE integrity and thus in nucleocytoplasmic compartmentalization. Minutes after NE rupture, chromosomal regions adjacent to the rupture site can show signs of DNA damage. NE membrane lesions are rapidly repaired by endosomal sorting complex required for transport-III (ESCRT-III) and vacuolar protein sorting-associated protein 4 (VPS4; step 3), by a process similar to NE resealing after mitosis (see also FIG. 3).

Endoplasmic reticulum-associated degradation (ERAD). A cellular quality-control pathway that targets misfolded proteins of the ER for ubiquitylation and subsequent degradation by the proteasome in the cytosol.

RING finger (Really interesting new gene finger). A specialized zinc-binding protein domain of 40–60 amino acids that mediates protein–protein interactions of factors involved in protein ubiquitylation.

F-Box proteins Proteins that contain a structural motif of approximately 50 amino acids called the F-box. They were first identified as substrate-specific adaptors of E3 ubiquitin ligase complexes that contain cullin1 and SKP1 (to collectively form the SCF complex).

that holds true for a wide range of mouse tissues and can be observed with cultured cells that have been grown on substrates of varying rigidity[53]. Thus, cells adapt their lamin content in response to the demands of their environment. Experiments that analysed the response of nuclei to deformation suggested that A-type lamins increase nuclear stiffness, whereas B-type lamins sustain nuclear elasticity[53–56]. Importantly, the integration of lamins into a highly interconnected, multivalent membrane–protein–chromatin network by INM-localized membrane proteins, and their physical linkage to the cytoskeleton via LINC complexes, allows the NE to withstand and transmit mechanical forces[57]. In addition, the condensed, INM-tethered heterochromatin contributes to nuclear stability and aids the nucleus to resist strain[58,59].

Force-induced molecular changes at the NE. A concept explaining mechanosensing at the molecular level entails force-induced conformational changes, resulting in altered protein–protein interactions or accessibility of proteins for post-translational modifications. The INM protein emerin contributes to the rapid stiffening of isolated nuclei when pulses of force are applied to the LINC complex component nesprin 1 (also known as SYNE1)[60] (FIG. 2a). Phosphorylation of emerin on Tyr residues by SRC kinase is a crucial aspect of the response to force. Interestingly, tension and the accompanying emerin phosphorylation strengthen the interaction between LINC complexes and A-type lamins[60]. Also, lamins themselves respond to forces, leading to changes in antibody accessibility of lamin A/C epitopes[61] or decreased phosphorylation of A-type lamins, potentially stabilizing lamin filaments[53]. In general, stiffening of the NE-associated protein meshwork might help to ensure the isotropic distribution of forces to prevent nuclear rupture and thereby protect the underlying chromatin.

The enrichment of LINC complexes and A-type lamins at sites of nuclear indentations is another immediate change in NE organization in response to force[62,63] (FIG. 2a). Besides their function in withstanding forces, these NE components also promote and sustain the activation of transcription factors that are involved in long-term adaptation to external forces and the regulation of cell fate[53,64–66]. For example, A-type lamins were proposed to be part of a positive feedback loop that enhances their own transcription via the nuclear

Box 2 | **Links between nuclear envelope remodelling, genetic diseases and cancer**

Mutations in nuclear envelope (NE) proteins result in a wide range of genetic disorders — collectively termed 'nuclear envelopathies' — that can either be tissue-specific or more systemic. Mutations in lamin A (LMNA), emerin (EMD), lamina-associated polypeptide 1 (LAP1) or nesprins cause degenerative diseases of tissues[162]. For instance, muscle cells, which are naturally exposed to high mechanical strain, are affected in cardiomyopathies and muscular dystrophies and the respective disease-causing mutations compromise NE stability and nucleocytoplasmic force transmission[192]. However, the same disease-causing mutations in lamin A/C also lead to perturbations of chromatin organization and epigenetic programming[164,193]. Notably, tissue-specific defects in nuclear envelopathies can be accompanied by changes in gene expression, which is exemplified by a lipodystrophy-causing mutation (Arg482Trp) in lamin A that perturbs its interaction with two regulatory factors that are involved in adipocyte differentiation, sterol regulatory element-binding protein 1 (SREBP1; also known as SREBF1) and fragile X mental retardation syndrome-related protein 1 (FXR1P; also known as FXR1)[194,195].

A number of systemic nuclear envelopathies can be attributed to defects in prelamin A processing. Mutations in the endoprotease zinc metalloproteinase Ste24 homologue (ZMPSTE24; also known as FACE1), the enzyme responsible for the processing of farnesylated prelamin A, provoke severe systemic disorders such as restrictive dermopathy associated with early neonatal death[196] or mandibuloacral dysplasia, which is characterized by a variety of abnormalities in bone development, skin pigmentation and fat distribution[197]. Similarly, the premature ageing disorder Hutchinson–Gilford progeria syndrome (HGPS) is caused by a mutation in *LMNA*, which results in the expression of a dominant lamin A isoform called progerin that remains farnesylated and accumulates at the NE[198,199]. Patients with progeria develop ageing-associated symptoms in many tissues, especially in those that are exposed to mechanical stress such as the cardiovascular system, bones and joints. At the cellular level, progerin expression alters nuclear morphology, heterochromatin organization and impairs redox homeostasis[200]. A recent study now suggests that these wide-ranging cellular defects might be triggered by repression of the nuclear factor erythroid 2-related factor 2 (NRF2) antioxidant pathway owing to sequestration of NRF2 on progerin[201]. Increased oxidative stress may render cells more dependent on the DNA damage response, which might be delayed owing to a reduced activation of the DNA repair factor NAD-dependent protein deacetylase sirtuin 6 (SIRT6) by progerin[202,203]. An atypical ageing syndrome that is similar to progeria (albeit lacking the cardiovascular deficiencies) is caused by a homozygous mutation in barrier-to-autointegration factor (*BAF*; also known as *BANF1*), which is an interaction partner of lamin A[204,205]. A comparison of the mechanisms that drive these progeroid syndromes might advance our molecular understanding of the specific cardiovascular deterioration that is a common cause of death in HGPS.

Even in the absence of genetic alterations, a loss of NE integrity may have detrimental consequences for health. This is exemplified by the irreversible NE rupture of micronuclei[206] that, in combination with delayed DNA replication in these structures[207], causes extensive DNA damage and may promote tumorigenesis. Micronuclei most commonly result from chromosome mis-segregation during mitosis. They contain fewer nuclear pore complexes, have defects in nucleocytoplasmic transport and replicate their DNA inefficiently and asynchronously with the primary nucleus[207], which causes premature chromatin compaction and DNA breaks at fragile sites during the next mitosis. Furthermore, many micronuclei undergo irreversible NE collapse during interphase progression, which inactivates replication and leads to massive damage on the exposed DNA, including DNA double-strand breaks[206–208]. During the next cell division, defective micronuclear DNA may eventually be reincorporated into primary nuclei and repaired, which leads to the random joining of DNA fragments — a phenomenon known as chromothripsis[208,209]. A catastrophic event such as chromothripsis may result in an instantaneous culmination of many genomic lesions. Whereas this will cause cellular dysfunction in most cases, rarely the new genetic landscape may confer a selective advantage for cancer evolution with reduced latency and increased aggressiveness.

sequestration of the retinoic acid receptor RAR-γ, which binds to retinoic acid-responsive elements in *LMNA* promoters, thereby helping cells to adapt to force load[53]. The potential physiological importance of mechano-responsive NE proteins is illustrated by recent analyses, which suggest that lamin A/C, emerin and nesprin 2 (also known as SYNE2) modulate the proliferation of vascular epithelial and muscle cells in arterial walls in response to cyclic shear stress that is associated with hypertension[67,68]. The critical role of these NE-located mechanosensors is further underscored by their malfunction in a range of genetic diseases such as muscular dystrophies and cardiomyopathy (BOX 2).

Adaptation and remodelling of the NE allows migration under confinement. NE remodelling and reorganization of the NE-associated cytoskeleton support the preparation by cells for directed movement[69,70]. For migration within a tissue, nuclei must possess the right balance between deformability and stiffness (FIG. 2b). In particular, when cells migrate through narrow constrictions, NE plasticity is required to allow for nuclear deformation to occur, whereas a certain level of NE rigidity is needed to prevent NE rupture. These properties are crucial for development, tissue repair, immune responses and haematopoiesis, and on the downside they may promote tissue invasion by cancer cells.

The A-type lamins play an important role in balancing plasticity and rigidity, as nuclei can only successfully deform during migration if they possess low enough levels of A-type lamins; however, too little lamin A enhances migration-associated apoptosis[54,56]. Strong deformation of the nucleus can cause NE rupture, which leads to perturbation of the nucleocytoplasmic diffusion barrier and rupture-induced DNA damage[71,72]. NE rupture is more frequently observed in lamin A/C-depleted cells or in patient-derived fibroblasts containing mutations in A-type lamins[73], which underscores the significance of an optimal lamin content for coping with migration-associated mechanical stress on the NE.

Retinoic acid receptor
A member of the nuclear receptor family of transcription factors that is activated by the binding of retinoic acid. It binds to retinoic acid-responsive elements as a heterodimer with a retinoic X receptor.

The quick recognition and repair of rupture-associated NE 'wounds' are equally important. The ESCRT-III machinery is rapidly recruited to sites of NE rupture and has a pivotal role in closing NE lesions[71,72] (FIG. 2c). Although DNA damage and NE repair pathways are typically activated on sensing the damage, extensive NE rupture may eventually lead to nuclear fragmentation, thereby challenging genome integrity and cell survival.

NE remodelling during mitosis

Extensive morphological reorganization of the NE accompanies mitotic spindle formation and chromosome segregation. Different solutions to how the mitotic spindle is formed have emerged during evolution. In closed mitosis, which is extensively studied in yeast, the spindle is assembled inside the nucleus. This is usually accompanied by the embedding of spindle pole bodies (SPBs) into the NE and NE remodelling during spindle elongation and nuclear division. In the case of cytoplasmic spindle assembly during open mitosis in higher eukaryotes, the NE must be dismantled in the process of NE breakdown (NEBD) to allow cytoplasmic microtubules access to chromatin. At the end of open mitosis, the NE is reformed and encloses all chromosomes within a single nucleus in each daughter cell.

NE remodelling during closed mitosis. As attachment sites for intranuclear spindle microtubules during closed mitosis, SPBs can be either temporarily embedded into fenestrae of the NE (as in *Schizosaccharomyces pombe*) or remain permanently anchored in the NE (as in *Saccharomyces cerevisiae*). SPB insertion into the NE displays striking similarities to NPC biogenesis. Both processes require INM–ONM fusion and the subsequent stabilization of a membrane pore. SPBs and NPCs share the transmembrane NUP NDC1 as an essential component[74], rely on membrane curvature-sensing and stabilizing proteins, such as reticulon-like protein 1 (Rtn1), Yip1 partner protein 1 (Yop1), Pom33 and Nap1-binding protein 1 (Nbp1)[37,75,76], and display biogenesis defects when membrane fluidity is altered[77,78].

Intranuclear spindle elongation during anaphase of closed mitosis is accompanied by changes in nuclear shape and an increase in NE surface area. A recent study revealed that the ability to expand the NE defines the mitotic programme of either closed or semi-open mitosis in two related species of fission yeast. In *S. pombe*, an increase in NE surface area is accomplished by cyclin-dependent kinase 1 (Cdk1)-dependent inactivation of the lipin Ned1. Lipin inactivation increases phospholipid synthesis and thereby allows for the mitotic expansion of the NE–ER network. By contrast, *Schizosaccharomyces japonicus*, which undergoes semi-open mitosis, does not regulate lipin activity, cannot expand its NE and breaks the NE at the nuclear equator for spindle elongation in anaphase[79]. This example illustrates how simple differences in protein activity can influence the chosen mode of mitosis and helps explain how the numerous mitotic programmes in eukaryotes (including many variations of semi-open mitosis) may have evolved.

Mechanisms of NE breakdown. When higher eukaryotic cells enter mitosis, the NE disassembles in the process of NEBD (FIG. 3). NPCs and the nuclear lamina are disintegrated and the connections between INM proteins and chromatin are broken. This enables the removal of membranes from chromatin and the dispersion of NE membrane proteins into the connected ER.

A burst of phosphorylation events disrupts protein–protein interactions within the NPC, the nuclear lamina and between NE proteins and chromatin in prophase. NPC disassembly is initiated by the release of soluble NUPs from NPCs, which coincides with the loss of the nuclear permeability barrier[80]. An important early event that promotes timely NE permeabilization is the hyperphosphorylation of the FG-NUP NUP98 by the concerted action of CDK1 and other mitotic kinases[81]. Liberation of chromatin from the NE depends on the phosphorylation of various INM and INM-associated proteins (FIG. 3b). This is exemplified by the role of vaccinia-related kinase 1 (VRK1) in disrupting the connections between LAP2, emerin, MAN1 domain (LEM domain) proteins and chromatin by phosphorylation of barrier-to-autointegration factor (BAF)[82,83], or by Aurora kinase B (AURKB) and CDK1-mediated release of lamin B receptor (LBR) from heterochromatin[84,85]. Similarly, phosphorylation of lamins by CDK1 and protein kinase C (PKC) promotes lamina disassembly and allows for the solubilization of A-type lamins and retraction of B-type lamins into the mitotic ER[86–89]. Notably, lipins also contribute to mitotic NE remodelling in human cells, although through different mechanisms compared with closed mitosis. The production of diacylglycerol (DAG) by lipins stimulates lamina disassembly via DAG-dependent activation of PKC[90,91]. In addition, lipin activity supports NEBD in *Caenorhabditis elegans* by balancing phospholipid synthesis to prevent the expansion of ER sheets around the NE[92,93].

The disassembly of the NE is closely coordinated with the formation of a bipolar mitotic spindle. In prophase, NPC-attached dynein motors contribute to centrosome separation by pulling on astral microtubules as centrosomes are pushed apart by kinesin-5 (EG5; also known as KIF11)[94,95]. Two independent pathways involving the dynein cofactors bicaudal D homologue 2 (BICD2) and NUDE/NUDEL–CENPF recruit dynein to NPCs in late G2 and prophase[96,97]. During prophase, dynein-dependent pulling forces on the nuclear surface, also aided by tearing on LINC complexes, generate membrane invaginations around the centrosomes and promote NE fenestration[98–101] (FIG. 3c). In prometaphase, when the connections between the NE and chromatin are broken, the NE–ER network becomes spatially separated from chromatin[98–101]. The ER is largely excluded from the spindle area in metaphase, a state that is maintained by the microtubule-binding ER proteins receptor expression-enhancing protein 3 (REEP3) and REEP4 (REF. 102). Recently, the mitotic ER was proposed to serve as a membranous spindle envelope that excludes organelles from the spindle area during semi-open mitosis in *Drosophila melanogaster* and perhaps also in human cells[103]. In the future, it will be key to clarify the functional importance of morphological changes in the NE–ER membrane network for mitotic progression.

ESCRT-III
(Endosomal sorting complex required for transport-III). An assembly of filamentous proteins that form spiral-shaped structures within annular membrane holes and mediate membrane scission, which results in the closure of membrane pores.

Spindle pole bodies
(SPBs). The microtubule-organizing centres in yeast that are functionally equivalent to the centrosomes in higher eukaryotes.

Semi-open mitosis
A form of mitosis in which the nuclear envelope is partially dismantled, accompanied by increased nuclear envelope permeability.

Cyclin-dependent kinase 1
(CDK1). A member of the family of cyclin-dependent protein kinases that are functionalized by complex formation with a cyclin protein. CDK1 in complex with cyclin B promotes entry into mitosis in mammalian cells.

Lipin
A member of the family of phosphatidate phosphatases that converts phosphatidic acid into diacylglycerol (DAG), which can be used for the production of storage lipids or structural phospholipids.

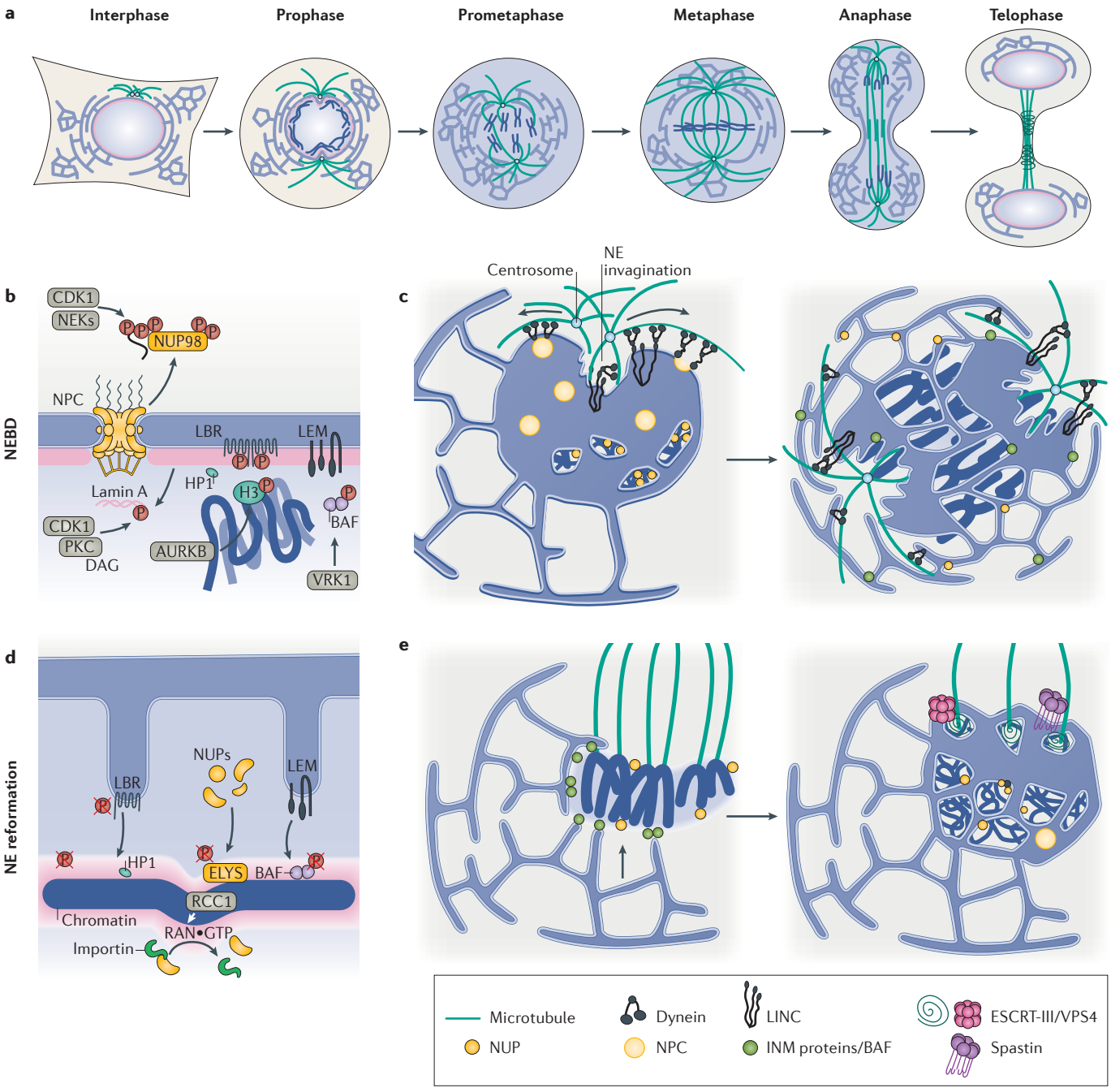
LAP2, emerin, MAN1 domain
(LEM domain). A bi-helical structural module found in the nucleoplasmic domain of some INM and nuclear proteins that mediates interaction with barrier-to-autointegration factor (BAF).

Barrier-to-autointegration factor
(BAF). A homodimeric DNA-binding protein that directly interacts with members of the LEM domain protein family.

Aurora kinase B
A member of the Aurora family of Ser/Thr kinases. A component of the chromosomal passenger complex that orchestrates several distinct steps of mitosis, including the fidelity of spindle assembly and cytokinesis.

Mechanisms of NE reassembly. The re-establishment of the nuclear boundary requires the reversal of mitotic phosphorylation of NE components, which is initiated by the inactivation of CDK1–cyclin B and the activation of counteracting protein phosphatases in anaphase (FIG. 3d). Starting in late anaphase, the NE membrane re-emerges from the mitotic ER by the gradual attraction of ER-embedded INM proteins to chromatin[104–106]. Not all INM proteins are recruited to the chromatin with similar kinetics, which may reflect differences in dephosphorylation kinetics and a varying dependence on chromatin reversion to its interphase configuration. This entails various processes, including Aurora B extraction from chromatin, changes in post-translational modifications of histones (for example, dephosphorylation and demethylation) as well as other alterations that are linked to chromatin decondensation[107–111].

Whether the ER approaches chromatin in the form of sheets or membrane tubules, and whether NPC insertion into the reforming NE occurs by their integration into flat NE cisternae or by membrane engulfment of chromatin-associated pre-pores, remains a matter of debate (for a discussion, see REF. 112). Importantly, membrane recruitment and NPC assembly are coordinated to avoid the formation of a closed NE that lacks NPCs[113–115]. NPC assembly is spatially guided by chromatin through the interaction



Nucleosomes
The fundamental packing units of chromatin, which comprise a segment of DNA and a core histone octamer.

Importins
RAN·GTP-binding nuclear transport receptors that recognize nuclear localization signals (NLSs) and mediate passage of NLS-containing proteins through nuclear pore complexes.

of the NPC assembly factor ELYS with nucleosomes and the release of NUPs from inhibitory interactions with importins by GTP-bound RAS-related nuclear protein (RAN·GTP) in the vicinity of chromatin[24,116–119]. Depletion of ELYS leads to the ectopic formation of NPC-like structures in annulate lamellae, which indicates that ELYS is not required for NPC formation per se, but for linking the process to chromatin. Interestingly, a recent study suggests that NPCs of annulate lamellae serve as a pool of immature NPCs which feed the rapid NE expansion during the short interphases that intersect the mitotic cycles in early *D. melanogaster* embryogenesis[120].

NE reassembly must ensure the inclusion of all chromosomes into the reforming nucleus but it must exclude material that is not destined to be nuclear, such as cytoplasmic organelles. It is the surface of the compact mass of late anaphase chromatin that directs the tight enclosure of chromosomes by membranes[121,122]. Anaphase chromosomes are more coalesced and axially shortened than metaphase chromosomes[123]. This dense configuration may help to prevent an invasion of membranes into chromatin, which can cause postmitotic NE aberrations such as NE wrinkles, nucleoplasmic reticulation and, in extreme cases, promote the singling out of chromosomes and cause deleterious micronucleation as a consequence (for details, see BOX 2). For instance, the co-depletion of REEP3 and REEP4 induces membrane accumulation on metaphase chromosomes and nucleoplasmic reticulation in daughter cell nuclei[102]. Defects in NE reassembly that include membrane invaginations and micronucleation were also described for either depletion of BAF[83,124] or a failure of BAF release from chromatin in mammalian cells or *C. elegans*[82,83]. How the dual functionality of BAF as a multivalent chromatin- and INM protein-binding factor supports faithful NE reformation remains to be explored.

As chromatin is engulfed by membranes, spindle microtubules remain connected to the chromatin mass, which prevents the formation of a closed nuclear membrane (FIG. 3e). NE sealing at the sites of microtubule intersection is coordinated with the disassembly of NE-penetrating microtubules and requires the ESCRT-III complex together with the microtubule-severing AAA-ATPase spastin[125,126]. Recruitment of the ESCRT-III machinery to the reforming NE may depend on charged multivesicular body protein 7 (CHMP7; a non-canonical ESCRT-III-like protein)[125,127] and/or ubiquitin fusion degradation protein 1 (UFD1; also known as UFD1L)[126], a ubiquitin-binding cofactor of the AAA-ATPase p97 that has been previously implicated in NE reformation as part of the p97–UFD1–NPL4 complex[110,128,129]. Whether the role of UFD1 in ESCRT-III recruitment is independent of p97 or is linked to its ubiquitin adaptor function for p97 awaits investigation. Clearly, the role of ESCRT-III in NE reformation underlines its emerging importance for a broad range of NE-associated remodelling events.

◀ Figure 3 | **Mechanisms governing nuclear envelope breakdown and reassembly in animal cells undergoing open mitosis. a** | During prophase, cells prepare for spindle formation by the separation of duplicated centrosomes and chromatin condensation. Inner nuclear membrane (INM) proteins are progressively phosphorylated (see panel **b**) to induce their dissociation from lamins (pink) and chromatin (dark blue). Disassembly of the nuclear lamina and of nuclear pore complexes (NPCs) is initiated, accompanied by changes in nuclear envelope (NE) permeability in late prophase. Nuclear and cytoplasmic components mix and NE membrane proteins are dispersed into the interconnected endoplasmic reticulum (ER). NE breakdown (NEBD) marks the transition into prometaphase. Kinetochores are captured by microtubules (green) and move to the midzone of the forming mitotic spindle. After all chromosomes have been organized at the metaphase plate and properly attached to microtubules, the separation of sister chromatids is triggered and anaphase is initiated. NE reformation starts by the re-binding of membranes to chromatin in late anaphase when the chromatin is most compact. Nuclear assembly continues during chromatin decondensation in telophase. At the end of telophase, a closed NE that contains NPCs has formed. Cytokinesis completes cell division and involves a role for endosomal sorting complex required for transport-III (ESCRT-III) in abscission. **b** | Phosphorylation (indicated by P) of nucleoporins (NUPs), lamins, INM proteins and chromatin-associated factors by protein kinases (cyclin-dependent kinase 1 (CDK1), Aurora kinase B (AURKB), vaccinia-related kinase 1 (VRK1), NIMA-related kinases (NEKs) and protein kinase C (PKC; activated by diacylglycerol (DAG)) disassembles the nuclear compartment boundary and allows chromatin to be released from the INM. **c** | NE-associated dynein generates pulling forces on astral microtubules that emanate from the centrosomes, leading to the formation of NE invaginations around centrosomes in prophase and facilitating NE fenestration at the transition into prometaphase. Microtubule-dependent tearing on linker of nucleoskeleton and cytoskeleton (LINC) complexes assists in the remodelling of the NE–ER network and the separation of membranes from chromatin. **d** | Reassembly of the nuclear boundary requires dephosphorylation of NE and chromatin-associated components. RAS-related nuclear protein (RAN)·GTP is generated on chromatin and spatially guides NPC reformation by triggering the local release of NUPs from inhibitory complexes with importins in the vicinity of chromatin. The NUP ELYS links NPC reformation to chromatin. **e** | In late anaphase, INM proteins regain their ability to bind to DNA and to chromatin-associated proteins such as barrier-to-autointegration factor (BAF) or heterochromatin protein 1 (HP1), enabling the recruitment of ER membranes. After the expansion of NE membranes on chromatin, some holes remain. These holes may either be closed by annular membrane fusion or be potentially filled by reforming NPCs. At sites where spindle microtubules penetrate the reforming NE, ESCRT-III and the AAA-ATPase spastin promote NE sealing and microtubule-severing in a coordinated fashion. H3, histone H3; LBR, lamin B receptor; LEM, LAP2, emerin, MAN1 domain-containing proteins; RCC1, regulator of chromosome condensation 1; VPS4, vacuolar protein sorting-associated protein 4.

Vesicular transport across the NE

NPCs can accommodate the transport of macromolecular complexes up to a size of 39 nm[130]. For many years, larger molecular assemblies were assumed to either remain within the nucleus or to require remodelling for passage through the NPC. The first evidence of an alternative route for large complexes to cross the NE emerged from studies on the nuclear egress of herpesvirus capsids by a process of vesicle budding and fusion through the NE[12,131]. Later, it became evident that herpesviruses may hijack a natural transport pathway that is used for the nuclear export of large RNP complexes[13].

Nuclear egress of large viruses by a vesicular transport pathway across the NE. Herpesviruses are enveloped, double-stranded DNA viruses that replicate inside the nucleus. The newly formed nucleocapsids must reach the cytoplasm in order to complete viral assembly. With a diameter of approximately 120 nm, these nucleocapsids are too large to pass through NPCs, and thus escape from the nucleus by vesicular transport across the NE[12] (FIG. 4). To initiate nuclear egress and allow access of viral capsids to the INM, the viral kinase pUS3 and the cellular kinase PKC phosphorylate nuclear lamins[132,133], which locally dissolves the lamina meshwork in a process that resembles lamina disassembly during mitotic entry.

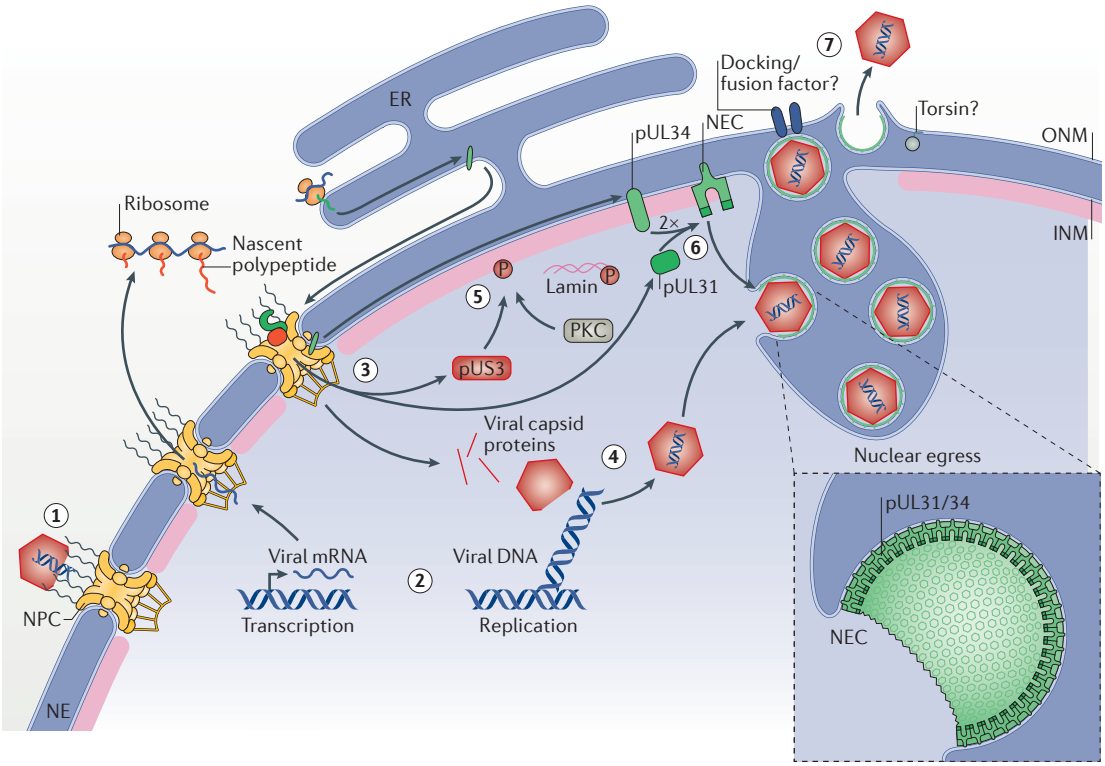


Figure 4 | **Nuclear egress of herpesviruses.** Herpesviruses are large, enveloped viruses that contain double-stranded DNA genomes. After de-envelopment during infection (not shown), nucleocapsids are transported to nuclear pore complexes (NPCs), where the viral DNA is released and translocated into the nucleus (step 1) for transcription and replication of the viral genome (step 2). Viral mRNAs are exported to the cytoplasm and translated. The newly synthesized viral proteins pUS3 and pUL31 are imported into the nucleus, whereas the tail-anchored membrane protein pUL34 is inserted into the endoplasmic reticulum (ER) membrane and targeted to the inner nuclear membrane (INM) (step 3). Capsid and other proteins assemble with the replicated viral DNA into large nucleocapsids (step 4). Nuclear egress of herpesvirus nucleocapsids occurs by vesicular transport across the nuclear envelope (NE) after the local disassembly of the nuclear lamina (pink), which is mediated by the viral kinase pUS3 in conjunction with the cellular kinase protein kinase C (PKC) that phosphorylate (indicated by P) nuclear lamins (step 5). Budding of viral capsids into the perinuclear space (PNS) is driven by the viral nuclear egress complex (NEC), which comprises pUL31 and pUL34. NECs assemble into a membrane coat (see inset) facing the viral capsid, followed by budding of vesicles into the PNS at sites of infolding of the INM (step 6). The fusion of these vesicles with the outer nuclear membrane (ONM) or ER membrane releases the nucleocapsids into the cytoplasm (step 7), potentially supported by ER lumenal AAA-ATPases of the torsin family and by unknown vesicle docking/fusion factors that reside in the ONM or the ER membrane. In the cytoplasm, herpesviruses then acquire their final membrane envelope by budding into membranes of the *trans*-Golgi network or early endosomes (not shown).

RAN·GTP
GTP-bound form of the small GTPase RAS-related nuclear protein (RAN) that confers directionality to nucleocytoplasmic transport. A high concentration of nuclear RAN·GTP, which is maintained by the chromatin-bound RAN guanine nucleotide exchange factor, facilitates unloading of transport cargo from importins in the nucleus.

Annulate lamellae
Stacks of endoplasmic reticulum membrane sheets that contain nuclear pore complexes.

Nucleoplasmic reticulation
Nuclear envelope-derived membrane invaginations, tubules or reticular structures that project into or traverse the nucleoplasm.

AAA-ATPase
(ATPases associated with diverse cellular activities-ATPase). A protein family defined by a structurally conserved ATPase domain that assembles into oligomeric rings. ATP hydrolysis is used to power the conformational remodelling of macromolecules.

Nuclear egress
An unusual vesicular transport pathway across the nuclear envelope that is used for nuclear export of herpesvirus particles.

Torsin family
A family of AAA-ATPases that reside in the ER lumen and the contiguous perinuclear space. An amino acid deletion in torsin 1A (TOR1A), TOR1AΔE, causes a severe movement disorder, early-onset dystonia.

The budding of vesicles into the perinuclear space requires the viral proteins pUL31 and pUL34 (in the alphaherpesvirinae subfamily), which together form the nuclear egress complex (NEC)[134,135]. NECs assemble into a hexagonal lattice that coats INM-derived vesicles on their inner surface[136–138]. Remarkably, the NEC is sufficient for vesicle formation and abscission *in vitro* and does not require additional energy input or cellular proteins[139]. However, host factors may contribute *in vivo*, as was suggested by the potential ubiquitylation-dependent role of ESCRT-III in the nuclear egress of a gammaherpesvirus, the Epstein–Barr virus[140,141]. To deliver nucleocapsids into the cytosol, vesicles that bud into the perinuclear space must specifically fuse with the ONM or ER membrane and not with the INM. The identity of the responsible docking and fusion machinery is unknown. Furthermore, it is unclear how vesicle budding from the INM is coordinated with vesicle fusion with the ONM to prevent rupture of the NE permeability barrier.

Candidate cellular factors that assist in nuclear egress include the metazoan AAA-ATPases of the torsin family. Overexpression of the ubiquitously expressed protein torsin 1A (TOR1A; also known as TORA) reduces herpesvirus production. Virus-like vesicles faultily enclosed by a double membrane accumulate in the cytoplasm, as if a second budding step was initiated instead of vesicle fusion with the ONM for de-envelopment[142]. In contrast to torsin overexpression, knockout of *TOR1A*, either alone or in combination with its close paralogue *TOR1B* (also known as *TORB*), only marginally reduces the replication of herpes simplex virus 1 (HSV-1)[143]. However, there are at least five torsin homologues in humans, and therefore redundancy with other torsins might explain the lack of a defect. The ATPase activity of torsins requires a direct interaction with either of their membrane-embedded activators lamina-associated protein 1 (LAP1; also known as TOR1AIP1) or lumenal domain-like LAP1 (LULL1; also known as TOR1AIP2)[144,145], which reside

in the INM and ER, respectively. Inactivation of *LULL1* reduces HSV-1 propagation, albeit at a step before nuclear egress, whereas knockout of *LAP1* does not alter viral replication[143]. Clearly, more work is required to illuminate the link between torsins and viral nuclear egress.

RNP granules, similar to viral capsids, are exported by vesicular transport through the NE. Export of large RNP granules by vesicular transport across the NE was first described in postsynaptic myonuclei of developing neuromuscular junctions (NMJs) in *D. melanogaster*[13] (FIG. 5a). Upon presynaptic stimulation, a fragment of the Wingless (Wg; a WNT orthologue) receptor Frizzled 2 (Fz2; also known as Dfz2) enters the nucleus and associates with RNP granules. These granules localize at the nuclear periphery and contain transcripts that encode postsynaptic proteins. RNP granule formation and budding depends on A-type lamins and atypical PKC, which may aid local remodelling of the nuclear lamina akin to herpesvirus egress. Electron microscopy studies revealed the presence of large evaginations of the INM into the perinuclear space that contained dense material, Fz2, RNA and lamin C[13]. Although RNP granule export and viral egress share many morphological features, RNP granule export requires an unknown cellular machinery that can substitute for the function of the viral NEC in INM budding. These cellular proteins may share some molecular attributes with the NEC, such as being able to assemble into lattices that drive INM deformation.

Several lines of evidence hint at an involvement of the torsins in the RNP granule export process in *D. melanogaster*. First, an ATPase-deficient torsin mutant was found to be enriched at the collared necks of vesicles budding from the INM into the perinuclear space, some of which were loaded with RNP granules[146]. Furthermore, inhibition of the single torsin in flies increased the number of these flask-shaped INM evaginations that contained RNP granules and impaired the delivery of critical mRNAs to postsynaptic sites. Based on these observations, torsin was proposed to promote membrane scission of budding vesicles at the INM. In cultured mammalian cells, overexpression of an ATPase-deficient mutant TOR1A induces the formation of NE herniations and stretches of closely apposed inner and outer nuclear membranes[147]. Often, these herniations are several hundred nanometres in diameter and remain connected to the INM by a collared neck, similar to the herniations that are associated with budding RNP granules. *Tor1a*-deficient mice or knock-in mice that express TOR1AΔE (a single glutamate deletion mutant that is associated with early onset dystonia) display evaginations of the INM into the perinuclear space specifically in neurons, probably because TOR1A is the predominant torsin in the developing brain[148]. Co-depletion of TOR1A and TOR1B or inactivation of LAP1 affects the NE in all tissues and cultured cells that were analysed[149]. These data point to an important general function of torsins in membrane remodelling steps at the NE.

Although a mechanistic understanding is lacking, the vesicular nuclear export pathway might allow for the exit of distinct types of over-sized cargo that are incompatible with translocation through NPCs. Interestingly, neurons of mice that harbour a conditional deletion of *Tor1a* in the central nervous system accumulate ubiquitin in NE herniations concomitant with an increased perinuclear localization of the ERAD-associated E3 ubiquitin ligase HRD1 (also known as SYVN1)[150]. It remains to be determined whether this observation provides the first glimpse of a new waste disposal pathway for intranuclear protein aggregates or NE proteins, and whether ubiquitin plays a mechanistic role in the formation of NE evaginations. A thorough analysis of the composition of INM-associated vesicles should provide insights into both the machinery that drives this pathway and the versatility of its cargo. It can be expected that the torsins will reveal many secrets about the physiological importance of NE remodelling.

NE remodelling and cellular differentiation

When cells differentiate, the spatial segregation of euchromatic and heterochromatic regions increases and heterochromatin progressively accumulates at the nuclear periphery and around nucleoli[151]. The peripheral enrichment of heterochromatin is largely determined by the sequential expression of LBR and lamin A/C, which are two major NE tethers for heterochromatin in mammalian cells[152]. At the same time, certain facultative LADs containing tissue-specific genes are released from the nuclear lamina for transcriptional activation during terminal differentiation, whereas pluripotency genes are repressed and eventually incorporated into LADs[153–157]. The reorganization of peripherally localized chromatin goes hand-in-hand with changes in the protein composition at the NE[158,159]. The rod photoreceptor cells of nocturnal mammals are a unique case that illustrates the functional importance of chromatin organization at the nuclear periphery — heterochromatin positioning is inverted in these cells by pausing LBR and lamin A/C expression to reduce light loss in the retina[152].

Below, we discuss a few examples that highlight how alterations in NE protein composition contribute to cell-type specific functions by influencing chromatin organization and gene expression, signalling, organization of NE–cytoskeletal interactions or the mechanical resilience of the nucleus.

NE composition influences myogenic differentiation and the functionality of NMJs. Myogenesis is promoted by an upregulation of the levels of NE membrane proteins[156,160,161]. These proteins include the ubiquitous LEM domain-containing proteins emerin (EMD) and LEMD2 (also known as LEM2) as well as the muscle-specific proteins NET39 (also known as PLPP7), TMEM38A (also known as TRICA) and wolframin (WFS1) (FIG. 5a), which contribute to lineage commitment by tissue-specific gene repositioning[156,160]. The tethering of chromatin regions to the nuclear periphery is accompanied by the enhanced repression of genes that are involved in muscle-cell progenitor proliferation. As the respective NE membrane proteins alone are insufficient for gene repression, other processes that accompany differentiation must also contribute.

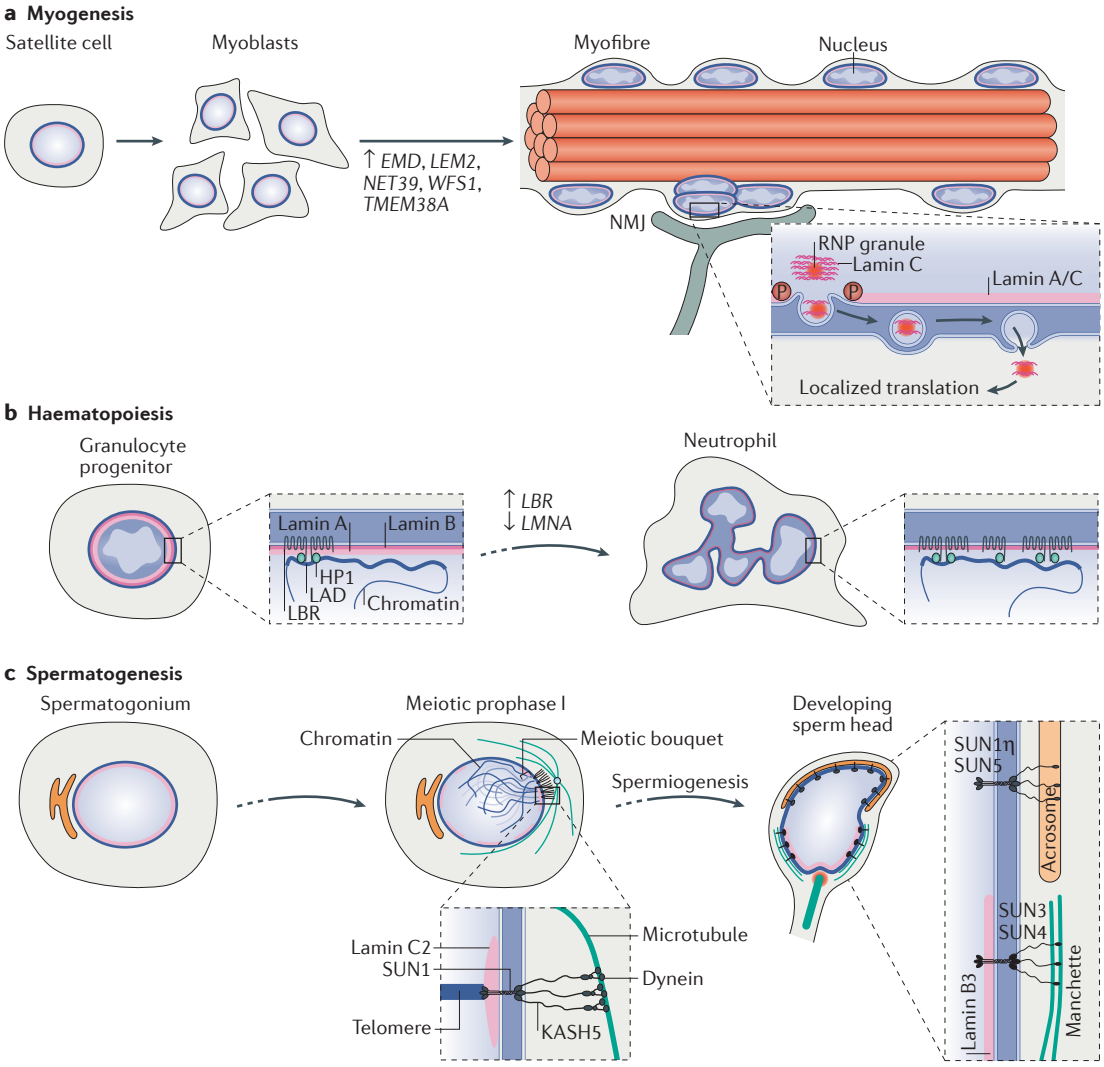


Figure 5 | **Nuclear envelope remodelling during cell differentiation. a** | Muscle stem cells — the so-called satellite cells — generate myoblasts that proliferate and undergo fusion to form multinucleated muscle fibres. During the differentiation of myoblasts, the expression of several genes that encode nuclear envelope (NE) proteins, including emerin (EMD) and LEM domain-containing protein 2 (LEM2), is upregulated. In mature muscle fibres, the nuclei are positioned at the periphery of the syncytium. Some nuclei are enriched at neuromuscular junctions (NMJs) and express mRNAs that encode proteins of the postsynapse. Certain mRNAs are exported from the nucleus as part of large ribonucleoprotein (RNP) granules by vesicular transport through the NE that is akin to the nuclear egress of viral capsids (see FIG. 4). This process involves NE remodelling, in particular the local depolymerization of the nuclear lamina (pink) through the phosphorylation of lamins (indicated by P). **b** | The nuclei of neutrophils possess a unique multilobed shape as a consequence of increased lamin B receptor (LBR) expression and decreased levels of lamin A/C (encoded by *LMNA*). Low levels of lamin A/C allow neutrophils to migrate through constricted microenvironments, whereas the increased level of LBR is responsible for the multilobed nuclear shape. **c** | Spermatogenesis involves germline-specific linker of nucleoskeleton and cytoskeleton (LINC) complexes that contribute to cellular reorganization. LINC complexes composed of SUN-domain containing protein 1 (SUN1) and KASH domain-containing protein 5 (KASH5) promote chromosome movements required for the pairing of homologous chromosomes during meiotic prophase I by linking telomeres to cytoplasmic dynein. Minus end-directed movement of dynein on microtubules is used to cluster and align LINC-coupled chromosomes into a so-called meiotic bouquet. Mobile lamin C2 plaques might help the nuclear membrane to withstand the forces that are associated with cytoskeletal pulling on chromosomes. Note that LINC-dependent meiotic chromosome bouquet formation also occurs in female meiosis. Spermiogenesis, the final step of male gametogenesis, is accompanied by nuclear restructuring in the developing sperm head. This process involves testis-specific LINC complexes that localize at opposite poles of the nucleus. LINC complexes that contain SUN5 and SUN1η are enriched near the acrosome at the anterior pole, whereas SUN3 and SUN4 together with lamin B3 localize to and function in the proximity of the posterior microtubule-based manchette. These distinct types of LINC complexes potentially serve to position and shape the sperm nucleus by interactions with cytoskeletal components, the acrosome and the manchette, respectively. Dashed arrows indicate multistep pathways. HP1, heterochromatin protein 1; LAD, lamina-associated domain; *NET39*, nuclear envelope transmembrane protein 39; *TMEM38A*, transmembrane protein 38A; *WFS1*, wolframin.

The connections between myogenic differentiation and the NE have received considerable attention since the discovery of muscular dystrophies that are associated with mutations in *LMNA* or *EMD* (BOX 2), such as Emery–Dreifuss muscular dystrophy (EDMD)[162]. A dystrophic phenotype arises when muscle fibres are chronically damaged and degenerate, which may be exacerbated by a compromised ability to regenerate. Skeletal muscles contain quiescent stem cells, the so-called satellite cells, which are responsible for muscle regeneration. Upon activation, satellite cells generate myoblasts, which proliferate and eventually undergo myogenic differentiation and fusion into myotubes. The differentiation of mouse myoblasts into myotubes *in vitro* is inhibited by the expression of lamin A that contains EDMD-causing mutations[163]. EDMD-associated mutations may perturb crucial pathways for cell cycle exit and myogenic differentiation by altering LAD organization and affecting downstream differentiation programmes that are driven by RB and MYOD[164–167].

The fusion of myoblasts into myotubes creates a syncytium containing hundreds of nuclei that are localized at the periphery of muscle fibres (FIG. 5a). Some nuclei are recruited directly to the developing NMJ, serving the expression of components for the postsynaptic apparatus through specialized transcription. Enrichment of nuclei at the NMJs and muscle innervation are severely impaired in *Lmna* knockout mice or mice expressing EDMD-associated lamin A/C mutants[168]. Notably, postsynaptic clustering of nuclei is also perturbed in *Sun1*/*Sun2* or *Syne1* knockout mice[169–171]. However, patients with cerebellar ataxia expressing mutant *SYNE1* (and also *Syne1* knockout mice) display nuclear mispositioning without compromised muscle function[172], indicating that nuclear mispositioning is not clinically relevant in terms of muscle function. Thus, the absence or mutation of A-type lamins probably causes the deterioration of NMJs and denervation by a mechanism that is independent of nuclear positioning; for example, by impairing the nuclear egress of mRNAs that encode crucial postsynaptic proteins[13,168] (FIG. 5a).

NE plasticity in neutrophils. Neutrophils are the most abundant phagocytic white blood cells. They circulate in the bloodstream and are readily recruited to sites of injury and inflammation. To do so, neutrophils must enter confined spaces in tissues, which demands marked plasticity of the nucleus as the largest organelle in the cell. Neutrophil nuclei attain their plasticity by expressing remarkably low levels of lamin A/C[55,56]. In addition, the nuclei of neutrophils are multilobed, which is a morphological hallmark that results from both a reduced level of A-type lamins and a strong upregulation of LBR[56] (FIG. 5b). Mutations that decrease LBR abundance lead to a benign autosomal-dominant disorder, Pelger–Huët anomaly, which is characterized by hypolobulated nuclei in neutrophils[173,174]. Consistent with a lack of clinical symptoms in carriers that are heterozygous for Pelger–Huët anomaly, high LBR levels and nuclear lobulation are dispensable for cell migration through narrow openings[56]. Thus, it is NE plasticity (attained by the low expression of A-type lamins) rather than nuclear shape that is important for the unperturbed migration of neutrophils to support their optimal functioning in immune responses.

NE remodelling associated with gametogenesis. The pairing of homologous chromosomes during meiotic prophase I is an essential step in gametogenesis. The initial clustering of chromosomes is facilitated by forces that are generated by microtubule motors on the cytoplasmic face of the NE, which are transmitted via LINC complexes to INM-tethered telomeres[175] (FIG. 5c). The resulting cluster of telomeres at the NE is called a 'meiotic bouquet'. In mammalian cells, bouquet formation involves the germ line-specific LINC complex protein KASH domain-containing protein 5 (KASH5) that binds dynein and, via the INM protein SUN1, couples the minus end-directed movement of the motor along microtubules to the telomeres. This process is essential for male and female fertility in mammals, as demonstrated by deletion of the implicated LINC complex constituents in mice[176–178].

Germ cells also possess a nuclear lamina of special composition. In contrast to differentiated somatic cells, 'meiotic' cells lack canonical A-type lamins. As chromosome movements during meiotic prophase are quite rapid (with rates of up to 100 nm s^{-1} (REF. 179)), a highly interconnected network of lamins could be an impediment. Remarkably, meiotic cells only express a short lamin C2 isoform, which forms mobile plaques surrounding the telomeres at the INM[180]. Although lamin C2 is not required for the bridging of telomeres and LINC complexes, it is essential for meiotic chromosome pairing[181]. Lamin C2 plaques may slide along the INM together with LINC-tethered telomeres and, at the same time, help the membrane resist the forces that are associated with cytoskeletal pulling on chromosomes.

Spermiogenesis (the final step of spermatogenesis) is an extreme case of cellular reorganisation that affects the nucleus. Here, the initially round nucleus of haploid spermatids becomes elongated and is localized to the anterior pole of the sperm. Nuclear restructuring involves the redistribution of a number of NE components to specific regions of the polarized nuclear surface (FIG. 5c). In particular, testis-specific LINC complexes accumulate at the opposing nuclear poles of the developing sperm head, potentially to aid in the positioning and shaping of the sperm nucleus by interactions with cytoskeletal components. Whereas SUN5 and SUN1η (a testis-specific isoform of SUN1) are enriched adjacent to the acrosome at the anterior pole of the nucleus, SUN3, SUN4 and the *LMNB2* splice variant lamin B3 localize in the vicinity of the microtubule-based manchette[182,183]. Here, SUN4 plays an essential role in manchette assembly, which may explain the requirement for it in male fertility[184,185].

Conclusions and perspectives

In recent years, several new processes that are associated with nuclear membrane remodelling and fusion have been discovered, including NE repair after rupture, NE autophagy and RNP budding. Similarly, NPC

RB
(Retinoblastoma protein). A tumour suppressor protein that inhibits cell cycle progression in its hypophosphorylated form.

MYOD
(Myoblast determination protein). A myogenic transcription factor and early marker for myogenic commitment.

Acrosome
A Golgi-derived intracellular organelle that is positioned on top of the anterior half of the sperm head.

Manchette
A transient structure built by microtubule bundles that surrounds the posterior part of the nucleus in the developing sperm head.

insertion into a closed NE requires membrane remodelling and fusion, although the underlying mechanism of pore formation remains a mystery. The question arises: do some of these processes rely on a related molecular mechanism? A number of commonalities have already been found between these local NE-remodelling events. In metazoan cells, the local phosphorylation-driven disintegration of the nuclear lamina represents an early step in many NE-remodelling events. Furthermore, ESCRT-III has emerged as a central player in some of these processes. Conceptually, one might expect that these NE-remodelling events would share other molecular components and perhaps a basic mechanistic principle. NPC insertion, for instance, could occur at the neck of a vesicle budding from the INM, akin to the vesicular transport pathway across the NE. Although our molecular understanding of local NE remodelling has progressed, a number of intriguing questions remain. How does NE lipid composition contribute to the processes described in this Review? Which factors drive membrane deformation and fusion events? How is ESCRT-III specifically recruited to the NE and does it function exclusively in membrane scission, as in other cellular contexts, or does it fulfil additional tasks? What is the function of the torsins and how do they work?

Besides these dynamic, local NE reorganization processes, there are striking changes in the composition of the NE that accompany and influence differentiation. Many NE proteins remain poorly characterized, especially those that are only expressed in specific tissues. A molecular understanding of their role may help to identify the underlying principles of the interplay between 3D chromatin organization, transcriptional regulation at the NE and cell fate determination.

Advances in genome engineering and microscopy may pave the way to answer some of these open questions. From a societal perspective, the various links between NE components and human diseases should encourage more studies of the impact of NE remodelling pathways on organismal homeostasis in mammals. The strong efforts of the field to identify and characterize the cellular machineries that are involved in NE remodelling will hopefully further advance our understanding of the aetiology of 'nuclear envelopathies' and aspects of pathological ageing (BOX 2).

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