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Nuclear envelope assembly and dynamics during development

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ABSTRACT

The nuclear envelope (NE) protects but also organizes the eukaryotic genome. In this review we will discuss recent literature on how the NE disassembles and reassembles, how it varies in surface area and protein composition and how this translates into chromatin organization and gene expression in the context of animal development.

1. Introduction

The nuclear envelope (NE) is an essential feature of the endomembrane system and a hallmark of eukaryotic cells. It serves as a barrier to protect the genome and separates biological processes within the nucleus from processes in the cytoplasm, such as translation. It is, however, not merely a fence between the nucleoplasm and cytoplasm: The NE organizes the genome and regulates gene expression, DNA repair and genome stability [1]. It executes regulated transport in and out of the nucleus, contributes to nuclear structural integrity and nuclear positioning in the cell, serves as an anchor for the centrosome and is implicated in signaling and mechanotransduction across the nuclear membranes [2]. The NE consists of two lipid bilayers, the outer and inner nuclear membrane and their associated proteins. The outer nuclear membrane is continuous with the endoplasmic reticulum and is fused with the inner nuclear membrane at nuclear pore complexes (NPCs), large proteinaceous channels that allow selective transport of cargoes as well as passive diffusion of smaller metabolites across the NE [3]. The inner nuclear membrane is populated by a unique set of proteins that are not present in the outer nuclear membrane and have dedicated functions in chromatin organization and gene expression [4]. In higher eukaryotes the nuclear lamina, a meshwork of intermediate filament proteins, underlies the inner nuclear membrane except at NPCs [5]. LINC (Linker of Nucleoskeleton and Cytoskeleton) complexes bridge the envelope to anchor the cytoskeleton with chromatin [6]. Thus the NE functions as both, a divider and a physical linker between the nucleus and cytoplasm.

2. NE composition

2.1. The NE membrane system

The membranes of the NE are a specialized endoplasmatic reticulum (ER) subdomain consisting of the outer nuclear membrane, which is continuous and functionally similar to the peripheral ER, and the inner nuclear membrane facing the nucleoplasm. The two membranes enclose the perinuclear space which is continuous with the ER lumen (Fig. 1a). Light and electron microscopy have shown that the NE contains invaginations reaching deep into the nucleus and forming a dynamic intranuclear network [7]. This so-called nucleoplasmic reticulum has been suggested to extend the functions of the NE into regions within the nucleus, contribute to efficient mRNA export [8], and regulate calcium signaling in subnuclear regions [9]. The NE appears to be significantly more fluid, deformable and elastic than the plasma membrane, providing a physical basis for the occurrence of the nucleoplasmic reticulum [10]. Its formation requires the incorporation of nascent membrane phospholipids and proteins, rather than the rearrangement of the pre-existing NE [11]. Generally, lipid metabolizing enzymes which produce lipids for the NE bilayer are associated with the surface of ER membranes, however recent findings document that the inner nuclear membrane can locally synthetize and store membrane lipids [12,13]. A key enzyme for phosphatidylcholine synthesis, PCYT1A, is localized in the nucleoplasm in yeast, fly and mammalian cells and translocates to the inner nuclear membrane when phosphatidylcholine levels are low, leading to its activation. This is crucial during *Drosophila* eye development where knockdown of a fly homologue of PCYT1A impairs rhabdomere formation [13]. Another inner nuclear membrane protein, the

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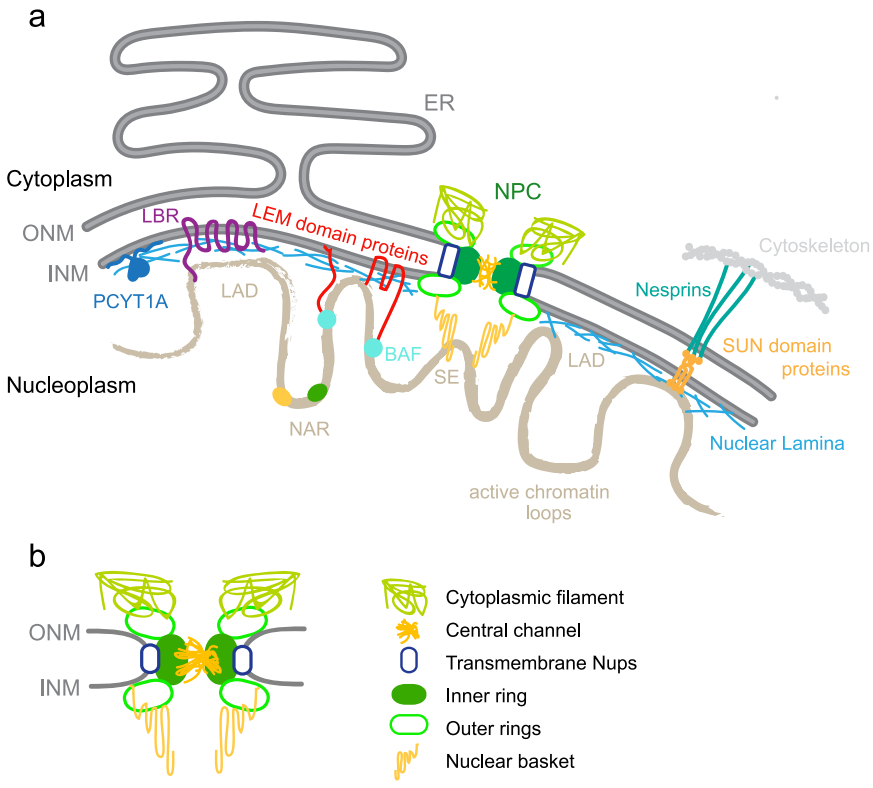

Fig. 1. The nuclear periphery in higher eukaryotes. **a** Inner nuclear membrane (INM) and outer nuclear membrane (ONM) are continuous with the ER network and are fused at NPCs. Towards the nucleoplasm the inner nuclear membrane is aligned by the lamina that attaches transcriptionally inactive lamina-associated domains (LADs) to the NE. Mobile nucleoporins bind active euchromatin at nucleoporin-associated regions (NARs) in the nucleoplasm while super enhancers (SE) attach to the NPC at the NE. Chromatin attachment at the inner nuclear membrane is also provided by LEM-domain proteins via barrier-to-autointegration factor (BAF) and other chromatin interactors, or by lamin B receptor (LBR). The inner nuclear membrane has an active lipid metabolism mediated by lamin B receptor and PCYT1A. LINC-complexes consist of SUN-domain proteins at the inner nuclear membrane and outer nuclear membrane bound Nesprins and bridge the cytoskeleton with the lamina and chromatin. **b** Schematic representation of the nuclear pore complex (NPC) and its subcomplexes. The NPC scaffold is composed from nucleoporins (Nups) of the inner and outer rings. Transmembrane Nups anchor the scaffold within the nuclear membrane. At the cytoplasmic side cytoplasmic filament Nups extend from the outer ring, while nuclear basket Nups attach on the nucleoplasmic side. Central channel Nups align the aquous channel.

lamin B receptor, is essential for cholesterol synthesis due to the Sterol C14 reductase activity in its C terminus. Mutations in the lamin B receptor gene can lead to Greenberg skeletal dysplasia, when homozygous, a perinatally lethal disorder [14]. This appears to be due to its enzymatic activity as NE integrity is unperturbed. Despite its localized lipid and cholesterol synthesis it is still unclear if the inner nuclear membrane has a different lipid composition in comparison to the outer nuclear membrane and ER membranes [15].

2.2. The nuclear lamina

In higher eukaryotes the nuclear lamina forms a filamentous meshwork consisting of type V intermediate filament proteins termed lamins, that lies between the inner nuclear membrane and chromatin (Fig. 1a). Two subtypes of lamins exist: The evolutionary older B-type lamin is expressed in all metazoans, while A-type lamins are largely restricted to vertebrates. The A-type lamins A and C arise from a single gene through alternative splicing, although some minor isoforms also exist Table 1 [5,16,17]. A and B-type lamins form distinct networks of 3.5 nm thick tetrameric filaments and have different specializations concerning their binding partners [18,19]. For example, Lamin C has been shown to interconnect NPCs, while Lamin A selectively associates with the LINC complex protein Sun1. B-type lamins are expressed in all cell types throughout development while A-type lamins are absent during early embryonic stages and in embryonic stem cells [20,21]. Moreover, while B-type lamins exclusively populate the nuclear lamina, A-type lamins are found in the lamina and the nucleoplasm and this interior pool depends on the non-NE resident LEM domain protein Lap2α (for review see [22]). The lamina mechanically supports the nucleus. It behaves like an elastic shell that renders the nucleus stiff, which is due to A-type lamins [23]. This has implications during differentiation: in embryonic stem cells with a B-type lamin only, the nuclear lamina is mechanically soft

Table 1
Lamins in mammalian development.

Lamin gene	Lamin proteins	Expression	Role in development	Reference
LMNA	A	Expressed in differentiated cells Absent in rod cells of nocturnal mammals	Essential for nuclear stiffness in differentiated cells Absence in rod cells correlates with improved night vision due to inverted chromatin architecture	[21,23,24]
	AΔ10 AΔ447 AΔ297	Minor isoforms expressed at very low levels	unknown	[16,131]
	C	Expressed in differentiated cells	Very similar to lamin A	[21,23,24]
	C2	Male and female germ line	Mediation of correct meiosis in germ cells	[130,132,133]
LMNB1	B1	Ubiquitously expressed from stem cells to differentiated cells	Supports nuclear integrity Role in brain development and neuronal differentiation	[134]
LMNB2	B2	Ubiquitously expressed from stem cells to differentiated cells	Similar to lamin B1 but with non-redundant roles in regulation of cell cycle and ploidy	[135,136]
	B3	Male germ line	Role in reorganization of the mammalian spermatid nucleus	[137–139]

but stiffens as cells differentiate and express A-type lamins [24]. Mutations in genes encoding for lamina proteins cause a wide range of tissue specific diseases called laminopathies [25]. As a prime attachment site for chromatin at the nuclear periphery the nuclear lamina has profound impacts on gene expression (see Section 5).

2.3. NE membrane proteins

The inner nuclear membrane is characterised by a unique set of integral and peripherally associated proteins in contrast to the outer nuclear membrane, which is functionally rather similar to the ER membranes (Fig. 1). The proteins of the inner nuclear membrane mediate the specialized functions of the NE like maintenance of nuclear architecture, force transmission, chromatin organization, control of transcription and DNA repair (reviewed in [4]). The core proteomic components of the NE and NPCs are detected across eukaryotic supergroups suggesting their descendance from the "Last Eukaryotic Common Ancestor" [26,27]. Proteomics and comparative genomics approaches suggest that the majority of NE associated proteins are remarkably divergent, suggesting specific functionalities of the NE in different organisms and tissues [28–30]. The transmembrane protein NET39 for example has muscle specific roles in NE integrity and gene expression and NET39 knockout mice die due to failed muscle growth [31].

Several inner nuclear membrane proteins can directly interact with the chromatin. These include the conserved family of LEM-domain proteins, named for the founding members LAP2, emerin and MAN1 [4]. Their LEM domain interacts with the conserved metazoan chromatin protein Barrier to Autointegration Factor (Fig. 1a) [32]. They are part of a complex interaction network formed by binding to each other as well as to A- and B-type lamins [33]. LEM-domain proteins have both general and individual roles in attaching chromatin regulators like Histone modifying enzymes or transcriptional repressors to the nuclear periphery. Another LEM-domain protein, Lem2 is crucially involved in NE sealing at the end of mitosis [34,35]. The transmembrane inner nuclear membrane protein lamin B receptor has been identified as lamin B binding protein (hence the name) but also interacts with chromatin in multiple ways. It is involved in heterochromatin tethering to the NE in developing tissues [21] (see Section 5.1).

Proteins of the LINC complex span the NE and are important for anchoring the nucleus to the cytoskeleton. They consist of SUN (Sad1p-UNC-84) domain proteins, integral membrane proteins of the inner nuclear membrane, which indirectly interact with chromatin [33]. In the NE-lumen SUN domains bind to the KASH domains of nesprins, transmembrane proteins of the outer nuclear membrane that extend into

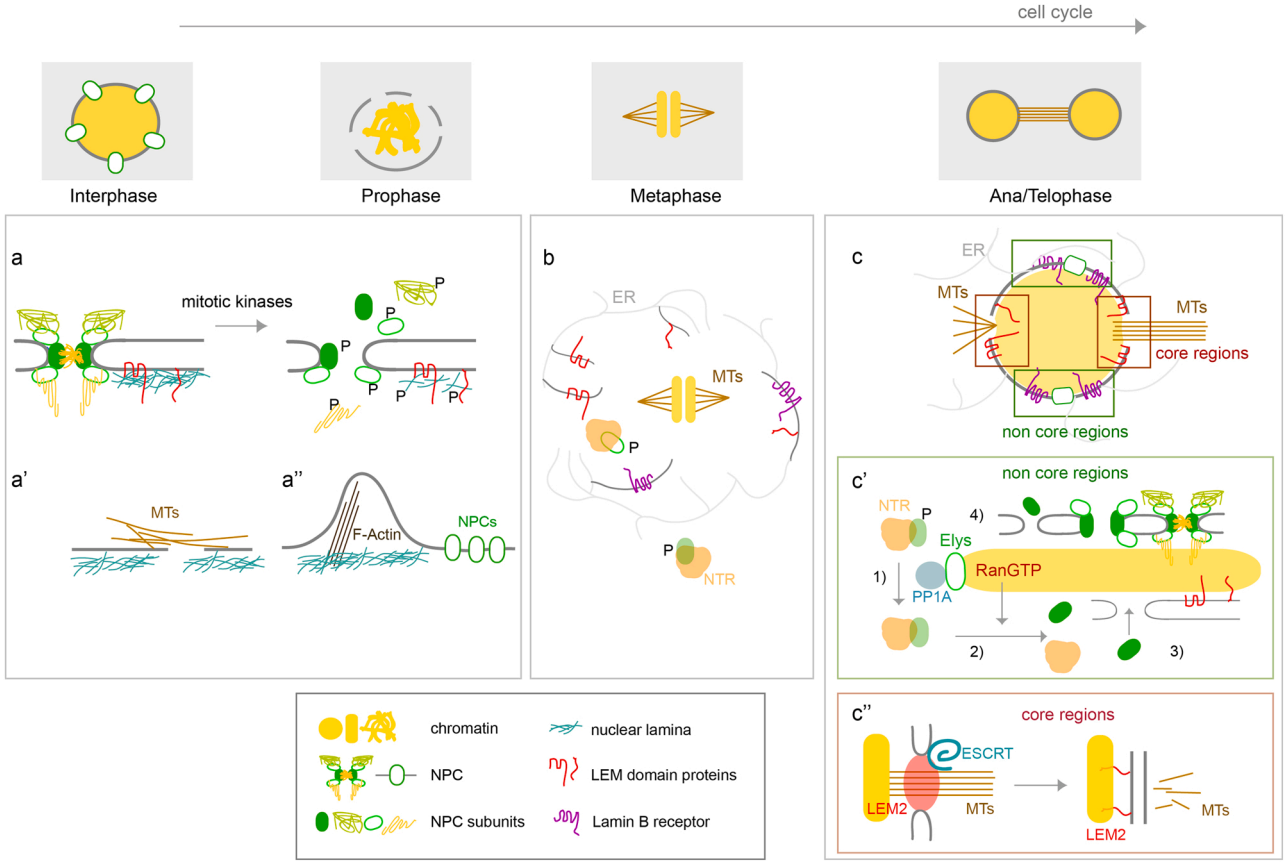

Fig. 2. Key events in NE disassembly and reassembly during open mitosis. **a** In prophase mitotic kinases phosphorylate Nucleoporins (Nups), lamins and nuclear membrane proteins, which renders the NE permeabel. Nup phosphorylation leads to disintegration of the NPC into its subunits. **a'-a''** The cytoskeleton assists NE-breakdown in prophase. In mammalian cells Microtubules (MTs) facilitate tearing of the NE from the cytoplasm (a') while in starfish oocytes F-actin polymerizes from the lamina at the nucleoplasmic leaflet into the NE, pushing NPCs to NE-stretches free of F-actin (a''). b In metaphase phosphorylated Nups or NPC subunits are kept soluble by binding to nuclear transport receptors (NTRs). The NE and its membrane proteins is retracted to the ER. **c** In ana and telophase the NE reforms unequally along the separated chromatids. NPC's reassemble in the "lateral non core regions", that contain Lamin B receptor but are devoid of LEM domain proteins. NPCs do not reassemble in core regions facing spindle MTs. **c'** Postmitotic NPC assembly is initiated by chromatin binding of the scaffold Nup Elys (1). In *C.elegans*, Elys recruits the phosphatase PP1A to sites of NPC reassembly on chromatin. RanGTP at chromatin releases dephophorylated nucleoporins from nuclear transport receptors (NTRs) and makes them available for their stepwise integration into the forming NPC (2), as membranes enclose daughter nuclei by interactions between NE membrane proteins and chromatin (3). (4) Postmitotic NPC assembly is believed to occur by stepwise incooperation of subunits into preexisting membrane gaps, that subsequently dilate and form the transport competent, mature NPC. **c''** At NE core regions spindle MTs pierce the reforming NE. Condensation of the LEM domain protein Lem2 at MTs recruits the ESCRT complex which is required to seal the NE membrane and induce MT clearance.

the cytoplasm and interact with the cytoskeleton. Hence, LINC complexes mechanically link the nuclear lamina and its associated chromatin with the cytoskeleton and, via integrins, ultimately to the extracellular matrix (Fig. 1a) [6]. Force transmission to chromosomes by LINC complexes is crucial for meiosis (see Section 5) and has been also shown to control cell differentiation: In epidermal stem cells, tension on the LINC complex and A-type lamins is high, but decreases upon differentiation. Keratinocytes lacking LINC complexes prematurely differentiate, suggesting that force transduction to the nucleus via LINC complexes is required to maintain keratinocyte progenitors [36]. There is also evidence that mechanotransduction via the LINC complex can regulate cell cycle progression: In *Drosophila* larval muscles LINC controls synchronized DNA replication in myofiber nuclei [37].

2.4. Nuclear pore complexes

2.4.1. NPC architecture and composition

NPCs are amongst the largest protein complexes in eukaryotic cells, in human cells they have a molecular mass of 120 MDa. In higher eukaryotes each NPC is composed of ~1000 copies from about 30 different Nucleoporins (Nups), most of them conserved across eukaryotes [38]. Multiple Nups assemble into a number of biochemically separable subcomplexes that combine in a modular fashion to give rise to the overall 8-fold symmetric NPC. The NPC scaffold is built from the inner ring which stabilizes fusion of the two nuclear membranes, and two outer rings containing protein complexes arranged in a Y-shape fashion at its cytoplasmic and nuclear side [3,39] (Fig. 1b). During the last decade the highly complex architecture of the NPC scaffold has been tackled in different species through a combination of cryogenic electron microscopy, biochemistry, X-ray crystallography, cross-link mass spectrometry and molecular modeling. Recent studies using cryo electron tomography in situ after Focused Ion Beam milling have revealed that the central channel is (a) wider than previously anticipated [40–43] and (b) can "breathe" in response to environmental conditions [42–45]. A small set of transmembrane Nups anchors the scaffold in the nuclear membrane. On either side of the symmetric scaffold different subcomplexes project towards the nucleoplasm or the cytoplasm respectively. On the nucleoplasmic side a structure called the nuclear basked is bound to the nuclear ring. The nuclear basket is an important site of interaction with chromatin and various factors that function in nuclear proximity to the NPC and modulates mRNA export through pores [46]. Opposite, long flexible filaments emanate from the cytoplasmic ring into the cytoplasm called cytoplasmic filaments (Fig. 1b) [3].

Fundamental for nucleo-cytoplasmic transport are intrinsically disordered regions in the central channel of the pore. They are rich in phenylalanine-glycine (FG) repeats that create a unique phase separated environment that only allows small molecules < 30–50 kDa to travel through the pore by passive diffusion [47]. Larger cargoes can only pass when bound to nuclear transport receptors, importins or exportins. Transport directionality is ensured by a sharp gradient of the nucleotide bound status of the small GTPase Ran. Nuclear transport activity plays an important role in development and in regulating cellular homeostasis [48] and can even vary within a single cell. In skeletal muscle cells which contain thousands of post-mitotic nuclei distributed in a common cytoplasm, gene expression varies dependent on their location within the muscle. These differences come about through differing nuclear import rates of proteins depending on the type of nuclear localization sequence they contain [49].

Similarly, the exact composition of the NPC can vary between different cell types and during development [50]. It is striking that Nups with documented roles in NPC assembly are dispensable in certain cells. The Y-complex protein Nup133 has an amphiphatic helix that can seed NPCs during interphase [51]. Despite being required beyond gastrulation [52], Nup133 is dispensable for interphase NPC assembly in mouse embryonic stem cells [53]. Changes in NPC composition have been shown to regulate cell differentiation. For example the transmembrane Nup gp210 is absent in NPCs from myoblasts and when its expression is induced it results in muscle differentiation in mammalian cells and zebrafish [54,55]. Mechanistically, gp210 changes expression patterns of genes involved in differentiation through direct interaction with the transcription factor myocyte enhancer factor 2 C (Mef2C) at NPCs. Alternatively it might support muscle cell differentiation by maintaining NE/ER homeostasis through its luminal domain [56]. Many other Nups are essential for embryogenesis and tissue differentiation with the obvious reason being that loss of certain Nups leads to impaired NPC integrity and reduced nucleocytoplasmic transport. However various Nups also have cell type- and tissue-specific functions, pointing towards NPC independent roles (for a comprehensive recent review see [50]).

2.4.2. NPC distribution

About 3000 NPCs can be found on the nuclear membrane of a mammalian tissue culture cell, although the exact number varies between cell types [57]. The total number appears to be negatively regulated by the NPC basket protein Tpr. Tpr recruits the MAP Kinase Erk which phosphorylates Nup153, a key Nucleoporin, when de-phosphorylated, for the assembly of new pores during interphase [58]. NPC numbers can vary at different stages of differentiation: Neural progenitor cells can give rise to multiple neuronal cell types with significantly different NPC numbers [59]. NPC biogenesis occurs mostly in proliferating cells and stops in differentiated cells where existing NPCs are maintained by slow turnover of their subcomplexes [60]. The composition of the lamin network or the inner nuclear membrane generally regulates NPC distribution and anchoring to the NE [19,61,62]. In flies, a striking transition in NPC distribution along the NE occurs concomitantly with the upregulation of the zygotic genome. In the earlier blastoderm stage NPCs can diffuse laterally resulting in an even distribution along the NE. NPCs get immobilized and cluster when embryos gastrulate, most likely by anchoring pores within the lamina [63]. This has been confirmed by super-resolution studies that show that in contrast to cultured cells, NPCs are nonrandomly distributed and congregate in gaps of the lamina network in many stages of *Drosophila* development [62].

3. Breaking and making

3.1. Mitotic NE remodeling

3.1.1. NE disassembly

Eukaryotes have developed different strategies to distribute the NE during mitosis. Most animals entirely dismantle their NE when they enter prophase and reform it *de novo* onto separated sister chromatids, a process referred to as "open mitosis" (Fig. 2). In the other extreme, yeast cells divide their nuclei within an intact NE in a "closed mitosis". However, the strict terminology "open" and "closed" might be more conceptual and many intermediate forms exist (discussed in [64]).

NE breakdown is the overture to open mitosis and initiated by phosphorylation dependent deconstruction of the NPCs and the lamina, which renders the NE leaky (Fig. 2a) [65]. Mitotic kinases hyperphosphorylate unstructured stretches in Nup98 and Nup35 that serve as interaction hubs within the inner ring and between subcomplexes, leading to the disassembly of the NPC [66,67]. NE breakdown is assisted by cytoskeletal elements: In mammalian cells microtubules facilitate tearing apart the NE [68], while a F-actin shell initiates NE breakdown in starfish oocytes (Fig. 2a) [69]. There, F-actin strikingly nucleates in the lamina and polymerizes into filopodia-like protrusions from the nucleoplasmic side that spike into NPC free regions. This pushes NPCs into adjacent membrane regions and ultimately may rupture the NE (Fig. 2a) [70]. In open mitosis, extensively studied in tissue culture cells, the NE membrane entirely disperses into the ER, although a membranous "spindle envelope" was suggested to repel organelles and large complexes from the spindle region in early mitosis [71]. Clearly a spindle envelope stays present in systems with a semi-closed mitosis: In

Drosophila embryos and larvae [72,73] NPCs disassemble, yet the fenestrated NE encases the spindle laterally throughout mitosis and is only open at the centrosomes. Recent work in flies suggests that the mode of mitosis can vary significantly even in the same organism: Nuclei in female germline stem cells divide with centrosomes within the confinements of an intact NE and even lamina [74]. The nature of the mitotic ER has been a matter of debate. Recent evidence favors a model where ER membranes are rather tubular than cisternal due to proteins containing Reticulon homology domains that stabilize high membrane curvatures present in tubules [75]. In turn enforced expression of Reticulons delays the reformation of a functional NE in anaphase [76]. After NPC disassembly the phosphorylated Nups are kept soluble (Fig. 2b) [77]. Their chaperoning by nuclear transport receptors counteracts promiscuous and fatal aggregation of the Nup intrinsically disordered regions during mitosis.

3.1.2. NE reassembly

In anaphase, NE constituents are dephosphorylated, allowing NE reformation. Chromatin associated RanGTP dissociates nuclear transport receptors from Nups and other NE components and thus directs NE and NPC reformation towards the daughter nuclei (Fig. 2c) [77]. While results obtained mainly in the *Xenopus* in vitro system have long argued for vesicles as the NE membrane source, live-imaging revealed that ER tubes contact chromatin and subsequently flatten out to form a closed NE [78]. Retention of inner nuclear membrane proteins by chromatin binding facilitates this reshaping. It is still unclear how membrane supply and NPC reformation are coordinated. Chou et al. recently suggested that scaffold Nups could populate membrane fenestrations throughout mitosis [79]. Super-resolution microscopy combined with modeling has provided detailed temporal maps of NPC disassembly and reassembly during mitosis [80]. Initially the Y-complex nucleoporin Elys has a key role: It possesses direct DNA binding activity and recruits the Y-complex onto chromatin [81,82]. In worm oocytes the Elys homolog Mel-28 binds to the catalytic subunit of Protein Phosphatase 1 thereby concentrating dephosphorylation activity required to remove mitotic phosphorylation on nucleoporins to sites of NE reformation (Fig. 2c) [83]. Ultrastructural studies performed in HeLa cells indicated that NPCs seed into small membrane fenestrations that extend in diameter as NPC subcomplexes are added in a stepwise manner [84]. *In vivo* post-mitotic NPC reassembly does not occur ubiquitously on the reforming NE but in lateral regions that do not face spindle or astral microtubules. These “non core” regions are distinct in inner nuclear membrane protein population from core regions (Fig. 2c) [85]. At core regions the inner nuclear membrane protein Lem2 phase separates along membrane penetrating spindle microtubules which triggers recruitment of the Endosomal Sorting Complex Required for Transport (ESCRT) [86], essential to constrict membrane gaps and seal the NE in telophase (Fig. 2c) [87,88]. Timely regulation of closure is provided via phosphorylation of the ESCRT adapter CHMP7 by the mitotic kinase CDK1, which prevents premature assembly of the ESCRT machinery by inhibiting its interaction with Lem2 [89].

3.2. NE holes and fusions during early development

After fertilization the parental pronuclei meet and subsequently undergo the first mitotic division of the zygote. Merging of the parental genomes is complicated by the in total four membranes in between them, in particular if NE membranes persist during semi-closed mitosis. Volume imaging in *C. elegans* zygotes led to exciting novel insights into this problem [90]. It revealed that at the intersection of the two parental NEs multiple, partially huge membrane fenestrations emerge in metaphase. These fenestrations allow the two genomes to approximate each other. Subsequently, NE membranes of the pronuclei fuse by sheet junctions that are topologically similar to three way junctions known from tubular ER. Fusion of NEs has also been demonstrated during pronuclear fusion in zebrafish. Key for this process is a transmembrane protein of the NE encoded by the gene *brambleberry (bram)* [91]. The Brambleberry protein is also involved in fusion of karyomeres, NE enclosed micronuclei that emerge in anaphase of blastomere embryos in fish and other species but resolve into one nucleus as mitosis ends. During anaphase Brambleberry accumulates in punctae at karyomere interfaces. In embryos devoid of maternally supplied *bram*, micronuclei persist through interphase. Brambleberry has homology to yeast Kar5p which is required for NE fusion in yeast mating, suggesting a similar molecular mechanism [91]. During *C. elegans* meiosis, material to reclose large scale NE-fenestrations is provided by the contiguous ER proximal to the meiotic spindle that acts in liaison with the ESCRT machinery to reform an impermeable NE [92]. However ER influx has to be controlled: In mutants of the NE-resident phosphatase CNEP-1 (C-terminal domain Nuclear Envelope Phosphatase 1) excess ER membranes invade the nuclear interior, a phenotype that is enhanced upon concomitant loss of the ESCRT adaptor *chmp7*. *Lem2/cnep-1* double mutants display the same phenotype, suggesting mechanistic similarities to NE reformation in mitotic Hela cells [92].

Large NE-fenestrations also accomplish en bloc integration of ER resident NPCs. This occurs when ER membranes feed the rapid expansion of the NE in the astonishingly fast interphases in *Drosophila* syncytial embryos [63]. Across metazoan NPCs are found not only at the NE but also in parallel ER sheets, a compartment termed annulate lamellae that was identified already in the 1950’s by classical transmission EM [93]. Volume imaging indicates that in fly embryos large fenestrations of the NE facilitate the insertion of overlying annulate lamellae membrane sheets in a process that surprisingly does not compromise the permeability barrier of the NE. Insertion might be facilitated by the lack of asymmetry within annulate lamellae resident NPCs, thus elevating any need for directionality of the insertion. This process is prominent during early, maternally controlled development [63] but more recently was also reported in gastrulating fly embryos and in larvae as well as during postmitotic NPC assembly in mammalian cells [94].

Apparently the early zygote tolerates the existence of large holes in the NE, seemingly risking the integrity of its permeability barrier. Moreover the rather prominent membrane influx from the ER indicates that proteomic composition of ER versus inner nuclear membrane might be similar at these early stages of development. A distinct inner nuclear membrane landscape, ready to organize and interpret the genome may emerge only at later stages.

4. NE growth

Already early on, it has been recognized that the size of a nucleus is proportional to the dimensions of the surrounding cell [95]. This framework postulates the existence of cytosolic factors that limit nuclear growth when being consumed. This is reflected in early embryos across metazoans where, during the rapid reductive cleavage divisions, nuclei get progressively smaller.

4.1. Addition of soluble NE constituents

To accompany changes in nuclear volume, the NE and its constituents have to adapt accordingly. This concerns the ER as the NE-membrane reservoir as well as building blocks of the lamina and of NPCs that have to be imported to the nucleus via nuclear transport receptors. It is thus not surprising that the nuclear-cytoplasmic transport system has emerged as a key regulator of nuclear size (reviewed in [96]). Recent work suggests an elegant model of how nuclear transport receptors scale cell and nuclear size [97]. During reductive divisions in early *Xenopus* embryos the nuclear transport receptor Importin α gets progressively sequestered to the plasma membrane by palmitoylation, which blocks the binding site for Importin α cargoes including lamins. Likely this progressive nuclear transport receptor-sequestration at the plasma membrane reduces nuclear import and contributes to shrinking of nuclei in early *Xenopus* embryos. A similar process operates in human

cells [97]. As mediators of nuclear transport, NPCs also impact on NE growth: In mammalian cells the scaffold Nup Elys regulates nuclear size by controlling NPC number, which is suppressed when nuclear transport is stimulated [98].

The principal reservoir to assemble NPCs onto postmitotic daughter nuclei is the pool of NPCs integrated in the mother NE, such that the number of NPCs has to double before the next mitosis [99]. In contrast to postmitotic pore formation, interphase assembly occurs in all eukaryotes, is stochastic, ubiquitous along the NE and takes place with a rather slow kinetics into a sealed double membrane. Carefully timed ultrastructural analysis of NPC progression in cryo-fixed cultured cells postulates an inside out assembly mechanism, where the inner nuclear membrane bends towards the outer nuclear membrane, presumably by local accumulation of Nups [100]. This provides a structural explanation to previous studies that had indicated that Nucleoporin import was necessary to form new pores [101]. Membrane bending capacity could come from amphiphatic helices of Nups 153, 53 and 133, all required for interphase assembly (reviewed in [3]) or/and Nucleoporin accumulation driven by FG-Nup condensation, a mechanism that would concomitantly ensure impermeability upon fusion with the outer nuclear membrane [102].

4.2. Membrane supply

There are not only soluble cytosolic molecules competent for nuclear import that determine how much a nucleus can grow. By artificially inducing asymmetric cell divisions or micro-dissection of sea urchin blastoderm embryos Mukherjee et al. have modulated cell size and nevertheless saw that nuclear size and growth rates were unaffected. More critical was the supply of membranes from the perinuclear ER into the NE [103]. However the amount of ER membranes that redistribute into the NE has to be tightly controlled: In *C. elegans* embryos depleted for the phosphatase CNEP-1, supernumerary ER sheets encase the NE and block its partial break down at mitotic onset [104]. CNEP-1 activates Lipin, a key regulator of ER-NE membrane composition [105]. Consequently lipin loss suppresses the formation of excess ER sheets in CNEP-1 mutants [104]. The importance of the associated ER pool for nuclear growth is also apparent in dividing *Drosophila* neuroblasts, stem cells of the central nervous system that divide asymmetrically into a big neuroblast and a small ganglion mother cell. Most of the perinuclear ER is inherited by the stem cell and enables an eminent growth of the neuroblast nucleus while the nucleus of the ganglion mother cell remains small [73]. In fission yeast the inner nuclear membrane protein Lem2 serves as a barrier to control membrane exchange between the NE and the ER [106]. Interestingly the ER protein Lnp1, homologous to mammalian Lunapark, represents a secondary, redundant checkpoint to prevent excessive nuclear growth or shrinkage [107]. It remains elusive to date if similar barrier mechanisms operate in higher eukaryotes.

Most transmembrane proteins of the inner nuclear membrane are co-translationally inserted into the ER membrane and then distribute to the outer nuclear membrane by diffusion. To reach the inner nuclear membrane, membrane proteins with extralumenal domains up to ~60kD translocate through NPCs and then get retained at the inner nuclear membrane by binding to nuclear partners [108]. While the import of soluble cargoes through NPCs relies on the activity of the small GTPase Ran, the diffusion-retention mechanism of inner nuclear membrane transmembrane proteins depends on the activity of atlastins, membrane-bound GTPases of the ER, that are required for proper maintenance of ER topology [109]. However, inner nuclear membrane targeting has also been suggested to occur by a nuclear transport receptor and Ran dependent import pathway [110].

5. The NE as chromatin organizer

5.1. NE proteins tether chromatin

The inner leaflet of the NE, together with the lamina, is a prime organizer of chromatin architecture. It has been a long standing notion that in the majority of differentiated cells transcriptionally inactive heterochromatin is enriched along the NE except at NPCs, while transcriptionally active euchromatin distributes in the nuclear interior (Fig. 1a). In human embryonic stem cells there is no heterochomatin, and chromatin appears to be functionally homogenous at the onset of development [111]. Upon differentiation animal cells express at least one of two molecular tethers, either lamin B receptor and/or A-type lamins, that attach heterochromatin to the nuclear periphery [21]. Loss of both tethers inverts overall chromatin architecture, with heterochromatin in the center and peripheral euchromatin. Mature rod photoreceptors of nocturnal mammals lack both, Lamin A/C and lamin B receptor and thus evolve an inverted chromatin organization. While this may be a disadvantage for higher order chromatin regulation, compacted heterochromatin in nuclei of the retina functions as a focusing lens that reduces light scattering and improves vision in night active animals [112]. In those species the originally conventional organization is inverted during terminal differentiation of rods in a process driven by high affinity interactions within heterochromatin, sufficient for discrete layering of chromatin by a phase separation process [113]. Similar organizing principles could apply for lamin B receptor mediated heterochromatin tethering at the NE: *Drosophila* Heterochromatin protein 1 (HP1), a binding partner of lamin B receptor, condenses in vitro and forms discrete foci with liquid characteristics as heterochromatin appears in early embryos [114]. Interestingly also euchromatin was recently suggested to form in a phase separation driven process at the onset of zygotic induction in zebrafish. There accumulating transcribed mRNAs trigger the formation of transcription foci which physically separate from heterochromatin [115].

5.2. Lamina associated domains and nucleoporin associated regions

Heterochromatin tethering at the nuclear periphery sequesters lamina-associated domains, DNA stretches of several hundred kilobases that are enriched in transcriptionally silenced loci and epigenetic marks indicative of repressed chromatin [116]. However lamina-associated domain tethering to the nuclear lamina is dynamic and can be released upon signaling inputs. When cardiac progenitors differentiate into cardiomyocytes, lineage specific genes are released from the nuclear lamina. Nuclear lamina-attachment is controlled by a histone deacetylase and loss of this protein results in precocious lineage determination [117]. Likewise, in flies the B-type lamin Dm0 is required to attach and thereby repress testis specific gene clusters at the nuclear lamina in somatic cells [118].

Peripheral heterochromatin aligns the nuclear lamina, but is generally exluded from the NE at NPCs. A striking example of heterochromatin exclusion by NPCs has recently been revealed during oncogene induced senescence in human cells, which regroups heterochromatin from the NE to the nucleoplasm. Responsible for the formation and maintenance of internal heterochromatin foci in oncogene induced senescence is an increased density of NPCs and in particular the basket Nup Tpr [119]. Already earlier Tpr has been shown to be instrumental for the heterochromatin exclusion zone at NPCs [120]. While in yeast many active loci are actually anchored at NPCs, the picture is less clear in higher eukaryotes. This is mainly due to the fact that especially non-scaffold Nups are mobile [121], can operate off-pore and localize to active genes in the nucleoplasm. In *Drosophila* Nup98, Nup62 [122,123] and nuclear basket nucleoporins [124] bind to and regulate nucleoporin-associated regions in the nuclear interior (Fig. 1a). Nucleoporin-associated regions are shorter in length than lamina-associated domains but are enriched for chromatin marks

Table 2
Nuclear Envelope proteins and their role in development.

Localization in NE	Protein		Constituent of	Model organism	Specific function	References
Lamina	B type lamins	Dm0	nuclear lamina	fly	represses testis specic genes in somatic cells	[118]
	A type lamins	Lamin A		mammals	anchors heterochromatin in differentiating cells	[21]
		Lamin C2		mouse	weakens lamina for chromosome pairing in meiosis	[130]
Nuclear membrane proteins	lamin B receptor		inner nuclear membrane	mammals	anchors heterochromatin in differentiating cells	[21]
	PCYT1A		nucleoplasm – inner nuclear membrane	fly	rhabdomere formation	[13]
	CTEN-1		nuclear membrane	worm	regulates ER/NE membrane flux in oocyte meiosis	[92]
	LINC proteins	various	nuclear membrane	human	repress keratinocyte differentiation	[36]
		KASH-5	outer nuclear membrane	mouse	chromosome pairing in meiosis	[128]
		SUN-1	inner nuclear membrane	mouse	chromosome pairing in meioisis	[128]
		MAJIN	inner nuclear membrane	mouse	telomere anchoring at LINC	[127]
	Nuclear Envelope Transmembrane proteins (NETs)	various	inner nuclear membrane	mammals	diverse specialized functions	[28]; rev in [4]
		NET39	inner nuclear membrane	mouse	muscle growth	[31]
	Brambleberry		nuclear membrane	fish, frog	karyomer fusion, pronuclear fusion	[91]
Nuclear Pore Complex	Nucleoporins	various	nuclear pore complex	several	diverse	rev in[50]
		Nup153 Mtor		fly	dosage compensation	[124]
		Nup153 Nup93		human	transcriptional control of super-enhancers	[125]
		Nup98 Nup62		fly	transcriptional regulation	[122,123]
		gp210		mouse, fish	muscle progenitor	[54–56]

indicative of active transcription. Transcriptional upregulation by basket Nups is of particular importance in dosage compensation, where gene expression levels from the fly male X chromosome are doubled [124]. In contrast to nucleoporin-associated regions, super-enhancers, "master regulator elements" that control the expression of key cell identity genes, have been found to bind Nup153 and Nup93 at NPCs in human cells (Fig. 1a). Consequently depletion of these Nups deregulates gene expression [125].

5.3. Force transmission during meiosis

In meiosis, the diploid chromosome set is halved and newly assorted in two consecutive rounds of mitosis. During the prolonged prophase of the first meiotic division the homologous chromosomes line up in pairs and this is a prerequisite for subsequent crossover between the homologues. The NE and in particular LINC complex proteins have a crucial conserved role in chromosome pairing and as such are essential for gametogenesis. LINC complexes bind to telomeres and thereby attach chromosomes to the NE. Pairing of homologous chromosomes is facilitated by cytoskeletal forces that are transferred via LINC complexes across the NE to chromosomes [126]. Meiosis specific factors ensure coupling of telomeres to the NE: For example, in mice telomere attachment to the gamete specific LINC protein SUN-1 requires expression of the transmembrane protein MAJIN that in turn contains DNA binding domains which interact with telomeric sequences [127]. SUN-1, in conjunction with KASH5 and the motor dynein, links the telomeres to microtubules that attach on the cytoplasmic side and generate force on the NE. Mice deficient for either of these genes are infertile due to meiotic arrest [128].

A potential impediment for chromosomal movement at the periphery is the lamina scaffold. In worms the single nematode lamin LMN-1 is phosphorylated analogous to mitosis which weakens the nuclear lamina and facilitates chromosome motion [129]. Mammals that have a more complex lamina composition express the meiosis specific splice variant Lamin C2, an A-type lamin compromised in filament crosslinking (Table 1) [130].

6. Conclusions

Remarkable progress has been made to better understand how the NE influences a whole variety of cellular processes. Improved high resolution imaging techniques continue to reveal the architecture of NE constituents in ever increasing detail and provide surprising insights. For example, it is striking that despite an overall conserved repertoire of nucleoporins, the architecture of the NPC scaffold varies significantly between eukaryotic species [42,43]. The functional consequences of such variations remain to be understood. Improved resolution could also reveal further sub-compartimentalization at the NE: For example condensates of the LEM-domain protein Lem2 are crucial to reseal the NE after mitosis [86], but eventually many more phase separated micro-environments along the NE may exist. Condensation of NE membrane proteins could be a way to trigger the formation of distinct chromatin domains at the nuclear periphery. In flies the lamin B receptor binding partner HP1 concentrates into immobile foci and thereby compacts heterochromatin as lamin B receptor expression commences during cellularisation [63,114]. Many components of the NE are functionally linked to developmental decisions or tissue differentation (Table 2). Their effects can be general as in the case of lamins that tether transcriptionally silent heterochromatin to the periphery in a variety of cell types. On the contrary, the specific regulation of NE-proteins could determine differentiation in a very restricted subset of cells. This is true for ubiquitous NE-constituents as the transmembrane nucleoporin gp210. In muscle progenitors of fish and mammals, NPCs lack gp210 and its expression induces muscle differentiation [54,55]. Alternatively, specialized cells induce particular NE proteins to achieve specific functions as for example pairing of homologous chromosomes in meiotic gametes [127].

The use of correlative light and electrone microscopy has allowed to unambigously link particular molecular players to certain ultrastructural features and Focused Ion Beam-Scanning Electron Microscopy (FIB-SEM) volume imaging enables us to literally fill our spatial gaps in understanding complex membrane topologies at the NE and the interconnected ER. These techniques have revealed that during earliest development large membrane fenestrations open the NE to faciltate

pronuclear fusion or meiotic divisions in worms or bulk incoperation of NPCs from the ER in *Drosophila*. It is entirely unclear how these several hundred nanometer spanning gaps are created, maintained, and controlled in size. This is even more remarkable with respect to the central function of the NE to guarantee a shielded nuclear compartment, which, surprisingly, appears dispensable in these contexts.

Certainly extending the application of these high resolution imaging techniques to genetically tractable metazoans at their key developmental transitions will continue to provide surprising insights into the regulatory potential of the NE.

Conflict of interest

The authors have no conflict of interest to declare.

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