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Till Disassembly Do Us Part: A Happy Marriage of Nuclear Envelope and Chromatin

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A characteristic feature of eukaryotic cells is the presence of nuclear envelope (NE) which separates genomic DNA from cytoplasm. NE is composed of inner nuclear membrane (INM), which interacts with chromatin, and outer nuclear membrane, which is connected to endoplasmic reticulum. Nuclear pore complexes are inserted into NE to form transport channels between nucleus and cytoplasm. In metazoan cells, an intermediate filament-based meshwork called as nuclear lamina exists between INM and chromatin. Sophisticated collaboration of these molecular machineries is necessary for the structure and functions of NE. Recent research advances have revealed that NE dynamically communicates with chromatin and cytoskeleton to control multiple nuclear functions. In this mini review, I briefly summarize the basic concepts and current topics of functional relationships between NE and chromatin.

Key words: chromatin, lamin, nuclear envelope, nuclear membrane, nucleus.

Abbreviations: BAF, barrier-to-autointegration factor; ER, endoplasmic reticulum; HIV-1, human immunodeficiency virus 1; INM, inner nuclear membrane; LAP2, lamina-associated polypeptide 2; LBR, lamin B receptor; MoMLV, Moloney murine leukaemia virus; NE, nuclear envelope; NPC, nuclear pore complex; ONM, outer nuclear membrane; PIC, preintegration complex.

TO HAVE AND TO HOLD THE CHROMATIN INSIDE: STRUCTURE AND ASSEMBLY OF NUCLEAR ENVELOPE

Nuclear envelope (NE) is composed of double concentric lipid bilayer membranes surrounding eukaryotic chromatin. Inner nuclear membrane (INM) faces toward and interacts with chromatin, and outer nuclear membrane (ONM) is connected to endoplasmic reticulum (ER) and cytoskeleton. The space between INM and ONM is called as NE lumen. Multiple units of nuclear pore complex (NPC), large multi-protein gating machinery, are inserted into NE to form molecular transport channels between nucleus and cytoplasm. In metazoan cells, an intra nuclear meshwork termed as nuclear lamina exists beneath INM and encloses chromatin. The main component of nuclear lamina is the polymerized form of lamin, a special class of intermediate filament protein. In mammals, lamin A and lamin C are splice variants of the same gene and often described as lamin A/C, whereas lamin B1 and lamin B2 are encoded by distinct genes. However, neither genomic nor microscopic analysis has identified lamins or nuclear lamina-like structures in lower eukaryotes such as yeasts. Due to space limitation, I mainly focus on the physiological roles of lamins and integral INM/ONM-associated proteins in mammals.

Distributions of integral membrane proteins in INM and ONM are clearly different, and targeting mechanisms of INM and ONM proteins are supposed to be distinct. Whereas soluble proteins are transported to their destinations immediately after translation depending on their localization signals, membrane-anchored proteins are bound to membrane structures during intracellular movement. Live cell imaging analyses using fluorescent protein fusions suggest that INM proteins are first translated and inserted into ER membrane, followed by lateral diffusion across ER and ONM membranes. These membrane proteins are thought to move into and out of nucleus by diffusion through NPC. If they bind to target molecules such as chromatin components and nuclear lamina, they become less mobile and accumulate at INM. In contrast, interactions with perinuclear materials will result in ONM localization of membrane proteins. In this model, intracellular localization of binding partners determine the destination of each membrane protein (reviewed in *1*, *2*). However, a recent study indicates that the nuclear entry of membrane proteins is an energy- and NPC-dependent rate-limiting step in mammalian cells (*3*). Moreover, the requirement of karyopherin-mediated import of integral INM proteins was reported in *Saccharomyces cerevisiae* (*4*) and in insect cells (*5*). Further studies will be necessary to fully elucidate these points.

In lower eukaryotes such as yeasts, NE does not break down during cell division (closed mitosis). In contrast, NE disassembles at metaphase in metazoan cells (open mitosis), and INM and ONM are dispersed among ER membranes (reviewed in *6*, *7*). This process is mainly mediated by the phosphorylation of key substrates (NPC components, lamins and INM proteins) by mitotic kinases such as Cdk1/cyclin B. Microtubules are also involved in the removal of membrane from chromatin.

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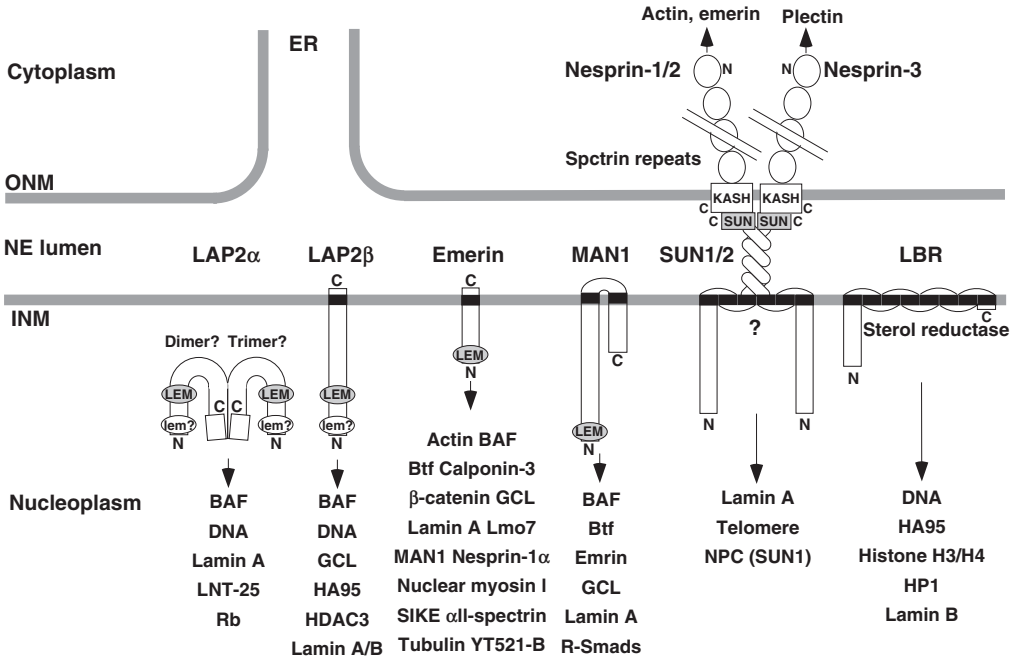

Fig. 1. **Schematic views of mammalian INM and ONM proteins.** Only selected members of mammalian INM and ONM proteins are shown, and arrows indicate their interacting partners. Conserved domains such as LEM, LEM-like (lem?), SUN and KASH domains are presented. In the case of LAP2α, a biochemical study suggests homo-trimeric structure (*71*), whereas the crystal structure of C-terminus is dimeric (*72*). SUN1 and SUN2 contain at least three putative transmembrane regions, but a recent report suggests that SUN1 transverses INM only once (*73*).

It is not yet clear whether these NE-derived membranes become fragmented vesicles or tubular networks. After nuclear disassembly, lamin B is involved in spindle assembly by forming a matrix-like network in a Ran-GTP-dependent manner (*8*). At the end of mitosis, dephosphorylation of key substrates by phosphatases such as protein phosphatase 1 initiates the re-association of membranes onto chromatin (*9*). Subsequently, formation of uniform membrane structures, re-establishment of NPC, and recovery of nucleocytoplasmic transport are necessary processes for complete NE reassembly. In this dynamic transition, passage through NPC is not required for integral membrane proteins to reach INM. Rather, membranes with higher affinity for chromatin are targeted to chromatin more quickly and eventually become INM, whereas membranes which do not interact with chromatin may become ER or ONM. It is suggested that NE reassembly is driven by specific interactions between membrane-associated proteins and chromatin. A recent study using *Xenopus* egg extracts indicates that the basic domains of vesicle-associated proteins directly bind to acidic DNA (*10*), although these proteins may not be necessarily membrane-integrated (*11*). INM proteins and NPC components are targeted to distinct regions of chromatin at different timings during telophase (*12*). Consequently, distributions of NPC, INM proteins and lamins across NE are initially uneven, but gradually become uniform during G1-S phase (*13*). Thus, NE structure is highly dynamic during cell cycle.

Only selected members of the well-characterized mammalian integral INM and ONM proteins, together with their binding partners, are summarized in Fig. 1. These molecular interactions play important roles for their correct localizations and physiological functions (reviewed in *1*, *2*, *14*, *15*). Lamina-associated polypeptide 2 (LAP2), emerin and MAN1 share a conserved motif named as LEM domain, which interacts with a small dsDNA-binding protein Barrier-to-Autointegration Factor (BAF). LAP2 is expressed as multiple splice variants, all containing N-terminal LEM and LEM-like domains. Most isoforms (LAP2β in this figure) are integral membrane proteins, whereas LAP2α is a nucleoplasmic protein without transmembrane region. SUN1 and SUN2 carry C-terminal SUN domain, which binds to KASH domain of a group of giant ONM proteins collectively called as Nesprins. Recent proteomic approaches have identified many new nuclear membrane-associated proteins (*16*, *17*). Also, more and more interaction partners are being discovered by yeast two hybrid and proteomic screenings. Further characterization of these molecules will surely enhance our knowledge of NE physiology.

FOR BETTER OR FOR WORSE VIRAL REPLICATION: NUCLEAR ENVELOPE AND LIFE CYCLES OF VIRUSES

To replicate in host cells, retrovirus first reverse-transcribes its RNA genome into DNA copy in cytoplasm, assembles several viral and cellular proteins to form a ribonucleoprotein complex termed as preintegration complex (PIC), and then tries to integrate viral DNA into host genome (reviewed in *18*). PICs of some retroviruses such as Moloney murine leukaemia virus (MoMLV) cannot pass through NPC, and NE disassembly

during cell division is required for such retroviruses to access host cell genome. Therefore, these viruses can replicate only in dividing cells. In contrast, PICs of human immunodeficiency virus 1 (HIV-1) and other lentiviruses carry karyophilic components and can be delivered through NPC into the nuclei of non-dividing cells. Nuclear and NE-associated proteins of host cells are also involved in these processes. BAF was identified as a host cell factor of PIC to inhibit retroviral autointegration, and LAP2α also collaborates with BAF to suppress MoMLV autointegration (*19*). Emerin was reported to be required for the integration of HIV-1 cDNA into host genome in macrophages (*20*), but this result was not reproduced by another study (*21*).

In the case of herpesvirus, capsid assembly and packaging of DNA genome initiates inside the nuclei of host cells. To escape from nucleus (nuclear egress), this viral capsid interacts with INM and wears a host-derived membrane to cover itself. Nuclear lamina and INM proteins act as physical barriers against this process. Herpesvirus uses specific viral proteins to recruit cellular protein kinase C, and dissolves NE structure by phosphorylating lamins and INM proteins (reviewed in *22*). Polyomavirus disrupts host NE structure with a viral protein which displaces heterochromatin protein 1 from lamin B receptor (LBR) (*23*).

FOR RICHER OR FOR POORER GENE DISTRIBUTION: NUCLEAR ENVELOPE AND TRANSCRIPTIONAL REGULATION

In various eukaryotic cells, gene-rich, transcriptionally active chromosomes are often found in the nuclear interior, whereas gene-poor, transcriptionally silent chromosomes are located at the nuclear periphery. Recent studies have started to reveal the molecular mechanisms underlying this phenomenon. One hypothesis is that INM proteins and lamins selectively interact with transcriptionally inactive heterochromatin. For example, LBR associates with heterochromatin through the binding to hypoacetylated histones H3/H4 (*24*, *25*), and a recent study identified that most of the ~500 lamin-binding genes in *Drosophila* are transcriptionally silent and lack histone marks (*26*). SUN1 and SUN2 are required for the anchoring of telomere at NE during meiosis (*27*, *28*). Alternatively, INM proteins may inhibit transcription at nuclear periphery by recruiting transcriptional repressors. LAP2β, emerin and MAN1 all bind to transcriptional repressor GCL (*29–31*). Emerin and MAN1 interact with death-promoting transcriptional repressor Btf (*31*, *32*). Emerin also binds to transcriptional regulator Lmo7 (*33*), splicing-associated factor YT521-B (*34*) and restricts the nuclear accumulation of β–catenin (*35*). LAP2β associates with histone deacetylase 3, which induces histone H4 deacetylation (*36*). Nucleoplasmic LAP2α forms a complex with Rb to repress E2F-dependent transcription (*37*, *38*). MAN1 binds to regulatory Smads to specifically antagonize transforming growth factor β/bone morphogenic protein-induced signalling pathway (*39–41*). Altogether, INM proteins and lamins appear to play important roles in the proper distribution of silent genes at the nuclear periphery in higher eukaryotes. In contrast, NPC directly associates with some actively transcribed genes in *S. cerevisiae*, and NPC is also involved in the dosage compensation of *Drosophila* X chromosome (reviewed in *42*). It will be interesting to examine whether this mechanism is generally conserved in other organisms.

NUCLEUS IN SICKNESS AND IN HEALTH: NUCLEAR ENVELOPE AND MAMMALIAN DISEASES

Any nuclear protein is normally hidden inside the cell and, when accidentally exposed, can be recognized as a foreign antigen by our immune system. Several NE proteins are recognized by the antisera from the patients of autoimmune diseases (reviewed in *43*). In leukaemia cells, gene rearrangements frequently generate chimeric proteins between some of NPC components and various proteins (including transcription factors and proto-oncogenes). These fusion proteins are supposed to be functionally involved in the pathogenesis of leukaemia (reviewed in *44*). In addition, genomic analyses have identified several NE proteins as responsible gene products for genetic diseases. Mutations and gene targeting experiments in mice have also revealed the physiological importance of NE proteins. The NE-related mammalian diseases are summarized in Table 1. Among these, mutations in lamin A are drawing interest because of the surprisingly variable clinical phenotypes (collectively called as 'laminopathies', reviewed in *45*, *46*). Lamin A is first synthesized as a C-terminally extended precursor form (prelamin A). After the farnesylation of Cys in its C-terminal CAAX motif, AAX residues are removed by proteolysis, and C-terminal farnesylated Cys is carboxymethylated. Subsequent endoproteolytic processing by a specific metalloprotease FACE-1/Zmpste24 removes the C-terminal 15 residues, and mature lamin A is not farnesylated. In the case of Hutchinson–Gilford progeria syndrome, the mutant lamin A (named as progerin) lacks the endoproteolytic processing site recognized by FACE-1/Zmpste24, and farnesylated C-terminus cannot be removed. Loss of FACE-1/Zmpste24 activity in human and mice also results in progeria, or clinically more severe restrictive dermopathy. Constitutive farnesylation of lamin A may be the pathogenic cause of these diseases and possible use of farnesyl transferase inhibitors as therapeutic reagents is currently under investigation. Inhibitors against HIV-1 protease also block FACE-1/Zmpste24 activity and induce the accumulation of farnesylated prelamin A *in vivo*, thereby explaining the lipodystrophy-like side effects of these drugs (*47*, *48*). However, pathogenic mechanisms of other forms of laminopathies are not yet clear. Information are still lacking for the molecular causes of other NE-related diseases, although functional analysis of each protein may give some hints. For example, developmental defects caused by MAN1 mutations may be due to deregulation of transforming growth factor β signalling (*49–51*). Disruption of Rb-MyoD transcription pathways and impaired muscle regeneration by lamin A/emerin mutations may be involved in the pathogenesis of Emery–Dreifuss muscular dystrophy (*52–55*). HEM/Greenberg skeletal dysplasia and ichthyosis, caused by LBR mutations, were initially suggested to be due to the loss of

Table 1. **NE-related mammalian diseases.**

Protein name (localization)	Human diseases (transmission type)	Mutant mice phenotypes (mutation type)	References
Lamin A (nuclear lamina)	Emery–Dreifuss muscular dystrophy (autosomal dominant or recessive) Dilated cardiomyopathy (autosomal dominant) Dunnigan type familial partial lipodystrophy (autosomal dominant) Limb-girdle muscular dystrophy (autosomal dominant) Charcot–Marie-Tooth disease (autosomal recessive) Mandibuloacral dysplasia (autosomal recessive) Atypical Werner syndrome (autosomal dominant) Hutchinson–Gilford progeria syndrome (sporadic) Generalized lipoatrophy (autosomal dominant) Restrictive dermopathy (sporadic)	Muscular dystrophy, dilated cardiomyopathy, impaired spermatogenesis (knock-out/homo) Dilated cardiomyopathy (N195K mutation/homo) Muscular dystrophy, dilated cardiomyopathy (H222P mutation/homo) Progeria-like symptoms (L530P mutation and exon skipping/homo) Progeria-like symptoms (progerin knock-in/homo>hetero) Healthy (lamin A-specific disruption/homo) Cardiac injury (heart-specific expression of M371K mutant transgene) Progressive loss of vascular smooth muscle cells in medial layer of large arteries (BAC-progerin transgene)	(*45*, *46*)
Lamin B1 (nuclear lamina)	Leukodystrophy (autosomal dominant)	Lethal at birth, abnormal lung development and bone ossification (gene-trap/homo)	(*58*, *59*)
Lamin B2 (nuclear lamina)	Acquired partial lipodystrophy (sporadic?)	Not tested	(*60*)
ALADIN (NPC)	Triple-A syndrome (autosomal recessive)	Not tested	(*61*)
Nup62 (NPC)	Infantile bilateral striatal necrosis (autosomal recessive)	Not tested	(*62*)
Emerin (INM)	Emery-Dreifuss muscular dystrophy (X-linked recessive)	Healthy, minimal motor and cardiac dysfunctions, nuclear-associated vacuoles, slight retardation of muscle regeneration (knock-out/homo)	(*53*,*55*, *63-65*)
LAP2α (nucleoplasm)	Dilated cardiomyopathy (autosomal dominant?)	Not tested	(*66*)
LBR (INM)	Pelger–Huët anomaly (autosomal dominant) HEM/Greenberg skeletal dysplasia (autosomal recessive)	Ichthyosis, loss of sterol reductase activity is compensated by DHCR14 (nonsense and frame-shift mutations/homo)	(*56*, *57*, *67*, *68*)
MAN1(INM)	Osteopoikilosis, Buschke-Ollendorff syndrome, melorheostosis (autosomal dominant)	Embryonic lethal at E10.5-11.5, defects in embryonic vasculature (gene-trap/homo)	(*49–51*)
SUN1 (INM)	Not found	Healthy, male/female sterility due to defective gametogenesis (knock-out/homo)	(*27*)
Nesprin-1 (ONM)	Pure cerebellar ataxia (autosomal recessive)	Healthy, defects in myonuclear anchorage (Nesprin-1 knock-out/homo) Healthy (Nesprin-2 knock-out/homo) Lethal at birth due to respiratory failure (Nesprin-1/2 knock-out/homo)	(*69*, *70*)

sterol Δ^{14} reductase activity (*56*). However, lack of LBR-dependent enzyme activity is compensated by another redundant enzyme DHCR14 *in vivo*, suggesting that these diseases are not due to impaired sterol metabolism (*57*).

Using cultured cells derived from human patients and mutant mice, as well as RNA interference technique, functional analyses of NE proteins at cellular levels are also making much progress. In many cases, cells with mutant or silenced NE proteins have abnormally shaped nuclei with lower mechanical stability and reduced stress response, and interacting partners show aberrant localizations. These cells often show different mRNA expression profiles, lower proliferation rates and higher tendencies to senescence and apoptosis. However, these cellular abnormalities themselves may not fully explain the clinical manifestations observed in human patients and animal models. To elucidate the molecular mechanisms of NE-related diseases, it will be necessary to consider not only protein functions but also tissue-specific expression patterns or organ/tissue-dependent environments.

TO LOVE AND TO CHERISH THE GENOME: FUTURE PERSPECTIVES

Although NE is an evolutionarily conserved structure, the precise regulatory mechanisms of NE functions are

significantly different among eukaryotic species. During evolution, each organism may have optimized its own NE depending on its genome size, cell size and life cycle. Recent innovations in genomic, proteomic and microscopic technologies have provided a wealth of knowledge of the NE components and functions. Future technical progress such as 'membrane lipidomics' and systems biology will help us solve remaining important questions. Understanding how NE protects chromatin and maintains nuclear functions will contribute to both basic and clinical sciences.

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