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Structural plasticity of the nuclear envelope and the endoplasmic reticulum

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The nuclear envelope is a double membrane structure, continuous with endoplasmic reticulum, and the morphological organization of both these structures is quite conservative. However, nuclear envelope and endoplasmic reticulum demonstrate distinct structural plasticity, i. e., based on common organization, cells may form various non-canonical membrane structures that are observed only in specialized types of cells or appear in different pathologies. In this review, we will discuss the mechanisms of the biogenesis of such non-canonical structures, and the possible role of this plasticity in the development of pathological processes.

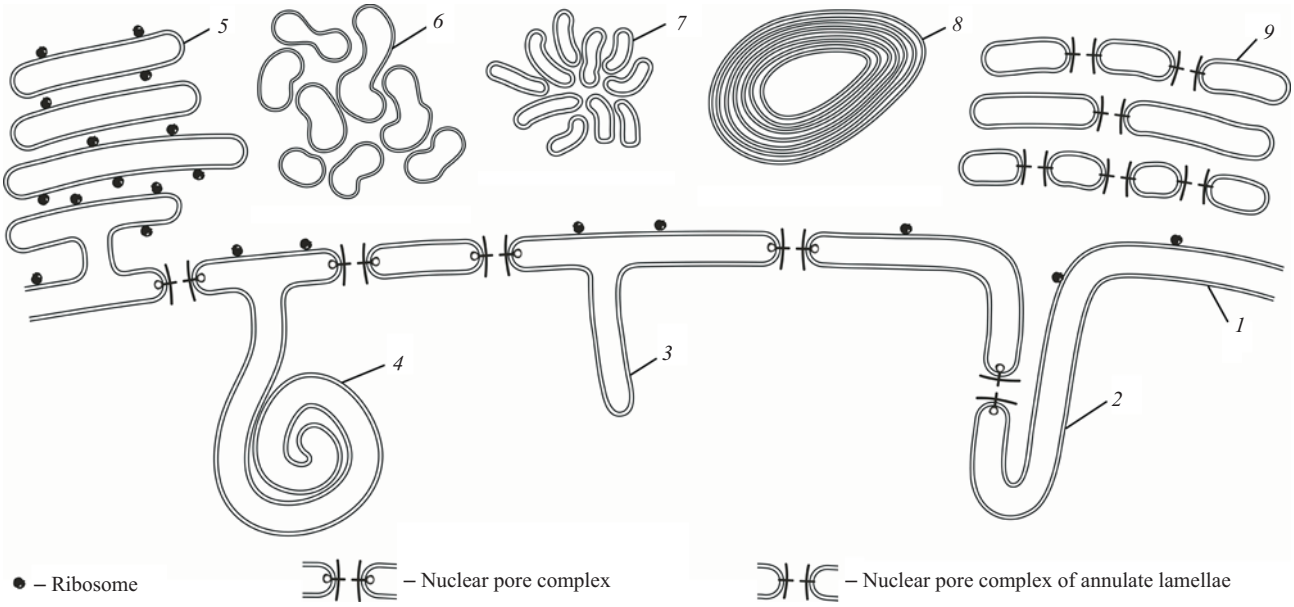
Keywords: nuclear envelope, endoplasmic reticulum, structural plasticity.

Introduction. The nuclear envelope (NE) is a double lipid bilayer consisting of the outer nuclear membrane (ONM), continuous with endoplasmic reticulum (ER), and inner nuclear membrane (INM). The morphological organization of NE and ER is quite conservative but based on this organization, cells may form various non-canonical membrane structures observed only in specialized types of cells or appearing in different pathologies (Figure). Recent studies have led to significant advances in the understanding of the biogenesis of such non-canonical structures, most notably in studies analyzing the overexpression of different proteins of NE and ER.

The nuclear envelope. The NE is formed by INM and ONM, which are separated by a periplasmic space. Although ONM is contiguous with ER, INM contains at least 100 unique components specific to this membrane [1–3].

Huge nuclear pore complexes (NPCs) are localized in perforations formed in NE membranes. NPCs are composed of multiple copies of ~ 30 distinct proteins (nucleoporins) arranged with eightfold radial symmetry, leading to an assembly of 500–1000 proteins with an estimated mass of ~ 125 MDa in vertebrates [4]. Recently, NPCs with ninefold symmetry that are found occasionally among the more typical eightfold symmetrical structures were described [5]. The yeast NPC organization was extensively investigated, and the molecular architecture was described using immuno-electron microscopy [6]. Altered expression of some nucleoporins affects both the nuclear size and shape. For example, deletion of yeast proteins Mlp1p and Mlp2p, structural components of the NPC basket, led to increased NPC mobility and clustering and the formation of misshapen nuclei that frequently exhibited NE blebs [7]. Nup136 overexpression in *Arabidopsis thaliana* increased nuclear size and elongation, whereas reduced Nup136 expression resulted in smaller, more spherical nuclei [8, 9].

NPCs control nuclear-cytoplasmic traffic. In some cases, NPCs do not provide a reliable separation of the nucleus and cytoplasm, *e. g.*, pore permeability increases during the development of viral infections, leading to the displacement of nuclear proteins into the cytoplasm and *vice versa* [10, 11]. It has also been shown



Structural complex of the nuclear envelope and the endoplasmic reticulum: *1* – nuclear envelope; *2* – invagination of the nuclear envelope; *3* – protrusion of the inner nuclear membrane; *4* – nucleoplasmic membrane structure (nucleoplasmic reticulum); *5* – rough endoplasmic reticulum; *6* – smooth endoplasmic reticulum; *7* – aggregate of membrane tubules; *8* – organized smooth endoplasmic reticulum (OSER); *9* – annulate lamellae (AL)

that pore permeability may increase during aging as a result of the destruction of long-lived nucleoporins [12].

Typically, traffic via NPCs is considered as the only way for cargoes to be transferred between the nucleus and the cytoplasm. However, some viruses are able to bypass NPCs in membrane vesicles that bud from the INM and merge with the ONM [13, 14]. A similar nuclear export process was recently described for large ribonucleoprotein particles involved in Wnt signaling in *Drosophila larvae* muscle cells [15]. The extent of the use of this nuclear export mechanism is currently unknown.

Plasticity of the NE. INM is adjacent to a thin (15–20 nm) protein layer, the nuclear lamina, which plays an important role in the formation and maintenance of the structural integrity of the cell nucleus. The lamina is composed of A- and B-type lamins, which belong to the type V intermediate filament family. Biochemical studies have shown that purified lamins can assemble *in vitro* into filamentous structures [16–18]. The mechanisms of the formation of the nuclear lamina *in vivo* are not well known.

Cells are capable of existing without lamin A, as it is known not to be expressed in embryonic cells [19]. B-type lamins are found in all cells; however studies using mice with knockout of both B-type lamins (B1 and B2) indicates the possibility that cells may exist without these proteins [20, 21].

An important parameter is the stoichiometry of A-type and B-type lamins. In liver and brain, A-type lamins have relatively low expression levels, whereas A-type lamins are increased in heart and muscle to withstand mechanical stresses and to limit potential disruption of chromatin [22]. Differentiation of embryonic stem cells was accompanied by increased level of A/C-type lamins [23, 24]. Downregulation of A-type lamins and concomitant irregularities in nuclear shape are exhibited in many cancers. For example, A-type lamins show low or no expression in small cell lung cancer cells [25–27]. In colon cancers [28], gastric cancers [29, 30], breast cancers [31, 32] and diffuse large B-cell lymphomas [33], the A-type lamin expression is also greatly reduced and correlates with increased recurrence of disease and a poor prognosis.

Lamin B1 overexpression leads to excessive production of the NE [34, 35], resulting in numerous invaginations. NE in such cells contains fewer nuclear pores [35] than in control cells. It appears that the excess NE is not a compensatory response but rather a consequence of lamin self-assembly, which is similar to self-assembly *in vitro* [16–18]. The formation of invaginations may be a consequence of excess surface area relative to a constant

nuclear volume and therefore a consequence purely driven by geometry. It should be stressed that the ER system is very poorly developed in cells overexpressing lamin B1, indicating that the NE growth is due to the ER membrane [35].

The overexpression of B-type lamin might be the cause of some diseases. For example, overexpression of the *Drosophila* ortholog of lamin B1 (Dm0) leads to neuronal cell death and a reduced life span [36]. It is also known that duplication of LMNB1 leads to neuronal demyelination and the development of autosomal dominant leukodystrophy [37].

The overexpression of lamin A does not produce significant growth of the NE but results in local reorganization of the NE, in particular, the formation of protrusions from the nuclear surface (nuclear blebs), were observed in cells overexpressing lamin A [35]. Importantly, nuclei of prostate cancer cells and some other cancer types contain nuclear blebs enriched in lamin A/C but deficient in lamin B [38, 39].

The overexpression of two transmembrane nucleoporins, Ndc1 and Pom121, produces formation of cytoplasmic aggregates of membrane tubules [35]. Any tubular structures are characterized by the presence of strong membrane bending, therefore one can assume that these nucleoporins either induce membrane bending or recruit proteins that bend membranes. It is important to note that Ndc1 [40–43] and Pom121 [44–46] play an important role in the *de novo* formation of new pore complexes, a process also conjugated with membrane bending.

Additionally, the structural organization of the NE might be affected not only by changing protein concentration but also by the changing the ability of proteins to interact with each other.

Recently, the role of protein SUN1 was demonstrated in the development of Hutchinson-Gilford progeria syndrome, a disease associated with a mutation of lamin A [47]. Mutant lamin A (progerin) has a high affinity for SUN1, leading to aberrant recruitment of progerin to the ER membranes during postmitotic assembly of the nuclear envelope. The dysregulated interaction of SUN1 and progerin during the NE reformation contributes to nuclear aberrancies typical to Hutchinson-Gilford progeria syndrome. This is a consequence of local but not total increases in protein concentration due to enhanced affinity of the protein to a structure at the moment of its formation.

Intranuclear membrane structures. INM can form small protrusions inside the nucleus [35]. Additionally, inside the nuclei of some tumor cells, compact clusters of membrane tubules have been described [48]. The functional significance of these intranuclear protrusions and intranuclear tubular complexes are currently unknown. Such structures are formed in large quantities after lamin A overexpression, particularly following the nucleoporin Pom121 overexpression [35]. Moreover, following the Pom121 overexpression, some cells were observed to contain globules with increased amounts of this protein within the nucleus. Using correlative light and electron microscopy, these complexes have been shown to be formed by membranes representing protrusions of the INM. Besides, such hypertrophic INM protrusions have been described to form nucleolar channel system [49, 50]. The nucleolar channel system consists of a set of intranuclear clusters of membrane tubules, which are located near the nuclear envelope or nucleoli. Such structures are identified in endometrial cells on 16–24 days of the menstrual cycle. The nucleolar channel system formation is induced by progesterone [51, 52]

Intranuclear membrane structures can be induced by the nucleolar protein Nopp140 [53] as well as proteins of NE. Following protein overexpression, intranuclear Nopp140-containing globules (R-rings) are observed. These complexes are formed by concentrically packed membranes which contain ER-specific membrane proteins. The morphology of these complexes and their proteins are very similar to those in the nucleolar channel system. In particular, both structures contain Nopp 140, which may be the major component that induces biogenesis of R-rings and of the nucleolar channel system [53]. Afterwards, it was also demonstrated that the formation of this system is complex and depends on another as yet unidentified protein [54]. Morphologically similar intranuclear membrane complexes have been observed in cells after prelamin A accumulation [55], overexpression of nucleoporin Nup153 [56], and lamin B2 [57].

The mechanisms of INM protrusion growth are poorly understood. The simplest assumption is that they form as a compensatory response to abundant formation

of INM (similar to the formation of NE invaginations after lamin B1 overexpression). However, it should be noted that the Pom121-induced protrusions are formed only after the cell passes through mitosis, *i. e.*, as a pathological response to the post-mitotic NE formation [35].

The NE of metazoan cells completely disintegrates during cell division to allow the mitotic spindle to access chromosomes. During mitosis, the majority of soluble NE proteins are distributed throughout the cytoplasm and transmembrane NE proteins reside in the mitotic ER [58–60]. It is important that membrane components are absent in the zone occupied by the mitotic spindle. It seems that the removal of membrane vesicles from the mitotic spindle determines the absence of membrane structures within the nuclei. It has been shown that the mitotic phosphorylation of the ER protein STIM1 is responsible for the dissociation of membrane vesicles from microtubules [61]. Non-phosphorylatable STIM1 leads to faulty localization of ER vesicles in mitosis, with vesicles localized inside the mitotic spindle. Additionally, the ER protein REEP3/4 was identified as having the ability to bind microtubules [62]. Depletion of this protein leads to the accumulation of ER vesicles on the surface of chromosomes, which in turn leads to the formation of intranuclear membrane structures in postmitotic cells [62]. Unfortunately, the nature of these structures has not been described, due to an absence of electron microscopic data. However, the results of these studies suggest that alterations of post-mitotic biogenesis of the NE may be a possible mechanism underlying the formation of intranuclear membrane structures.

The endoplasmic reticulum. ER is a highly dynamic cellular compartment, and its organization differs between cell types. In cultured cells, ER forms a network of membrane structures defined as either ribosome-covered (rough ER) or ribosome-free (smooth ER). The ER components can be divided into two distinct morphological types, cisternae and tubules, which are the major components of rough and smooth ER, respectively. ER is able to change its structural organization depending on the physiological state of the cell. A classic example of the fast reorganization of ER is the development of a smooth ER system in cells in response to phenobarbital [63].

The structural organization of ER and the possibility of structural transitions between different forms of ER depend on reticulons and DP1/Yop1p proteins, which are responsible for the formation of ER tubules, *i. e.*, ER components with highly curved membranes [64]. These proteins specifically act to induce curvature by inserting into the outer leaflet of the membrane [65]. The overexpression of certain reticulon proteins leads to the assembly of long tubules, whereas the absence of both reticulons and Yop1p in yeast leads to the loss of tubular ER [64]. Importantly, these proteins are excluded from ER sheets and NE, which may be considered as a flat ER sheet; however, reticulons have been shown to be involved in NPC assembly, most likely through the creation of a NE pore [66, 67].

Plasticity of endoplasmic reticulum. The nuclear membrane is an integral structural part of ER, which in turn is structurally and functionally closely associated with the Golgi complex. For a long time, both the Golgi and ER were considered stable structures; however, observations of live cells have demonstrated that the material in these compartments are constantly and rapidly exchanged [68], so that this macroscopically stable structure is formed by dynamic components. Morphological organization of ER and the Golgi complex depends on the balance of inflow and outflow components. For example, inhibition of the component inflow from ER leads to disassembly of the Golgi complex [69].

In cultured cells, ER forms a network of branching tubular structures and cisternae. In some situations, this network may be partially transformed into the so-called organized smooth ER (OSER), which may have different morphologies but is always characterized by an ordered packing of the membranes. Such structures are described after treatment with toxic substances [70–72]. Of particular interest is the fact that OSER can be formed after overexpression of certain proteins of the ER and NE [72–79].

OSER formation can be caused by dynamic interactions between cytoplasmic domains of the membrane proteins [78]. Some proteins cannot induce OSER formation but are able to form homodimers after fusion of the cytosolic domain with either GFP or YFP and gain the ability to induce the formation of OSER [78, 80]. This has been exploited to assess the tendency of fluorescent proteins to oligomerize under physiologic conditions [81].

The interactions leading to the reorganization of ER and formation of OSER have been shown to be weak – thus cytochrome b(5) demonstrated a lateral mobility in the membrane and is able to move freely inside and between OSER and the rest of the ER [78]. Some proteins of the nuclear envelope are capable of inducing reorganization of the ER network. Expression of the INM protein, Lap2β, leads to the development of OSER complexes formed with numerous tightly packed ER membranes [79]. Despite the high packing density of the membranes, Lap2β retained high lateral mobility. Low lateral mobility was described for YFP-tagged langerin, a protein required for the biogenesis of Birbeck granules, the characteristic organelles of Langerhans cells [80]. However, in this case, the formation of OSER was caused by the YFP oligomerization.

The OSER formation may be induced by the overexpression of different proteins, suggesting that this process is nonspecific. Moreover, there are some similarities between these complexes and intranuclear membrane complexes. Neither of these structures result from a compensatory response; instead, they result from the ability of abundant proteins to induce an excessive membrane modification (bending, collapse, stacking, *etc*.). Such membrane structures may be formed by the action of membrane proteins that have lost their ability to be exported from the ER due to mutation. Such pathological phenotypes, in particular, have been observed in a mouse model of Charcot-Marie-Tooth disease [82] and torsion dystonia [83].

Nucleoporins are localized not only in NE but also in the cytoplasmic stacks of membrane cisternae pierced by numerous pore complexes. Such complexes are called annulate lamellae (AL). AL have been described in the cytoplasm of a wide variety of cells, notably in oocytes, embryonic cells, and rapidly dividing cells including many types of tumor cells. Prolonged exposure to sublethal doses of the antimitotic drugs colchicine and vinblastine sulfate induces AL in diverse cell types and species [84]. AL are rarely found in the nucleoplasm, for example, in rat trophoblast cells at the definitive stage of differentiation [85].

Over the years, a variety of roles have been ascribed to AL [84], with the prevalent consensus that AL are stockpiles of excess nucleoporins that support subsequent, rapid cell divisions. In support of this theory, the major fraction of the nucleoporin Nup62 is localized inside AL [86] in Xenopus stage VI oocytes. However, in *Drosophila* embryos, AL have only a minor role in storing excess maternally contributed nucleoporins [87]. This is indicative of the fact that AL have functions unrelated to the preservation of excess nucleoporins, such as changing ER properties. In particular, it was shown that NPCs within AL suppress local Ca^{2+} signaling activity of the ER [88].

The expression of individual proteins normally does not lead to the appearance of additional AL. The only example of such induction was described for Pom121-overexpressing cells [89]. However, using correlative light and electron microscopy, it was demonstrated that Pom121-containing cytoplasmic complexes are formed by membrane tubules and do not contain NPCs, *i. e*., they are not AL [35]. In this regard, it should be noted that some reports indicate AL do not contain Pom121 [90].

Conclusions. NE and ER demonstrate high structural plasticity and the ability to vary according to the physiological conditions and during the development of pathological processes. Heterogeneity in the organization of these structures may depend on changes in the global or local concentrations of the individual components. This has been confirmed with numerous data showing changes in membrane structures following overexpression of NE and ER proteins. The available data suggest that both NE and ER demonstrate an apparent structural plasticity, leading to physiological cell adaptation to changes in the external environment, specialized functions in differentiated cells or the development of pathological processes.

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Структурна пластичність ядерної оболонки і ендоплазматичного ретикулуму

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Резюме

Ядерна оболонка – двомембранна структура, неперервна з ендоплазматичним ретикулумом, причому морфологічна організація цих структур досить консервативна. Однак для ядерної оболонки і ендоплазматичного ретикулуму характерна виражена струк-

турна пластичність, тобто на основі спільної організації в клітинах можуть формуватися різні неканонічні структури, які виявляються або в спеціалізованих клітинах, або за розвитку деяких патологій. У представленому огляді розглянуто механізми біогенезу подібних неканонічних структур, а також можливу роль структурної пластичності у розвитку патологічних процесів.

Ключові слова: ядерна оболонка, ендоплазматичний ретикулум, структурна пластичність.

Структурная пластичность ядерной оболочки и эндоплазматического ретикулума

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Резюме

Ядерная оболочка – двухмембранная структура, непрерывная с эндоплазматическим ретикулумом, причем морфологическая организация этих структур достаточно консервативна. Однако для ядерной оболочки и эндоплазматического ретикулума характерна выраженная структурная пластичность, т. е. на основе общей организации в клетках могут формироваться различные неканонические структуры, выявляющиеся либо в специализированных клетках, либо при развитии некоторых патологий. В настоящем обзоре рассмотрены механизмы биогенеза подобных неканонических структур, а также возможная роль структурной пластичности в развитии патологических процессов.

Ключевые слова: ядерная оболочка, эндоплазматический ретикулум, структурная пластичность.

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