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REVIEWS

Origin and Early Evolution of the Nuclear Envelope

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Abstract—The origin of the nuclear envelope is a milestone in the eukaryotic evolution. The nuclear envelope separates the nucleus from cytoplasm and provides selective traffic between them. It is the most prominent structure in modern eukaryotes, which has no analogues in prokaryotes. Here, we overview different theories of eukaryogenesis and contemplate the data concerning possible ways of the formation of the nuclear envelope and nuclear pore complex.

Keywords: nucleus, nuclear envelope, nuclear pore complex, eukaryogenesis, LECA

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INTRODUCTION

The origin of eukaryotic cell is one of the most intriguing and enigmatic issues of cell biology because of the conspicuous morphological differences between modern prokaryotes and eukaryotes. The origin of the nucleus is still one of the important and unclear phenomenon in the eukaryote evolution. Existing models explaining the origin of the nucleus could be divided in two main groups: endosymbiotic models and models of autokaryogenesis [1]. Models of the first group suggest that a eukaryotic cell appeared as a result of symbiosis between two ancestral forms, i.e., one symbiont became a nucleus and the other one provided cytoplasm. Alternative models of autokaryogenesis suggest that the nucleus appeared as a result of a gradual differentiation of the internal membrane system of the ancestral cell (see the figure).

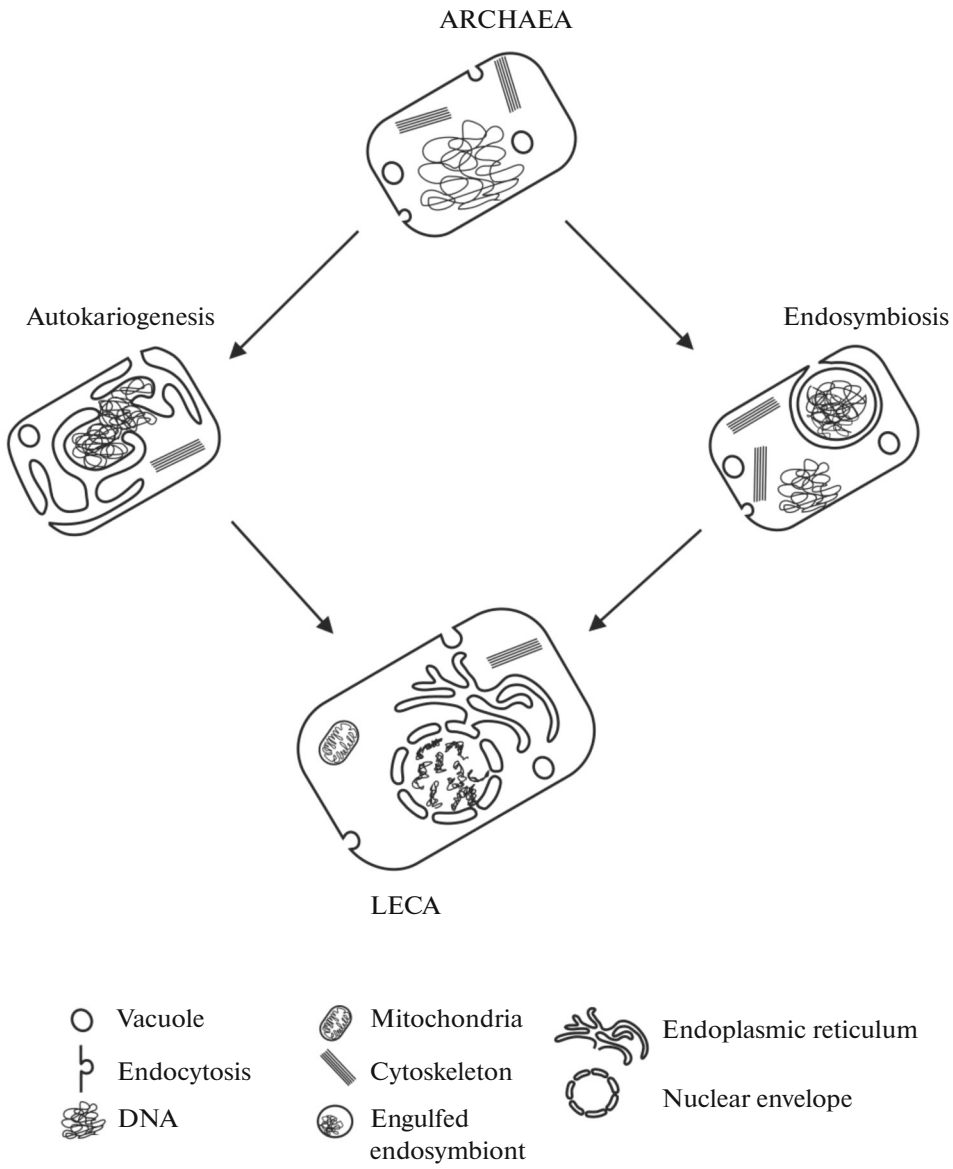
Recent studies of the genome of the sea archaea *Lokiarchaeota*, which have certain features of the eukaryotes, support the idea of a complex morphological organization of the ancestral form [2, 3]. In particular, their genome encodes similar to eukaryotic actin and gelsolin proteins, ESCRT-III complex, and small Ras-like GTP-ases. This suggests that these archaea possess cytoskeleton and an intricate system of the intracellular membranes and may be capable of phagocytosis. However, these assumptions remain hypothetical due to the lack of the information on structural organization of *Lokiarchaeota*.

Thus, on the basis of the latest data it can be proposed that the eukaryote ancestor was quite a complex organism and that the transition from prokaryotes to eukaryotes was not an unlikely event, as it could seem earlier [4–6].

ENDOSYMBIOTIC MODELS OF THE NUCLEUS ORIGIN

According to endosymbiotic theories, nucleus appeared as a result of the engulfment of a prokaryotic cell or virus by a host cell, followed by a sequential transformation of the engulfed organism into the nucleus. Russian biologist D.S. Mereschkowsky was the first to propose the endosymbiotic origin of the nucleus in his article [7], which was recently translated into English [8]. He believed that the nucleus evolved from a prokaryotic cell engulfed by an amoeboid cell (a prokaryotic cell gave rise to the nucleus, and an amoeboid cell, to the cytoplasm). Later the ideas of the endosymbiotic origin of the nucleus were developed by other authors [9–14]. Moreira and Lopez-Garcia modified the initial model employing the principle of anaerobic syntrophy (H_2-dependence) and postulated that the cytoplasm appeared as a result of the membrane fusion of several δ-proteobacteria around a methanogenic archaebacterium that developed into the nucleus [15, 16].

The formation of a cellular compartment surrounded by a continuous bilayer membrane would be a logical result of endosymbiosis. However, the tight connection between the endoplasmic reticulum and nuclear membrane, as well as the formation of the nuclear pore complexes still has to be explained by the endosymbiosis theories [17–21]. In modern eukaryotes, endoplasmic reticulum and nuclear membrane are parts of the same vacuolar system. Thus, overex-



Two main models describing a possible origin of a cell nucleus.

pression of nuclear membrane proteins can lead to changes in the endoplasmic reticulum structure [22–24]. In modern eukaryotes nuclear pore complexes can be formed de novo [25–27]; however, in all likelihood, this formation mechanism could evolve from pre-existing structures of the nuclear pore complexes.

In order to reconcile these facts with endosymbiotic theories, a new model was proposed assuming that the nucleus appeared as a result of the entrapment of α-proteobacteria by the archaebacteria [28]. According to this theory, a host cell (archeabacteria) increased the surface of contact with the protomitochondria (α-proteobacteria) via multiple protrusions of the outer membrane in order to make the exchange of molecules more efficient [28]. Gradually growing protrusions completely surrounded the α-proteobacteria and formed a long network of channels, which later became an inner nuclear membrane and the endoplasmic reticulum of eukaryotes, and the openings between the protrusions were occupied by the nuclear pore complexes. However, this model is not yet verified experimentally.

MODELS OF AUTOKARYOGENESIS

The most known model of autokaryogenesis suggests that the nuclear membrane and endoplasmic reticulum evolved from invaginations of plasma membrane of a prokaryotic cell [29–32]. Large genome of the ancestral eukaryotic organism could have played the key role in the evolution of the nuclear membrane. Linear chromosomes carrying the packed genome

were able to interact via their telomere regions with multiple invaginations of the plasma membrane, a precursor of the endoplasmic reticulum [33].

An endospore model can be regarded as a special case of the autokaryogenesis concept. According to this model, nucleus appeared as a result of an abnormal cell division, during which one of the sister cells was engulfed by the second sister cell, as it occurs in Gram-positive bacteria during the endospores formation [34].

One more interesting model postulates that the nuclear membrane arose in an archaebacteria cell containing mitochondria from the membranes of lipid vesicles of the bacteria [35]. In any case, the developed system of membranes within the cell could play an important role in the formation of the nuclear envelope. Thus, autokaryogenesis models are able to explain the origin of the membrane component of the nuclear envelope. The computer modeling shows that even a fragmentary nuclear membrane without nuclear pore complexes could considerably restrict the diffusion within the cell and favor the formation of protein concentration gradients between the nucleus and cytoplasm (for example, gradients of proteins interacting with chromatin) [36].

EVOLUTION OF THE NUCLEAR PORE COMPLEX

The appearance of the physical barrier between the genome and surrounding cytoplasm led to the formation of another important system, i.e., a system of the nuclear pore complexes providing a selective transport of components between the nucleus and cytoplasm in a eukaryotic cells.

Nuclear pore complex of modern eukaryotes consists of approximately 30 different proteins called nucleoporins [37, 38]. According to their functions, nucleoporins can be grouped into three categories: (1) membrane nucleoporins that anchor the whole complex in the membrane; (2) scaffold nucleoporins forming the framework of the nuclear pore complex; (3) barrier nucleoporins providing a selective transport of macromolecules through the nuclear pore complex [38].

Recently a significant progress has been made in determining the atomic structure of multiple scaffold nucleoporins. Interestingly, six scaffold nucleoporins display similarities in their 3D structure with subunits of COPII (coat protein II), a coatomer complex transporting vesicles from the endoplasmic reticulum to the Golgi complex. Despite a low homology of the amino acid sequences of nucleoporins Nup84, Nup125(C), and Nic96, they share a similar U-shaped architecture with Sec31, a component of complex Sec13/31 of the COPII coatomer complex [41–46]. Furthermore, the pattern of the Sec31 positioning in between the propeller blades of Sec13 can be found in heterodimers of Nup145(C)-Sec13 and Nup85-Seh1 [41, 46–48]. In addition, antiparallel packaging of complex Nup84-Nup145(C) resembles the organization of Sec31 dimer within Sec13/31 [42, 48]. Therefore, it is likely that these six scaffolding nucleoporins (comprising ~60% of the scaffold layer) and elements of the COPII coatomer have a common ancestor.

The evolutionary origin of other scaffold nucleoporins remains unclear. The structure of Nup170, Nup133 and Nup120 [49–52] has no obvious homology with known vesicular proteins. However, it was shown that these nucleoporins share weak similarities between each other [53] and are characterized by rich interaction network with the membrane proteins of the nuclear pore complex. Nup170 and Nup157 from the yeast, as well as nucleoporin Nup155 of the vertebrates, form multiple direct contacts with membrane nucleoporins [54–56]. All three proteins, yNup120, vNup133, and yNup170, contain helices mediating direct contacts with the lipid layer of the membrane [57, 58]. Interactions between scaffold nucleoporins and proteins of the nuclear envelope resemble binding of the adaptors of the COP/clathrin coats to the proteins of cargo vesicles. It is possible that some of the scaffold nucleoporins are evolutionary related with the adaptor proteins of cargo vesicles; otherwise, it can be an example of the functional analogy.

Homologues of membrane nucleoporins also could be found among transmembrane proteins. A luminal domain of gp210 displays similarity with an extracellular part of intimin-like transmembrane proteins [59, 60], while a luminal domain of yeast protein Pom152 resembles cadherins, proteins of the plasma membrane [61]. Thus, it is possible that the membrane nucleoporins originated from the proteins involved in sorting of macromolecules on the cell membrane surface.

Selective exchange of macromolecules between cytoplasm and nucleoplasm are conducted by special nucleoporins, which are enriched with the phenylalanine (F) and glycine (G) repeats (FG-repeats). Specific interactions between FG-repeats and karyopherins define the selectivity of transport between nucleus and cytoplasm [62]. Albeit there is no obvious homology between FG-rich nucleoporins and the proteins of the COP/clathrin coats, FG-rich nucleoporins are able to interact both with soluble molecules and with transmembrane proteins [63, 64]. This functionally resembles the COP/clathrin coat proteins that act as filters to selectively enrich the forming vesicles with molecular cargo.

Interaction of nucleoporin's FG-repeats with the transport nuclear receptors, β-karyopherins, is important for the proteins transport through the nuclear pore complex. β-Karyopherins either directly bind protein molecules or bind protein via adaptors called α-karyopherins [65, 66]. A complex consisting of β-karyopherin and cargo molecule interacts with FG-repeats of nucleoporins and the cargo molecule is translocated through the nuclear pore complex. Analyses

of the structure and amino acid sequences revealed a considerable similarity between β-karyopherins and the adaptor proteins of coatomer complex α and β [59]. In addition, the architecture of karyopherins resembles spatial structure of nucleoporins [61, 67], and nucleoporins Nup188 and Nup192, similar to β-karyopherins, interact with FG-repeats [68]. This may suggest that nucleoporins, karyopherins, and proteins of the coatomer complex are evolutionary related.

LAST EUKARYOTIC COMMON ANCESTOR (LECA)

Last eukaryotic common ancestor (LECA) is a hypothetical organism, from which all modern eukaryotes evolved. Due to the paucity of the paleontological data, reconstruction of a possible organization of LECA is performed by methods of molecular paleontology [4].

LECA probably had a linear genome packed into chromosomes, and its size could considerably exceed the size of genomes of modern bacteria and archaea [69]. A systematical analysis of genome duplications in eukaryotes revealed that LECA's genome contained hundreds of gene duplications, especially duplication of genes involved in the protein turnover [70–72]. On the basis of the comparative analysis of the genomes of various eukaryotic groups it was proposed that the LECA genome was enriched in introns and the intron density in its genome was much higher than in genomes of modern free living eukaryotes [73–76]. It is possible that the nucleus formation was required for the separation of splicing and translation processes [77]. However, an opposite scenario is also possible: the intron spread became achievable only after the formation of the nuclear membrane separating the nuclear and cytoplasmic compartments [78]. In both cases, the presence of splicing supports the idea that the nuclear envelope in LECA ensured the selectivity of the import and export of macromolecules.

Multiple alignment of nuclear membrane proteins of different eukaryotic supergroups suggests that LECA possessed proteins with LEM-domains [59], which are present in modern eukaryotes and are involved in interactions with chromatin, telomeres [79–82] and repressed genes of rDNA [83]. Transmembrane protein LUMA interacting with nuclear proteins SUN2, lamins, and emerin [84, 85] is conserved in three eukaryotic supergroups and also in bacteria [84, 86], suggesting that LUMA might have been already present in LECA [86]. However, in silico studies did not identify any homologues of lamins in LECA [87].

LECA proteome could also contain proteins of the nuclear pore complex. Analysis of 60 eukaryotic genomes from 5 supergroups suggested that LECA was probably carrying 23–26 out of 30 nucleoporins of modern eukaryotes [88]. Among the reconstructed nucleoporins were gp120 and Ndc1, which anchor nuclear pore complex to the membrane, as well as Tpr, Nup50, and Nup153 that form "basket" of the nuclear pore complex. Last three proteins bind lamins directly in modern eukaryotes [89]. Besides, proteins Tpr and Nup153 interact with chromatin and are involved in regulation of gene expression [6].

LECA might also possess a developed system of inner membranes. It is possible that endoplasmic reticulum of LECA contained chaperones, proteins responsible for the correct formation of a secondary structure, reorganization of disulfide bridges, N-glycosylation, and a reverse translocation of incorrectly packed proteins [90]. Endoplasmic reticulum of LECA was able to form peroxisomes typical of the eukaryotes [91]. According to the reconstruction data, LECA could possess the Golgi complex with stacked cisternae structure [92] and, like modern eukaryotes, could perform a vesicular transport of proteins and processing of N-glycans [93]. The prevalence of the clathrin-mediated mechanism of the vesicle transport from Golgi complex to the cell membrane among Trypanosomatids, Apicomplexa, and plants suggest the possibility that this particular mechanism can be regarded a basic one in all eukaryotes and most probably originally emerged in LECA [94].

Main components of the actin [95, 96] and tubulin [97] cytoskeleton, as well as associated motor proteins, such as kinesins [98], myosins [99], and dyneins [100, 101] were also reconstructed in LECA using bioinformatical approach. Supposedly, LECA had a flagellum, which fulfilled both sensor and locomotion functions [102].

Since LECA possessed a complex and developed cytoskeleton, it could likely be able to transport molecules into the cell via endocytosis. It is conceivable that in the process of endocytosis an α-proteobacterium could get inside the cell and subsequently become a mitochondrion [103, 104]. Since all known eukaryotes contain mitochondria, it was suggested that mitochondria were acquired by LECA before the nucleus formation [105–107].

All data obtained by molecular paleontology supports the idea that LECA was a more complex and multifunctional organism than prokaryotes and was characterized by the presence of mitochondria; differentiated endoplasmic system; actinomyosin- and tubulin-based cytoskeleton; flagellum; a system of nucleocytoplasmic transport, and endocytosis. A big genome of LECA possibly was organized in linear chromosomes subcompartmentalized into hetero- and euchromatin by specialized proteins [4].

CONCLUSIONS

Metagenomic data analysis provided a lot of new information about possible ways of early evolution of eukaryotes. Comparative analysis of genes and group of genes encoding proteins involved in certain physio-

logical process in bacteria, archaea, and eukaryotes uncovered common features of the processes and helped to trace the origin of different cell structures of eukaryotes. The available data suggests that the ancestors of eukaryotes possessed complex systems of membranes, which gave rise to the nuclear membrane.

Proteins can travel through the whole volume of a prokaryotic cell; however, the situation changes after the formation of cell compartments separated by the membranes. Thus, a special system required for the protein sorting and transport appeared with the nucleus formation, as the proteins involved in nuclear processes should get easily inside the nucleus, while the cytoplasmic proteins should stay out of the nucleus. In order to distinguish proteins for the nuclear import or export in the cell, two different signals are necessary: nuclear localization signal and nuclear export signal. These signals – short amino acid sequences incorporated into the proteins – interact with karyopherins and provide the translocation of a protein to or from the nucleus. However, the origin of both signals is still unknown.

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