

# A Review on Theories on the Origin of the Nucleus in Modern Eukaryotes

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## ABSTRACT

Nucleus (plural nuclei) is the Latin term for the central organelle of eukaryotic cells. While the building blocks of eukaryotic cells (humans, plants and amoebas) feature command centers containing DNA, prokaryotes (Eubacteria and *Archaeobacteria*) do not. This membrane-bound nucleus has played an indispensable role in the diversification of today's multicellular life, and the uncertainty surrounding its evolution has long been a puzzle for scientists studying the evolution of modern organisms. Emergence of the nucleus and our own origin are quite interlinked. Over the years, the subject of the origin of the eukaryotic nucleus has been discussed in depth by microbiologists, evolutionary biologists, cell biologists, etc., and even though the subject has brought many biologists together, their studies continue to produce different perspectives of the birth of the nucleus. We discuss here primarily theories arguing for the prokaryotic or viral origin of the nucleus, but also investigate reductive or gemmate theory which suggests that the origin of the nucleus dates back to the Last Universal Common Ancestor (LUCA), and that prokaryotes are a product of reductive evolution. Finally, we take a brief glance at the domain cell theory of life supporting the LUCA as the origin of the nucleus. In concordance with the domain cell theory, we also concluded that the origin of the nucleus rooted from the last universal common ancestor and all three domains of life evolved separately.

**Keywords:** Nucleus; Prokaryote; Eukaryote; Evolution; Last universal common ancestor

## ABBREVIATIONS

LUCA: The Last Universal Common Ancestor; LECA: The Last Eukaryotic Common Ancestor; NE: Nuclear Envelope; NPCs: Nuclear Pore Complexes; PVC Superphylum: Planctomycetes-Verrucomicrobia-Chlamydiae superphylum; OI model: Outside-in Model; IO Model: Inside-Out Model

## INTRODUCTION

In general, the nucleus is defined as the driving force behind the complexity of eukaryotic cells [1,2], and its emergence was probably the most prominent step in cellular evolution. In 1831, the opaque area in the orchid cells as both the areola and nucleus, although the latter would become the globally accepted term [3].

Studies conducted over the years have suggested that the nucleus is the result of a giant evolutionary innovation in eukaryotic

cells, since each nucleus is surrounded by a double lipid-layer membrane with thousands of sophisticated protein complexes that are known as Nuclear Pore Complexes (NPCs) [4,5]. NPCs control molecular traffic inside and outside the organelle [6]. Inside the nucleus, polymerases and other special enzymes turn the protein-coding message of DNA into RNA. Other proteins process the RNA strand to ensure the accuracy of the message transmission to ribosomes located outside the nucleus. As a result, the unique structure of the nuclear envelope leads to the separation of the transcription and translation processes, and provides a high-quality control mechanism for eukaryotic cells [7,8]. The picture in prokaryotes, however, is quite different, since DNA, RNA, ribosomes and proteins work together within the main cell compartment [9,10]. Immediately after DNA transcription, nearby proteins begin translating the newly synthesized RNA into a new protein [11]. These processes have led to speculations about the evolution of complex life.

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For many years, two opposing theories on the early eukaryotic evolution and the origin of the nucleus have dominated [2]. Endosymbiosis and autogenously-based theories suggest that the prokaryotic ancestor gradually, or via endosymbiosis developed such eukaryotic features as the nucleus [12-15] while reductive evolution-based theories assert that eukaryote-like cells predate bacteria and *Archaea*. According to this theory, a prokaryote emerged when a eukaryotic cell lost its nucleus and developed the bacterial cell wall that is present in modern bacteria [16]. Comparisons of fully sequenced microbial genomes introduced new data to this argument, showing that eukaryotes contained both archaeal and bacterial genes. Archaeal genes in eukaryotes are involved in the processing of genetic information [4] while bacteriogenics are mainly responsible for metabolic and basic functions [5].

This task division originated from an ancient symbiotic partnership and the friendly merging of bacteria and *Archaea* [6]. Highlighting the existence of a nucleus or nucleus-like structure surrounded by a double membrane in *Gemmata obscuriglobus* bacterial species [7]. In 2001, a new concept in eukaryogenesis was proposed by virologist in his famous article "Viral eukaryogenesis: Was the Ancestor of the Nucleus a Complex DNA Virus?", in which DNA viruses was introduced as the origin of the nucleus [8].

The common suggestion of all theories in this field is the necessity of the nucleus for the evolution of present-day eukaryotes. Scientists have thus investigated new techniques that would allow them to explain the relationship between microorganisms that have gone much further back in time. Here, we will review the proposed models regarding the origin of the nuclear compartment, and discuss the available data in detail.

## LITERATURE REVIEW

### Theories arguing for the prokaryotic origin of the nucleus (Prokaryotes first hypotheses)

Eukaryogenesis has led to the formation of organisms with completely different lifestyles and morphologies from prokaryotes, and it is assumed that the diversity of eukaryotes is partially or completely attributable to the presence of the nucleus [9].

A comparison of eukaryotic and prokaryotic cells reveals a large number of structural (e.g. Nuclear envelope, NPCs) and procession (e.g. phagocytosis, exocytosis) differences [10]. The earliest theories related to eukaryogenesis suggest that eukaryotes are actually descendants of prokaryotes. The end symbiotic- and autogenously-based models of the origin of the nucleus are the most widely accepted concepts [11]. Although there is general consensus among these models that mitochondria and chloroplast are symbioses rather than cell organelles [11,12], the question of how the nucleus of eukaryotic cells emerged has long been a matter of controversy.

Endosymbiotic theory has been shaped based on a fusion event, in which a unicellular free-living prokaryote was swallowed by another prokaryote. In this case, the engulfed prokaryote

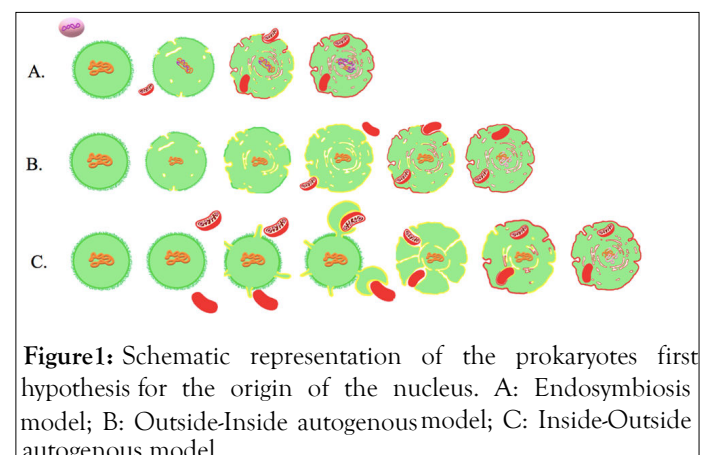
represents the nucleus and the encapsulated prokaryote is the source of the cytoplasm [13]. The autogenously models, on the other hand, assert that the progressive development of a single protoeukaryotic ancestor led to the birth of the nucleus [14].

In this section, the source of the nucleus in both endosymbiosis and autogenous models will be thoroughly investigated, and in addition, the conventional autogenous Outside-Inside (OI) models will be compared with the newly proposed autogenous Inside-Outside (IO) alternative.

**Endosymbiotic theory:** The endosymbiotic hypothesis is chronologically the oldest theory, being focused primarily on prokaryotic progenitors in terms of the origin of mitochondria and plastids. The endosymbiotic origin of chloroplasts was first introduced in 1883 [15] and was then developed by the Russian botanist Konstantin Mereschkowski in his study in Russia: "The nature and origins of chromatophores in the plant kingdom" in 1905 [16] and "The Theory of Two Plasms as the Basis of Symbiogenesis, a New Study of the Origins of Organisms" in 1910 [17]. Afterwards, the origin of mitochondria with endosymbiosis [18].

A few years later, the founder of serial endosymbiosis theory, published an article entitled "On the Origin of Mitosing Cell", describing the process of eukaryogenesis, substantiated with microbiological evidence, in *Theoretical Biology* in 1967 [19]. In the article, the endosymbiosis theory and hypothesized that the three basic organelles in eukaryotes (mitochondria, photosynthetic plastids and nuclei) were once free-living prokaryotic cells [13,19], and claimed that (endo) symbiosis was the most important factor in the formation of eukaryotic cells (the source of the nucleus) [9,13]. She was perhaps the first person to combine endosymbiotic theory with eukaryogenesis.

Analogically, endosymbiotic-based models suggest that the nucleus, plastids and mitochondria emerged as a result of sequential phagocytosis and serial endosymbiosis [20]. According to these models, the birth of a eukaryotic cell requires a host cell to entrap an endosymbiont (Figures 1A-1C).



**Figure 1:** Schematic representation of the prokaryotes first hypothesis for the origin of the nucleus. A: Endosymbiosis model; B: Outside-Inside autogenous model; C: Inside-Outside autogenous model.

**Endosymbiosis model:** Symbiosis between a eubacteria and an *Archaea* caused the birth of the nucleus. Following the merging of mitochondria ancestor with this union, the first eukaryotic cell emerged [6].

**Outside-inside autogenous model:** The supposed order for the development of the nucleus begins with the evolution of endo/phagocytosis system. Afterwards, the generation of an endomembrane system caused the formation of NE and NPCs. This model suggests that the mitochondria acquisition occurred after the formation of an internal endomembrane system [33].

**Inside-outside autogenous model:** In the IO model, which known as the mitochondrion-first scenario, the order of cellular innovation is assumed in the opposite direction to OI-based models. According to this model, the formation of extracellular blebs around the mitochondrion ancestor was the first step in the formation of the nucleus [14]. Both IO and OI autogenous models, however, acknowledge that a gradual increase in the complexity of the archaeal ancestor led to the birth of the nucleus.

Different endosymbiotic models have suggested that the host (source of cytoplasm) may be an *Archaea* [8,13], a gamma-proteobacterium or a Planctomycetes [21,22]. In the same way, an *Archaea* [22,23], a Spirochet or a large DNA virus [8,13,24] have been considered as endosymbiont (the source of the nucleus). In general, it is quite difficult to define the order of symbionts, and to determine which symbiont (the source of nucleus or mitochondria) was engulfed earlier. As an exception, however, the syntrophic consortium model proposes that the three members of the symbiotic community (cytoplasm, nucleus and mitochondria) fused together simultaneously [25,26]. Within this model, hydrogen transfer between symbionts introduced as a selective force may have led to the emergence of the nucleus. In this model, the endosymbiosis between methanogenic archaeobacteria and hydrogen-producing  $\alpha$ -proteobacteria has been defined as the origin of eukaryotes [25]. The proposed anaerobic methane oxidizers, however, seem to be phylogenetically more like methanogens than  $\alpha$ -proteobacteria [27].

Considering the collected data from recent phylogenomic and biochemical analyses of the mitochondria and chloroplast genome, scientists agree that modern eukaryotes were previously chimeras, formed via the integration of at least two cell types (an engulfed fast-evolving  $\alpha$ -proteobacteria bacterium that transformed into mitochondria and the host that contained it) [28]. Due to the absence of such a convincing phylogenetic signature of the nuclear genome, however, the transformation of prokaryotic endosymbiont into a nucleus seems an unlikely process for the origin of the nucleus [29].

Moreover, endosymbiotic models fail to provide any supplemental or logical explanation for the structural continuity of the nuclear envelope at the junction of its inner and outer membranes. Furthermore, these models have not clarified how a host cell could lose its own transcriptional and translational mechanisms, and instead adopt the mechanism of the endosymbiont [5,29,30].

The origin of eukaryotic cells, and especially the formation process of the nuclear envelope, has yet to be fully understood in endosymbiosis-based models. The gap in the eukaryogenesis process was attempted to be filled by a new set of hypotheses, known as "autogenous" models.

**Autogenous models:** One common feature of endosymbiotic and autogenous models is that they both propose a prokaryotic progenitor as the origin of eukaryotes. Autogenous models assume, however, that the nucleus was formed by progressive structural modification in a single prokaryotic lineage [10] and arose de novo in the cytosol of a proto-eukaryotic ancestor in response to selective forces [12]. Though the endosymbiotic models suggest that the fusion of at least three different cellular ancestries (source of cytoplasm, nucleus and mitochondria) is required for eukaryogenesis, autogenous models suppose that the fusion corresponds to the union of two ancestries - the source of mitochondria and cytoplasm [10].

Numerous autogenous models have been put forward to explain the origin of eukaryotes and their generation process [14,31,32]. Based on the cellular topology of the prokaryote-to-eukaryote transition, the autogenous models (the traditional Outside-In [OI] and newly proposed Inside-Out [IO] model) will be discussed in the following sections.

**OI model:** Several OI models have been proposed that assume that a wall-free prokaryotic cell with a single membrane-bound is the progenitor of eukaryotes [31-33]. The ability of a cell to generate an internal vesicle by invagination the outer plasma membrane (perhaps for feeding) is the starting point of the OI-based hypothesis, assuming that the intracellular membrane system evolved before the nucleus through primitive phagocytosis in Figures 1A-1C, and that the nuclear compartment derived from this pre-existing intracellular membrane system [31,34,35]. The most common and known (the most described in textbooks) OI model for the origin of the nucleus was put forward in 1975 [33], who suggested that the mechanism of compartmentation was essential in the prevention of DNA degradation by motor molecules [36].

Another matter relates to how cells gained the phagocytosis ability required for the formation of a cytoskeleton in the cell. The OI autogenous hypothesis suggests that, most probably, the proto-eukaryotic ancestor also possessed a cytoskeleton that was indispensable for phagocytosis [1,37] and was necessary for structural integrity of the cell and its response to osmotic challenges [38]. This may be supported by phylogenetic data collected from the genome of the Lokiarchaeota (the sister of Eukarya), which contains more eukaryotic-like genes that lead to the emergence of the universal features of eukaryotes, such as the cytoskeleton, membrane remodeling and vesicle formation [39-41].

The weakest aspect of all OI models is their failure to fully explain the birth of the nuclear compartment and the structure of NPCs. Baum, the founder of IO model, suggested two predictive ways in which the nuclear envelope could have been formed based on OI models. In the first case, the ribosome-free ER vesicles enclosed the chromatin, and the non-fused points in some regions became the source of NPCs. Alternatively, a single ER vesicle surrounded the chromatin in a concave curvature shape, and the non-closure points of the vesicle formed a primitive NPC, and by stabilizing this primitive NPC, the selection promoted the formation of additional pores via an unknown procedure. In either way, NPCs prevent the complete

surrounding of chromatin by the nuclear envelope, and regulate material exchange between the nucleoplasm and cytoplasm [10].

**IO models:** According to early phylogenetic studies, OI models generally suggest that mitochondria arise in cells with a nucleus [32,33], which means that mitochondria emerged later [42]. Indeed, there are a number of groups of eukaryotes that lack mitochondrion, such as *Giardia lamblia* [43]. A molecular analysis of their genome, however, revealed the presence of mitochondrial genes, which implies the presence of mitochondria in their evolutionary past. In addition, more recent phylogenetic data revealed the presence of mitochondria in the Last Eukaryotic Common Ancestor (LECA) [44,45]. All these new data led to the formulation of new autogenous models (IO) based on the precedence of mitochondria acquisition to the nucleus in eukaryotic cells [46-48].

Like OI models, in IO models, the development of membrane protrusions following the disappearance of the glycoprotein-rich cell wall of proto-eukaryotic ancestor was also necessary for nuclear evolution [14]. In contrast to the OI models, the IO model assumes that the ability of prokaryotes to form outward protrusions [49-53] brought about an increase in the surface area of the cell (Figures 1A-1C), which enhanced the cell accessibility of external materials and the ability of the cell to entrap the free-living ancestor of mitochondria. The progenitors of NPCs (especially outer ring nucleoporins) and the LINC complex played an important role in the stability of these outward protrusions and their lateral expansion. Following the disappearance of the cell wall in the proto-eukaryotic cell, extracellular blebs formed a continuous eukaryotic plasma membrane that provided control over secretion and was a barrier to external threats. This model suggests that the nucleus is actually composed of a single bounding membrane that is equivalent to the monolayer plasma membrane of the wall-free archaeal ancestor cell folded by NPCs [14]. This implies that the nucleus is one of the most ancient parts of eukaryotic cells.

The IO model also elicits a conserved nuclear remodeling mechanism for the loss of the nuclear compartment during open mitosis and the local breakdown of the NE in closed mitosis [54]. It also suggests a plausible mechanism for the insertion of new NPCs into the nuclear envelope during the interphase that is similar to the process in which outward protrusions are generated in the ancestor cell. As time passed, the NPCs' progenitor proteins gained a new function and regulated the transport of materials across the nuclear envelope [14].

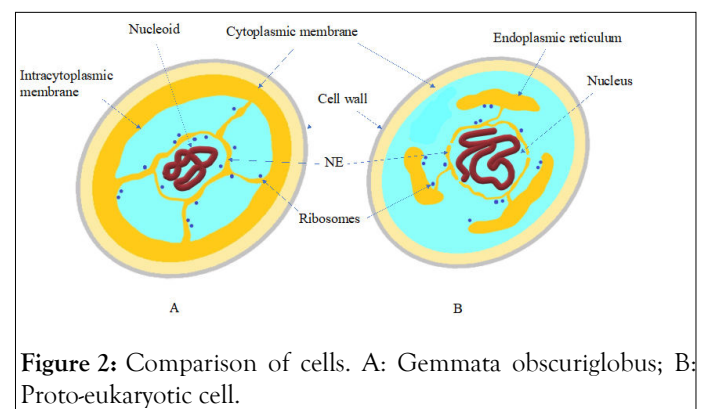
Similarly, ER originated from the negative gaps among these protrusions, and the fusing of adjacent blebs generated a continuous network that was homologous to the ER and NE lumen of modern eukaryotes [14]. With the significant advances in structural and biochemical analysis, it was found that: (a) A structural homology exists between several nucleoporins and vesicle coat proteins such as clathrin/adaptin, COPI, and COPII [55,56]; (b) There is a similar  $\alpha$ -helical solenoid and  $\beta$ -propeller/ $\alpha$ -solenoid signature in outer ring Nups and membrane-coating complexes -such as clathrin/adaptin [57]; (c) These increase the possibility of the co-evolution of coat proteins with several

nucleoporins from a common ancestor [58-60] and render the IO autogenous-based theory possible.

### Theories suggesting that the nucleus originated from the last universal common ancestor (Gemmata or reductive evolution model)

All symbiosis and autogenous models assume that bacteria and *Archaea* appeared earlier than eukaryotes in the tree of life, although the homology-based reductive theory of John Fuerst offered a different perspective of eukaryogenesis.

In 1984, it was shown that the nuclear material of eubacterium *Gemmata obscuriglobus*, a member of phylum Planctomycetes, was wrapped by a membrane [61], while 7 years later, in 1991, the existence of two nuclear membranes, surrounded the DNA-containing nucleoid in freshwater *G. obscuriglobus* using sophisticated electron microscopy techniques [7]. This observation challenged the traditional classification of organisms as "prokaryote and eukaryote" based on the structural features of the cell (Figures 2A and 2B).



**Figure 2:** Comparison of cells. A: *Gemmata obscuriglobus*; B: Proto-eukaryotic cell.

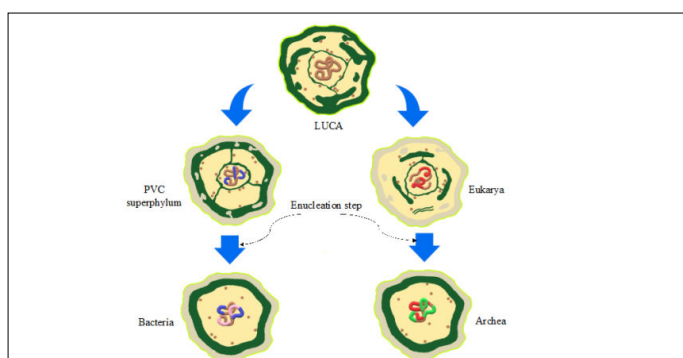
The similarity between proto-eukaryotic cell and gemmata like cell suggests that planctomycetes evolved via reductive evolution from a eukaryote-like LUCA ancestor or a proto-eukaryotic cell.

A further investigation of *G. obscuriglobus* revealed the existence of an endocytosis-like process behind the uptake of proteins into the cell which was not previously identified in Bacteria or *Archaea* [62]. Moreover, *G. obscuriglobus* has been found to possess some internal membrane-bounded compartments that include pore-like structures similar to eukaryotic nuclear pores, and with eight-fold rotational symmetry [63]. Subsequently, a bioinformatic analysis of proteomic data identified common structural domains in some of the *G. obscuriglobus* proteins and eukaryotic membrane coat proteins involved in both vesicle-trafficking systems and in NPCs [64-66]. The occurrence of such paradigmatic eukaryotic features in *G. obscuriglobus* and in several related bacteria in the Planctomycetes-Verrucomicrobia-Chlamydiae (PVC) superphylum suggest three hypotheses:

- Symbiosis had occurred between a compartmentalized PVC bacterium (host) and an *Archaea* (source of the nucleus) [65]. Endosymbiosis-based theories are discussed earlier in the study.
- There is a possible homology between PVC superphylum and eukaryotes [65,67,68], and while there is a lack of any firm evidence establishing the homologous relationship between PVC phylum and eukaryotes [69]. Mcinerney et al. suggested

this similarity between PVC superphylum and eukaryotes was analogous given the lack of molecular homology [70]. There is insufficient evidence to either rule out homology or to confirm the analogy [67]. Interestingly, regarded the eukaryotic signature proteins as remnants of the LUCA that played a crucial role in the early evolution of the nucleated Bacteria and Eukarya [71].

- The birth of the nucleus could date back to the proto-eukaryote-like Last Universal Common Ancestor (LUCA), but subsequently disappeared from the Bacteria (except PVC superphylum) and *Archaea* domains [72]. This suggestion is consistent with the Nuclear Compartment Commonality (NuCom) hypothesis, which assumes that both bacteria and eukarya are descended from nucleated organisms [71,72]. Ancient, the presence of highly conserved proteins from the LUCA with a complex cell biology favor NuCom hypothesis, and imply that eukarya have always been nucleated [71]. It has been suggested that the emergence of a nuclear compartment enclosed by a membrane was essential for the evolution of DNA replication in ancestor cell by inhibiting the other molecules from interfering in the process. According to this hypothesis, the enucleation process (loss of the nucleus) of eukarya during reductive evolution brought about the formation of the *Archaea* domain. In the same way, typical bacterial phyla emerged when the nucleus in some members of the PVC superphylum disappeared (Figure 3) [72]. For example, Proteobacteria may have descended from Verrucomicrobia [73]. Support for this theory is provided by phylogenetic information, based on the highly conserved regions of the 16S rDNA phylogenies and proteomic analysis, which reveals PVC superphylum to be the most ancient bacteria [74] and the presence of a nucleus in this group, reveals their deep ancestry from LUCA.



**Figure 3:** Overview of nuclear compartment commonality (NuCom) hypothesis for the origin of the nucleus.

This model posits that the ancestor of both the Bacteria and Eukarya-Archaea domains included a primitive nuclear compartment. The process of reductive evolution, termed Enucleation, brought about the loss of the nucleus in some Bacteria and Eukarya. The Enucleated members of the PVC superphylum resulted in the formation of modern Bacterial phyla, and enucleated Eukarya gave rise to the Archaeal domain [72].

Even though these alternative models depicting the origin of the nucleus had considerable impact, they were protested by

William and Embley due to the unfulfillment of the topological state of the nucleus in planctomycetes [75]. Moreover, it was proposed that the intracytoplasmic (ICM) membranes in the PVC superphylum may be a specialized physiological adaptation for the enhancement of anaerobic ammonium oxidation (anammox) [76].

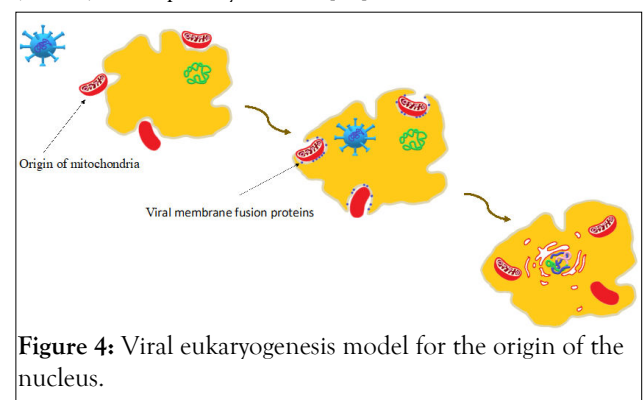
Despite the criticisms of Fuerst's reductive evolutionary model, it was sufficient to weaken the symbiotic hypothesis for the origin of modern eukaryotes in terms of known biological mechanisms [22,76,77].

### Theories arguing the viral origin of the nucleus

Though, viruses are known to be one of the major components of the biosphere, and have been considered alive following several recent investigations [78,79], the universal tree of life is divided into three cellular domains (*Archaea*, Bacteria, and Eukarya) [80], from which viruses have been excluded.

The viral eukaryogenesis theory and the possible link between the virus and the origin of the nucleus were reported simultaneously in 2001. According to the viral eukaryogenesis theory, a complex DNA virus is introduced as a new candidate for the origin of the nucleus [8,24]. This study suggested that viruses are ancient, and was quite common in the primordial soup [2]. The existence of viruses such as the icosahedral small virus Sputnik, which are able to infect members of the three domains of life [79], leads to an assumption that viral lineages probably originated independently before the time of LUCA, and have played an important role in evolutionary transition [81-83].

Viral eukaryogenesis is a form of endosymbiosis. In this model, it is postulated that the source of eukaryotic cytoplasm was an infected archaeon by a virus [84,85]. According to this model, a virus entered inside the archeal host cell and generates an intracellular compartment (viral factory) following the fusion of viral envelope with host membrane. The formation of viral factory which contained a large linear chromosome and enzymes (required for transcription, capping/polyadenylation, and the transfer of the mRNA into the host cytoplasm) increased the efficiency of viral replication and protect the virus against host defenses. The permanent residency of the virus inside the host was critical in eukaryogenesis, as the viral fusion proteins helped the host engulf other bacteria [8,86]. When the virus that had acquired genes from the host (*Archaea*) and its endosymbiont (eubacteria) DNA through lateral gene transfer evolved into an organelle (Figure 4), the First Eukaryotic Nuclear Ancestor (FENA) subsequently evolved [87].



**Figure 4:** Viral eukaryogenesis model for the origin of the nucleus.

The syntrophic association between wall-free archaeal host and CO<sub>2</sub>/ hydrogen-producing bacteria (syntroph) was an obligatory mutualism. The infection of the host cell by a complex DNA virus and its persistent residency inside the host cell is the most important step in viral eukaryogenesis. The viral membrane fusion proteins come in view on the cell membrane of the host and aided the phagocytosis of the syntroph. The three-lineage consortium led to the birth of the nucleus containing linear DNA [8,86].

The crucial factor in favor of such DNA viruses as FENA is the similar biochemical and genetic features of FENA to the nucleus of the eukaryotic cell, which are not found in any prokaryotic cells. These features can be listed as:

- mRNA capping
- Linear chromosomes
- Uncoupling the transcription from translation
- Membrane-bound structures
- Dissociation of the membrane during replication
- Reverse transcriptase/telomeres activity [8,86,88].

All these findings support the notion that the eukaryotic nucleus evolved from a DNA virus, although there is as yet no clear explanation for the accumulation of genetic material within the viral compartment rather than the cytoplasm of the prokaryote [29].

### Domain cell theory of life

The universally accepted cell theory of Schleiden and Schwann suggests that all living organisms are single or multi-cellular [89], and that all cells are generated from a pre-existing cell by division [90].

Based on the principles of cell theory, the domain cell theory of life proposes that three domains (*Archaea*, Bacteria and Eukarya) in Carl Woese's universal tree [80,91,92] be regarded as three different cellular types, and that each domain be considered distinct in terms of their evolutionary process, genetic content and membrane type (cell or nuclear membrane). Thus, the organisms of each of the three domains maintain their unique identities throughout the evolutionary process. According to domain cell theory, all prokaryote-to-eukaryote-based theories are invalid, since a member of a domain cannot give rise to members of other domains of life [71,93,94]. This theory partially supports the NuCom hypothesis, and introduces LUCA as the origin of the nucleus [95].

## DISCUSSION

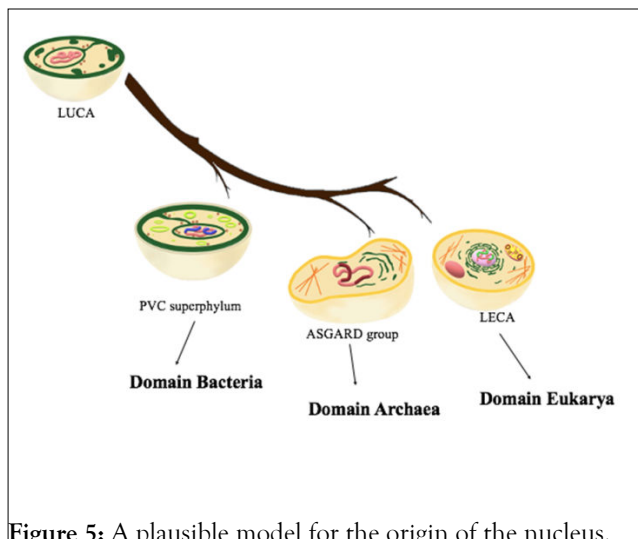
The enigmatic structure of the nucleus has led to the emergence of various models explaining its origins. Indeed, the birth of the nucleus is the source of extraordinary diversity in the eukaryotic world, from single-celled micro-organisms to multicellular plants, fungi and animals. Phylogenetic analyses and comparative genomics have provided valuable information for the tracing of the evolutionary process of the nucleus, and have shown the eukaryotic genome to be a combination of archaeal

and proteobacterial genomes. Subsequently, a new aspect of nucleus evolution came into focus regarding the archaeal and bacterial symbiotic origin of the nucleus, although there is no clear explanation for the structures of NE, NPCs and linear chromosomes in this concept. Furthermore, the absence of a plausible mechanism or evidence of an additional genome donor, unlike in endosymbiotic-based theories, have seriously challenged such models. Unlike endosymbiotic theories, autogenous models are widely accepted for their compartmentalization of DNA in an archaeal ancestor via internal changes. This model was particularly well-supported following the seminal discovery of the Asgard group of *Archaea*, which seems to be the closest relative to eukaryotes, as members of this group contain eukaryotic signature genes and are able to produce membrane vesicles and extracellular protrusions. That said, autogenous theories may be seriously called into question when it comes to the origin of the acyl chains attached to the glycerol-3-phosphate (G3P) in the membranes of eukaryotes and most of the bacteria, which differ completely from the ether-linked membranes of *Archaea*. Furthermore, there is a lack of homology between the enzymes involved in phospholipids biosynthesis in *Archaea* and Eukaryotes. According to some studies, endosymbiotic and lateral gene transfer between the mitochondria and the host is the source of the bacteria-like fatty acid in eukaryotes, though the possibility of the existence of Archaeal membrane genes in LUCA enhance the possibility of reductive evolution, through which these genes have been lost to the Domain Bacteria and Eukarya.

The complex endomembrane systems and the structures determined as nuclei in planctomycetes gave rise to the birth of reductive evolution-based theories, in which it was suggested that the nucleus already existed in the LUCA, and that the prokaryote lineage had evolved from this nucleated ancestor through reductive evolution. Additionally, the intracellular structure of the PVC superphylum revealed that this phylum could be in an intermediate form in evolutionary transitions, as otherwise, the nucleus would no longer be a distinguishing characteristic of eukaryotes.

Moreover, although there is a lack of sufficient evidence in support of the viral eukaryogenesis theory, viruses should also be considered as possible forerunners of the nucleus, since viruses are very ancient and have the ability to transfer genes among organisms.

The existence of eukaryote-like characteristics in some members of the Archaeal (particularly Asgard group) and Bacterial (PVC superphylum) domains indicate that they may be the earliest relatives of eukaryotes. Moreover, the commonality of the genes in the three domains of life may date back to LUCA, before the domains separated. Down through the years, prokaryotes have lost most of them, and developed new features, possibly in response to various evolutionary pressures, thus enhancing their resistance and compatibility (Figure 5).



**Figure 5:** A plausible model for the origin of the nucleus.

Each of the three domains of life derived from a nucleated ancestor (LUCA) separately. LECA (Last Eukaryotic Common Ancestor) is the ancestor of modern compartmentalized eukaryotic cell. The ancient ASGARD group gave rise to the domain *Archaea*, and modern bacteria are descended from the PVC superphylum.

## CONCLUSION

In the present study, we reviewed several heterodox hypotheses regarding the origin of the nucleus. The rationale behind the historical models (prokaryote-first scenario) is that the complex structure of the Eukarya may have derived from simpler organisms (prokaryotes), although there is no experimental support for this rationale, and it cannot be reproduced in the laboratory. It would seem that theories suggesting that the nucleus originated from last universal common ancestor are more plausible, and fit in with Carl Woese's Tree of life. In support of this, the domain-cell theory of life, which suggests the independence of the three primary domains of life, would seem quite logical, as no intermediate species between these domains has yet been discovered.

## LIMITATIONS AND RECOMMENDATIONS

The origin of the nucleus remains an open question, and further analysis will be required to test the above-mentioned alternatives. The further investigation of the diversity of simple and single-celled (unicellular) prokaryotes could aid researchers in gaining vivid insight into the early stages of evolution. Increasing our genome sequence knowledge from a larger prokaryotic fraction, combined with comprehensive phylogenetic methods, could strongly change our understanding of nuclear evolution, and may pave the way for the demystification of the birth of nucleus.

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## CONFLICT OF INTEREST

The authors declare no competing or financial interests.

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