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Review

Archaebacterial ancestor of eukaryotes and mitochondriogenesis

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Division of the ancestral prokaryotic genome into two circular double-stranded deoxyribonucleic acid (DNA) molecules by genetic recombination, is a basis for the future separate evolution of the nuclear and mitochondrial gene compartment. This suggests monophyletic origin of both mitochondrion and nucleus. Presumed organism which genome undergoes genetic recombination has to be searched among an aerobic, oxygen non-producing archaeon with no rigid cell wall, but a plasma membrane, probably an crenarchaeota containing functional bacteriochlorophyll a synthase gene and histones. In this proposal, origin of eukaryotes occur by a three-steps. First, replication fork pauses and collapses generating a breakage in the genome of archaeal ancestor of eukaryotes. Second, the double-strand break can be repaired intergenomically by complementary strands invasion. Third, this duplicated genome can be fissioned into two compartments by reciprocal genetic recombination. Scenario is accomplished by aberrant fission of the inner membane surrounding separately those two compartments.

Key words: Origin of nucleus, origin of mitochondrion.

INTRODUCTION

Archaebacterial ancestor of eukaryotes

Organisms are clasiffied into three Domains and into one of six Kingdoms of life. These Kingdoms are Archaebacteria, Eubacteria, Protista, Fungi, Plantae and Animalia. There is opinion that Archaebacteria (Archaea) have an ancestor in common with eukaryots, which has been shown by a phylogenic analysis based upon nucleotide and amino-acid sequences comparison showing deep archaeal root of eukaryots (Woese et al., 1990). Archaea and eukaryotes have many common characters, notably obligately co-translation secretion of N-linked glycoproteins, signal recognition particle with 7S ribonucleic acid (RNA) and translation-arrested domain, eight-subunit chaperonin, protein-splited transfer ribo-nucleic acid (tRNA) introns, core histons (Cubonova et al., 2005), small nucleolar ribonucleo-proteins, exosomes and similar replication, repair, transcription and tran-slation processing, tRNA maturation (Schierling et al., 2002).

Archaeal-derived genes are significantly more likely to be essential to eukaryotic viability, are more highly expressed, and are significantly more highly connected and more central in the eukaryotic protein interaction network than that of eubacterial origin (Cotton and Mcinerney, 2010.). This importance reflects these genes' origin as the ancestral nuclear component of the eukaryotic genome. These findings hold irrespective of whether the genes have an informational or operational function. So that, and this is very important as we will seen in the new theory of evolution of mitochondrion and plastids, many features of eukaryotic genes with prokaryotic homologs can be explained by their origin, rather than their function.

The endosymbiont theory proposes that mitochondria and chloroplasts originated as bacterial symbionts within a nucleus-containing host cell (xenogenous origin), rather than formed from within the cell itself (autogenous origin).

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A number of structural and biochemical features shared by organelles and bacteria, arguing that those similirarities could reflect an origin of organelles through a series of bacterial endosymbiosis. Recent studies have provided insights that challenge the traditional serial endosymbiosis-based view of how the eukaryotic cell and its mitochondrion came to be (Gray et al., 1999). These date raise possibility that this organelle originated at essentially the same time as the nuclear component, supporting monophyletic origin of both, nucleus and mitochondrion. But, should be born in mind that three billions of years are passed after mitochondrion has originated, and that mitochondrial genome is slowly evolving one. At a time of development of endosymbiotic theory little has been known regarding Archaeal genome organization and gene content.

One of the obstacle in interpreting 'Only Archaeal origin' of eukaryotes is a membrane composition. The most recent unexpected discovery is a *Ignicoccus*, only archaeal genus known today whose cells possess an outer membrane. The examples of the *planctomycetes* (from Martin, 2005), as well as that of *Ignicoccus*, in which the cytosol is surrounded by two complete and distinct membranes (Kupar et al., 2010; Rachel et al., 2002), indicate that new membrane system can arise, surprisingly, *de novo* in evolution, at least in prokaryotes. All three known species in the crenarchaeota genus *Ignicoccus* lack rigid cell walls. Another problem regarding membrane discrepancy that separetes archaebacteria from eubacteria and eukaryotes are isoprene ethers versus fatty acids esters and their glycerol configuration (Figure 1). The lipid issue is dealt with by assuming that the nuclear membrane synthesis pathway functionaly replaced the membrane synthesis pathway of the archaebacterial. The archaeal isoprene synthesis pathway itself was not replaced in eukaryotes, it was retained for synthesis of sterols, quinone tails and dolichol phosphate. However, regardless of whether lipid replacement occured in ancestral eukaryotes or in ancestral archaebacteria, lipid replacement has occured in evolution, the question is therefore not 'if' it occured, but 'where'.

Regarding the evolution of the nuclear pore, they could come later in nuclear origin, which is consistent with the pattern of duplication events suggested here. Another surprise, in *Ignicoccus*, adenosine triphosphate (ATP) synthase and H_2:sulfur oxidoreductase complexes of this organism are located on the inner side of outer membrane. These two enzyme complexes are mandatory for the generation of an electrochemical gradient and for ATP synthesis. It was known for some time that archaea have an ATP synthase different from the F1F0 ATP synthase found in eubacteria, mitochondria and chloroplasts: the A1A0 synthase (Lewalter and Muller, 2006), but evolutionary closely related to eukaryal V1V0 ATP synthase.

Methanogenic archaea produce two primary ion gradients: Na^+, H^+ and couple both of them to synthesis of ATP. It was assumed that the enzymes have different ion specifities: Na^+ for the F1F0 ATP synthese and H^+ for the A1A0 ATP synthase. Further finding of F1F0 ATP synthase genes in archaea (Sumi et al., 1997; Saum et al., 2009; Muller et al., 2005) solve this suspition. ATPases with unusual membrane-embedded rotor subunuts were found in both F1F0 and A1A0 ATP synthases. The rotor subunit *c* of A1A0 ATPases is similar to subunit c from F0. Suprisingly, multiplied *c* subunits have been found in some archaea. Extraordinary features and exeptional structural and functional variability in the rotor of ATP synthase may have arisen as an adaptation to different cellular needs and the extreme physicochemical conditions in the early history of life.

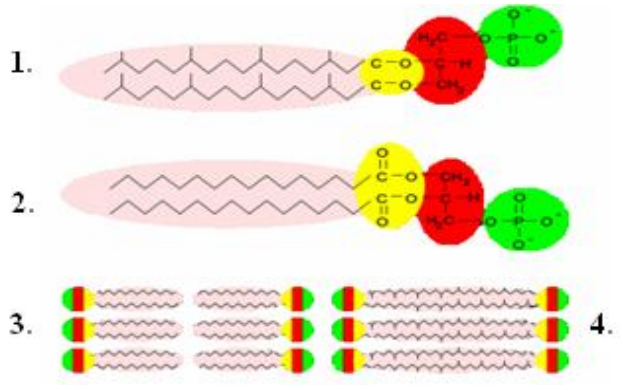

Figure 1. Membrane structure. 1.an archaeal phospholipid with isoprene chains,ether linkages, L-gycerol moiety and phosphate group. 2. a bacterial or eukaryotic phospholipid with fatty acid chains, ester linkage and D-glycerol moiety. 3. lipid bilayer of bacteria and eukaryotes, 4. lipid monolayer of some archaea.

The cell structure of *Ignicoccus* is unlike that of any known prokaryot but stricingly similar to that of eukaryotes. These differences make *I.hospitalis* a prime candidate for being a eukaryotic ancestor. But, we can expect another surprise from archaebacterial genome sequencing and gene content.

Archaea is a fascinating and divers group of organisms with deep roots overlapping those of eukaryots. So, it is inteligent to search for the origin of eukaryots within those group of microorganisms. Genome evolve by nucleotide aquisition, mutation and genetic recombination. Gene duplication plays a major role in the gene modeling. The duplication of deoxytibonucleic acid (DNA) and faithful segregation of newly replicated chromosomes at cell division is frequently dependent on recombinational processes.

Whole-genome duplication, followed by massive gene loss and specialization has long been postulated as a powerful mechanism of evolutionary inovation. Genomic duplication has been proposed as an advantageous path to evolutionary progress, bacause duplicated genes can

supply genetic raw material for the emergence of new function through the forces of mutation and natural selection. Typical example of whole-genome duplication is a yeast *Saccharomyces cerevisiae* (Kellis et al., 2004). The primary evidence that duplication has played vital role in the evolution of new gene functions is the widespread existence of gene families. Members of a gene family that share a common ancestor as a result of a duplication event are denoted as being paralogous, distinguishing them from orthologous genes in different genomes which share common ancestor as a result of a speciation event. Paralogous genes can often be found clustered within a genome, although dispersed paralogues, often with more diverse functions, are also common.

A kay intermediate in general racombination is a structure in which two double-stranded DNA molecule are covalently linked by a single-stranded crossover characteristic of a Hollidy junction. When DNA molecules are circular, the recombinant structure take the form of a biparental figure eight. The maturation of figure-eight molecules in prokaryots is characterized by the formation and recovery of both parental and recombinant types. Biparental figure eight behave as recombinant intermediates that can be resolved into mature recombinants (West et al., 1983). In this process, DNA gyrase interlocks duplex DNA circules and resolves catenanes DNA into component monomers (Kreuzer and Cozzarelli, 1980). DNA gyrase relaxes supercoiled DNA in an ATP-independent manner (Yamashiro and Yamagishi, 2005). In the domain of Archaea, DNA gyrase is occasionally found, but exists.

The fact that replication, recombination, chromosome segregation and cell division are linked together, tell us that once upon a time existed unique DNA sequence that code for all those processes, reflecting ancient compact genome organization. Evolutionary modeling of those sequence are the basis for functional separation of those four processes. Prokaryotic features of mitochondria are results of slow mutation rate of coding sequences, unlike the non-coding regions of DNA. Mitochondrial genome does not have non-coding sequences, as a results of compact genome organization, vestige of the compact organization of first pragenome replicon.

According to the gene origin, two functionally energo-matabolic pathways can be distinguished: nitrogen fixation, respiration, and photosynthesis; carbohydrate metabolism: glycolisis (hexose), pentoso-phosphate cycle and tricarboxylic cycle. It is hard to imagine free-living archaeal ancestor of the first proto-eukaryot without both groups of metabolisms, except photosynthesis. Recent discoveries in the molecular biology and new DNA sequencing data has been show that Archaea possesses a genetic apparatus for multiple types of energetic activity. Genes for glycolitic (Embden-Meyerhof-Parnas) pathway (Ronimus and Morgan, 2003), reductive tri-carboxylic acid cicle (Baliga et al., 2005), reductive pentose phosphate cycle (Soderberg, 2005), Entner-Dudoroff pathway (Canback et al., 2002), Fe-hydrogenasa catalitic H_2 production (Kanai et al., 2003), the sulfate assimilation (Teske et al., 2003), nitrogen fixation (Chein and Zinder, 1996), are widely distributed among Archaea and they are often considered a central to the origin of metabolisms. Gene for cytochrome oxidase, which presence indicates that aerobic metabolism is possible in an eviroment with a low level of oxygen, was present in common ancestor of archaea and eubacteria (Castresana et al., 1994). This means that aerobic respiration was a monophyletic and ancient enzymatic system before oxygenic photosynthesis.

Ribulose bisphosphate carboxylase, central enzyme in carbon fixation, is present in archaeal genomes (Soderberg, 2005). Genetic apparatus of the electron transport chain (complex I-V), which are responsible for oxidative phosphorylation, are examined in archaeon *Natromonas pharaonic* (Falb et al., 2005). Genes for NADH- dehydrogenase type II, succinate dehydrogenase, terminal oxidase, ATP synthase and equvalent for cytochrome-C reductase, have been identified. Experimantal studies provide the existence of a functional respiratory chain in these archaeon. And finaly, archaea can performe oxygen non-producing carotinoide based photosynthesis, so they posses a primeval photosynthetic operon (including gene for bacteriochlorophyll a synthase) which is the basis for the future photosynthetic replicon and plant's photosynthesis.

Whole-genome sequencing has reveald several cases where prokaryotic genomes have more than one large replicon. When second largest replicon approaches the size of the largest replicon, a chromosome splits to form a secondary chromosome. Genome of the archaeal ancestor of eukaryotes (AAE) might be organized up of two replicons. Presence of two replicons in AAE correlates with the distribution of the majority of housekeeping functions in its chromosome. At the level of compact genome organization, recombination/ repair, replication and cell division were brought together functionally and physically, because they evolved from a single gene with multiple functions (ancestor sequence of the recA, kaiC, dnaB).

Recombination evolved in prokaryots not only as a means to exchange genetic information but also as a DNA repair process. Recombinational DNA repair is associated with replication, every time bidirectional recombinational repair replication is initiated at oriC, there is a chance that fork encounted a situation requiring repair. Common ancestor gene for herA, dnm-like gene, ftsZ, ftsK, cdc6 from one side and dnaG, recA, resT, from the other side, where encoded by a single operon sequence with dual function: (dnaG +recA + resT) + (ftsZ + herA + cdc6). In the presumed archaeal ancestor of the first proto-eukaryot (AAE), this operon is placed at the level of oriC. To allow functional polarization, genes participated in energy production and ribosomal operon

with elongation factors, are encoded by the 'mitochondrial' replicon and others, luxury genes, by 'nuclear' replicon, something like in the *Nitrosomonas europea* (Chain, 2003), for example. It may be that bilateral inverse symmetry is a vestige of kindship between chromosomal halves, where one half of the genome begat the other via an ancient whole-genome inverse duplication event (Sanchez and Jose, 2002).

Bidirectional replication from an internal origin forms a circular head-to-head, tail-to-tail dimer with two DNA monomers covalently linked at the terC. During AAE's whole-genome duplication it can be that replication fork pauses and collapses causing double-strand break, after bidirectional replication is terminated, to promote compartmentalization, there is no generation of two daughter genomes. Resolution in terC continued, after strand break, by strands invasions and homologous recombination. Such type of duplication from oriC to terC, could explain compartmentalization of the functionally polarized AAE's genome by subsequent reciprocal genetic recombination at the level of oriC (Stupar, 2006, 2007).

MITOCHONDRIAL ORIGIN

This proposal are based on the existence and development of single evolutionary line of cells, which genome is a basis for existence of the contemporary compartments (nuclear, mitochondrial, plastids, hydrogenosomes), and infrastructuraly already prepared possibility for future ribosomale gene compartment apearance. This is an autogenous way of evolution of free-living and independent organisms, that is, 'Archaeal only origin of eukaryotes'. Last universal common ancestor (LUCA), had about 3,500 genes, so that after the duplication had about 7,000. Integrity of the duplicated LUCA's genome would be disturbed so that the genome has to be inevitably divided. LUCA of eukaryotes has to be search among crenarchaeota with no rigid cell wall, but a plasma membrane, containing gene for bacteriochlorophylle a synthase, as a part of the primeval photosynthetic operon. Bacteriochlorophylle a synthase is a functional gene engaged not in photosynthesis, but in the membrane's lipides processing. The LUCA's does not exist any more since with the ending of his function, ends its existence.

In prokaryots, cell division occurs through binary fission and is driven by the formation of the septum. Septum formation structurally altered envelope, so that inner membrane is connected closely to the cell wall and outer membrane layer (De Souza and Gueiros, 2006). A network of proteins interactions must be carefully tuned, both in time and space, in order to allow the correct and timely generation of two identical daughter cells. Genetic rearrangement, and mutation or change of time and level of expression of the genes participating in septum formation, could cause separated inner and outer membrane fission. ftsZ and dnm1-like genes did not necessary tuned when both are recruted to constriction site, indicating that inner and outer dividing machineries are not in tight association during the late stage of cell division (Erickson, 2000). Surely, addition of new DNA sequences, either in "mitochondrial", either in "nuclear" replicon, can cause this dramatic event that is, fission of two replicons, this 'additionaly' new sequences arose by genome duplication. Dynamin regulates membrane squeezing and peroxisomal (organele surrounded by one membrane) fission (Fujimoto et al., 2005). In that way, AAE's inner membrane becomes proto-nuclear and proto-mitochondrial outer unique membrane of the resulting proto-eukaryot (for the time before evolution of endomembranes and endosceleton of mature eukaryote). The scenario reaches culminating point: on one side there is a AAE's whole-genome duplication (with homologous strands invasions and reciprocal recombination) and on the other side, partial cell fission, including only inner membrane invagination and squeezing. Resolution in terC, by strans invasion, was followed by the resolution in oriC, still attached to the inner membrane probably at the mesosome level; two oriC pairs at the corresponding repeated sequence, probably mt-telomere like *div*-sequence (Stupar, 2008a, b; Vidović, 2010) allowing a reciprocal genetic recombina-tion to generate two duplicated, functionally separated genomes. Hydrogenosome genome of *Nyctotherus ovalis* hybridizes with genomic DNA which terminates in a G3T4G3(T4G4)5 repeat that is very similar to the telomere sequences (Akhamova et al., 1998). This can be good candidate for *div* sequence.

Invagination of the inner membrane continued, after genome fission, and then envelops each of the replicon separately, in that way it give rise a two new compartments (Figure 2). The initiation of replication in Archaea occurs through loading of the minichromosome maintenance protein (Mcm), which can activated cell division cycle protein Cdc6. In the most Archaea cdc6 gene is adjanced to the origin of replication. Frequent exposure to DNA demage results in frequent recombination and genomic rearrangemants. It can be that initiation of the replication overlaped with these genomic rearrangement. If direct repeat sequences are near or at the origin of replication this can lead to the functional segregation by genetic recombination, when maximal capacity of the pragenome has been reached.

Coupling replication, cdc6 gene activation and pragenome rearrangement this can lead to the fission of the 'nuclear' from the 'mitochondrial' gene content. The nuclear membrane is contiguous single lipid bilayer that has an outer face and inner face, as a vestige of the ancient AAE's inner membrane invagination around the 'nuclear' replicon. While the appearance of nuclear pores, place where the nuclear membrane goes around the corner connecting the inner and outer surface, it is just a

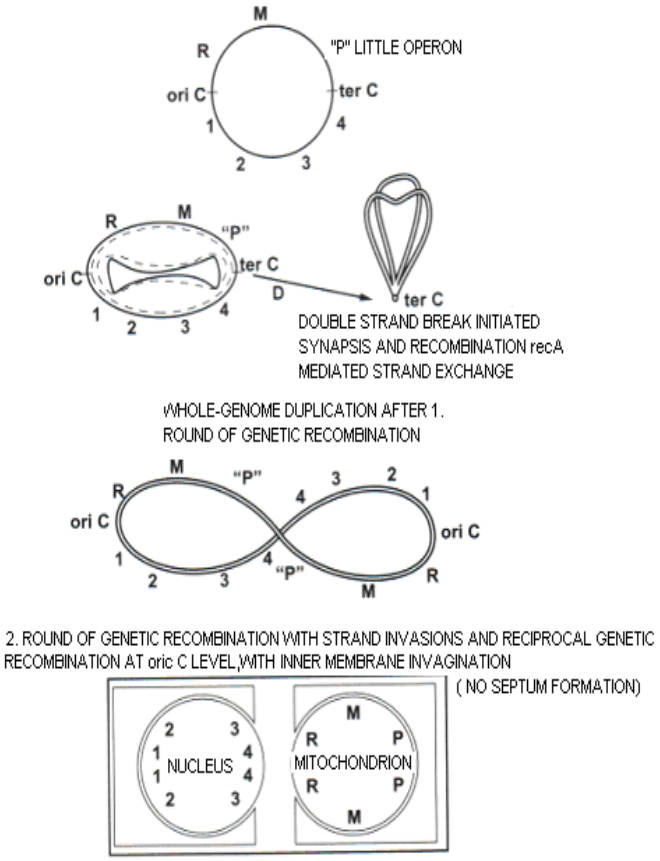

Figure 2. Set of the subsequent steps leading to the fission of the eukaryotic common ancestor genome into nuclear and mitochondrial compartment and origin of the eukaryotes. 1, 2, 3, 4-different operons in the nucleus; M and R-different mitochondrial operona, P-primeval photosynthetic operon.

matter of organizational nature. The example of crenarchaeon *Ignicoccous* (Kupar et al., 2010; Rachel et al., 2002) indicate that new membrane system can arise *de novo* in evolution, at least in crenarcheaotes. Another problem regarding membrane is discrepancy that separates archaebacteria from eubacteria and eukaryotes (isoprene ethers versus fatty acid esters and their glycerol configuration). The isoprene synthesis pathway of Achaea was retained in eukaryotes for synthesis of sterols, quinone tails and dolichol phosphate, but replaced for the eukaryotic membrane lipids synthesis pathway, which provides continuity of the transition from Achaea to eukaryotes.

DNA duplication take place early in the evolution, after evolution by nucleotide acquisition was terminated. DNA duplication has an ancient and continuing process during evolution. The types of sequences at the break-points as well as their superposition with the replication map suggest that spontaneous duplication result from replication accidents and repair of this replication-dependent double-strand break in AAE's genome could be the origin of eukaryotes, which correlate with existence of div sequences (Stupar, 2006). Mitochondrial telomeres play essentially the same biological roles as their chromosomal counterparts (ensure the complete replication, mask the ends from DNA repair machinery and protect them from exonucleolytic degradation and/or end-to-end fusions) because they have same origine and results from original DNA sequence and processing.

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