Biologia Serbica, 2017, 39(1):32-40

DOI 10.5281/zenodo.826619

Minireview

Interaction between mitochondrial and nuclear genomes: the role in life-history evolution

Biljana Stojković[1,2,*] and Mirko Đorđević[2]

[1]*Institute of Zoology, Faculty of Biology, University of Belgrade, Studentski trg 16, Belgrade 11000, Serbia*

[2]*Department of Evolutionary Biology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Bulevar despota Stefana 142, Belgrade 11060, Serbia*

Summary. The evolution of eukaryotes is based on dynamic coevolutionary interactions between the two genomes, nuclear (nDNA) and mitochondrial (mtDNA). Current evidence suggests that the origin of eukaryotes corresponds to the origin of mitochondria. The primary center of adenosine triphosphate (ATP) production, the process of oxidative phosphorylation (OXPHOS), is based on the functioning of four large protein complexes that are responsible for the proton gradient across the inner mitochondrial membrane. These complexes in the electron transport chain (ETC) are composed of polypeptides encoded by both mitochondrial and nuclear genes. In order to preserve the uncompromised functionality of mitochondria, i.e. the adequate coupling of all interacting subunits in OXPHOS, the two genomes had to coevolve. In other words, mitonuclear compatibilities are required for optimal life-history of an organism because even minor biochemical inefficiency can have major fitness consequences by modulating energetic efficiency and oxidative stress levels. The link between life-history evolution and mitonuclear interactions is deeply rooted within the mechanisms of energy metabolism. The coevolved epistatic interactions between mitochondria and nucleus determine the amount of energy available for all biological functions. Selective optimization of one life-history function (e.g. reproduction) may come at the cost of reduced competence for somatic maintenance, viability and survival due to mutually exclusive energy allocation to distinct functions. Different approaches in investigating the central roles of mitochondrial metabolic processes and mitonuclear epistasis in life-history evolution are discussed in this paper.

Keywords: life-history evolution, mitochondria, mtDNA, nDNA, nucleus, OXPHOS.

INTRODUCTION

The eukaryotic cell has two obligate genomes – one mitochondrial (mtDNA) and the other nuclear (nDNA). Current evidence indicates that mitochondria, organelles that provide energy to the cell, were derived from an alphaproteobacterial endosymbiont (Bacteria domain) that evolved within a host cell of Archaean domain origin (Gray et al. 1999; Pittis and Gabaldón 2016). This ancient symbiosis between the two prokaryotes gave rise to a new type of organisms – eukaryotes. It has been widely recognized that mitochondria provided the orders for the required magnitude of increase in the amount of metabolic energy per gene, which was necessary for the evolution of eukaryote-specific traits (Lane and Martin 2010). Prokaryotes do not have that amount of energy at their disposal and this explains "why the origin of eukaryotes corresponds to the origin of mitochondria" (Martin et al. 2015). On account of mitochondria, a novel type of cell gained the bioenergetic means for both an increase in genome size and the evolution of complexity in genome architecture, cell structure and multicellularity (Lynch and Walsh 2007; Archibald 2014).

Several competing hypotheses, however, disagree on the details in the evolutionary steps that led to the appearance of eukaryotes. According to Pittis and Gabaldón (2016), these diverse scenarios could be grouped into either mito-early or mito-late perspectives. The first group presumes that the host archaea was a simple cell and that eukaryogenesis was triggered by the entrance of the endosymbiont and intense recombination between the two prokaryotic genomes. On the other hand, according to the mito-late hypotheses, the significant complexity of a proto-eukaryotic cell, which origi-

*Corresponding author, e-mail: bilja@bio.bg.ac.rs

nated from the Archaea domain, predated mitochondrial endosymbiosis (see review in Embley and Martin 2006). Recently, a wide phylogenomic study was performed in order to reveal the taxonomic origin of different genes in eukaryotes – whether they are of bacterial or archaeal origin (Pittis and Gabaldón 2016). This study has found that the latest massive genetic contribution to eukaryotes (dated at approximately 2 billion years ago) was indeed related to the bacterial origin (most particularly alphaproteobacterial). Moreover, it has been shown that proteins coded by these genes have a mitochondrial localization and roles in energy production. This is scientific evidence that supported the endosymbiotic origin of mitochondria. The more ancient archaeal contribution to eukaryotes comprises of genes whose proteins are associated with nuclear structures and informational processes (replication, transcription and translation). These results are also in accord with the endosymbiotic theory for eukaryote origin, i.e., the evidence that eukaryotes are rooted within the Archaea domain. However, it seems that the prokaryotic proteome of the endomembrane system preceded the appearance of mitochondria. The origin of these genes is a taxonomic mixture of archaeal and bacterial genomes (other than alphaproteobacteria) suggesting that the archaeal host was involved in serial symbiotic associations with different partners before mitochondrial acquisition. These ancient symbiotic events produced a complex archaeal genome already harboring many pathways of bacterial origin (Koonin and Yutin 2014). Therefore, although mitochondrial endosymbiosis was a crucial step in eukaryogenesis, the archaeal host could have already been a complex cell – a proto-eukaryotic cell.

Classical endosymbiotic theory was based on the premise that the benefit of the endosymbiotic origin of mitochondria was founded in oxygen utilization (Margulis et al. 2006; Martin et al. 2015). However, some eukaryotes have anaerobic forms of mitochondria – hydrogenosomes. Starting from the point that mitochondria and hydrogenosomes share a common ancestor, Martin and Müller (1998) formulated the "hydrogen hypothesis" according to which the primitive endosymbiont was a facultative anaerobe that could have been involved both in aerobic and in anaerobic metabolism. One of the confirmations of this hypothesis is the fact that aerobic and anaerobic forms interleave on the eukaryotic phylogenetic tree, leading to the conclusion that the evolution of the endosymbiont had proceeded in diverse ways in different eukaryotic lineages depending on environmental and metabolic demands. Some lineages, grouped within the taxon Archezoa, have even lost mitochondria during their evolution (Poole and Penny 2007).

Regardless of the details in the evolutionary pathway that resulted in the emergence of the eukaryotic cell, it is widely accepted that the acquisition of the endosymbiont triggered dynamic recombinations and gene exchange between archaeal and bacterial partners. The major trends in evolution of the two eukaryotic genomes were: (i) reduction in mtDNA size, and (ii) translocation of the original mitochondrial genes to the nuclear genome. Namely, the host cell acquired genetic information from the endosymbiont by horizontal gene transfer. Many of these genes now function to encode proteins of the nucleus and cytosol (Allen 2003). Information that remained within the mitochondrial genomes of most animals consists of 22 tRNAs, 2 ribosomal RNAs and 13 protein-coding genes (Björkholm 2015).

This inequality in the relationship between the two genomes raises an important question as to why mitochondria even contain a genome. In other words: "Why do mitochondria (and chloroplasts) require their own separate genetic systems when other organelles that share the same cytoplasm, such as peroxisomes and lysosomes, do not?" (Alberts et al. 1997). It is known that mtDNA protein-coding genes play a crucial role in energy production. As will be explained in more detail in the next section, polypeptides encoded by these mitochondrial genes are parts of the large molecular complexes involved in oxidative phosphorylation (OXPHOS) – a process that ultimately results in ATP production. Because of this close collaboration in energy metabolism, which is necessary for all living functions, OXPHOS is an example of the most direct epistatic interaction between mitochondrial and nuclear genes.

To explain what could be the selective advantage for the eukaryotic cell to retain cytoplasmic location (i.e. within the mitochondria) of some genes, Allen (2003) formulated the CoRR (co-location for redox regulation) hypothesis. He proposed that these genes are coding for proteins whose "function in electron transfer demands rapid, direct and unconditional redox regulatory control of their biosynthesis". Knowing that OXPHOS is taking place in mitochondria, other ways of transcriptional regulation would be selectively disadvantageous because of the postponed reaction to the changed energy status in the cell, decreased energy efficiency and the harmful side effects of electron transport operating on wrong substrates. In accord with the endosymbiotic theory of eukaryotic origin, it is widely accepted that direct redox control of the expression of genes within bioenergetic organelles, such as mitochondria and chloroplasts, is evolutionarily conserved from the bacterial genomes from which these organelles originated.

Mitonuclear coevolution and oxidative phosphorylation

The history of endosymbiotic gene transfer from mtDNA to nucleus during the eukaryotic evolution has led to a distribution of work between the two genomes but also to the significant differences in biological and population-genetics properties among the genomes. Firstly, mitochondrial genomes experience a much higher rate of mutation than the nucleus due to their high replication rate and lower ef-

fectiveness of repair mechanisms. Secondly, due to the strict maternal inheritance and almost complete absence of recombination between diverse mitochondrial genomes (i.e. the whole genome behaves as a single, nonrecombining locus), the effective population size (*Ne*) of mitochondrial DNA is just a quarter of the size of the nuclear genome. The implication of this mitochondrial specificity is that the efficacy of selection in molding mtDNA evolution is diminished. In other words, there is an expectation that the genetic drift, and not natural selection, has an extensive role in shaping mtDNA variance across generations. More specifically, it has been assumed that most of the segregating mtDNA variation is likely to be selectively neutral or near-neutral (Ballard and Rand 2005). Purifying selection should swiftly remove deleterious or fix beneficial mutation in the mitochondrial genome in order to ensure uncompromised mitochondrial function in bioenergetics processes, and, as a result, all the remaining variance in mtDNA sequences within a population should be neutral and exposed to stochastic evolutionary mechanisms, such as genetic drift.

Contrary to these theoretical expectations, however, the sizable effects of mitochondrial genetic variation on the core life-history phenotypes (see later) have been demonstrated by several in-depth studies (Meiklejohn et al. 2013; Immonen et al. 2016). Also, a growing number of studies have indicated that mitochondrial genetic effects might be context-dependent on the environment in which they are measured (Dowling et al. 2007, 2010; Arnqvist et al. 2010). These results, which are not expected under the assumption of neutrality, have led to the conclusion that at least some genetic variants in mtDNA haplotypes are associated with fitness (that is, selectively recognizable). One of the examples of linking functional changes in mtDNA genes to a better adjustment to environmental conditions is the study of the bar-headed goose (*Anser indicus*). This bird can migrate over the Himalayas and sustain high metabolic rates due to the adaptations at multiple levels of organizations (Bishop 2015). Among the potentially adaptive differences observed between bar-headed goose and low-altitude geese is a single amino acid substitution in the mitochondrial gene COX3 (cytochrome c oxidase subunit 3), which is a core subunit of Complex IV of OXPHOS (Scott et al. 2011). This substitution potentially enables mitochondria to maintain redox balance in response to limitations and fluctuations in their oxygen supply during extreme flights (Scott et al. 2011). Although many studies offer strong examples of the mechanistic link between functional changes in mtDNA genes and ecophysiological phenotype, further analyses are needed to investigate how nucleotide substitutions in mtDNA affect the biochemistry of OXPHOS complexes.

Another feature of mitochondrial genetics is that the diminutive size of the mitochondrial genome imposes its high dependence on nucleus-encoded proteins. It was estimated that approximately 1500 nDNA-encoded proteins are needed for maintaining mitochondrial functions, such as the replication of mtDNA or transcription of mitochondrial genes (Ryan and Hoogenraad 2007). Moreover, essential cell functions such as OXPHOS and mitochondrial translation are hinged on the coordinated interactions between mitochondrial and nDNA-encoded products. For example, the primary center of ATP production, the OXPHOS process, is based on the functioning of four large protein complexes that are responsible for the proton gradient across the inner mitochondrial membrane (Fig. 1). This gradient is used by the fifth complex (ATP synthase) to generate ATP from adenosine diphosphate (ADP) and free phosphate. Complexes I-IV form the multi-subunit electron transport chain (ETC) through which electrons are transferred from electron donors (NADH and $FADH_2$) to electron acceptors (such as oxygen) in a series of redox reactions that release energy. Among the 80 subunits in ETC complexes and ATP synthase only 13 are mtDNA-encoded. Specifically, complex I (NADH:ubiquinone oxidoreductase) consists of 37 nDNA- and 7 mtDNA-encoded subunits; complex II (succinate:ubiquinone oxidoreductase) has only 4 subunits all coded by nuclear genes; complex III (ubiquinol:cytochrome c oxidoreductase) consists of 10 nucleus- and 1 mitochondrial-encoded polypeptides; complex IV (cytochrome c oxidase, COX) has 10 nDNA- and 3 mtDNA-encoded subunits; and ATP synthase is made up of 12 nDNA- and 2 mtDNA-encoded polypeptides. Complex II, which is completely of nuclear origin, is also involved in the tricarboxylic acid (TCA) cycle and has an important role in adjusting respiration with organisms' energetic needs because the TCA cycle is the final common metabolic pathway for providing energy from various metabolites (Dröse 2013).

In addition to serving as the 'powerhouse of the cell', the OXPHOS complex is also the main production site of a by-product of normal cell metabolism – reactive oxygen species (ROS). The source of the most intracellular ROS is the superoxide ($O_2^{\cdot-}$) which is generated by the oxygen reduction during mitochondrial electron transport. Superoxide is converted to hydrogen peroxide (H_2O_2) and O_2 by superoxide dismutases (SODs), which can be reused to generate superoxide. The effects of these highly reactive molecules are dose-dependent, and at high levels ROS will damage macromolecules such as proteins, lipids and nucleic acids. However, at low levels, they function as signaling molecules that regulate a wide variety of essential biological processes (Finkel 2012). For instance, ROS are biologically important in a variety of physiological systems, including adaptation to hypoxia, regulation of autophagy, immunity, differentiation and longevity (Sena and Chandel 2012 and references therein). So, at low levels, ROS may be important in metabolic adaptation, while high intensity of ROS production damages macromolecules and can signal cell death via induction of apoptosis or autophagy. This has led to the viewpoint that ROS might have an important role in communication between mitochondrial

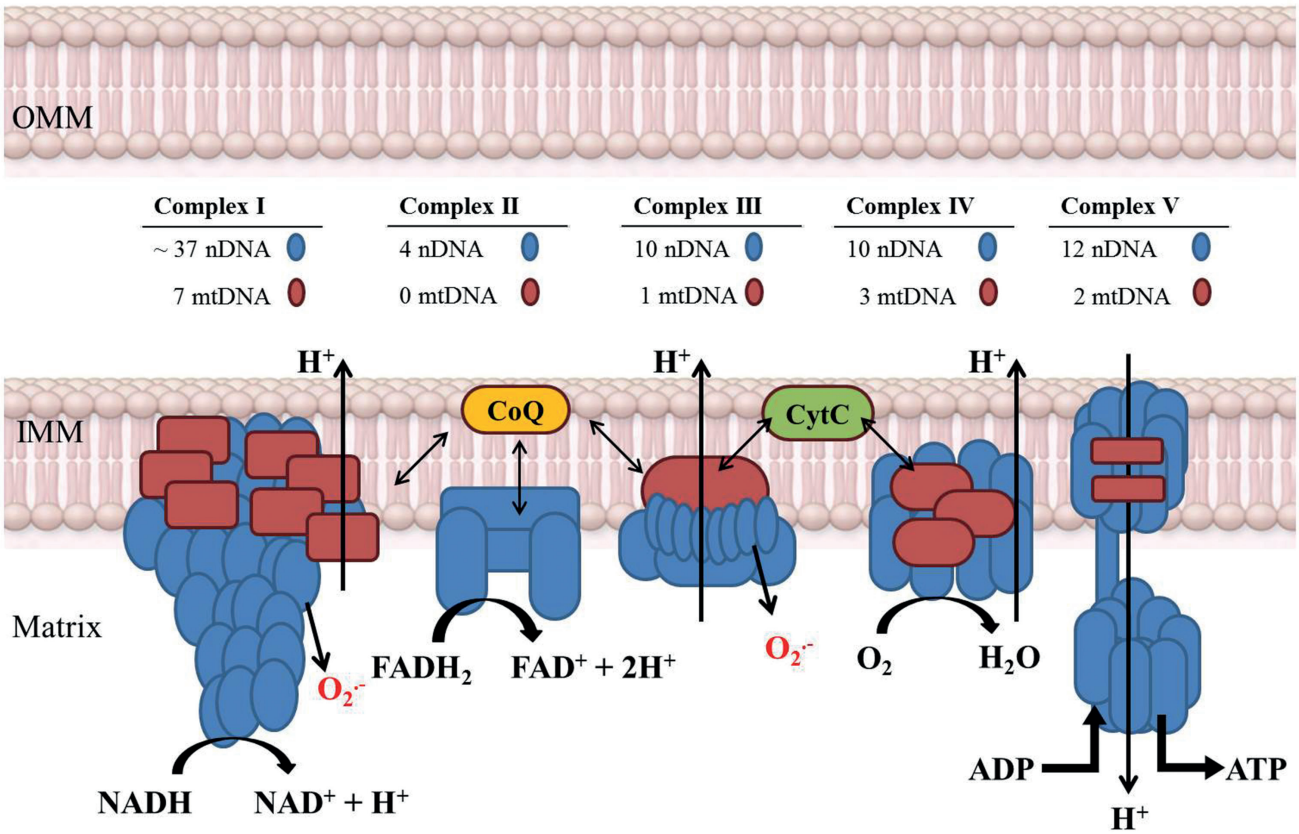

Fig. 1. Schematic model of the oxidative phosphorylation process (OXPHOS) and the production of reactive oxygen species (ROS). ATP is generated by oxidative phosphorylation conducted by the four complexes of the ETC and ATP synthase (Complex V) located in the inner mitochondrial membrane (IMM). Superoxide ($O_2^{\cdot-}$) is an abundant ROS in the cell and it is generated as the by-product of the electron transport of Complexes I and III. The origin of the subunits of the complexes and their number are given in the tables (mitochondrial-encoded polypeptides (mtDNA) are in red, nuclear-encoded polypeptides (nDNA) are in blue). OMM – outer mitochondrial membrane; CytC – cytochrome C; CoQ – coenzyme Q10.

function and other cellular processes in order to maintain homeostasis and promote adaptation to stress.

In the light of the notion that even minor biochemical inefficiencies in OXPHOS functioning, due to mitonuclear incompatibility, could modulate energy production and/or oxidative stress levels in the cell, strong selective pressures should optimize and maintain optimal mitonuclear allele combinations. In other words, specific patterns of mitonuclear coevolution should be expected within each population under diverse environmental conditions and over the evolutionary time (see review in Levin and Mishmar 2015). If these presumptions are true, then any disturbance in the coevolved mitonuclear genomes should have deleterious consequences on mitochondrial bioenergetics and life-history (fitness) traits. The results of several studies on diverse and phylogenetically distant taxons (e.g. yeast, invertebrates and mammals) lend support to the model of mitonuclear coadaptation discussed above (Wolff et al. 2016). In the next section, the significance of mitonuclear interactions for the evolution of diverse phenotypes will be discussed.

Life-history theory and mitonuclear interaction

In modern evolutionary theory, there is a growing interest in the idea that energy metabolism plays an important functional role in determining the evolution of life-history strategies in all biological species. Here, the major generalizations of life-history theory will be presented in order to understand how the patterns of mitonuclear coevolution, which lies at the heart of organismal energy production, could affect the ways in which the life cycles of diverse taxa evolve.

The fundamental biological principle presumes that the acquisition of external resources is necessary for producing energy and materials for all the biological processes that enable individuals to develop, grow, live and reproduce. Several essential life-history traits basically determine the life-history strategy that is specific to each species, population and individual: size at birth, growth pattern, age at maturity, size at maturity, number, size and sex ratio of offspring and lifespan (Stearns 1992). The two extreme life-histories in animals can illustrate the great variety of combinations in life-history schedules and growth forms. At one end, there are species

that mature early and reproduce quickly, have small body size, produce a large number of eggs and live short lives (e.g. insects), and at the other end of the life-history spectrum are species that take several years to mature, with large individuals that have a small number of offspring and live substantially longer (e.g. many mammals). It is important to note that between these extremes, there is a great variety of different life-history strategies in animals, and also that within each species and population there is a considerable amount of individual variation in life-history traits (see review in Stojković 2011).

These considerations raise the question as to why so many diverse life-history strategies exist. An ultimately superior organism (named the 'Darwinian demon'; Law 1979) would be completely mature at birth; it would continuously produce a large number of high quality offspring, and it would live forever. The existence of such a 'demon' is not possible for at least two reasons. First, an organism can acquire a finite amount of resources, and second, the portion of the resources that are allocated to one biological function decreases the amount of resources that can be allocated to another. In other words, biological processes within an individual compete directly with one another for limited resources, and this phenomenon is called physiological trade-off (Stearns 1992). It is clear that different ecological environments impose diverse selective pressures that determine the pathways of adaptive evolution of life-history strategies in each population. The adaptive strategy in one environment depends on an optimal allocation balance between organismal functions in which the fitness of an individual depends on its ability to allocate resources in reproduction while simultaneously maximizing its chance of surviving to reproduce (Roff and Fairbairn 2007). The genotypes that have the combination of life-history traits, which is optimal for certain ecological conditions, will be favored by natural selection, and the specific genetic/epigenetic mechanisms that underlie adaptive life-history strategy will evolve (population/genetic selective responses of negative correlations between life-history traits are termed microevolutionary trade-offs; Stearns 1992).

The link between life-history evolution and mitonuclear interactions is deeply rooted within the mechanisms of energy metabolism. It is the close collaboration among mitochondria and nucleus that initially determine the amount of energy available for all biological functions. Furthermore, the life-history theory suggests that selective optimization of reproduction-related traits and activities in one environment may come at the cost of reduced competence for somatic maintenance, viability and survival due to mutually exclusive energy allocation to different functions (Adler et al. 2016).

There are several different approaches to investigating energy processes as the proximate cause of trade-off between life-history traits. One of the most important components in these considerations is the concept of free radical production (and oxidative stress), which is the by-product of oxidative metabolism. According to Speakman et al. (2015), different tissues and macromolecular targets of oxidative stress respond differently during the whole life cycle and especially during the reproductive period when energy is largely allocated to reproduction. This line of research is based on the hypothesis that there are differential strategies in allocating energy for maintenance and repair mechanisms toward different tissues in an age-specific manner. The physiological basis of the evolution of specific life-history trade-offs should be largely founded on the strategy of which tissues will be protected and which will be left vulnerable to oxidative damage during the lifetime of an individual (see review in Speakman et al. 2015). The pace-of-life syndrome (POLS) hypothesis suggests that the rate of individual metabolism, which shows intrapopulation variation, may influence life-history traits (Reznick 2013). It is expected that animals living at a faster metabolic rate evolved a so-called "live-fast-die-young" strategy characterized by fast development, early reproduction and short lifespan because of increased production of ROS in mitochondria and consequent intracellular molecular damage and accelerated ageing (e.g. Berger et al. 2014).

Recent evidence corroborates the hypothesis that mitonuclear interactions and tight coevolution underpin expression of the key life-history phenotypes (Wolff et al. 2016). Elegantly designed experimental hybridization between *Tigriopus californicus* copepods from geographically isolated populations (Santa Cruz and San Diego), with mtDNA divergence exceeding 18%, has resulted in mitochondrial dysfunction and deleterious life-history consequences due to the intergenomic incompatibilities (Burton 1998). In particular, interpopulation hybrids showed slower development, reduced fecundity and viability, elevated oxidative damage, as well as decreased ETC complex activity (Elison and Burton 2006). However, despite showing that mitonuclear compatibilities are required for the optimal expression of life-history traits, what remains uncertain are the roles of evolutionary processes and pressures on such traits in modeling mitochondrial evolution and mitonuclear coevolution. Namely, although these mitonuclear incompatibilities probably represent indirect evidence of selection in different environments, detailed information about the evolutionary mechanisms responsible for shaping observed genetic variation is lacking (Rand et al. 2004). One way for resolving the above contentions can be found in the protocols of laboratory-based experimental evolution.

Laboratory evolution protocols for studying mitonuclear coevolution

Experimental evolution is the study of evolutionary processes that occur in laboratory populations that are studied across multiple generations under defined and reproducible conditions (Garland and Rose 2009). Contrary to artificial selection, where the experimenter breeds indi-

viduals with specific traits or genotypes, thereby enforcing a predetermined relation between desired traits/genotypes and fitness, in experimental evolution, genetic and physiological changes occur during the process of adaptation to regime-specific conditions.

Protocols of laboratory-based experimental evolution can give insights into the trade-offs between life-history traits. During the 30 years of laboratory evolution, experimental populations of the bean beetle, *Acanthoscelides obtectus*, were selected to reproduce either early (E lines) or late (L lines) in their adult life. This evolutionary procedure was designed in order to reveal complex patterns of life-history evolution and the underlying genetic and physiological changes that were accompanied by observed phenotypic changes. In addition, such an approach enabled the detailed analyses of the roles of mitonuclear interactions in the evolution of specific life-history strategies. The phenotypic changes that resulted from the long-term evolution within the two selection regimes (E and L lines) were dramatic. After more than 190 generations of selection for late reproduction, the beetles showed a decrease in early fecundity and doubled their lifespan in comparison to the populations that were selected for early reproduction (E line) (Đorđević et al. 2015; Đorđević 2016). Previous studies of these unique lines have also shown that E/L selection regimes have led to significant divergence in body size, metabolite composition, growth rate, resistance to oxidative stress and several other life-history traits (Lazarević et al. 2012, 2013). Furthermore, recent findings suggested that the age-dependent selection generated differences in mitochondrial and nuclear haplotype frequencies, as well as in mitochondrial bioenergetics (Đorđević et al. 2017; Stojković et al. 2017). Selection for a long life and late reproduction generated positive selection for one specific mitochondrial haplotype, which was fixed in most of the L lines, whereas selection for reproduction early in life (E lines) favored two distinct mt-haplotypes and eliminated the L-specific haplotype (Stojković et al. 2017). This sharp genetic divergence between the two regimes clearly demonstrated that the adaptive evolution of life-history strategies involved mitochondrial genomes.

The results on *A. obtectus* laboratory populations and several similar experimental models (Rose et al. 2002) demonstrated that an experimental evolution approach was important in studying evolutionary and physiological theories of ageing, but also that they were convenient model systems for investigating the relative contribution of nuclear and mitochondrial genes and their epistatic interactions in the evolutionary response of life-history and energy metabolism.

To analyze the fitness consequences of disrupted mitonuclear coadapted genetic combinations, specific experimental lines of *A. obtectus* were created. Maternal inheritance and lack of recombination allow experimental disassociation of the maternal mtDNA from its native nuclear genome and introgression of specific mtDNA into a distinct nuclear background. Namely, if a female with a specific mtDNA haplotype is repeatedly backcrossed for 14 generations to the paternal genotype, the resulting offspring should have maternal mtDNA and 99.9% of paternal nDNA. This underpins the technique of repeated introgressive backcrossing, which was used to generate the mitonuclear introgression lines in which E and L mitochondrial genomes were expressed in distinct nuclear DNA backgrounds (i.e. E and L) (Fig. 2). The logic behind this procedure was the following: if the observed differences in E and L life-history strategies and mitochondrial bioenergetics were shaped by mitonuclear epistasis, then two hypotheses could be made: (i) in the lines with disrupted mitonuclear interaction (i.e. EL and LE lines), the activity of ETC complexes should be reduced in comparison with undisrupted (native) genotype (i.e. EE and LL lines), and (ii) the beetles from EL and LE lines should exhibit lower life-history performance (and consequent decrease in net fitness) relative to the individuals containing native mitonuclear combinations – EE and LL lines.

Both hypotheses were confirmed in two experiments on the bean beetles. Firstly, disruption of the coevolved mitonu-

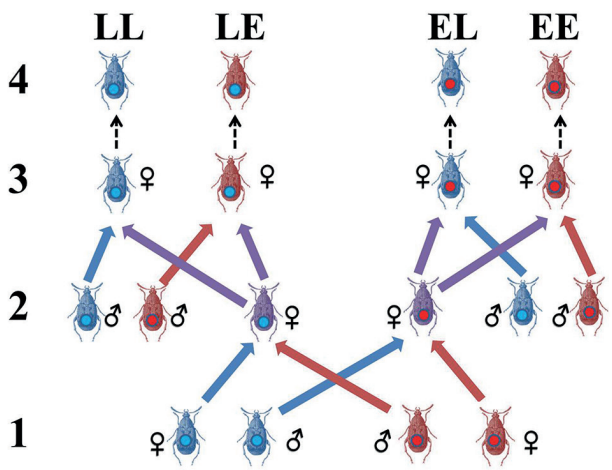

Fig. 2. Schematic presentation of the repeated introgressive backcrossing design that was used to construct mitonuclear lines with disrupted and reconstituted mitonuclear interactions. (1) In parental generation females from E (E nuclear genetic background, red beetle) and L (L nuclear genetic background, blue beetle) selection regimes were mated with males from the opposite regime. Small red and blue circles inside the beetles represent mitochondria derived from either E or L regimes, respectively. (2) Beetles from F1 generation (purple beetles) have maternal mtDNA, 50% of maternal nuclear background and 50% of paternal nuclear background. Virgin F1 females were then divided into two subgroups. (3) In one subgroup, virgin females were backcrossed to males from the maternal selection regime, whereas in the second subgroup, they were backcrossed to males that originated from the paternal selection regime. (4) After 14 generations of repeated backcrossing, more than 99.99% of the original nuclear background should have been replaced. All descendants from both isofemale groups have same maternal mtDNA, but differ in their nuclear genetic background.

clear gene combinations invoked a depression of ETC complex activity in three ETC complexes encoded by both mitochondrial and nuclear genomes (complexes I, III and IV) (Đorđević et al. 2017). Secondly, the assay on life-histories in disrupted and native *A. obtectus* laboratory lines showed that impaired mitonuclear cross-talk mainly affected preadult life-history traits – egg-to-adult viability was significantly decreased and preadult development was significantly prolonged, indicating the serious consequences of lower activity in ETC complexes on early ontogenesis due to the disruption of coevolved mitonuclear gene combinations. Surprisingly, no deleterious effects of mitonuclear impairment on adult life-history traits (fecundity and lifespan of virgin beetles) were observed (Đorđević et al. 2015).

A possible explanation for these results could be found in Lane's threshold model for mitonuclear match (Lane 2011). This model is the most comprehensive theoretical concept connecting energy metabolism, i.e. mitonuclear epistasis, with life-history theory. Here, the central postulate is that a severe mismatch, which raises the errors in the energetic system above the threshold of mitochondrial functioning, will increase oxidative stress, causing higher lethality during embryonic and larval development. On the other hand, a mild mitonuclear mismatch, below the threshold of energetic functioning, which does not compromise the development, will evoke compensatory stress-response processes that could compensate for disrupted mitochondrial function (Fig. 3). Since the selection for a mitonuclear match begins with the first stages of ontogenesis (immediately after fertilization), when the energy-demanding processes of intensive cell cleavage and differentiation start, preadult stages of the bean beetle's life cycle could represent a kind of "intergenomic mismatch control point". At this control point, all the beetles with mitonuclear mismatch above the threshold were eliminated during their larval development, whereas individuals carrying moderate functional impairment were "masked" with the compensatory effect of stress-response processes. Under these predictions, it could be expected that beetles that reached adulthood had unchanged adult traits in comparison to control mitonuclear lines. Interestingly, however, a shorter lifespan was observed in "mismatched" adults who were involved in energy demanding reproductive activities. It could be hypothesized that reproduction provoked additional ROS production and pushed a free-radical leak above the threshold, leading to apoptosis and lifespan reduction. According to Dowling (2009), ROS production in mitochondria could be considered "the central mediator in the evolution of life-history trade-offs."

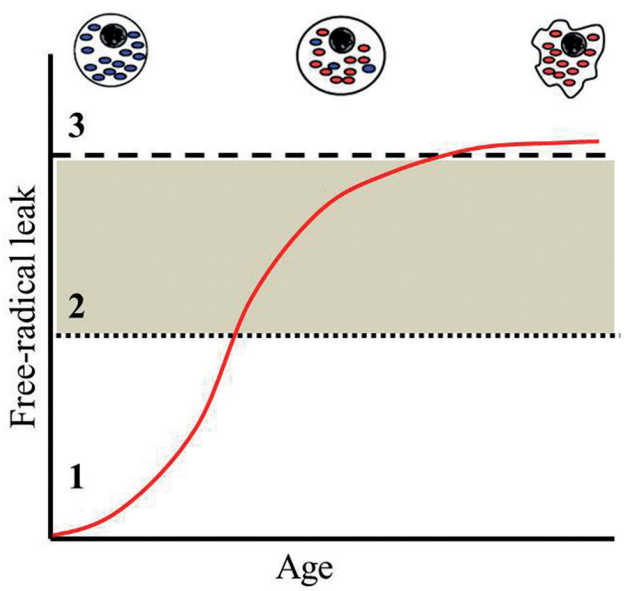

Fig. 3. Diagram of the threshold model for mitonuclear match (Lane 2011). (1) Optimal concentrations of ROS are needed to maintain cellular homeostasis. (2) Concentrations of ROS below the threshold modulate protective, stress-response pathways, resulting in positive effects on life-history traits. (3) ROS levels above the threshold trigger a toxic runaway process and apoptosis.

Conclusions

The evolution of eukaryotes was, and still is, based on dynamic coevolutionary interactions between the two genomes – nuclear, rooted from within domain Archaea, and mitochondrial that originated from the Bacteria domain. It has become increasingly clear that this ancient endosymbiosis created the unique evolutionary situation in which the two genomes became mutually dependent on each other. On the one hand, mtDNA replication and transcription completely depend on proteins encoded by nuclear genes. On the other hand, the evolution of large and complex nuclear genomes is essentially supported by the energy produced by mitochondria. This reflexive relationship between the two genomes has traced the pathways of evolution of all specific eukaryotic traits, including the life-history strategies of multicellular organisms. Although the role of the haploid mitochondrial genome in the evolution of life-histories has often been dismissed because of its small size and the presumed neutrality of its genetic variability, a growing body of experimental studies has now unveiled evidence that mtDNA effects, expressed through intergenomic epistatic interactions with nDNA, could be crucial to the past and ongoing evolution of life-histories. Clearly, the balance between energy production, molecular damage and antioxidative defense lies at the heart of life-history trade-offs through energy allocation into body maintenance (and hence future survival) and reproduction.

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