The First Mitochondrial Genomics and Evolution SMBE-Satellite Meeting: A New Scientific Symbiosis

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Abstract

The central role of the mitochondrion for cellular and organismal metabolism is well known, yet its functional role in evolution has rarely been featured in leading international conferences. Moreover, the contribution of mitochondrial genetics to complex disease phenotypes is particularly important, and although major advances have been made in the field of genomics, mitochondrial genomic data have in many cases been overlooked. Accumulating data and new knowledge support a major contribution of this maternally inherited genome, and its interactions with the nucleus, to both major evolutionary processes and diverse disease phenotypes. These advances encouraged us to assemble the first Mitochondrial Genomics and Evolution (MGE) meeting—an SMBE satellite and Israeli Science foundation international conference (Israel, September 2017). Here, we report the content and outcome of the MGE meeting (https://www.mge2017.com/; last accessed November 5, 2017).

Key words: evolution, genomics, mitochondria, mitochondrial DNA.

Mitochondria are organelles which are pivotal to ATP production and cellular metabolism. As descendants of endosymbiotic alphaproteobacteria, extant mitochondria retained many bacterial-like features, such as double membranes, their own genome (mtDNA), bacteriophage-like transcription, and unique translation machineries (Lane and Martin 2010; Allen 2015). This unique former free-living prokaryote, which virtually defines all eukaryotes, has equally attracted the attention of both medical geneticists and evolutionary biologists. Specifically, mitochondrial dysfunction was found to be central to the development of a variety of human disorders (Vafai and Mootha 2012; Wallace 2016; Marom et al. 2017), whereas also playing a role in major evolutionary events in animals and plants, including adaptive responses (Rand 2008; Lane and Martin 2010; Burton et al. 2013; Dowling 2014; Levin et al. 2014) and the emergence of new species (Gershoni et al. 2009).

Despite the importance of mitochondria to life, research in the fields of animal and plant genomics, using high throughput genome-wide sequencing technologies, frequently overlook mitochondrial genetics and evolution, and even excluded mtDNA sequencing reads from analysis (Pesole et al. 2012). The main reason for overlooking the mtDNA likely relates to the high mtDNA copy number within most samples and the frequent misperception that the small size of the mitochondrial genome may preclude its significant impact on health and disease. The former frequently results in overrepresentation of mtDNA reads in sequencing outputs, thus reducing the read coverage of other genomic regions (Rensch et al. 2016). Therefore, much effort has been invested in reducing

mitochondrial read coverage either during library preparation (Wu et al. 2016) or during data analyses (Buenrostro et al. 2015). These efforts underline the poor representation of mitochondrial genomics not only in the main genomics research arena but also in various other fields of investigation. As a result, mitochondrial genomics and evolution is often underrepresented in mainstream scientific meetings, whereas meetings dedicated to mitochondrial research are often focused on the physiological impact of mitochondrial dysfunction in disease rather than on mitochondrial genomics. Novel genomics technologies have revolutionized the field of genomics, however, their application to the study of mitochondrial gene functions is new. Recent studies have applied diverse methods focusing on mitochondrial gene expression using RNA-seq (Rackham et al. 2016; Kuznetsova et al. 2017), nascent RNA transcript analysis by PRO-seq (Blumberg et al. 2017), and mtDNA transcription factor binding sites by ChIP-seq (Blumberg et al. 2014). Whole-exome and whole-genome sequencing have been employed to screen for phenotype-causing mutations in the nuclear genome (Vafai and Mootha 2012; Abrams et al. 2015), to study inheritance of mixed mtDNA populations (heteroplasmy) (Goto et al. 2011; Avital et al. 2012; Payne et al. 2013; Rebolledo-Jaramillo et al. 2014), and to decipher the structure of abnormal mitochondrial genomes (Lavrov and Pett 2016; Yahalomi et al. 2017). These technologies have enormous applications for the study of mitochondrial genetics and evolution and provide new insights into the diversity of life driven by the evolution of the mitochondrial genome.

In contrast to biomedical researchers, molecular evolutionists frequently focus on the mitochondrial genome as a neutral marker to trace ancient migrations or dispersal and less on the direct phenotypic implications of mitochondrial genetic variation. Nevertheless, the accumulating evidence indicates that interactions between elements encoded by the mitochondrial and nuclear genomes can have major phenotypic consequences. In fact, there has been a gradual realization that mitochondrial genomics may play a major role in evolutionary transitions and adaptive responses, possibly underlying some cases of speciation following the Dobzhansky–Muller model of hybrid breakdown (Gershoni et al. 2009; Burton et al. 2013; Bar-Yaacov et al. 2015).

The gap between biomedical research recognizing the important phenotypic effects of mitonuclear interactions and the limited understanding of its evolutionary consequences strongly motivated us to stimulate discussion among a group of researchers from the fields of genomics, molecular evolution and mitochondrial biology (supplementary table S1, Supplementary Material online) in a combined **scientific meeting entitled "Mitochondrial Genomics and Evolution" (abbreviated to MGE)**, held in the exotic location of the Ein-Gedi oasis, Israel (September 3–6) (conference website: https://www.mge2017.com/; last accessed November 5, 2017). We were fortunate that this new conference topic attracted the attention of the Society for Molecular Biology and Evolution (SMBE), who provided support as a satellite SMBE meeting. This positive response was matched by equal enthusiasm from the Israeli Science foundation, Israeli Ministry of Science and Technology, and the Company of Biologists (see Acknowledgments), thus significantly facilitating the success of this meeting.

The focal topics discussed at the meeting included (fig. 1):

A. The beginning of life and the mitochondria.
B. Uniparental inheritance of the mitochondria—always?
C. Mito-nuclear coevolution.
D. The evolution of mitochondrial activity and regulation
E. The evolution of the mitochondrial genome: genome organization and intracellular dynamics.

The sessions (supplementary figure S1, Supplementary Material online) were preceded by a plenary keynote lecture given by **Douglas C. Wallace** (Children Hospital of Pennsylvania, U-Penn) (presented by **Dan Mishmar**, Ben-Gurion University of the Negev) who uniquely combines evolutionary genomics along with evolutionary medicinal approaches to study the contribution of the mitochondrion to the molecular basis of complex disorders. Each of the above-mentioned topics were discussed by representative scientists from different institutes around the world working on a wide variety of organisms, including fungi, plants, protists, and animals. In the frame of the first session, chaired by **Nick Lane** (University College London) and **Oren Ostersetzer-Biran** (Hebrew University), the role of the mitochondria in the early development of eukaryotes was discussed. The session first highlighted the requirement for a core bioenergetic genome in mitochondria, which needs to be colocated with bioenergetic membranes for redox regulation. Secondly, we discussed the impact of gene loss from proto-mitochondria, which allowed the enormous expansion of the nuclear genome during early eukaryotic evolution. The specialization of mitochondrial genomes in relation to bioenergetic membranes satisfied the high energetic needs of nuclear gene expression. Thirdly, and accordingly, we discussed the unique challenges for natural selection acting on oxidative phosphorylation genes which are encoded in all complex eukaryotes by two asymmetric genomes, that need to produce energy in response to diverse external environments (demonstrated in the frame of thermal adaptation in *Drosophila*). The impact of such constraints on the tremendous variation in mtDNA architectures across eukaryotes was discussed, including the expansion of group II introns in plants and lower animal forms.

Mitochondria are characterized by a uniparental mode of inheritance (UPI), which was the topic of the second session, chaired by **Andrew Pomiankowski** (University College London). Selection against low-frequency mutational variants is weak as their fitness effects are buffered by the multiploid nature of mtDNA—deep sequencing has confirmed universal

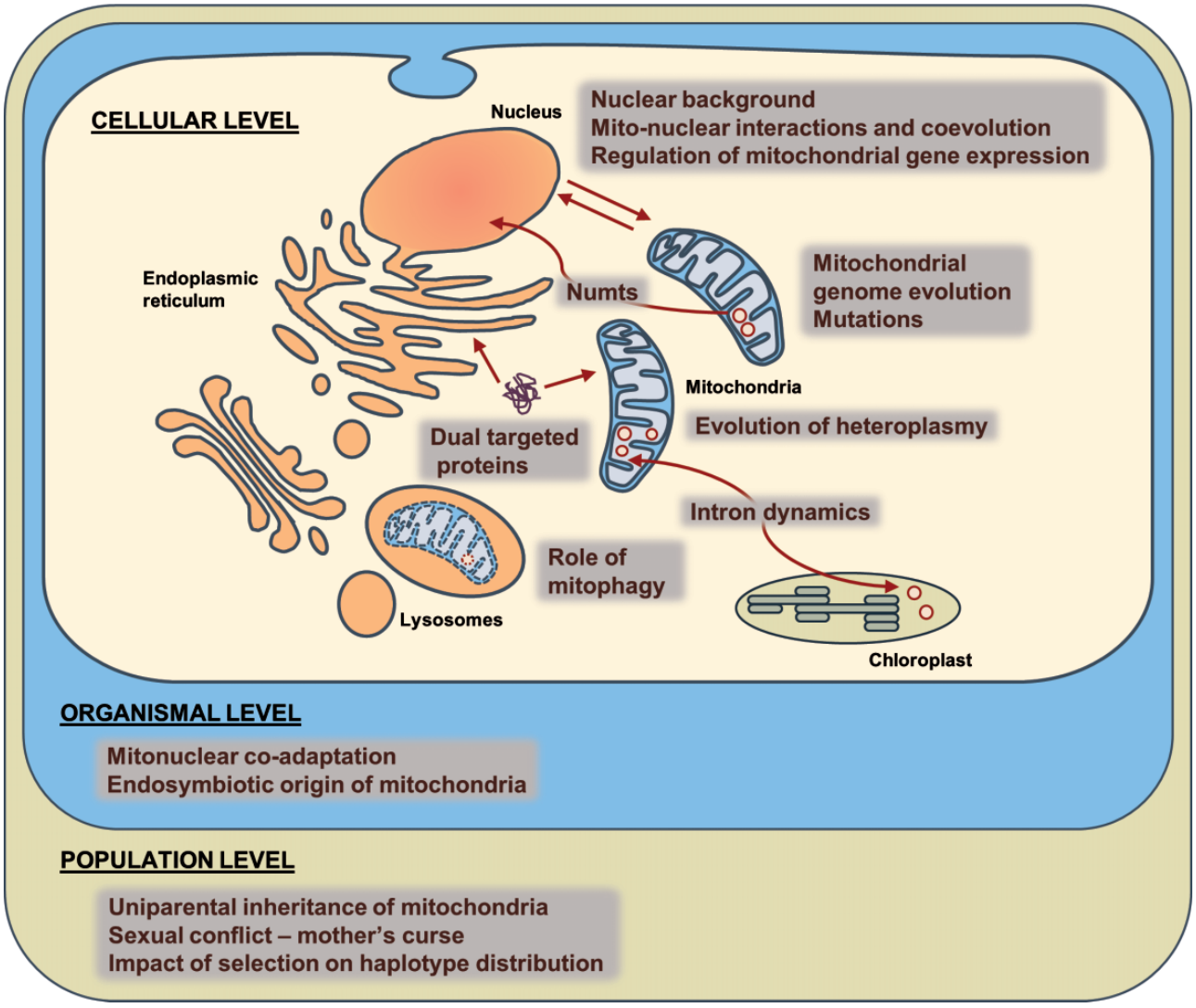

Fig. 1.—Principal topics discussed at the first Mitochondrial Genomics and Evolution satellite meeting. Topics are indicated within gray boxes.

low-level heteroplasmy. UPI helps by generating greater variation in mutation number among gametes and resulting zygotes, allowing a stronger evolutionary reduction in mutation load in the long term. During the session, it was suggested that other aspects of oogenesis are designs to increase variability and overcome the build-up of mutations (such as the so-called "bottleneck," the massive expansion of mtDNA numbers in eggs, and atresia). Selfish mtDNA mutations (those that have a replicative advantage within cells, but at a cost to organismal fitness) ramp up the need for organismal-level counter adaptations like UPI, but it remains unclear just how prevalent they are in nature. To address this, parental mtDNA sequencing has uncovered many more cases where paternal mitochondria slip through during fertilization (e.g., wild carrot), creating extensive heteroplasmy in the resulting offspring. This aligns with theory that predicts weak paternal control of mtDNA transmission, favoring some degree of paternal leakage. Two of the talks presented the most bizarre example of this—doubly uniparental inheritance of the mitochondrial genome in bivalve mussels, where male and female mitochondrial genomes are both inherited despite differing in up to 50% of their sequence. UPI also leads to the prediction of so-called mother's curse, dysfunction of mitochondrial activity in males, revealed by incompatibilities between mitochondria on some nuclear genetic backgrounds, but was questioned in other talks during the conferences.

The third session, which focused on mitonuclear coevolution, was cochaired by **Ronald Burton** (University of California, San Diego) and **Göran Arnqvist** (Uppsala University, Sweden). This session highlighted the emerging insight that epistatic interactions between the mtDNA and the nuclear genome are more complex than once thought, extending beyond mitochondrial energy production to all aspects of mtDNA replication, transcription, and translation.

Although there are relatively few protein-coding genes in the mtDNA, mitochondrial function requires importing more than a thousand nuclear-derived proteins. Recent evidence indicates that many of these nuclear-derived proteins show elevated rates of evolution compared with other nuclear genes, apparently a coevolutionary response to rapid mtDNA evolution. DNA elements with a regulatory role may also affect the performance of certain mitonuclear genotype combinations, further adding to the potential complexity. To name a few contributions, oral presentations focusing on more phenotypic experimental approaches, such as those that use controlled crosses between known mitonuclear types, were brought together with more mechanistic and comparative contributions focusing on mitochondrial mutations and computational approaches to understanding the evolution of mitonuclear interactions and the role of introns and other forms of noncoding DNA. The general conclusion was that mitonuclear interactions and coevolution is clearly fundamental to selection that shape the evolutionary dynamics of the mtDNA which, in turn, impacts evolution of the nuclear genome. The meeting participants were left with the current challenge to unravel various aspects of the apparent complexity of such interactions.

The fourth session, chaired by **Aleksandra Filipovska** (University of Western Australia, Australia) focused on the role of mitochondrial genomics in the study of mtDNA replication, transcription, and posttranscriptional regulation by a range of factors and nucleic-acid binding proteins. The speakers in this session discussed the variation of mitochondrial heteroplasmy in diverse tissues and organisms, the posttranscriptional regulation of mitochondrial RNAs in models of health and disease, potential epigenetic regulation, and new genomic and transcriptomic technological developments that are increasingly valuable to dissect the mechanisms that regulate mitochondrial gene expression. The correlation between nuclear and mitochondrial gene expression was examined to emphasize the interdependence of the two genomes that relies on their communication via diverse antero- and retrograde signaling networks.

The final (fifth) session, chaired by **Dorothée Huchon** (Tel Aviv University, Israel) discussed variability in mtDNA size, organization, and dynamics among and within organisms, during the course of evolution and during the lifespan of an organism. In the first part of the session, factors that affect the transmission of heteroplasmy were discussed. This topic was approached from both population genetics and molecular cell biology point of views. For example, the impact of maternal age on the heteroplasmy was studied in the human population. At the cellular level, mitophagy regulation of heteroplasmy was studied in *Caenorhabditis elegans* and in yeast. The evolution of dual targeted proteins, that is, proteins that reside both in the mitochondria and in other subcellular compartments, was also discussed as well as the selective pressures acting upon such proteins. The second part of the session focused on the sequence and structural diversity of the mitochondrial genomes of model and nonmodel organisms harboring both circular, fragmented, or linear mtDNAs. Finally, the impact of mitochondrial introns as markers for phylogenetic studies, and on sequencing difficulties in organisms with diverse mitochondrial genome organization were discussed.

The genomics and evolutionary flavor of the meeting integrated new and exciting studies on model and nonmodel organisms from all kingdoms of life. The diverse fields of the participating scientists included population and molecular genetics, cell biology and ecology, enabling the speakers and poster presenters to identify synergies and common technologies that would advance their future research endeavors and promoted networks for new collaborative efforts. The discussion throughout the meeting elevated beyond the conceptual level, providing valuable insights and interpretation of new paradigms, results, and methodologies. The MGE conference provided the platform to meeting between researchers from diverse fields that usually attend different meetings and may not be up-to-date on the progress outside their niche fields. This strategy enabled an unprecedented opportunity for collaboration and discussion that may not have been possible previously.

The vast majority of eukaryotes cannot sustain life without mitochondria. In addition to producing the major cellular energy currency (ATP), mitochondria are essential for the breakdown of fats and carbohydrates, the biosynthesis of nucleotides, hormones, the regulation of programmed cell death, redox regulation, and scavenging of reactive oxygen species. As this biological system developed at the dawn of eukaryote evolution, many emerging questions about their role in different organisms, were addressed during the MGE meeting. We hope that the unique platform created at the MGE conference will continue in the coming years, and will nourish interdisciplinary topics in mitochondrial genomics and evolution. We also hope that fruitful cross-field discussions at the MGE conference will set the grounds to formation of new interdisciplinary meetings, combining evolutionary research with molecular biology, genomics, and transcriptomics.

Supplementary Material

Supplementary data are available at *Genome Biology and Evolution* online.

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