Opinion Article

Are maternal mitochondria the selfish entities that are masters of the cells of eukaryotic multicellular organisms?

Luigi F. Agnati,1,* Peter W. Barlow,2 E. Baldelli1 and Frantisek Baluška3

1Department of BioMedical Sciences; University of Modena and IRRCS Lido VE; Modena, Italy; 2School of Biological Sciences; University of Bristol; Bristol, UK; 3Department of Cellular and Molecular Botany; University of Bonn; Bonn, Germany

Key words: complexity, embedded internal milieu, Energide, evolution, maternal mitochondria, prokaryote-eukaryote transition, order

The Energide concept, as well as the endosymbiotic theory of eukaryotic cell organization and evolution, proposes that present-day cells of eukaryotic organisms are mosaics of specialized and cooperating units, or organelles. Some of these units were originally free-living prokaryotes, which were engulfed during evolutionary time. Mitochondria represent one of these types of previously independent organisms, the Energide, is another type. This new perspective on the organization of the cell has been further expanded to reveal the concept of a public milieu, the cytosol, in which Energides and mitochondria live, each with their own private internal milieu. The present paper discusses how the endosymbiotic theory implicates a new hypothesis about the hierarchical and communicational organization of the integrated prokaryotic components of the eukaryotic cell and provides a new angle from which to consider the theory of evolution and its bearing upon cellular complexity. Thus, it is proposed that the “selfish gene” hypothesis of Dawkins1 is not the only possible perspective for comprehending genomic and cellular evolution. Our proposal is that maternal mitochondria are the selfish “master” entities of the eukaryotic cell with respect not only to their propagation from cell-to-cell and from generation-to-generation but also to their regulation of all other cellular functions. However, it should be recognized that the concept of “master” and “servant” cell components is a metaphor; in present-day living organisms their organelar components are considered to be interdependent and inseparable.

Introduction

The concept of ‘Energide’, originally proposed in 1892 by Julius Sachs,2 demands revisions not only of the classical concept of cell,2-4 but also of the equally classical concept of the “internal milieu”.5 According to the most recent version of the Energide concept,6 the combination of nucleus and microtubular cytoskeleton is the fundamental and universal unit of eukaryotic life. The complementary endosymbiotic theory of the cell due to Margulis6 maintains that mitochondria were originally free-living prokaryotic organisms (e.g., proteobacteria), which became engulfed and integrated within either an archael or a primitive eukaryotic host. The transition from being an autonomous proto-bacterium to becoming a subordinate host (nuclear)-controlled organelle was pivotal in the evolution of the eukaryotic cell (for a discussion of alternative hypotheses describing the origin of eukaryotic cell and evolution of mitochondria, see Gray et al.8).

Recent analyses of the genomes of eukaryotic nuclei and cytoplasmic mitochondria have revealed that the last universal common ancestors of the organelar components of eukaryotic cells were formed by cell-cell mergings or fusions. Now that we have a more complete and holistic view of eukaryotic cells, we can see that it is characterized by a distinct duality, or dialectic, recognizable in the complementarity of (originally the antagonism between) cellular structures and processes. Thus, at the level of the cell, the Energide (guest) is complemented by a Cell Periphery Complex (host). At the level of the genome, eubacterial features complement archaebacterial features; the cytoskeleton is composed of complementary tubulin (Guest) and actin (Host); membrane flow is comprised of exocytosis (Guest) and endocytosis (Host) which complement each other, and cell division integrates the complementary processes of mitosis and cytokinesis.2,3 At the level of the genome, eubacterial features complement archaebacterial features.

These complementary features strongly suggest that the most ancient eukaryotic cell was generated from the merger/fusion of at least three proto-cell organisms and that the eukaryotic genome is the result of the merger of at least two proto-genomes (reviewed in refs. 2–4). It has been suggested that this universal and ancestral “Host/Guest” cell consortium “enslaved” at least two other types of cells that entered it via a predatory phagocytosis.2,9 Thereby, a new even more complex endosymbiotic cell emerged consisting of diverse organelles.

Remarkable is that mitochondria, although enslaved by their host, have retained most of their prokaryotic biochemistry despite the fact that they harbour only a remnant of the genome which their eubacterial predecessor possessed. This view implies that two processes have paved the way for the evolution of eukaryotic cells which now have a greater degree of complexity than their ancestors. Importantly, this hypothesis has the consequence that such cells would disobey the
usual tenets of Darwinian evolution due, notably, to the processes of lateral gene transfer (also called horizontal gene transfer) and endosymbiosis. Each of these processes, both individually and together, have played a crucial role in the evolution of complex eukaryotic cells and has endowed them with nuclei. Lateral gene transfer (LGT) is a process by which an organism incorporates genetic material from another organism without being the offspring of that organism. This phenomenon is still in operation in eukaryotic cells, and is a ubiquitous and continuing natural process which pervades the dynamics of nuclear DNA within and between diverse organisms. Moreover, it is still occurring between the mitochondria and the nucleus of cells. Analysis of genome DNA sequences reveals that ever since the incorporation of cellular organelles into a “host” cell, organelar DNA has constantly bombarded the nucleus of the host, and that DNA is transferred by LGT from the genome of organelles to the nucleus at frequencies that were previously thought impossible.

As underlined by Baluska et al., evolution of complex eukaryotic cells not only provides us with an important paradigm for the elusive nature of living matter but also suggests why living entities should have evolved from a low level of complexity to one that is higher. Here we remark that the strength of the Darwinian evolutionary theory is its ability to explain how adaptation comes about, driven as it is by variation, competition and selection, but that the theory could also probably find important complements in the endosymbiotic theory and in Kauffman’s proposal that there is a tendency by variation, competition and selection, but that the theory could also probably find important complements in the endosymbiotic theory and in Kauffman’s proposal that there is a tendency inherent to living matter to acquire order and hence to develop more complex forms—i.e., the selective sieve that creates the most efficient combinations of molecular modules at the sub-cellular level. At the cellular level there is a similar “sieving” of related features realize their full meaning only within the framework of order.

The Present Hypothesis

The present hypothesis posits that the precursor of the Energide as well as several other small prokaryote bodies colonized a large proto-cell and found within it a suitable internal milieu. Then, as indicated above, there were intraorganellar forces that had to be balanced, namely the competitive forces of the ingested prokaryotic units within this shared internal milieu. Out of this new balanced state came the need for positive interactions between all those units which had been ingested in order to survive in an endosymbiotic relation with the host prokaryote. A second force also had to be reconciled: the often antagonistic relationship between the new composite organism (or cell) and its external and potentially hostile environment.

Wallace states that “Life is the interplay between structure, energy and information.” To this can be added the idea that these interrelated features realize their full meaning only within the framework of order. Inevitably, a further question is whether order is better conserved by containment of the system within a heterarchic or a hierarchic organizational structure; that is, whether all components of a ‘cell’ are of equal ‘strength’ and cooperate (heterarchy), or whether one component is dominant and regulates the function of subordinate components (hierarchy). A hierarchical order would necessarily invoke a master entity. To discern such an entity would require analysis of the inter-organellar symbiotic interactions and thereby discover cui maxime prodest.

On the basis of these premises, the hypothesis is put forward that, for multicellular organisms, cellular order is hierarchical, and that the “master” entity of the eukaryotic cell is not the Energide (i.e., nucleus with associated microtubules), as was previously supposed, but the
maternal mitochondrion. Hence, a Copernican Revolution seems inevitable for the understanding of the biology of eukaryotic cells in multicellular organisms. The intracellular organelles no longer revolve around a nuclear "sun", but everything revolves instead around a maternal mitochondrial "sun". Thus, while Dawkins has formulated the important theory of the selfish gene (nuclear DNA), the present hypothesis maintains that, during the evolutionary descent of present-day eukaryotic animals and hence of humans, and perhaps plants also, the selfish entity that promotes its own conservation is the maternal mitochondrion.

Data and deductions. Some data and deductions which support the present hypothesis centre around mitochondrial biology and are as follows:

- Mammalian mtDNA is maternally inherited. This phenomenon was probably a late development in evolutionary time and did not apply in early eukaryotic organisms. However, in the modern eukaryotes the mitochondria of mammalian sperm are destroyed in the fertilized oocyte; they are ubiquitinated inside the oocyte cytoplasm and later subjected to proteolysis during pre-implantation development of the embryo. That mitochondria have an exclusive maternal origin, implies that mammalian organisms defend their gender-based singularity. Thus, the mitochondria move from one generation to the next unopposed by any recombination resulting from sexual mechanics. This is in contradistinction to the male Energide which mixes its nDNA with that of the female Energide following sexual fertilization of the oocyte. While this assumption is generally accepted, some authors have pointed out that, in some cases, a paternal inheritance of mitochondria is possible.

Supporting this view is a case report describing a 28-year-old man with most of the mitochondria in his muscles inherited not from his mother but from his father. However, besides special cases such as the one mentioned, it should be accepted that males are dead-ends for mitochondria (due to their destruction at fertilization) and this has consequences for the human sex ratio. Supporting this view is a case report describing a 28-year-old man with most of the mitochondria in his muscles inherited not from his mother but from his father. However, besides special cases such as the one mentioned, it should be accepted that males are dead-ends for mitochondria (due to their destruction at fertilization) and this has consequences for the human sex ratio.

- Plant mitochondria are maternally inherited. Recent work shows that in the thale cress, Arabidopsis thaliana, the mitochondria of sperm cells, brought into the egg cell during the double fertilization, are destroyed. Those that remain are of maternal origin. There are also observations from electron microscopy which show that, in barley, the mitochondria of the sperm are ejected from these cells before the sperm participate in fertilization.

- Mitochondria maintain power over the life and death of a cell because they have the controlling hand in programmed cell death by releasing proteins such as cytochrome c. This can explain why human cells dedicate well over 100 nuclear genes to the maintenance of mtDNA that encodes only 13 proteins. In fact, three main hypotheses have been put forward to explain why genes for certain mitochondrial membrane subunits of the oxidative phosphorylation complexes (OXPHOS) have been retained in the mtDNA. These hypotheses are not mutually exclusive and each has some experimental support. However, it should be considered, as mentioned above, that the mtDNA-encoded polypeptides give overall control of the mitochondrial energy supply by which the eukaryotic cell is sustained, and even holds the key to cellular life and death and maybe to organismal life and death also. As Wallace points out, all mtDNA analyzed to date contain cob and cox1 genes, which are central to the coupling of electron transport with proton pumping via complexes III and IV. A consequence of our hypothesis is the proposal that, during evolution, mitochondria, while they have maintained possession of some crucial genes, they may nevertheless have transferred most of their mtDNA to the "servant" nDNA that is the product of the combined male and female Energide brought into being by sexual fertilization. In addition to hypothetical selfish action of the mitochondrial "master" unloading part of its genetic burden onto the nuclear "servant", the transfer of endosymbiont genes to the host genome is also a consequence of the well-documented observation that, in isolated endosymbiotic genomes, degenerative evolution and inevitable loss of DNA-based information is an unavoidable consequence of the increasing mutational load.

- Mitochondria can evolve as colonies within the eukaryotic cell, i.e., in a privileged environment (Fig. 1). As beautifully stated by Wallace, "once the nuclear cytosol and mitochondrial endosymbiosis became established, the cytosol became the mitochondrial universe." It follows that in a multi-cellular organism mitochondria enjoy their own "embedded milieu" (i.e., the internal environment of the prokaryotic mitochondrial ancestor that lies embedded within the internal milieu of the host cytoplasm), which protects them from the surrounding "classical internal milieu," or cytosol, provided by the original host organelle, or cell. Obviously, this is true for the Energide and also for the other endosymbiotic organelles; each of their organelar "cytoplasts" is also an embedded milieu within the cytosol. Thus, the host's classical internal milieu harbours, embedded within it, one Energide with its cytoplasm, as well as a colony of interacting mitochondria each with its own internal milieu.

- Mitochondrial DNA can mutate more rapidly than nDNA—animal mtDNAs have been found to have a high mutation rate, evolving about 20 times faster than nDNA sequences with analogous coding sequences. Mitochondria can more easily discard the unfavorable mutations since they are always organized as a dynamic colony, or chondriome, of 10^2 or 10^3 organelles within each eukaryotic cell. The relevance of the proper functioning of the chondriome is underlined by several findings of particular interest. For example, recent data show a cause-effect relationship between amyloid β over-production and alterations in mitochondrial dynamics. Thus, it has been demonstrated that the amyloid precursor protein (APP), through amyloid β production, causes an imbalance of mitochondrial fission/fusion that results in mitochondrial fragmentation and abnormal distribution. This, in turn, contributes to mitochondrial and neural dysfunction.

Thus, not only might mitochondria be defective in supplying energy to neurons, but also alterations to the processes of mitochondrial fission can lead to apoptosis and neurodegeneration. These data may shed some light on the still unclear etiologies of sporadic Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, which are among the most common neurodegenerative diseases and seem to have mitochondrial alterations as one of the causative factors.

- Transmission of heteroplasmic mtDNA deletions from a mother organism to its offspring is rare, whereas transmission of heteroplasmic point mutations is common in human pedigrees. The uneven distribution of mutated mtDNA among siblings has been attributed to a bottleneck phenomenon during mammalian oogenesis. This is still unexplained.

- Mitochondria can sometimes move from one eukaryotic cell to another within one and the same organism and thereby reach a more
Maternal mitochondria: selfish entities that are masters of eukaryotic cell?

Two phenomena should be considered to broaden the more conservative form of neo-Darwinism of evolution, namely endosymbiosis and lateral gene transfer, LGT. They have, nevertheless, been of paramount importance in the acquisition of cellular complexity by eukaryotic cells. It is proposed that Jacob’s far-reaching concept of evolution acting not as an engineer but as a tinker, using materials at its disposal to produce a new entity, 26 can be extended from the molecular level up to the level of entire organisms.

This view is in agreement with the statement of Russell and Aloy, 27 who propose that a key concept in biological system design is modularity; thus, modularity in relation to tinkering means that nature is continually reusing both the design principles as well as the modules of structure to which are coupled metabolic processes in the construction of new forms. This basic logic is apparent at nearly all levels, from the four bases making up the genetic code to the hierarchical organization of ecosystems. 27 In the present paper, it is suggested that modularity is advantageous to the tinkering process by which the assemblage of endosymbiotic “contraptions” came into being during eukaryotic phylogeny. It is proposed, therefore, that different primitive
organisms have been used by the evolutionary tinker as the modular building blocks for the assembly of a new endosymbiotic type of cell with an increased complexity and out of which more complex living systems can emerge. This mode of evolution recalls how “tesserae” are put together to construct a mosaic; or, at an even higher level, how intelligent animals consciously co-opt inanimate objects as tools for the enhancement of their mode of living.

Thus, present-day eukaryotic cells are a hierarchical mosaic of cooperating specialized units. It follows that a hierarchical order of modules within a cell (or at any level) would imply that there is a ranking of these constituent units (with respect to their complexity or bonding energy) in operation. Accordingly, criteria can be found to assess the leading or dominant component in a ranked series of organelles. We consider four such criteria:

- Unbroken linear descendent through successive cell generations.
- Control of energy production.
- Possibility of by-passing, and therefore of surviving, cell death.
- Regulation of cell death, life being the default position.

According to these criteria mitochondria are the “master” entities of the eukaryotic cells of multicellular organisms, and all other organelles are ‘servant’ entities (the Energide and everything else).

A fifth criterion is forthcoming from the answer to the question concerning which of the endosymbionts acquires the maximal advantage from the cooperation of organelles within a hierarchically ordered eukaryotic cell? Mitochondria represent the most numerous and cooperative of cellular organelles. Hence they can exploit, in an efficient way, all the other milieu embedded within an endosymbiotic cell. Basically, they have delegated to all the other organelles the task of maintaining a constant internal milieu—that cytosolic milieu which was originally supplied by the host cytoplasm. This they do with the aid of three controls: energy balance, fusion with self-assembly of their own mitochondrial structure, and selective apoptosis of the cells containing them. Furthermore, mtDNA influences sex determination, as it has been shown that in early embryos mitochondria can kill or feminize males by initiating apoptosis in important gender-related cell lineages. Thus, a genetic conflict exists between mitochondrial genes, which are maternally inherited, and nuclear genes, which are biparentally inherited. A mitochondrion would prefer that all the organisms that propagate them should be female. But apart from the above-mentioned processes (i.e., endosymbiosis and lateral gene transfer) should be analyzed against Kauffman’s proposal that Darwinian evolution should conform to Darwinian evolution, the increase in complexity of eukaryotic cells and, hence, of the increased scope for organogenesis which can be achieved by the second pattern disobey the tenets of Darwinian evolution. However, each pattern should be evaluated in the context of Kauffman’s proposal that simple and complex systems exhibit order spontaneously.

Thus, present-day eukaryotic cells are a hierarchical mosaic of cooperating specialized units. It follows that a hierarchical order of modules within a cell (or at any level) would imply that there is a ranking of these constituent units (with respect to their complexity or bonding energy) in operation. Accordingly, criteria can be found to assess the leading or dominant component in a ranked series of organelles. We consider four such criteria:

- Unbroken linear descendent through successive cell generations.
- Control of energy production.
- Possibility of by-passing, and therefore of surviving, cell death.
- Regulation of cell death, life being the default position.

According to these criteria mitochondria are the “master” entities of the eukaryotic cells of multicellular organisms, and all other organelles are ‘servant’ entities (the Energide and everything else).

A fifth criterion is forthcoming from the answer to the question concerning which of the endosymbionts acquires the maximal advantage from the cooperation of organelles within a hierarchically ordered eukaryotic cell? Mitochondria represent the most numerous and cooperative of cellular organelles. Hence they can exploit, in an efficient way, all the other milieu embedded within an endosymbiotic cell. Basically, they have delegated to all the other organelles the task of maintaining a constant internal milieu—that cytosolic milieu which was originally supplied by the host cytoplasm. This they do with the aid of three controls: energy balance, fusion with self-assembly of their own mitochondrial structure, and selective apoptosis of the cells containing them. Furthermore, mtDNA influences sex determination, as it has been shown that in early embryos mitochondria can kill or feminize males by initiating apoptosis in important gender-related cell lineages. Thus, a genetic conflict exists between mitochondrial genes, which are maternally inherited, and nuclear genes, which are biparentally inherited. A mitochondrion would prefer that all the organisms that propagate them should be female. But apart from these two processes (i.e., endosymbiosis and lateral gene transfer) should be analyzed against Kauffman’s proposal that Darwinian evolution should conform to Darwinian evolution, the increase in complexity of eukaryotic cells and, hence, of the increased scope for organogenesis which can be achieved by the second pattern disobey the tenets of Darwinian evolution. However, each pattern should be evaluated in the context of Kauffman’s proposal that simple and complex systems exhibit order spontaneously.

Stuart Kauffman suggests that Darwin’s view is inadequate, since the source of order in the great branching tree of life itself is not the result of a single force: natural selection. We propose that the two above-mentioned processes (i.e., endosymbiosis and lateral gene transfer) should be analyzed against Kauffman’s proposal that selection achieves and maintains complex systems poised on the boundary, or edge, between order and chaos. These two processes could be viewed as instruments used by the “evolutionary tinker” since, as Jacob asserts, evolution tinkers together contraptions. Jacob’s simile of tinkering provides a very suggestive insight of the way in which evolution might operate, but it leaves open one basic question: is tinkering...
founded only on the accidental encounter of various components within one and the same construction (same-level, intracellular tinkering)? Or could it be that two previously independent constructions (organisms) would fuse together (higher-level, intercellular tinkering)? Such an action would then lead to a single new assemblage which, in turn, would yield to further inter-cellular tinkering, but now with an increased range of parts that allows more efficient exploitation of the environment than was possible previously. In our opinion, it can be surmised that chance may be an important factor in this and in any other process. Although the nature of chance, or hazard, is mysterious, we can say that, in the present context, it regulates the rate at which independent organisms become tinkerered, or fused, together.

However, chance operates within limits imposed by the order with which complex systems are inherently endowed. It may be surmised that there is even a propensity towards order (order is attractive), and that this ordering property, together with chance, contribute to some of the improbable phenomena revealed within a phylogeny. Nevertheless, at higher levels of living matter other factors besides chance and the attractiveness of order (which might be a metaphor for metabolic efficiency coupled with morphological plasticity) come into play. Let us, for example, consider again the scenario we have been pursuing—the evolutionary tinker’s use of mitochondrion and Energide. In the atmosphere of the Earth, during the first phases of the emergence of life, there was a progressive enrichment of oxygen—a toxic element for anaerobic organisms. It may be surmised that a relatively privileged environment permitting the survival of anaerobic organisms would be created by enclosing within them of a prokaryotic pre-endosymbiotic colony because the constituent organelles would consume oxygen and maintain its tension at a relatively low level. Obviously, this could have been one of the functional processes brought about by chance and the tinkering process which brought together the Energide and the mitochondria within a host cell. Chance lay in the predator-prey relationship of organisms which later generated a respective host-guest relationship within the newly tinkerered endosymbiotic cell.

Final comments on the present hypothesis. According to the present hypothesis, there has been not only a competitive coevolution between cytoplasmic genetic elements and nDNA, but also a master role has been conferred upon mitochondria. These have assumed a selfish control even of the human organism from fertilization through to the early-embryo stage and thence to the adult life. All these stages of development are biased to favor survival and propagation of the maternal mitochondria. The maternal mitochondria are nothing but prokaryotes which exert a powerful control over the endosymbiotic status of the eukaryotic cell.

A strong deduction can therefore be drawn from such a hypothesis: The increased complexity of multi-cellular organisms, during phylogeny, has been due to natural selection favoring adaptation to the external environment by means of the maintenance of the classical internal milieu of the endosymbiotic cell, using the mechanism of homeostasis. The classical internal milieu is obviously also an important requisite for the constancy of the proposed embedded milieu belonging to mitochondria, and vice versa.

It may also be surmised that, just as the physico-chemical parameters of the classical internal milieu are basic indices for monitoring the state of a multi-cellular organism, so the analogous parameters of the embedded milieu will have a similar importance for the assessment of the state of mitochondrial colonies. The relevance of this view is stressed by the demonstration that an increasing number of human diseases are caused by mutations in mtDNA.5,35 That is, the state of the embedded mitochondrial colony bears no longer an optimum relationship with the state of the classical internal milieu. Because altered mitochondrial states have been proposed to play a role in ageing36,37 and in carcinogenesis,38 it may be conjectured that a new field of research regarding multicellular organisms will arise. It will inevitably include the investigation of how mitochondria, because of their role in controlling nDNA, affect cognition. In agreement with this view it has been demonstrated that the mitochondrial haplotype has a great impact on brain cognitive function.39 Furthermore, it has been shown that mtDNA, via interactions with nuclear DNA, can modify learning, exploratory behavior, sensory development and the anatomy of the brain. The effects of mtDNA alterations persist into old age, increasing in magnitude as organisms (there is evidence for this from mice) become older.40 Thus, it is not unexpected that complex patterns of behavior will emerge, e.g., the reproductive behaviors of females within a species or group because they are the primary bearers of mitochondria.17 It should be noted that female susceptibility to male manipulations may persist (and evolve) because of the indirect advantage to the female selection for those males which are good in manipulating females.41 Even propensities for male homosexuality and male infertility have been proposed to be governed by mitochondria.17

In conclusion, we are convinced that this new perspective on the eukaryotic cells will provide new clues to allow a better understanding not only of the logic of living systems but also of the logic of evolution and the attainment of higher biological complexity. It will also pose additional scientific questions for biology, as well as lead to the design of critical experiments which will bring us closer to the control of devastating diseases such as cancer, Alzheimer’s, Parkinson’s, and many more which, as indicated above, might eventually be discovered to be due to pathological alterations to the hierarchical order that governs mitochondria, Energides and the Cell Periphery Complexes within endosymbiotic eukaryotic cells.

References
1. Dawkins R. The Selfish Gene. Oxford: Oxford University Press 1999.
2. Balasila F, Volkmann D, Barlow PW. Cell-cell channels and their implications for Cell Theory. In Cell-Cell Channels, Balasila F, Volkmann D, Barlow PW, (eds), Georgetown and New York: Landes Bioscience and Springer Verlag 2006; 1-18.
3. Balasila F, Volkmann D, Barlow PW. Cell bodies in a cage. Nature 2004; 428:371.
4. Balasila F, Volkmann D, Barlow PW. Eukaryotic cells and their Cell Bodies: Cell Theory revisited. Ann Bot 2004; 94:9-32.
5. Agnati LF, Fanz K, Balasila F, Guidolin D. Implications of the ‘Energide’ concept for communication and information handling in the central nervous system. J Neurol Transm 2008; In press (PMID: 19221689).
6. Margulis L. Serial endosymbiotic theory (SET) and composite individuality. Transition from bacterial to eukaryotic genomes. Microbiol Today 2004; 31:172-4.
7. Osterweis KW, Nunnari J. The division of endosymbiotic organelles. Science 2003; 302:1698-704.
8. Gray MW, Burger G, Lang BF. Mitochondrial evolution. Science 1999; 283:1476-81.
9. Wallace DC. Why do we still have a maternally inherited mitochondrial DNA? Insights from evolutionary medicine. Annu Rev Biochem 2007; 76:781-821.
10. Timmins JN, Ayliffe MA, Huang CY, Martín W. Endosymbiotic gene transfer: organelle genomes forge eukaryotic chromosomes. Nat Rev Genet 2004; 5:123-35.
11. Turner C, Killoran C, Thomas NS, Rosenberg M, Chuchanowa NA, Johnston J, et al. Human genetic disease caused by de novo mitochondrial-nuclear DNA transfer. Hum Genet 2003; 112:303-9.
12. Wulf K. Insertion of mitochondrial DNA in the chromosomes—a cause for cancer and aging? Endocytob Cell Res 1996; 11:211-8.
Maternal mitochondria: selfish entities that are masters of eukaryotic cell?

13. Neupert W, Herrmann JM. Translocation of proteins into mitochondria. Annu Rev Biochem 2007; 76:723-49.
14. Ryan MT, Hoogentaa NJ. Mitochondrial-nuclear communications Annu Rev Biochem 2007; 76:701-22.
15. Bomhahn L, Eyer-Walker A, Smith NH, Smith JM. Mitochondrial Steve: paternal inheritance of mitochondria in humans. Trends Ecol Evol 2003; 18:2-4.
16. Schwartz M, Vissing J. Paternal inheritance of mitochondrial DNA. N Engl J Med 2002; 347:576-80.
17. Zeh JA, Zeh DW. Maternal inheritance, sexual conflict and the maladapted male. Trends Genet 2005; 21:281-6.
18. Matsushima R, Hamamara Y, Higashiyama T, Arimura S, Sodmergen, Tsutsumi N, et al. Mitochondrial dynamics in plant male gametophyte visualized by fluorescent live imaging. Plant Cell Physiol 2008; 49:1074-83.
19. Mogenon HL, Rusche ML. Quantitative ultrastructural analysis of barley sperm I. Occurrence and mechanism of cytoplasm and organelle reduction and the question of sperm dimorphism. Protoplasma 1985; 128:1-13.
20. Scharz G. The magic garden. Annu Rev Biochem 2007; 76:673-8.
21. Wang X, Su B, Siedlak SL, Moreira PI, Fujinoka H, Wang Y, et al. Amyloid-β overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fusion/fission proteins. Proc Natl Acad USA 2008; 105:19318-23.
22. Newmeyer DD, Ferguson-Miller S. Mitochondria: releasing power for life and unleashing the machineries of death. Cell 2003; 112:481-90.
23. Schon EA, Manfredi G. Neuronal degeneration and mitochondrial dysfunction. J Clin Invest 2003; 111:303-12.
24. Delivani P, Martin SJ. Mitochondrial membrane remodeling in apoptotic: an inside story. Cell Death Differ 2006; 13:2007-10.
25. Coerdia A. Mitochondrial transfer between eukaryotic animal cells and its physiologic role. Rejuev Res 2006; 9:450-4.
26. Jacob F. Evolution and tinkering. Science 1977; 196:1161-6.
27. Russell RB, Aloy P. Targeting and tinkering with interaction networks. Nat Chem Biol 2008; 4:666-73.
28. Rand DM. Mitochondrial genetics of aging: intergenicomic conflict resolution. Sci Aging Know Environ 2005; 45:5.
29. Budar F, Touzet P, De Paepre R. The nucleo-mitochondrial conflict in cytoplasmic male sterilities revisited. Genetica 2003; 117:3-16.
30. Kuhn T. The Structure of Scientific Revolutions. Chicago: The University of Chicago Press 1996.
31. Agnati LF, Genedani S, Leo G, Rivera A, Guidolin D, Fuxe K. One century of progress in neuroscience founded on Golgi and Cajal’s outstanding experimental and theoretical contributions. Brain Res Rev 2007; 55:1-89.
32. Kaufman SA. The Origin of Order. New York: Oxford University Press 1993.
33. Jacob F. Molecular tinkering in evolution. In: Bendall DS, (ed), Evolution from Molecules to Men. Cambridge: Cambridge University Press 1983.
34. Zeviani M, Antozzi C. Mitochondrial disorders. Mol Hum Reprod 1997; 3:133-48.
35. Wallace DC, Brown MD, Lott MT. Mitochondrial DNA variation in human evolution and disease. Gene 1999; 238:211-30.
36. Wallace DC. Mitochondrial DNA in aging and disease. Sci Am 1997; 277:40-7.
37. Pak JW, Herbst A, Bua E, Gokey N, McKenzie D, Aiken JM. Mitochondrial DNA mutations as a fundamental mechanism in physiological declines associated with aging. Aging Cell 2003; 2:1-7.
38. Penta JS, Johnson FM, Wachman JT, Copeland WC. Mitochondrial DNA in human malignancy. Mutat Res 2001; 488:119-33.
39. Roubertoux PL, Marcet B, Slayter F, Verrier B. Mitochondrial DNA (mtDNA) and behavior: interaction between mitochondrial and nuclear genes, preliminary results from microarrays. Behav Genet 2003; 33:717.
40. Roubertoux PL, Slayter F, Carlier M, Marcet B, Maarouf-Veray F, Chérief C, et al. Mitochondrial DNA modifies cognition in interaction with the nuclear genome and age in mice. Nat Genet 2003; 35:65-9.
41. Cordero C, Eberhard WG. Female choice of sexually antagonistic male adaptations: a critical review of some current research. J Evol Biol 2003; 16:1-6.