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Beyond Retrograde and Anterograde Signaling: Mitochondrial – Nuclear Interactions as a means for Evolutionary Adaptation and Contemporary Disease Susceptibility

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Abstract

While there is general agreement that most forms of common disease develop as a consequence of a combination of factors, including genetic, environmental, and behavioral contributors, the actual mechanistic basis of how these factors initiate or promote diabetes, cancer, neurodegenerative, and cardiovascular diseases in some individuals while not in others with seemingly identical risk factor profiles, is not clearly understood. In this respect, consideration of the potential role for mitochondrial genetics, damage, and function in influencing common disease susceptibility seems merited, given that the prehistoric challenges were the original factors that molded cellular function, and these were based upon the mitochondrial-nuclear relationships which were established during evolutionary history. These interactions were likely refined during prehistoric environmental selection events that today, are largely absent. Contemporary risk factors such as diet, sedentary lifestyle and increased longevity that influence our susceptibility to a variety of chronic diseases were not part of the dynamics that defined the processes of mitochondrial – nuclear interaction, and thus, cell function. Consequently, the prehistoric challenges that contributed to cell functionality and evolution should be considered when interpreting and designing experimental data and strategies. Although several molecular epidemiologic studies have generally supported this notion, studies that probe beyond these associations are required. Such investigation will mark the *initial steps* for mechanistically addressing the provocative concept that contemporary human disease susceptibility is the result of prehistoric selection events for mitochondrial-nuclear function that increased the probability for survival and reproductive success during evolution.

Keywords

Mitochondria; Bioenergetics; Oxidants; Disease susceptibility

The genetic basis for common diseases associated with metabolism is generally appreciated as being complex. Overall, disease susceptibility is considered to be an interactive consequence of multiple modifiable (behavioral, lifestyle) and non-modifiable (genetic) factors, however, the actual mechanistic basis of this interaction is not clearly understood. The “common disease – common variants” hypothesis argues that common forms of disease involve multiple genes, each with a different effect that interact with other genes or environmental factors that modify their actions, contributing to individual disease susceptibility [1]. While this concept is important in that it introduces the notion of gene

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groups that can influence disease susceptibility and also provides a plausible explanation for differences in individual disease susceptibility, it is not yet evident whether it satisfactorily encompasses basic questions about risk for common diseases, such as ethnic disparity and why risk increases with age.

In this respect, mitochondrial genetics and biology could act in a complementary fashion with nuclear genetics to more lucidly explain individual disease susceptibility. Douglas Wallace proposed that mitochondrial DNA (mtDNA) missense mutations accumulated in humans as they migrated from Africa, and that these mutations changed aspects of mitochondrial bioenergetics that contributed to the establishment of human populations at more northern latitudes [2;3]. As described in this review, it is proposed that the prehistoric factors driving these selective changes in the mtDNA were the adaptations of cellular bioenergetics to increase fecundity under conditions of changing environmental challenges. Because the environment of “modern” humans has dramatically changed from our prehistoric ancestors, these prehistoric mtDNA mutations influence contemporary disease susceptibility. The following discussion will attempt to summarize the tenets of the “Mitochondrial paradigm for disease” and current evidence consistent and inconsistent with this paradigm.

MITOCHONDRIAL ORIGINS AND FUNCTIONS

While there is still controversy regarding the specific mechanics and nature of endosymbiotic origins of the eukaryotic cells, it is generally agreed that mitochondria are ancient bacterial endosymbionts, which were originally endocytosed by a larger, anaerobic nucleated cell (proto-eukaryote), that gave the resulting proto-eukaryotic organism a selective advantage for survival. Interestingly, while the basis of this advantage has historically been thought to be aerobic metabolism, this is now being challenged in that it may have originally been related to hydrogen or carbon compound based metabolism [4–9]. Nevertheless, in the presence of photosynthetic organisms, the atmosphere of the Precambrian world became increasingly oxygen laden, and aerobic mitochondria evolved. Hence, the observed compartmentalization of anaerobic (glycolytic) versus aerobic (mitochondrial) metabolism seen in cells today represents historical evidence of their past origins as endosymbionts. Considered in this light, it is possible that the ancestors of the mitochondrion and nucleus were likely to be on more equal terms in regulating cell function than commonly contemplated today.

By virtue of their origins as aerobic bacteria, mitochondria have their own DNA, RNA, and protein synthesis systems. Each cell contains hundreds to thousands of mitochondria and each mitochondrion contains multiple copies of a double stranded, closed circular, maternally inherited mtDNA. Interestingly, while it has been previously speculated that the reasons for this maternal inheritance were due to the location (sperm midpiece) and low numbers of paternal mtDNA copies versus maternal, recent evidence also suggests that the paternal mtDNA is degraded by fertilization triggered autophagy [10;11]. In humans, the mtDNA is 16,569 base pairs in size [12]. The mtDNA in our proto-eukaryotic ancestors was significantly larger in genetic complement, but transfer of mtDNA encoded genes to the nucleus has occurred over the 1.5 – 2 billion years since the origin of the eukaryotic cell, and today the mammalian mtDNA encodes 13 polypeptides, two rRNAs (12S and 16S) and 22 tRNAs that are essential for OXPHOS and proper cell function. Consequently, a unique feature of the molecular machinery controlling cellular bioenergetics is that electron transport and oxidative phosphorylation proteins are encoded by both nuclear and mitochondrial genomes. Whereas the nucleus encodes ~1500 mitochondrial proteins and the mtDNA only 13, the mtDNA retained key structural subunits required for the catalytic activity for NADH-ubiquinone oxidoreductase (commonly referred to as NADH

dehydrogenase), ubiquinone-cytochrome c oxidoreductase (also referred to as cytochrome c reductase or the bc_1 complex), cytochrome c oxidase, and ATP synthase. Accordingly, mutations in these mtDNA encoded subunits could alter features in mitochondrial metabolism or economy (bioenergetic function) [13]. Pathogenic mtDNA mutations have been associated with numerous types of diseases, including neurodegeneration, neuromuscular disease, deafness, blindness, diabetes, and cardiovascular disease [14]. However, the focus of this mini-review is upon the potential influence of mtDNA sequence variation that is not considered to be pathogenic, but polymorphic, upon mitochondrial function and disease susceptibility.

Historically, mitochondria have been characterized as “cellular powerplants”. In actuality, they are multifunctional organelles, and serve as the sites for electron transport, oxidative phosphorylation (OXPHOS), the citric acid cycle, β-oxidation, steroidogenesis, and many other important cellular functions including growth, oxidant generation and programmed cell death [13]. In some cells, the mitochondrion may serve as a source of regulated oxidant generation for cell signaling, whereas it will serve as an oxidative energetic source in others, or, a combination of these functions in still others. Mitochondria generate molecular energy (ATP), thermal energy (heat), and superoxide ($O_2^{\cdot -}$) by utilizing electron flow generated from metabolism of cellular carbohydrates and fats (Figure 1). Nearly half of the energy released during electron flow is used to generate a transmembrane electrochemical gradient across the mitochondrial inner membrane; the potential energy in this gradient is used by ATP synthase to generate ATP. Energy lost during the formation of the transmembrane potential generates heat. Under conditions of high membrane potential, electrons can interact with oxygen to form $O_2^{\cdot -}$, which is a fundamental building block for oxidant formation in the mitochondrion. Superoxide can be converted to highly diffusible hydrogen peroxide (H_2O_2) which functions as a redox signaling molecule, or in the presence of nitric oxide ($^{\cdot}NO$), reacts at diffusion limited rates to form the oxidant peroxynitrite ($ONOO^-$)[15]. In the mitochondrion, $ONOO^-$ will likely react with CO_2 (CO_2 is generated in the citric acid cycle) to form the nitrating agent, nitrosperoxycarbonate ($ONOOCO_2^-$) [16;17].

MITOCHONDRIAL ECONOMY

The ability of the mitochondrion to convert caloric energy into ATP influences non-ATP related processes (e.g. heat and oxidant production). Mitochondria that are highly economical in generating ATP with a minimal loss of caloric energy to heat are also more prone to produce $O_2^{\cdot -}$ under conditions of high membrane potentials and low energy demand compared to those less coupled or economical [13]. Consequently, while economical mitochondria generate ATP with less expenditure of energy (calories), they also have a greater propensity to generate oxidants under conditions of low energetic demand and high caloric intake (Figure 2). In addition to the basic mechanisms of energy generation associated with electron transport and the production of a transmembrane potential, several constantly changing factors such as local concentrations of O_2, reactive species, mitochondrial antioxidants, cytokine concentrations, metabolic reducing equivalent availability, cellular energetic demand, uncoupling protein (UCP) activities, and overall organelle integrity influence mitochondrial economy [18].

MTDNA MUTATION AND ADAPTATION DURING PREHISTORY

It has been proposed that environmental factors influenced prehistoric human radiation patterns and survival by selecting for aspects of mitochondrial function (ATP production and thermogenesis) [2;3;19]. As prehistoric humans moved northward out of Africa they encountered climatic and dietary changes that played a role in the selective pressures of survival and reproduction [20;21]. It has been noted that as prehistoric humans migrated

northward they accumulated mtDNA missense mutations that have been proposed to have altered mitochondrial bioenergetics and thus, economy [2;19]. These mtDNA mutations decreased mitochondrial economy resulting in the greater generation of heat/calorie consumed [2;3;19]; this apparent decrease in efficiency was tolerated due to the changes in diet also encountered – as humans moved from Africa, their diet changed from a low protein, low fat vegetarian diet to a high protein, high fat diet consisting of animal fats [20;21]. Hence, the decreased ATP generation/calorie (due to increased heat production) was offset by increased caloric intake associated with animal fats. It is therefore suggested that mitochondrial economy (via mtDNA mutation) significantly influenced survival and thus reproductive potential in prehistoric humans, in response to changes in the environment and diet.

The concept that changes in mitochondrial function allowed adaptation is not exclusive to *Homo sapiens* – the 13-lined ground squirrel (S*permophilus lateralis*) upregulates mtDNA encoded NADH dehydrogenase mRNA during hibernation [22] which occurs concomitant with decreased metabolic rate and core body temperature compared to non-hibernating levels [23]. MtDNA-encoded ubiquinone-cytochrome c oxidoreductase subunits in *S. lateralis* liver mitochondria have also been reported to altered during hibernation, which may decrease the capacity of that electron transport complex [24]. Similarly, it has been shown that the bar-headed goose (*Anser indicus*) has evolved more subsarcolemmal mitochondria bordering capillaries with increased densities and numbers of oxidative fibers that enable them to sustain flight at high altitudes (up to 9000 m or 30,000 ft) compared to low altitude birds [25]. This adaptation is associated with decreased maximal cytochrome c oxidase activity, and a higher affinity of the enzyme for reduced cytochrome c that appears to be associated with a mutation in the mtDNA encoded subunit III for cytochrome c oxidase that may alter the structure of the enzyme complex that accounts for increased economy and high-altitude adaptation [26]. Examination of the mtDNA encoded subunits across placental mammals is currently underway to determine the degree of “adaptive” evolution which may provide useful information regarding key mtDNA mutations and their role on evolution in terms of cellular function [27].

CONTEMPORARY IMPLICATIONS OF MTDNA MUTATIONS SELECTED FOR DURING PREHISTORIC ADAPTATION

Western society has all too frequently become characterized by a sedentary lifestyle and excessive diet. In terms of mitochondrial bioenergetics, this has become problematic because a low energy demand and chronic high caloric intake were not factors under which mtDNA mutations became fixed in the human population during human prehistory. Mitochondria that harbor mtDNA mutations associated with greater economy will generate increased oxidants under conditions of excessive caloric intake and physical inactivity compared to those with mtDNA mutations linked to decreased mitochondrial economy, and therefore the former (greater mitochondrial economy) will be more prone to succumb to diseases connected to oxidative stress, whereas the latter (decreased mitochondrial economy) will be comparatively less susceptible, yet not completely immune. Chronic, excessive caloric intake and physical inactivity will still result in sustained mitochondrial oxidant generation over time even in mitochondria having decreased economy which will result in cell damage and dysfunction. Hence, disease susceptibility associated with oxidative stress will represent interplay between mtDNA genetic background, diet, exercise, and other environmental factors such as smoking or exposure to other environmental oxidants.

Evidence consistent with this provocative notion is still being gathered. In addition to the original studies that link mtDNA mutations with human disease, several studies have shown

that specific mtDNA mutations and genetic backgrounds are associated with increased risk for diseases thought or known to have an environmental component in humans [28–37]. MtDNA genetic background can influence tumor growth and age-related deafness [32;38], and has been shown to co-segregate with longevity in humans [34;35]. While it is hypothesized that mtDNAs associated with increased economy will be associated with certain types of cancer and neurodegenerative diseases associated with somatic mutation or oxidative stress, it has been also suggested that mtDNAs associated with “cold adaptation” (e.g. less economical) will be associated with increased life span, but increased predilection for clinical illnesses potentially associated with energetics such as blindness and central nervous system (CNS) defects [19].

Cybrid culture studies have provided conflicting results supporting the concept that the mtDNA influences cellular bioenergetics [39–42]. However, these studies by necessity have had to utilize transformed or immortalized cell lines and therefore do not exactly represent *in vivo* circumstances. Studies utilizing conplastic strains of mice (mice having different nuclear and mitochondrial genetic backgrounds, generated by breeding two different strains to generate F_1 females and backcrossing them and subsequent filial female generations onto the nuclear background of the paternal strain), suggest that mtDNA background does influence aspects of cognition, behavior, reproductive behavior, and susceptibility to autoimmune disease [43–46]. A potential issue with even this approach is that if the mtDNA alters organelle economy (bioenergetics) which can affect numerous nuclear genes, the mtDNA may also play a role in modulating nuclear gene expression and perhaps play a role in allelic segregation and assortment during meiosis. If this is the case, it would represent another historical clue regarding the evolution of the eukaryotic cell and endosymbiosis, and thus, provide the basis for an additional paradigm in that the mtDNA influences the selection of certain nuclear – mitochondrial gene combinations and mitochondrial retrograde signaling [47–49]. If true, this would have significant implications regarding the use of transgenics (or the creation of congenics) derived from different strains of mice.

MITOCHONDRIAL OXIDANT PRODUCTION

The concept that mitochondrial oxidant production is simply a consequence of energy production and serves as a primary, chronic source of cellular stress that causes disease development seems logical when considered from a contemporary viewpoint. However, from an evolutionary perspective and in reality, mitochondrial oxidants likely serve as signals for mitochondrial – nuclear interaction which evolved to increased cell survival under conditions of limited caloric availability. Whether under conditions of caloric scarcity or plentitude, a system with a facile feedback/signaling mechanism (redox signaling) linked to energy requirements and caloric availability would be advantageous. Consequently, mitochondrial oxidants likely served as stimuli for insulin production and signaling molecules associated with insulin signaling pathways in non-insulin producing tissues. In the presence of abundant calories and low energy demand, mitochondria increased mitochondrial oxidant production, triggering signaling pathways leading to storage of calories [50–54]. As food availability became low and/or energy demand increased, oxidant production and caloric storage would decrease. Interestingly, studies have shown that mitochondrial oxidants or the alteration of mitochondrial UCP levels affect insulin secretion and sensitivity [51;55–57]. Although studies have shown that mitochondrial oxidants can inhibit insulin production and sensitivity, they usually employ conditions of chronic hyperglycemia and therefore do not represent the original prehistoric conditions that were likely present during the establishment of mitochondrial – nuclear communication. Nevertheless, a connection does clearly seem to exist between mitochondrial oxidants, insulin secretion and insulin signaling [50;58–61].

Mitochondrial oxidants are generated during electron transport, when O_2 picks up electrons from the ubiquinone site in ubiquinone – cytochrome c oxidoreductase and flavin mononucleotide group of NADH dehydrogenase to generate $O_2^{\cdot-}$ [62–66]. In the mitochondrion, $O_2^{\cdot-}$ can be converted to H_2O_2 by mitochondrial manganese superoxide dismutase (MnSOD or SOD2). It has been estimated that mitochondrial H_2O_2 generation represents up to 2% of the total mitochondrial oxygen consumption under basal conditions and fluxes in mitochondrial H_2O_2 can be influenced by pharmaceuticals, inhibitors of respiration, uncouplers, redox cycling molecules, and by either endogenous or exogenous environmental changes [63;67–71]. This H_2O_2 produced by the mitochondrion acts as a redox signaling molecule that can stimulate growth and survival pathways or intrinsic apoptotic pathways, at low or high H_2O_2 concentrations, respectively [72–76].

Mitochondria may regulate many genes involved in cellular defense and immunological response via the generation of ROS that act as intermediate second messengers for NFκB activation by tumor necrosis factor alpha (TNFα) and interleukin – 1 [77–80]. Inhibition of mitochondrial respiration blocks H_2O_2 – induced transactivation of the endothelial growth factor receptor and stimulation of downstream targets [81]. As a result, antioxidant expression and cytokines such as TNF-α influence the steady state levels of specific mitochondrial oxidants, and therefore play a role in the modulation of mitochondrial mediated redox signaling. Cytokines such as platelet derived growth factor (PDGF) and TNFα directly or secondarily alter cellular oxidant production via mitochondrial pathways [82–84]. As with mitochondrial economy, oxidant generation from the mitochondrion is influenced by the concentrations of reactive species within the organelle, electron transport efficiency, availability of metabolic reducing equivalents (NADH and $FADH_2$), UCP levels and activities, and organelle integrity. For example, nitric oxide ($^{\cdot}NO$) reversibly binds cytochrome c oxidase and can regulate its activity, influencing ATP production and O_2 consumption [85–87]. Whereas lower $^{\cdot}NO$ concentrations can influence oxygen O_2 diffusion and modest $O_2^{\cdot-}$ generation, higher concentrations can lead to greater $O_2^{\cdot-}$ generation and related $ONOO^-$ formation triggering cytoxicity [88].

FUTURE IMPLICATIONS

Greater discernment of the factors that shaped original mitochondrial function, and how mitochondrial – nuclear interaction worked will lead to greater appreciation and understanding of the actual role of the mitochondrion in the cell. Perhaps because the mtDNA in humans encodes only 37 genes compared to the estimated ~23,000 in the nucleus, this has led to the general perception that the answer for a genetic basis for common disease susceptibility and development would more likely lie within the nuclear genome. However, the mitochondrion and nucleus were originally both unique genetic entities that entered into a symbiotic relationship, and hence, were probably once more balanced than we completely understand. Since changes in key subunits in electron transport may alter mitochondria economy, which includes oxidant production, one mtDNA mutation can ultimately have a multitude of effects on nuclear gene expression due to redox signaling mechanisms.

Interpretation and designing experiments directed at understanding how mitochondrial – nuclear functionality evolved will undoubtedly lead to greater understanding of disease pathology because they will provide greater understanding of the basis of mitochondrial – nuclear interaction, and therefore the etiology of disease. In order to successfully achieve these aims however it will require basic experimental studies to utilize “normal” or non-diseased models that examine their response to various stimuli commonly thought to be the initial harbingers for disease risk. A potential pitfall in many translational studies today is that they rely on experimental models that represent disease states, and therefore may not

provide information on the original role(s) of the mitochondrion in the cell. Overall, a greater understanding of how the original relationships between the mitochondrion and the nucleus evolved to allow for the adaptation of cell function will facilitate discovery of the mechanisms of how common disease develops.

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List of Abbreviations

ATP	adenosine triphosphate
CNS	central nervous system
CO_2	carbon dioxide
H_2O_2	hydrogen peroxide
MnSOD	manganese superoxide dismutase
mtDNA	mitochondrial DNA
NADH	nicotinamide adenine dinucleotide, reduced form
$^{\cdot}NO$	nitric oxide
O_2	oxygen
$O_2^{\cdot-}$	superoxide
$ONOO^-$	peroxynitrite
OXPHOS	oxidative phosphorylation
PDGF	platelet derived growth factor
SOD2	manganese superoxide dismutase
TNF-α	tumor necrosis factor alpha

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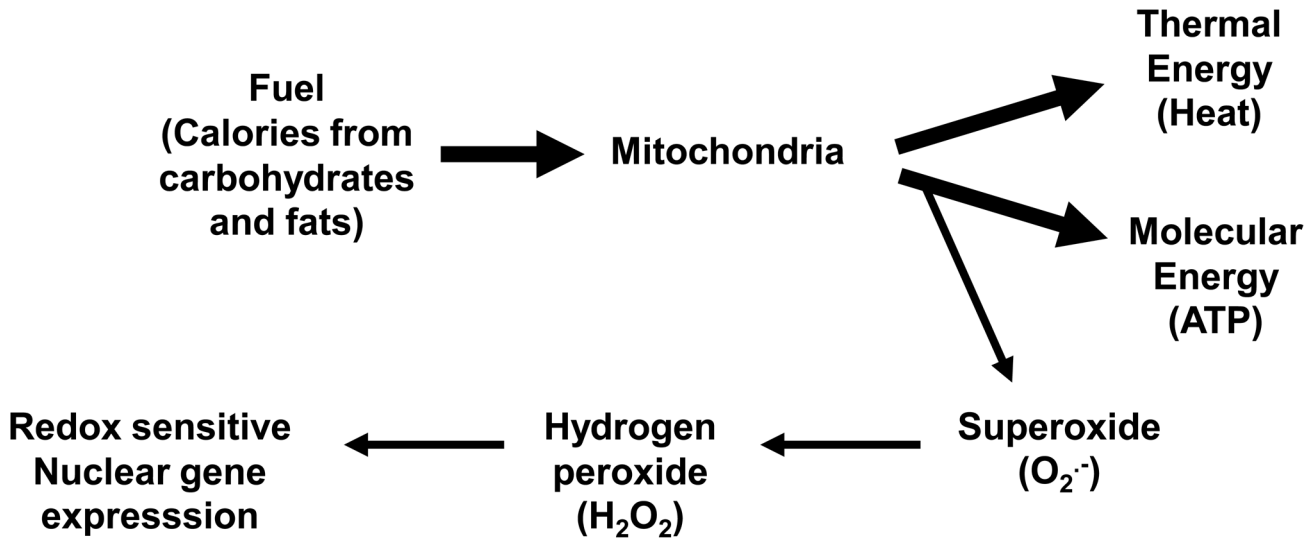
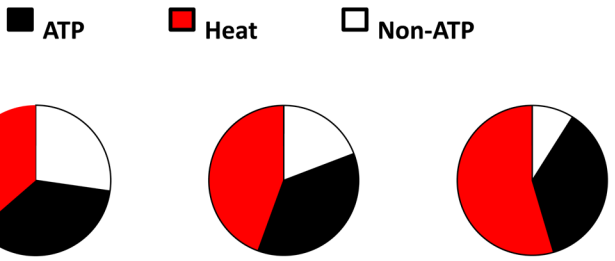


Figure 1.

Schematic summarizing the basic mitochondrial functions. By utilizing electron flow generated from metabolism of carbohydrates and fats, mitochondria generate thermal energy (heat), molecular energy (ATP), and superoxide ($O_2^{\cdot -}$). Energy lost during the transfer of electrons from electron transport generates heat, and the potential energy retained in the transmembrane electrochemical gradient across the mitochondrial inner membrane is used to generate ATP. Electrons also interact with oxygen to form superoxide ($O_2^{\cdot -}$) that can be converted to highly diffusible hydrogen peroxide (H_2O_2) which functions as a redox signaling molecule that can influence redox sensitive signaling pathways and nuclear gene expression. Mitochondrial oxidant production is increased under conditions of high membrane potential.



Mitochondrial Economy	50%	45%	40%
ATP (molecules)/kcal	4.11×10^{22}	3.70×10^{22}	3.29×10^{22}
Total caloric intake (kcal)	2750	2750	2750
Total ATP demand (molecules)	8.22×10^{25}	8.22×10^{25}	8.22×10^{25}
Total calories required to meet ATP demand	2000	2222	2500
Calories used for ATP generation	1000	1000	1000
Caloric energy lost in the form of heat	1000	1222	1500
Excess kcal	750	528	250
% Calories used for ATP demand	36.36%	36.36%	36.36%
% Calories used for heat	36.36 %	44.44 %	54.55 %
% Calories used for non-ATP production (excess kcal)	27.27 %	19.19 %	9 %

Figure 2.

Hypothetical presentation of how differences in mitochondrial economy influence caloric utilization. Mitochondria with different economies have different capacities for generating ATP/kilo-calorie (kcal) consumed (where 50%, 45%, or 40% of the energy from electron flow is utilized for generating ATP in the hypothetical examples), and therefore those with lower economies will consume more calories to meet energetic demands (with an increased release of caloric energy as heat). It is assumed that electron flow is equal between mitochondria having different economies. A related consequence is that under conditions of excessive caloric consumption (excess kcal) relative to energy demand, mitochondria with higher economies will generate greater amounts of mitochondrial oxidants (a component non-ATP production). ATP/kcal calculations are based upon 1 mole of ATP (6.023×10^{23} molecules) = 7.33 kcal. Hence 1 kcal = 8.22×10^{22} molecules of ATP assuming 100% economy. This value is used to estimate ATP/kcal for 50%, 45% and 40% (4.11×10^{22}, 3.70×10^{22} and 3.29×10^{22}, respectively) economies. Total caloric consumption is 2750 kcal. Total ATP demand of 8.22×10^{25} molecules, based upon a demand of 1000 kcal assuming 50% economy, hence decreased economy (45% and 40%) requires utilization of more calories to meet ATP demand. Caloric energy lost in the form of heat is determined by subtracting calories required to meet a demand of 8.22×10^{25} ATP under conditions of 100% economy (1000 kcal, or, calories used for ATP generation) from “Total calories required to meet ATP demand” for each economy. Percentages of calories used for heat generation, ATP and non-ATP production are determined by dividing kcal used to for heat, ATP generation, and excess kcal, respectively, by total caloric intake (2750 kcal). Pie charts illustrate percentages.