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THE MITOCHONDRIAL PARADIGM FOR CARDIOVASCULAR DISEASE SUSCEPTIBILITY AND CELLULAR FUNCTION: A COMPLEMENTARY CONCEPT TO MENDELIAN GENETICS

David M. Kryzwanski^{1,*}, Douglas Moellering^{2,*}, Jessica L. Fetterman¹, Kimberly J. Dunham-Snary¹, Melissa J. Sammy¹, and Scott W. Ballinger^{1,3}

¹The University of Alabama at Birmingham, Department of Pathology, Division of Molecular and Cellular Pathology, Birmingham, AL 35294

²The University of Alabama at Birmingham, Department of Nutrition Sciences, Birmingham, AL 35294

Abstract

While there is general agreement that cardiovascular disease (CVD) development is influenced by a combination of genetic, environmental, and behavioral contributors, the actual mechanistic basis of how these factors initiate or promote CVD development in some individuals while others with identical risk profiles do not, is not clearly understood. This review considers the potential role for mitochondrial genetics and function in determining CVD susceptibility from the standpoint that the original features that molded cellular function were based upon mitochondrial-nuclear relationships established millions of years ago and were likely refined during prehistoric environmental selection events that today, are largely absent. Consequently, contemporary risk factors that influence our susceptibility to a variety of age-related diseases, including CVD were probably not part of the dynamics that defined the processes of mitochondrial – nuclear interaction, and thus, cell function. In this regard, the selective conditions that contributed to cellular functionality and evolution should be given more consideration when interpreting and designing experimental data and strategies. Finally, future studies that probe beyond epidemiologic associations are required. These studies will serve as the *initial steps* for addressing the provocative concept that contemporary human disease susceptibility is the result of selection events for mitochondrial function that increased chances for prehistoric human survival and reproductive success.

With the exception of the worldwide Spanish influenza epidemic of 1918, cardiovascular disease (CVD) has been the leading cause of mortality and morbidity in the United States every year since 1900¹. Consequently, many studies have investigated the potential causes of cardiovascular disease, and it is generally accepted that oxidative stress mediated changes within the cardiovascular milieu are among the most popular postulated mechanisms of CVD development^{2–7}. Oxidative stress is caused by a collective grouping of reactive oxygen and nitrogen species (ROS and RNS, respectively) that are capable of disrupting cell function and exerting cytotoxic effects when generated in amounts beyond the antioxidant capacity of the cell. The concept that oxidative stress is important in the pathogenesis of CVD was conceived from studies that noted the cytotoxic and atherogenic properties of oxidized LDL (oxLDL) cholesterol^{8–12}. Subsequently, it became apparent that vascular dysfunction can be linked to increased oxidant stress; oxidant stress can have several

³To whom correspondence should be addressed: Scott W. Ballinger, PhD, Department of Pathology, Division of Molecular and Cellular Pathology, G019F Volker Hall, 1530 3rd Avenue South, Birmingham, AL 35294-0019.

*Contributed equally to this manuscript

biological effects, including the peroxidation of polyunsaturated fatty acids in membrane or plasma lipoproteins, direct inhibition of mitochondrial respiratory chain enzymes, inactivation of membrane sodium channels, and DNA damage^{2, 3, 5-7, 13-22}. These findings are consistent with the notion that CVD risk factors increase oxidative stress and contribute to a pro-inflammatory environment^{5, 11, 12, 23-35}. Whereas the majority of these studies regard atherosclerotic disease, oxidative stress also has been implicated as an important factor in many other forms of cardiovascular related maladies, including hypertension and cardiometabolic disease/syndrome.³⁶⁻³⁹ Although atherosclerosis and hypertension are often a pathologies ultimately associated with cardiometabolic syndrome, individuals with hypertension or atherosclerosis do not always have cardiometabolic disease. The classic traits of visceral obesity and insulin resistance are associated with cardiometabolic syndrome, although other traits typically linked with metabolic syndrome are common as well. Multiple early definitions of metabolic syndrome have been related from different organizations including: the International Diabetes Federation (IDF)⁴⁰, the revised National Cholesterol Education Program (NCEP; ATP III criteria)⁴¹, the World Health Organization (WHO)⁴², and the European Group for the Study of Insulin Resistance (EGIR)⁴³. Based on a joint interim statement in 2009 from the American Heart Association (AHA), National Heart Lung Blood Institute (NHLBI), World Health Federation, International Atherosclerosis Society, International Association for the Study of Obesity, and International Diabetes Federation (IDF) consensus statement⁴⁴, the criteria for clinical diagnosis of the metabolic syndrome include having three of five of the following (or drug treatment for them): some form of insulin resistance (impaired glucose tolerance or impaired fasting glucose [≥ 100 mg/dL]), hypertension [systolic ≥ 130 and/or diastolic ≥ 85 mm Hg], dyslipidemia (higher triglycerides [≥ 150 mg/dL, 1.7 mmol/L], and lower HDL [males < 40 mg/dL, 1.0 mmol/L; females < 50 mg/dL, 1.3 mmol/L]) and country-specific elevated waist circumference and abdominal obesity (USA, AHA/NHLBI ATP III thresholds: males 94–102 cm; females 80–88 cm) and all of these risk factors have been linked to oxidative stress^{45, 46, 47, 48}. Among the potential cellular origins of oxidative stress, studies have shown multiple sources to be important, including NAD(P)H oxidase, xanthine oxidase, and myeloperoxidase^{13, 49-60}. More recently, the mitochondrion, both a source and target of oxidants related to cardiovascular disease development, has garnered attention^{61-64, 65-73}.

THE MECHANISMS OF INDIVIDUAL CVD SUSCEPTIBILITY ARE NOT CLEARLY UNDERSTOOD

While significant progress in understanding the pathology, progression and development of CVD has been made, the determinants of why some individuals with identical CVD risk factor profiles develop disease while others will not, are not clearly understood. Currently, less than 5% of CVD appears to result from single mutations, such as those regulating lipoprotein synthesis^{74, 75}. It has been estimated that 70%–80% of CVD is attributable to modifiable, non-genetic factors, which is consistent with the notion that environmental factors heavily influence the risk of disease development⁷⁴. In addition to endogenous and environmental risk factors (i.e., hypercholesterolemia and tobacco smoke exposure, respectively), CVD susceptibility is also increased by age, family history⁷⁶⁻⁸¹, and ethnicity (reviewed in⁸². Some studies have shown that differences in cardiovascular function exist between racial groups, however the basis of these differences is currently unclear⁸³⁻⁸⁸. Consequently, it is thought that CVD is a multi-factorial disorder that involves both environmental and genetic factors^{89, 90}. A corollary of this idea however, is that individual response to environmental factors can be genetically influenced.

The Mendelian concept, or the “common disease, common variants” hypothesis suggests that common forms of disease such as CVD have a multi-factorial and polygenic basis:

genetic variants present in many normal individuals, each with a relatively small effect, alone or in combination with modifier genes and environmental factors contribute to overall CVD risk^{89, 90}. Hence, it has been hypothesized that multiple genes involved in vascular regulation, lipoprotein metabolism, inflammation, metabolic control and redox tone (the balance between oxidant generation and neutralization by antioxidants) and their interaction with risk factors influence CVD susceptibility^{77, 78}. In this regard, studies have looked for connections between polymorphic gene mutations and CVD development. However, many original associations were lost in larger scale studies, or were not as predictive for risk as plasma markers such as cholesterol levels^{75, 91–97}. Consequently, while important in advancing the understanding of gene “groups” that may be involved in influencing predilection to disease development, the underlying genetic and physiologic basis of why these differences exist is not well understood.

Because CVD usually develops over decades, its etiology should entail subtle changes in the vascular/endothelial environment over time, collectively resulting in the initiation and progression of disease. Therefore features of CVD development should involve genetic and cellular mechanisms that: i) play important roles in multiple cell functions involving the regulation and expression of multiple genes (e.g., growth, death, signaling, and bioenergetics); ii) are capable of gradual decline or dysfunction over time (an “aging” mechanism); iii) are susceptible to oxidative damage (risk factors), and; iv) explain risk associated with ethnicity.

The mitochondrion and its genome may account for these features in CVD development. The mitochondrion: i) is a multifunctional organelle which is a central focal point for proper cell function due to its role in energy production, cell growth, apoptosis, thermogenesis and redox signaling^{98–102}; ii) has an “aging” mechanism – there are thousands of copies of mitochondrial DNA (mtDNA) per cell, allowing for the accumulation of mtDNA mutations and damage over time that cause an age-related decline in mitochondrial function^{103, 104}; iii) is vulnerable contemporary CVD risk factors and oxidative stress which increase mitochondrial damage and alter function in cardiovascular tissues^{61–64}, and; iv) harbors the mtDNA which displays marked regional variation and has proven useful in population and molecular anthropological studies¹⁰⁵. By contrast, most ancient nDNA polymorphisms are common to all global populations¹⁰⁶. Similarly, maternal family history of cardiovascular disease has also been reported to convey greater risk than paternal history^{77–81}. Although this association is controversial and has been suggested to be due to offspring – maternal nutritional effects that were experienced *in utero*^{107, 108}, studies of *in utero* risk factor exposure have shown mtDNA damage⁶⁴. Consequently, these observations are consistent with the notion that mitochondria play significant roles in the etiology of CVD.

MITOCHONDRIA ARE MULTIFUNCTIONAL ORGANELLES

Mitochondria are ancient bacterial endosymbionts with their own DNA, RNA, and protein synthesis systems¹⁰⁹. Mitochondria 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 death¹⁰². In fact, the primary function of the mitochondrion is dependent upon the current requirements and environment of the cell. For instance, the primary function of a mitochondrion within an endothelial cell may be the regulated generation of oxidants for cell signaling, whereas within a cardiac myocyte, it may be the generation of ATP, or, a combination of functions therein (e.g. ATP and oxidant generation). This unique feature of mitochondrial functional biology makes it the central focal point in terms of the mechanistic basis of many forms of age-related diseases, including CVD.

Mitochondria fundamentally execute the conversion of caloric energy into molecular energy, thermal energy, and oxidants (Figure 1). They achieve these tasks by coupling electron transport with proton translocation and OXPHOS. The energy released during the movement of electrons along the electron transport chain is used to pump protons across the inner membrane at complexes I, III, and IV, which creates a transmembrane electrochemical gradient. This potential energy is utilized by ATP synthase (complex V) to condense ADP and P_1 to form ATP. The energy not utilized for proton pumping is lost in the form of heat (thermogenesis). Electrons are also donated directly to oxygen (O_2) during electron transport to form superoxide ($O_2^{\cdot-}$) which can be converted to hydrogen peroxide (H_2O_2) and contribute to cell redox signaling processes, or in the presence of nitric oxide ($\cdot NO$), form peroxynitrite ($ONOO^-$), an oxidant which can react with carbon dioxide (CO_2) to form nitrosperoxycarbonate ($ONOOCO_2^-$), a nitrating agent^{24, 110}.

Each cell contains hundreds to thousands of mitochondria and each mitochondrion contains 5 – 10 copies of maternally inherited mtDNA. The mammalian mtDNA encodes 13 polypeptides, two rRNAs (12S and 16S) and 22 tRNAs that are essential for OXPHOS and proper cell function (Figure 2). The nucleus encodes all the remaining mitochondrial proteins for the organelle. Interestingly, the mtDNA retained key structural subunits required for the catalytic activity for four of the five OXPHOS enzyme complexes (I, III, IV and V). Consequently, mutations in these mtDNA encoded subunits could alter features in mitochondrial metabolism or economy (bioenergetic function).

MITOCHONDRIAL ECONOMY

Mitochondrial economy describes how the organelle utilizes the oxygen it consumes in terms of molecular (ATP) and thermal energy production, plus oxidant generation. This economy is therefore dependent upon a myriad of factors including local concentrations of both reactive nitrogen and oxygen species, mitochondrial antioxidants, cytokines, electron transport efficiency, metabolic reducing equivalent availability (NADH, $FADH_2$, and those from β -oxidation of fatty acids), cellular energetic demand, uncoupling protein (UCP) activities, and overall organelle integrity (damage to membranes, DNA, and proteins). Among these factors, electron transport efficiency as it relates to overall “mitochondrial economy” has received limited attention and has not been considered seriously in relation to CVD development. Mitochondria that utilize less oxygen to generate the same amount of ATP compared to mitochondria that use more oxygen for ATP production are, relatively speaking, more economical. Hence, economical mitochondria will have a higher ATP/ O_2 compared to those that are relatively less economical. Under conditions of excess substrate and low energetic demand (positive energy balance), mitochondria with high ATP/ O_2 will have a greater proportion of electron carriers in a reduced state (occupied by electrons) compared to those with lower ATP/ O_2 and thus, will be more prone to donate electrons to oxygen to form oxidants and are suggested to include African haplotypes (Figure 3, higher mitochondrial economy). However, under chronic conditions of substrate excess and low energetic demand even mitochondria that are less economical will generate increased oxidants. Mitochondria with low ATP/ O_2 utilize more electrons and O_2 to generate ATP, resulting in greater energy loss in the form of heat compared to those with higher ATP/ O_2 and are suggested to include Eurasian and northern migratory haplotypes (Figure 3, lower mitochondrial economy).

PREHISTORIC SELECTION, MITOCHONDRIAL ECONOMY AND EVOLUTION

As humans migrated from Africa, they encountered changes in climate and diet as they moved northward^{111, 112}. To successfully survive and reach reproductive age, it was necessary to develop a biological system to deal with these challenges. Consequently,

selective pressures on prehistoric humans were exclusively related to reproductive success and survival of their offspring to reproductive age. Post-reproductive challenges beyond the successful rearing of offspring to reproductive age, were not major selective pressures in a genetically adaptive sense. As our ancestors moved northward, they accumulated a greater frequency of mtDNA missense mutations relative to silent substitutions^{100, 113}. It has been proposed that these mutations altered aspects of mitochondrial economy that enabled these northern migrants to generate more heat/calorie consumed^{99, 100, 113}. These changes were tolerated because the diet of these migrants changed from a low protein, low fat vegetarian diet to a high protein, high fat diet consisting of animal fats^{111, 112}; hence, the decreased ATP generation/calorie (due to increased heat production) associated with these mtDNAs may have been offset by higher caloric intake. Consequently, by changing aspects of mitochondrial function in settings of warm climates and vegetarian diets to a system designed to be more thermogenic in a setting of cold climates with increased caloric intake, these changes in mitochondrial function may have contributed to increased probability for survival of the young to reproductive age.

Changes in mitochondrial function and/or protein levels associated with specific animal adaptations in vertebrates have been previously noted. For example, hibernating 13-lined ground squirrels (*Spermophilus lateralis*) demonstrate upregulated *nad2* (mitochondrial-encoded ETC complex I subunit) mRNA in heart, liver, and skeletal muscle during hibernation¹¹⁴ coincidental with 95% decreased metabolic rate compared to resting levels and decreased core body temperature maintained below 10°C¹¹⁵. Smaller mtDNA-encoded cytochrome *b* and *c* spectra in *S. lateralis* liver mitochondria have also been reported during hibernation, which may decrease the capacity of complex III¹¹⁶ affecting ROS formation and CVD¹¹⁷, mtDNA damage, and retrograde signaling (discussed below in “THE IMPLICATIONS OF THE MITOCHONDRIAL PARADIGM...AND DISEASE DEVELOPMENT”). In an avian model, the bar-headed goose (*Anser indicus*) that migrates over the Himalayas (altitudes up to 9000 meters) must sustain high metabolic rates in the context of severe hypoxia. *A. indicus* has evolved more subsarcolemmal mitochondria bordering capillaries with increased densities within increased numbers of oxidative fibers, enabling them to sustain high metabolic rates for flight under hypoxic conditions compared to low altitude birds¹¹⁸. This evolutionary adaptation to hypoxia has more recently been shown to involve decreased maximal cytochrome c oxidase (COX) activity, a higher affinity of COX for reduced cytochrome c, and proportional decreases in COX3/COX1 and COX4/COX3 protein expression. The decreased COX3 subunit (mtDNA encoded) in the bar-headed goose also has a nonsynonymous substitution at a conserved site in vertebrates, which based on structural modeling suggests it would alter the interactions of COX3 and COX1 accounting for the increased economy and evolutionary mechanisms of high-altitude adaptation¹¹⁹. Finally, although not extensively studied, aspects of adaptive evolution of the mtDNA encoded subunits across placental mammals has been examined, potentially providing a framework for future characterization of mtDNA mutations in regard to their impact on cellular function and physiology¹²⁰.

MITOCHONDRIAL OXIDANT PRODUCTION

The perception that mitochondrial oxidant production is analogous to “pollution” or an unnecessary by-product of electron transport is inaccurate. While many reports have implicated mitochondrial oxidant generation as an important form of cellular stress that contributes to disease development, which is certainly a correct interpretation^{65, 66, 121–137, 65, 66, 68, 70, 72, 138–145}, it also reflects a contemporary viewpoint. Mitochondrial produced oxidants most likely originally served as a signaling system for the benefit of the host (the eukaryotic cell), a concept that has not been widely contemplated. From an evolutionary perspective, the cellular functions of the mitochondrion developed

over millions of years of endosymbiosis with its nucleated host. Because it is possible that our proto-eukaryotic ancestors spent a significant amount of time during their evolutionary existence under conditions of limited caloric availability, they likely evolved systems of mitochondrial – nuclear interactions designed for increased survival and reproductive success under conditions of punctuated caloric restriction. Consequently, selection for a system that had a rapid feedback/signaling mechanism (production of oxidants) linked to energy production that would induce caloric storage when energetic demands were met would be strong. This notion would suggest that mitochondrial oxidants may have originally served as stimuli for i) insulin production and ii) signaling molecules for insulin signaling pathways in non-insulin producing tissues. Hence, the mitochondrial oxidants may have initially served as a means for regulating caloric utilization and storage. Under conditions of excess substrate and low cellular energetic requirements (positive energy balance), mitochondria would increase oxidant production, triggering signaling pathways that would have led to storage of calories^{146–150}. As energy demand increased or food availability became low, mitochondrial oxidant production would decrease, as would caloric storage pathways. In this regard, studies have shown that mitochondrial oxidant generation or the alteration of mitochondrial UCP levels can impact insulin secretion and also affect aspects of insulin sensitivity^{68, 147, 151, 152}. While many studies have also shown that mitochondrial oxidant production inhibits insulin production and sensitivity, these studies are often performed under chronic conditions of hyperglycemia and therefore represent contemporary stress factors rather than prehistoric. Regardless, studies have shown that a connection exists between mitochondrial oxidant production and insulin secretion^{153, 154}, and more recent work suggests that oxidants impact insulin signaling pathways in non-insulin producing tissues^{146, 155, 156}. A final consideration is that these systems were designed to increase survival for reproductive purposes and hence, may function more robustly in the young (by virtue of their importance for survival and from a gene pool perspective). This concept is supported by the observation that insulin sensitivity is higher in the young compared to old¹⁵⁷.

THE IMPLICATIONS OF THE MITOCHONDRIAL PARADIGM FOR CONTEMPORARY SOCIETY AND CONCEPTS OF DISEASE DEVELOPMENT

As previously discussed, it has been hypothesized that mtDNA mutations fixed into prehistoric populations altered aspects of mitochondrial economy that enabled our ancestors to survive and reproduce at different geographic latitudes and diets¹⁰⁰. Today, these variants in mitochondrial function may influence individual disease susceptibility due to differences in mitochondrial oxidant production related to mtDNA haplotype^{100, 158}. With the development of greater physical inactivity, increased lifespan and excessive caloric intake seen in Western societies, these variants in mitochondrial function and genetics may influence predisposition towards disease development. Individuals with greater mitochondrial economy will have increased basal levels of endogenous mitochondrial oxidant stress under conditions of excessive caloric intake, physical inactivity (positive energy balance, Figure 3) and exposure to CVD risk factors compared to those with less economy and thus, will appear more susceptible to diseases related to oxidative stress such as CVD. Furthermore, those individuals with less mitochondrial economy will appear less susceptible to diseases related to oxidative stress, yet will not be completely immune to such disease under conditions of high caloric intake and/or physical inactivity (Figure 3). Chronic, excessive caloric intake and low energetic demands will still result in sustained mitochondrial oxidant generation over time that will induce cellular damage; hence even those individuals with lower mitochondrial economy will potentially develop CVD or cardiometabolic diseases with persistent exposure to these stressors. Conversely, individuals harboring mitochondria with greater economy will be more tolerant towards caloric

restriction compared to those having less economy (Figure 3, negative energy balance). This of course, sets up the dilemma that individuals more prone for weight gain under conditions of positive energy balance will be also more resistant to weight loss under conditions of negative energy balance although it has been shown that regular steady exercise may prevent or diminish the influence of mtDNA haplotype on some physiologic measures including aerobic capacity¹⁵⁹ and ROS-induced damage to skeletal muscle¹⁶⁰.

Evidence supporting these concepts is becoming recognized; several studies have shown that specific mtDNA mutations and haplotypes are associated with differences in oxygen consumption, increased risk for diseases thought or known to have an environmental component (e.g., deafness, blindness, Alzheimer's disease, diabetes and cancer)^{104, 160–181}. Similarly, studies have shown that the mtDNA haplotype can influence tumor growth and age-related deafness in mice^{182, 183}. It has also been suggested that human longevity significantly co-segregates with mtDNA haplotypes that have temperate and arctic origins^{174, 175}, yet they may have increased predilection for clinical illnesses associated with energetic insufficiencies such as blindness and CNS defects¹⁰⁰. Alternatively, mitochondrial haplotypes thought to be associated with increased mitochondrial economy may be more prone to certain types of cancer and age-related diseases associated with oxidative stress and/or somatic mutation^{100, 182}. More recent studies suggest a link between mtDNA haplotypes and CVD in certain populations¹⁸⁴. While studies in cybrid culture have provided conflicting results regarding the concept that the mtDNA influences cellular bioenergetics^{158, 185–187}, studies in conplastic strains of mice suggest that mtDNA background influences aspects of cognition, behavior, reproductive behavior, and susceptibility to autoimmune disease^{188–191}. An extension of the concept that the mtDNA alters organelle economy (bioenergetics) which influences disease susceptibility is that it may also play a role in modulating nuclear gene expression since the majority of proteins functioning within the mitochondrion are encoded by the nucleus. 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^{192–194}. If true, this would have serious implications regarding the use of transgenics derived from different strains of mice (e.g., backcrossing one strain on the background of another) and there are likely to be tissue-specific effects on mitochondrial-nuclear signaling^{195–197} influenced by energy balance, ROS, exercise, and diet.

THE ROLE OF DIET AND MITOCHONDRIAL FUNCTION

The composition and caloric content of the diet likely influence mitochondrial and cellular interactions. Excessive caloric intake without increased energy expenditure (a net positive energy balance), will result in increased weight gain, oxidant stress and disease risk. Whilst the effects of positive energy balance on mitochondrial function are a matter of debate concerning the question of whether mitochondrial dysfunction or positive energy balance drives the development of insulin resistance, diabetes, and cardiometabolic diseases^{198–202}, it is evident that caloric restriction decreases mitochondrial oxidant production and cardiovascular risk^{203–205}. Interestingly, it has also been shown that methionine restriction without caloric restriction can decrease mitochondrial oxidant production and mtDNA damage in rodents^{206–208}, while the same percent of carbohydrate does not^{209, 210}. In contrast, methionine supplementation in rats has been shown to increase ROS production and mtDNA damage in rat liver but not the heart²¹¹. Diets with higher unsaturated/polyunsaturated fat content (*ie.* fats from natural vegetable oils, nuts, and fish) compared to those with higher saturated fat (pork, beef, chicken, dairy, eggs, coconut oil, and some seafood) have been shown to decrease CVD^{212–215}, and decrease mitochondrial ROS

production²¹⁶. Polyphenols such as resveratrol contained in red grapes, red wine, and peanuts have been shown to induce mitochondrial biogenesis through activation of sirtuin 1 (NAD-dependent deacetylase sirtuin-1 or SIRT1) and peroxisome proliferator-activated receptor γ coactivator 1- α (PGC-1 α)²¹⁷, improving health, survival and decreasing diabetic complications^{218, 219}. Coincidental with dietary and mitochondrial interactions are conflicting reports regarding low-carbohydrate versus low-fat diets and their effects on disease progression. Ketogenic diets, high-fat with adequate protein and low-carbohydrates, mimic caloric restriction by forcing the body to burn fats rather than carbohydrates and have been shown to decrease mitochondrial ROS production through increased NADH oxidation²²⁰. Ketogenic diets are clinically used to treat many acute and chronic neurological diseases such as stroke²²¹, epilepsy^{222, 223}, mitochondrial myopathy²²⁴ and cardiovascular disease²²⁵.

The interaction of diet on mitochondrial function and bioenergetics in general involves the capability of the mitochondria to effectively and rapidly signal to the cell that excess reducing equivalents exist (high cytosolic NADH/NAD⁺ and ATP/AMP). This has been shown to occur in both rodents and humans through low level mitochondrial ROS generation^{146, 226}. Hoehn *et. al.* also demonstrated increased MnSOD expression improved glucose and insulin tolerance in mice fed high fat diets compared to controls¹⁴⁶. Further, evidence from that study suggests that mitochondrial ROS production (which would be higher under conditions of excess reducing equivalent availability and low ATP demand) may serve as a cell signal that decreases GLUT4 translocation to the cellular plasma membrane and induces temporary insulin resistance (by limiting cellular glucose uptake) in adipocytes and myotubes¹⁴⁶. Decreased influx of glucose would decrease NADH/NAD⁺, increase AMP/ATP, stimulate increased flux of electrons through the electron transport chain (ETC), decrease membrane potential and decrease ROS formation. However, under conditions of persistent positive energy balance, individuals with increased adiposity would also supply reducing equivalents via β -oxidation, and chronic ROS formation would ensue, contributing to post-translational oxidation of lipids, proteins and mtDNA, down regulation of metabolism, and vicious cycle of ROS-mediated mitochondrial dysfunction.

Under positive energy balance, excess reduced carbohydrates, fats and other foodstuffs lead to a chronic cellular redox shift toward an overload of reduced cytosolic NADH creating a 'reductive stress'²²⁷. Elevated levels of these high energy electron carriers, NADH and the reduced form of flavin adenine dinucleotide, FADH₂, would come from glycolysis and the Krebs cycle. Under these circumstances, most dehydrogenases and all NAD⁺-dependent enzymes would function abnormally because of the relative deficiency of NAD⁺ and inhibitory feedback mechanisms well described in most biochemistry text books. The NADH/NAD varies in response to changes in metabolism^{228–230} and is often used as a measure of the intracellular redox or metabolic state of the organism²³¹. Since NADH cannot penetrate the inner mitochondrial membrane directly, various shuttling mechanisms exist to transport the NADH reducing equivalents into the mitochondria for oxidation. The malate-aspartate shuttle is required in yeast for increased life span mediated through calorie restriction²³². Mitochondrial glycerol-3-phosphate shuttle also helps to funnel cytosolic reducing equivalents to the mitochondria for respiration²³³ and when knocked out in plants has been shown to increase the NADH/NAD ratio²³⁴.

Carbohydrate metabolism generates a ratio of 5 NADH/FADH₂ (per pyruvate), while fat metabolism generates a ratio of 2 NADH/FADH₂ (per acetyl CoA) which feed into the ETC at complex I for NADH and succinate dehydrogenase (complex II) for FADH₂. These reducing equivalents converge on coenzyme Q and complex III. Mitochondrial oxidant production has been shown to originate from complexes I and III of the electron transport chain (ETC)^{235–239} through both forward and reverse electron flux^{240, 241}. Hence, under

conditions of excess reducing equivalents and low energy demand (positive energy balance), a “bottleneck” can occur at coenzyme Q and complex III that increases cytosolic NADH/NAD⁺, mitochondrial membrane potential, and ROS formation²⁴². Moreover, it is possible that these effects are compounded in overweight individuals by virtue of their increased adiposity which further contributes to reducing equivalent availability through β -oxidation. Consistent with the notion that coenzyme Q may play an important role in modulating the effects of excess reducing equivalent availability are reports that mitochondrially-targeted coenzyme Q supplementation protects against endogenous oxidative stress²⁴³ and that supplementation of Co-Q has helped alleviate myopathic symptoms²⁴⁴. Interestingly, coenzyme Q deficiency may exacerbate cardiometabolic²⁴⁵, neurological²⁴⁶, and other diseases including diabetes and cancer²⁴⁷. It has also been reported that coenzyme Q deficiency induces mitochondrial degradation by mitophagy²⁴⁸.

SUMMARY

While there has been significant progress in understanding the pathological processes involved in CVD progression and development, the continuing status of CVD as the leading cause of death and morbidity in the Western world for the past century implies a lack of understanding regarding the basis of individual CVD susceptibility. Numerous studies have delineated important CVD risk factors, and although there is general agreement that they share a common feature of increasing vascular oxidant stress, the actual mechanistic basis of how they initiate or promote CVD development in some individuals and not in others with identical risk profiles, is not clearly understood. It is widely thought that CVD development is influenced by a combination of genetic, environmental, and behavioral factors that influence an individual’s biological response to known disease risk factors. A consideration currently lacking from these analyses is the potential role for mitochondrial genetics and function in determining CVD susceptibility. The mitochondrion is directly involved in the inter-relative aspects of caloric conversion to energy, thermogenic output, and oxidant production, and has been previously shown in numerous studies to be associated with cardiovascular dysfunction. Another aspect not commonly considered is that mitochondrial-nuclear relationships were established millions of years ago and were likely refined during prehistoric environmental selection events that today, are largely absent. By contrast, contemporary risk factors that influence our susceptibility to a variety of age-related diseases, including CVD were probably not part of the “equation” so to speak, that defined the processes of mitochondrial – nuclear interaction. Consequently, these diseases which are mostly post-reproductive are the by-product of our rapidly changing environment induced by technology; an environment for which our eukaryotic system was not designed. In this regard, the selective conditions that contributed to cellular functionality and evolution should be given more consideration when interpreting and designing experimental data and strategies. Finally, future studies that probe beyond epidemiologic/molecular epidemiologic associations are required. These studies will serve as the *initial steps* for addressing the provocative concept that contemporary human disease susceptibility is the result of selection events for mitochondrial function that increased chances for prehistoric human survival and reproductive success.

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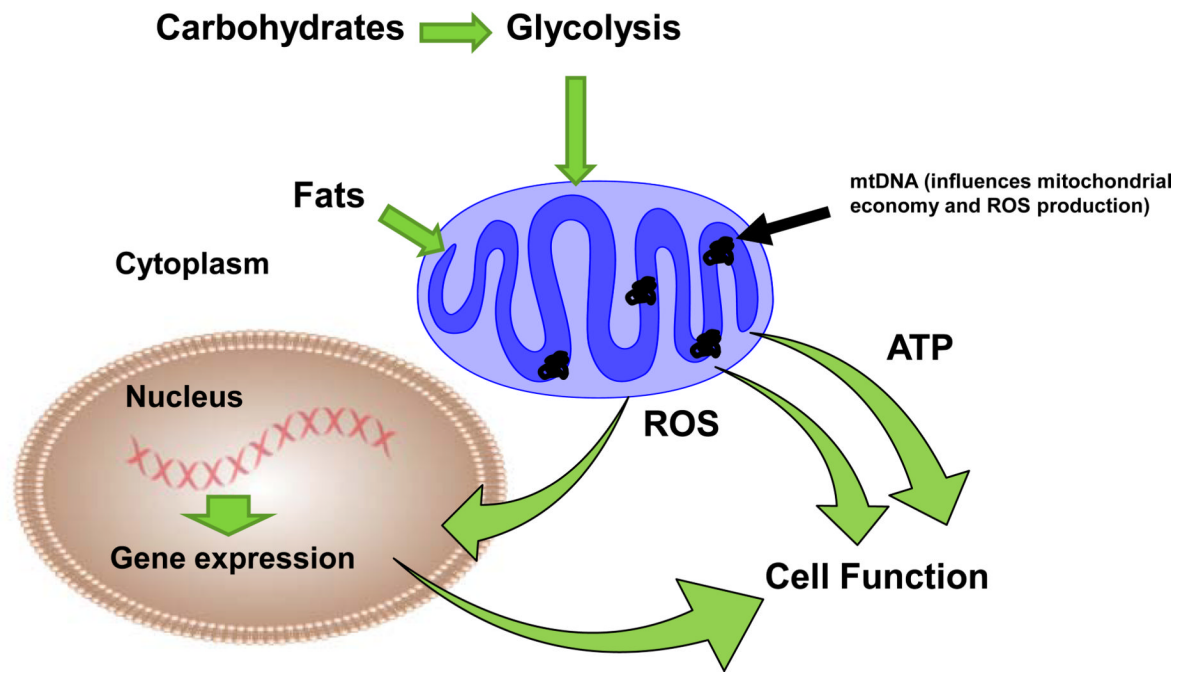
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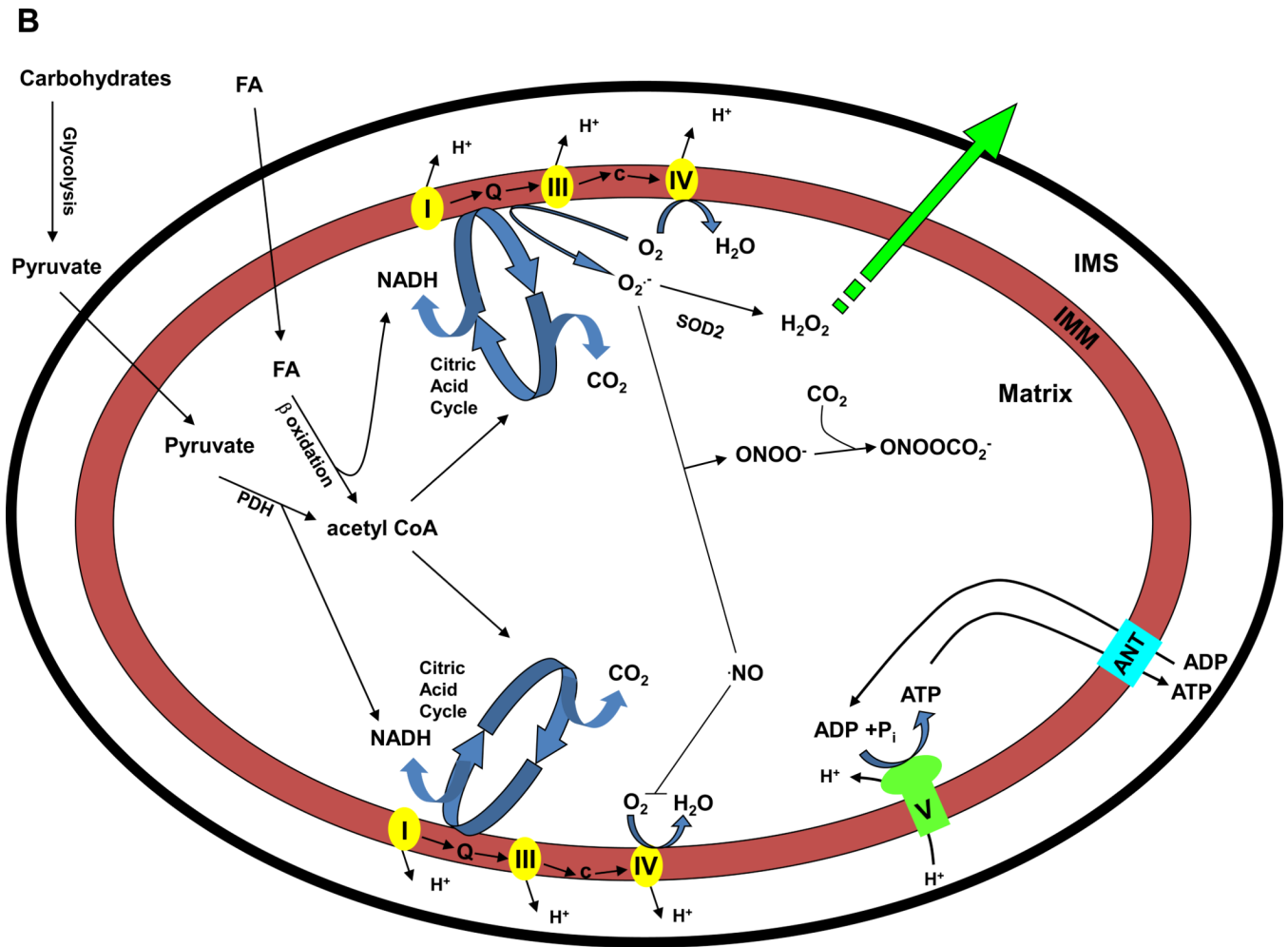
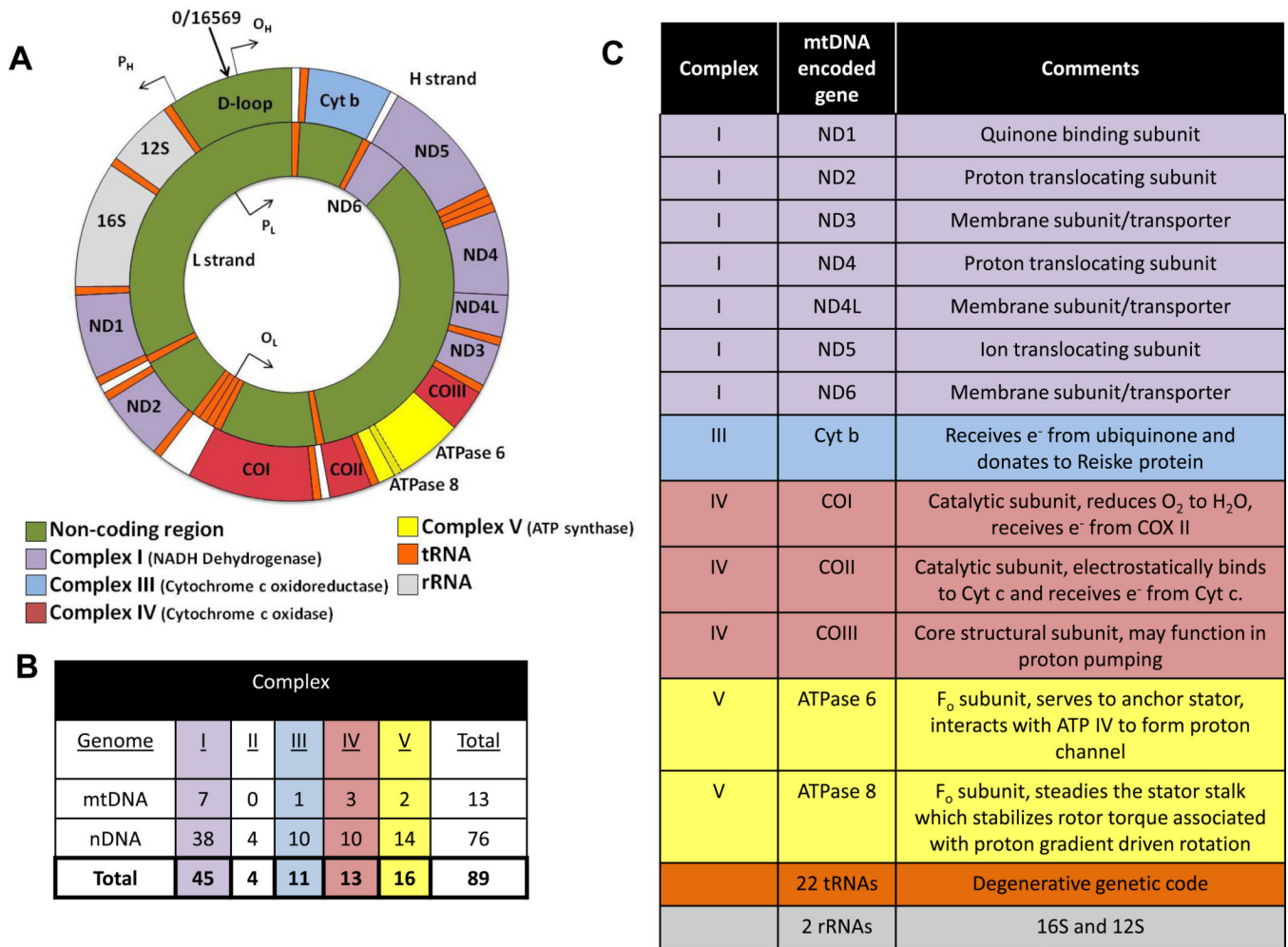


Figure 1.

A) Fundamental aspects of mitochondrial function. Caloric energy (carbohydrates and fats) are converted into molecular (ATP) and thermal (heat, energy lost during electron transport) energy and oxidants (reactive oxygen species-ROS). While ATP is utilized for energy requiring cell functions, mitochondrial generated ROS influence redox cell signaling processes, including induction of nuclear gene expression (via redox sensitive transcription factors) which contribute to cell function. Differences in mtDNA sequences are proposed to influence mitochondrial oxygen utilization (economy) and ROS production that impact cell function. The conversion of caloric energy into these respective components is dependent on overall organelle economy (influenced by the mtDNA encoded subunits), degree of positive or negative energy balance and uncoupling proteins. ATP and ROS are utilized for cellular functions (energy requiring processes and redox signaling); mitochondrial ROS also serve as a means for communication to the nuclear compartment and regulation of certain nuclear genes. **B)** Carbohydrates are metabolized to glucose that is further converted to pyruvate (glycolysis) in the cytoplasm and transported into the mitochondrion. Acetyl CoA is formed from pyruvate via oxidative decarboxylation (pyruvate dehydrogenase), where it enters the citric acid cycle that yields reducing equivalents (NADH and FADH_2) for electron transport located within the mitochondrial inner membrane. NADH is oxidized at complex I (NADH:Coenzyme Q oxidoreductase or NADH dehydrogenase) of the transport chain while FADH_2 is oxidized at complex II (Succinate:Coenzyme Q oxidoreductase or Succinate dehydrogenase, part of the citric acid cycle). Electrons are next passed to Coenzyme Q (Q).

Complex III (Coenzyme Q: Cytochrome c oxidoreductase or Cytochrome bc₁ complex) passes electrons from reduced coenzyme Q (Q) to cytochrome c (c), a peripheral membrane protein that alternately binds cytochrome c₁ (of complex III) and to complex IV (Cytochrome c oxidase). Complex IV catalyzes the one electron oxidations of four consecutive reduced cytochrome c molecules and the concomitant four electron reduction of one O₂ molecule to yield H₂O. During electron transport, protons are pumped across the inner membrane from the matrix into the intermembrane space, creating an electrochemical gradient. The free energy resulting from this gradient is utilized to condense a molecule of inorganic phosphate (P_i) with ADP at complex V (ATP synthase or F₁F₀ – ATPase) to yield ATP. ATP is subsequently transported out of the matrix by the inner membrane bound adenine nucleotide translocase (ANT) with the exchange of ADP. Fats bypass glycolytic metabolism in the cytoplasm and undergo β-oxidation in the mitochondrion to yield acetyl CoA (plus NADH and FADH₂ per cycle of oxidation), which enters the citric acid cycle to generate substrates for electron transport. During electron transport, superoxide (O₂^{·-}) is generated when electrons are added to O₂; O₂^{·-} is converted to hydrogen peroxide (H₂O₂) in the mitochondrion by manganese superoxide dismutase (MnSOD or SOD2). H₂O₂ (which is freely diffusible) can participate in cell signaling processes (H₂O₂ levels are regulated by a number of antioxidants within the mitochondrion and the cell, not illustrated). Alternatively, O₂^{·-} reacts with nitric oxide (·NO) to form peroxynitrite (ONOO⁻), an oxidant, which in the presence of carbon dioxide (CO₂) forms nitrosoperoxycarbonate (ONOOCO₂⁻), a nitrating agent.

**Figure 2.**

A) Sequence organization of the mammalian mtDNA. Colors indicate mtDNA encoded subunits for respective electron transport complexes, ATP synthase, tRNAs and rRNAs. ATPase 6 and 8 subunits overlap in sequence. The origins of heavy strand (guanosine rich) and light strand DNA synthesis are indicated by O_H and O_L, respectively. Transcriptional promoters for the heavy and light strands are represented by P_H and P_L, respectively. The D-loop (displacement loop) is a ~1 kb non-coding region within the mtDNA. The mtDNA genetic code is highly degenerate, so that only 22 are required for protein translation. When uridine is in the wobble position, all four members of a codon family can be read by one mitochondrial tRNA, whereas pairs of codons can be read when guanine or uridine is in the wobble position. Hence, 8 mitochondrial tRNAs recognize four member codon families, while 14 tRNAs recognize codon pairs. **B)** Table presenting the number of mtDNA and nDNA encoded subunits for each electron transport complex (I–IV) and ATP synthase (V) in the mammalian mtDNA. **C)** Table summarizing the known (or putative) function of each of the mtDNA encoded genes.

Mitochondrial Economy	Energy Balance	
	Positive (Caloric Excess)	Negative (Caloric restriction)
Higher	Increased oxidant generation (+++), increased propensity for weight gain and insulin resistance. Increased risk for diseases associated with oxidative stress and inflammation.	Greater tolerance for caloric restriction and starvation.
Lower	Increased (++) oxidant generation, decreased propensity for weight gain and insulin resistance*. Increased risk for diseases associated with energetic balance*.	Less tolerance for caloric restriction and starvation*.

Figure 3.

Table summarizing the anticipated characteristics of cells/tissues/individuals harboring mitochondria having higher or lower economy in regard to cellular-tissue oxidant generation and individual propensity for weight gain under positive or negative energy balance. An asterisk (*) indicates relative to higher economy, however under conditions of persistent positive energy balance, even cells/tissues/individuals with decreased (lower) mitochondrial economy will exhibit the same features as those with higher economy due to chronic stress. It is predicted that these features will be related to specific mtDNA sequences, or shared mutations between mtDNA haplotypes (representing mtDNA haplogroups).