Dysregulated mitochondrial and chloroplast bioenergetics from a translational medical perspective (Review)

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Abstract. Mitochondria and chloroplasts represent endosymbiotic models of complex organelle development, driven by intense evolutionary pressure to provide exponentially enhanced ATP-dependent energy production functionally linked to cellular respiration and photosynthesis. Within the realm of translational medicine, it has become compellingly evident that mitochondrial dysfunction, resulting in compromised cellular bioenergetics, represents a key causative factor in the etiology and persistence of major diseases afflicting human populations. As a pathophysiological consequence of enhanced oxygen utilization that is functionally uncoupled from the oxidative phosphorylation of ADP, significant levels of reactive oxygen species (ROS) may be generated within mitochondria and chloroplasts, which may effectively compromise cellular energy production following prolonged stress/inflammatory conditions. Empirically determined homologies in biochemical pathways, and their respective encoding gene sequences between chloroplasts and mitochondria, suggest common origins via entrapped primordial bacterial ancestors. From evolutionary and developmental perspectives, the elucidation of multiple biochemical and molecular relationships responsible for errorless bioenergetics within mitochondrial and plastid complexes will most certainly enhance the depth of translational approaches to ameliorate or even prevent the destructive effects of multiple disease states. The selective choice of discussion points contained within the present review is designed to provide theoretical bases and translational insights into the pathophysiology of human diseases from a perspective of dysregulated mitochondrial bioenergetics with special reference to chloroplast biology.

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1. Introduction

Mitochondria and chloroplasts represent endosymbiotic models of complex organelle development driven by the evolutionary modification of permanently enslaved primordial bacteria, to provide exponentially enhanced ATP-dependent energy production functionally linked to cellular respiration and photosynthesis (1-4). Over diverse eukaryotic phyla mitochondria and chloroplasts, either alone or together, provide a concerted amplification of cellular energy production via conserved biochemical pathways that have been positively enhanced in their catalytic and regulatory capacities during evolution.

It has been well established in the scientific literature that the cellular dysregulation of these two distinct organelles may generate potentially dangerous reactive oxygen species (ROS) due to compromised complex bioenergetics energy production, systemic oxidative stress and compounded pro-inflammatory processes in animals (5-11). Importantly, the genetically- or biochemically-mediated failure of mitochondrial function in human populations represents a potentially dire event in the etiology of major disease states that include type II diabetes, atherosclerosis, rheumatoid arthritis, Alzheimer's disease and cancer progression (12-28). These compelling mechanistic and clinical data suggest that the extent of mitochondrial/chloroplast regulatory signaling may vary over the lifetime of the eukaryotic cell and/or on a moment to moment basis, according to physiological demand and bioenergetics requirements (28-30).

Interestingly, a tumor cell may be viewed as a phenotypic reversion to the last common eukaryotic ancestor of the host cell, i.e., a facultative anaerobic microbe with unlimited replication potential (31). For example, anaerobic mitochondria in gill cilia of *Mytilus edulis* have evolved to utilize the phenotype of a facultative anaerobe, demonstrating that this primitive type of respiration has been evolutionarily conserved (32,33). Accordingly, anaerobically functioning mitochondria may represent a re-emergence or evolutionary retrofit of primordial metabolic processes and a reasonably posed scientific question

may relate to the frequency of this state-dependent phenomenon during the lifetime of an organism (2).

2. Co-identities within mitochondria and chloroplasts

It becomes readily apparent that the basic architectonic features of the mitochondrion also permit discrete microenvironments with specialized and autonomously segregated biochemical pathways (34). Given the spectrum of evolutionarily conserved chemical substrates and signaling molecules within TCA (Krebs) cycles and respiratory complexes of functional mitochondria across diverse cell types, it is not surprising that additional points of regulation are continuously emerging (3,35). Furthermore, the presence of functional mitochondria in both plant and animal cells underlines the molecular identities of shared regulatory, bioenergetics and chemical substrate pathways (3,35). The primacy of optimized energy processing in both plant and animal cells is supported by the observation that functional chloroplasts are found in selected animal cell types. The discovery of kleptoplasty, i.e., the dual expression of functional mitochondria and chloroplasts within specialized non-photosynthetic host cells has been extensively studied in the metazoan sacoglossan sea slug (36-39). The sacoglossan sea slug extracts and incorporates functional chloroplasts from Ulvophyceae into selected gut cell types (40), thereby allowing derived 'food' sources to be accumulated over time. The dependence on specific strains of algae suggests that strong adaptation mechanisms underlie the successful realization of bidirectional regulatory processes responsible for these requisite synergistic cellular phenomena (41). In conclusion, the dual expression of mitochondria and functional chloroplasts within specialized animal cells indicates a high degree of biochemical identity, stereo selectivity, and conformational matching that are the likely keys to their functional presence and essential endosymbiotic activities for over 2.5 billion years.

Interestingly, the ability of a phototroph to function intracellularly within a representative invertebrate, i.e., the sacoglossan sea slug, was identified as a unique phenomenon unlikely to occur in vertebrates (36-40). This working hypothesis, however, was overturned by the observation of internalized algae within embryonic tissues of the spotted salamander (42) and suggests that developmental processes within a vertebrate organism may also require photosynthetic endosymbiosis as an internal regulator. In effect, it appears that green algae and spotted salamander embryos have established an intimate endosymbiotic relationship that permit algae to invade the embryonic tissues and cells of the salamander and eventually degrade as the larvae develop over time (42). Although endosymbiotic algal cells go through degradation, the cells can also encyst on the inner capsule wall which is detected through 18s rDNA amplification in the reproductive tracts of the adult salamanders, thereby allowing for generational transfer of genes (42). Due to the dense accumulation of algae within the embryo, a distinct green color is exhibited, which leads to beneficial effects for the embryo. Requisite physiological effects include lowering embryonic mortality, a larger embryo size and earlier hatching times. It is still unclear as to whether the algae and the embryo have a true bidirectional symbiotic relationship, as there is evidence that the algae have no increase in oxygen levels, although they may benefit from the embryos when their nitrogenous waste is released. In any event, this phenomenon defines a distinctive relationship between developmental processes in a defined vertebrate organism and eukaryotic algae.

A careful examination of the biomedical literature has yielded many examples of biochemical and molecular commonalities between mitochondria and chloroplasts with regard to energy production. A prime biochemical example is the Q_o motif in cytochrome *b* (cyt b), formally known as the PEWY motif in mitochondrial complexes that possesses a high degree of catalytic importance within ordered electron transport complexes. Comprehensive evolutionary sequence analysis of the cyt b Q_o motif shows significant substitution within the tetra peptide sequence (PDWY, PPWF, PVWY and PEWY) according to phylogenetically specific patterns (43). The Q_o motif has been identified as PEWY in mitochondria and chloroplasts, as PDWY in Gram-positive bacteria, Deinococcus-Thermus and halo archaea, and as PVWY in β- and γ-proteobacteria patterns (43). It appears that the differential expression of PEWY by mitochondria and chloroplasts and PDWY by Gram-positive bacteria is functionally entrained to the redox potential of quinone, thereby reflecting an evolutionary modification from low to high potential electron-transfer systems in the emerging oxygenic atmosphere (43). The molecular evolution of the catalytic Q_o quinol oxidation site of cyt b complexes, in particular the tetra peptide PEWY sequence, functionally underlies the common retention of a chemiosmotic proton gradient mechanism for ATP synthesis in cellular respiration and photosynthesis.

In plants, the dynamic relationship between photosynthetic and respiratory processes can vary according to physiological or developmental demands. For example, when tomato fruit ripen, their chloroplasts are functionally differentiated into photosynthetically inactive chromoplasts that can produce ATP through a process known as chromo respiration (44). Similar to mitochondrial respiration, heightened O_2 consumption is driven by the concentrations of reduced NADH and NADPH as key electron donors, and is sensitive to the plastid terminal oxidase inhibitor, octyl gallate. Isolated chromoplasts are also sensitive to the cytochrome b_6f complex inhibitor, 2,5-dibromo-3-methyl-6-isoproply-p-benzoquinone, thereby indicating heightened electron transport coupled to ATP production concurrent with the ripening process (44). Finally, the number of functionally active mitochondria in fruit tissue was observed to decrease during ripening, consistent with the enhanced contribution of chromoplasts to total ATP production (44).

The essential role of molecular oxygen as the ultimate acceptor in the electron transport chain in animal and plant mitochondria is critically dependent on the integrity of cellular respiratory processes. In contrast to animal systems, it has been well established that plants lack active transport machinery to achieve adequate O_2 distribution to all cellular compartments, since gradients within plant tissues are vulnerable to severe hypoxic perturbations with potential dire functional endpoints. In effect, plants require different physiological responses to manage temporal variations in O_2 saturation with metabolic adaptations in energy requirements. Thus, an altered physiological demand under hypoxic stress may be coupled to the activation of the cellular glycolytic pathway to generate

substrate level ATP production when oxidative phosphorylation is compromised. Therefore, the regulated production of ATP, via anaerobic respiratory mechanisms, requires the co-ordinate recruitment of biochemical and molecular components of the oxygen-sensing pathway in plants, notably selective gene expression of different isoforms of glycolytic enzymes that are functionally adapted to hypoxic conditions, as well as the activation of transcription factors that regulate individual members of other hypoxia-inducible genes (45,46).

In this regard, cellular O_2 concentrations have been demonstrated to regulate the expression of group VII ethylene response factors (ERFVIIs), a family of plant-specific transcription factors that are stabilized during hypoxia, but degraded during normoxic conditions, via targeting to the N-end rule pathway of selective proteolysis (46-49). ERFVIIs are subsequently involved in the regulation of hypoxia-inducible genes that include *HRE1* and *HRE2*, thereby providing an adaptive homeostatic sensor of O_2 deprivation in plants. The N-end rule signaling pathway represents a cellular response mechanism that requires ubiquitin ligation linked to proteasome degradation via covalent modification of N-terminal amino acids. A recent study determined that the conserved N-terminal domain of ERFVIIs also distinguishes them as nitric oxide (NO)-dependent substrates of the N-end rule pathway of targeted proteolysis (50). It therefore appears that the state-dependent expression of ERFVIIs coordinately regulates homeostatic sensing to O_2 concentration, as well as key NO-dependent cellular processes.

Finally, the array of complex control mechanisms by which organelle gene expression (OGE) promotes respiration, photosynthesis and plant development is actively under investigation (51). Presently, several required components have been identified that are functionally associated with OGE processes. Nuclear-encoded proteins play important roles in OGE by promoting various required functions such as splicing, transcription, RNA processing and the regulation of translational processes. Normative OGE is regulated by the family of mitochondrial transcription termination factors (mTERF), and the observed dual regulatory targeting of nuclear mitochondrial and chloroplast gene expression by mTERF proteins, supports contentions of convergent evolutionary development. In conclusion, the dual regulatory targeting of mitochondrial and chloroplast gene expression by mTERF proteins to promote optimal energy production and oxygen consumption further advances the evolutionary importance of OGE processes.

It is now established that a similar set of functional genes are encoded in both the plastid and mitochondrial genomes that express catalytically conserved protein subunits within the electron transport chain (52). This implies that OGE processes are critically linked to shared stereo-selective enzyme reactions within common biochemical pathways (41). As an example of parallel and convergent evolution (52), ongoing processes that determine biologically meaningful modification of the OGE may be entrained to regulatory stability of intracellular and intra-mitochondrial redox potential. As such, any hypothesis of the evolutionary modification of the coordinate regulation of redox potential should predict discrete cellular loci for membrane proteins that are functionally related to respiratory and/or photosynthetic processes (52). Furthermore, the dual evolution of the plastid and mitochondria genomes will effectively drive the retention of functionally similar set of ribosomal protein genes which are functionally required for proper ribosomal assembly.

3. Antibiotic usage and mitochondrial dysfunction from an evolutionary perspective

Clinically employed classes of antibiotics represent the primary arsenal of chemical agents used to treat bacterial infections. Between 1940 and 1962, 20 novel classes of antibiotics were discovered and vary with regard to their structure and mechanism of action (53). The bactericidal effects of various antibiotics are possibly mediated by the induction of damaging ROS (54,55). A recent key study determined that bactericidal antibiotics elevate O_2 consumption, thereby altering bacterial redox physiology to produce lethal concentrations of ROS (55). As a critical control, the bactericidal efficacy of antibiotics was observed to decrease under strict anaerobic conditions, an effect that could be reversed by exposure to O_2 or equivalent electron acceptors. The overall importance of these observations relates to an expanded mechanism of action, whereby bactericidal antibiotics promote complex redox alterations that contribute to cellular damage and death, while also underlining a common evolutionary and developmental linkage between primordial bacteria and mitochondria (56,57).

Despite their number and various mechanisms of action, bacterial resistance has markedly limited widespread unrestricted usage of previously efficacious antibiotics (58). As alluded to above, additional limitations on the usage of certain classes of antibiotics relates to their documented side-effects functionally linked to mitochondrial dysfunction. As a prime example, aminoglycoside antibiotics used to treat infections of the inner ear (59) have been shown to irreversibly damage sensory hair cells due to the excessive production of mitochondria-derived ROS (3,18,24,29,60-62). Furthermore, the widely used class of tetracycline derivatives presents significant risk to patients with compromised mitochondrial functioning (63) due to established inhibitory effects on mitochondrial translational activities, including targeting of ribosomal RNA (64) that result in 'proteotoxic' stress and compensatory changes in nuclear gene expression (65). Interestingly, the selective targeting of mitochondrial translational apparatus by low concentrations of tetracyclines may in fact reiterate the evolutionary and developmental links between mitochondria and proteobacteria expression (65,66).

The glycopeptide antibiotic vancomycin chloride is widely used for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Nephrotoxicity, however, has been observed as a major adverse effect of vancomycin usage, thereby limiting the utility of the antibiotic in selected cases (67). A proposed mechanism of action was derived from a recent *in vitro* study demonstrating vancomycin-induced apoptotic renal tubular cell death driven by enhanced mitochondrial-derived ROS production linked to the inhibition of mitochondrial complex I activity (68). The results of this study were complemented by those of an earlier study demonstrating enhancements in complement-related and pro-inflammatory gene expression associated with oxidative cellular damage in kidney tissues of female rats following the administration of high concentrations of vancomycin (69).

It is worth noting that 'reverse engineering' of antibiotic-induced mitochondrial dysfunction has been proposed and pre-clinically employed as a therapeutic strategy against various malignant cell types, including cancer stem cells (70-74). Importantly, several classes of FDA-approved, widely employed, antibiotics including the erythromycins, the tetracyclines and the glycylcyclines have been shown to be highly effective anti-proliferative agents against cancer stem cells in 12 different cell lines via the inhibition of mitochondrial biogenesis linked to anabolic processes (74). Interestingly, in this same study, the authors proposed to treat cancer according to an infectious disease paradigm, utilizing a therapeutic regimen consisting of mitochondrial targeting by selected antibiotics. As a corollary, it has been recently demonstrated that the widely administered tetracycline analog, doxycycline, downregulates DNA repair mechanisms in cancer stem cells that are functionally linked to the maintenance of mtDNA integrity and copy number (72). Mechanistically, it was also shown that doxycycline treatment quantitatively reduced nuclear respiratory factor (NRF)1/2-mediated antioxidant responses and effectively inhibited multiple cancer stem cell signaling pathways. By contrast, the broad spectrum antibiotic, chloramphenicol, previously demonstrated to inhibit both mitochondrial protein expression and ATP production, may stimulate tumor progression via the activation of c-Jun N-terminal kinase (JNK) and phosphoinositide 3-kinase (PI3K) signaling pathways, leading to enhanced matrix metalloproteinase-13 region (MMP-13) gene expression (75,76). In conclusion, the translational potential of selected classes of antibiotics as anti-cancer agents must be evaluated by multiple physiological criteria, including inhibition of normative mitochondrial functioning.

4. Antibiotic usage and acute behavioral disorders: Potential association with mitochondrial dysfunction

A 2002 publication reviewed the incidence of acute manic episodes subsequent to antibiotic usage, subsequently termed 'antibiomania', as documented in 21 published studies, 82 cases reported by the World Health Organization (WHO), and unpublished data supplied by the Food and Drug Administration (FDA) (77). In total, usage of the erythromycin derivative, clarithromycin, was implicated in 28% of reported cases, whereas usage of the fluoroquinolones ciprofloxacin and ofloxacin was implicated in 27% of reported cases. These reports were consistent with unpublished FDA data indicating clarithromycin and ciprofloxacin usage to be most frequently associated with the development of acute manic episodes and were supported by additional studies exclusively focusing on the involvement of ciprofloxacin (78-80), oflaxocin (81) and clarithromycin (82,83) in the induction of acute psychotic episodes.

Mechanistically, it has been proposed that the stereoselective binding of ciprofloxacin to a mitochondrion-associated subtype of the NMDA receptor (84) promotes psycho-affective behavioral effects similar to those produced by the administration of dissociative anesthetics via the calcium-dependent excitation of hippocampal subfields (85). Conversely, the ciprofloxacin/fluoriquinolone-mediated inhibition of GABA-ergic signaling, partially driven via the production of mitochondrial ROS (86), has been shown to result in excitatory pro-convulsive neuronal activation as a putative contributing factor to the presentation of acute psychotic episodes (87-89). Subsequent case reports have observed acute psychotic/manic episodes following the administration of the nitroimidazole antibiotic, metronidazole (81), the mixed folate inhibitor/sulfonamide antibiotic cotrimoxazole (90-92), and the third generation cephalosporin derivatives ceftazidime (93) and ceftriaxone (94). Based on the diversity of the chemical structure and mode of action inherent to each class of antibiotic, a generalized downregulation of mitochondrial bioenergetics may account for the integrated psycho-affective behavioral effects observed in the string of case reports cited above. It would also appear likely that previous studies linking the acute psychotic effects of fluoroquinolones to interactions with NMDA and/or GABA-ergic neural transmission can be attributed to acute metabolic rundown due to severe mitochondrial inhibition (78-81).

5. Mitochondrial dysfunction in psychiatric disorders

The emergence of a highly efficient mitochondrial-driven ATP production appears to be a requisite component for the development of evolutionary diverse networking systems within the central nervous system (CNS) of higher animals, e.g., cognition appears to be rare. The manifestation of compromised cellular energy production, either due to oxidative stress and compounded pro-inflammation, hypoxia or genetically- or biochemically-determined mitochondrial abnormalities represents a major contributing factor to the symptomatology of major psychiatric illnesses, including major depressive disorder, bipolar disorder and schizophrenia (1,62,95). As a corollary, increases in the prevalence of neuropsychiatric disorders within aging adult populations suggest that the proto-symbiotic relationship of cellular mitochondria to compounded CNS energy production linked to entrainment of complex behaviors may be markedly altered within the lifetime of an individual. As with other metabolic processes, aberrantly high levels of ROS have been linked to cell death and degeneration in relatively diverse CNS pathophysiologies, including Alzheimer's disease, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD) and bipolar personality disorder (BPD) (96-102).

Mechanistically, causative factors involved in acute and chronic CNS damage linked to complex behavioral sequelae include high levels of mitochondrial-associated pro-oxidant iron functionally linked to lipid peroxidation (103-106) and ultimately enhanced endonuclease-mediated DNA fragmentation (107). Enhanced mitochondrial uptake of calcium linked to enhanced ROS production (108-112) has been established as a key causative factor in neurodegenerative conditions (98,113-120), as well as major psychiatric illnesses including schizophrenia (SCZ) (99,101,121-123). Chronic oxidative stress in conjunction with altered NO-mediated signaling pathways has also been proposed as a significant contributing factor in the pathophysiology of SCZ-related behaviors (124,125) and in the etiology of BPD (126). Etiological factors involving mitochondrial dysfunction in the presentation of BPD- and SCZ-related symptomatologies reveals a reduction in the gene expression of essential electron transport chain subunits (127).

Dysfunctional GMP-PKG signaling (116,128,129) and NOX2-mediated processes (130) also are causative factors in the pathogenesis of diverse psychiatric disorders (130).

Abnormalities associated with the electron transport chain system and the mitochondrial complex may be involved in the etiology of autism spectrum disorder (ASD) (102,131,132). Additional mitochondrial-associated pathophysiological factors in the development of ASD include altered pyruvate dehydrogenase activity and mtDNA copy numbers and enhanced oxidative stress (102,131,133,134). Finally, CNS antioxidant glutathione deficiency has also been functionally linked to autistic behaviors (131,135) and in SCZ and BPD (136).

In light of the above, we previously hypothesized that the multi-enzyme biosynthetic pathway responsible for endogenous morphine in animal cells may be similarly compromised in neuropsychiatric disorders due to their dependence on dopamine as a major synthetic precursor (137,138). Morphine administration engenders inhibitory effects on neuronal excitation and associated integrated behaviors that are consistent with coordinate regulatory activities on mitochondrial respiration, O_2 consumption, and aerobic ATP synthesis (139). Furthermore, the metabolic effects of endogenous morphine on CNS mitochondrial functions are selectively mediated by a novel 6-transmembrane domain GPCR, the mu-3 opiate receptor subtype, that is functionally coupled to constitutive NO production and release (139-145). The multi-faceted regulatory role of mitochondrial NO on O_2 consumption, oxidative phosphorylation, and ATP production reinforce the biological importance of morphine-coupled regulatory responses in integrated CNS behavioral pathways and their dysregulation in oxidative stress-associated neuropsychiatric disorders (95). Accordingly, endogenous morphine expression, which exerts its cellular actions via novel membrane G-coupled receptors, is directly responsible for overall cellular integrity via its regulation of mitochondrial respiration and functional linkage to NO production and release (138).

6. Conclusions and translational insights

As noted earlier, the dual expression of mitochondria and functional chloroplasts within specialized animal cells indicates a high degree of biochemical identity, stereoselectivity and conformational matching that are the likely keys to their functional presence, tolerance and essential endosymbiotic activities for billions of years (3,35,41,146,147). It has been recently proposed that archaebacterial and eubacterial precursors led to the origin of eukaryotes (148,149). Mitochondria arose via bidirectional endosymbiotic selection processes from an entrapped α-proteobacterium within a primordial eukaryotic cell (149,150). Plastids arose in a similar manner, but from an entrapped cyanobacterium within a eukaryotic precursor cell (149). Hence, eukaryotic cell types of higher organisms were evolutionarily fashioned to express autonomously contained bioenergetics processing centers in the form or mitochondria or chloroplasts.

The developmental primacy of photosynthesis was probably due to abundant sunlight and the coincident appearance of requisite photovoltaic chemical processes. Furthermore, the global abundance of reduced carbon in the form of glucose with concurrent expansion of atmospheric O_2 concentration introduced a major change in the biosphere, thereby driving evolutionary development of complex cellular respiratory processes along with major potential problems involving O_2 toxicity. In light of these changes, both photosynthetic and respiratory processes were driven by the potential for endosymbiotic protobacteria to evolve into semi-autonomous cellular organelles with concentrated catalytic foci expressed as highly ordered membrane protein complexes capable of errorless electron transport.

It has been proposed that the respiratory 'bacterium' evolved and remained in place because of its existential brokerage of molecular oxygen and the use of glucose as an initial fuel source within the metabolic pathway terminating in chemiosmotic ATP production. In this regard, photosynthetic priming events promoted evolutionary acceleration of intracellular membrane differentiation, selective for plastid-like structures. This major contention is supported by the observation that many organelles can be found in both plant and animal cells and that their molecular biology/bioenergetics share basic chemical processes (3,35,41).

Concerted biochemical and molecular investigation of the human gut microbiome is necessary to elucidate complex regulatory activities that directly affect diverse physiological activities of the 'host' organism (151-153). Given this multifaceted complex nature of the relationship between gut bacteria and humoral CNS factors, it is a highly reasonable contention that the gut microbiome is playing a role in the initiation and sustainability of normal and abnormal behaviors (153). Whereas normative microbiome activities represent key contributing factors to ongoing diverse physiological activities, severe perturbations of gut microbiota resulting in mucosal dysbiosis (154,155) are associated with pathological conditions that include gastrointestinal disease, obesity, and type II diabetes and ASD (156). The regulatory influences of the human gut microbiome also extend to immune activation and neuro-immune communication. In a pathophysiological setting, microbiotic dysregulation may inappropriately stimulate macrophage penetration into the CNS, with concurrent activation of proinflammatory processes involving activated microglia (157). Counter-intuitively, given the 10X greater number of gut bacteria in comparison to eukaryotic cells, which also contain evolutionarily derived mitochondria, it would appear that the summated populations of 'simple' organisms may in fact regulate the ultimate fate of our genetic material. In sum, it has become compellingly apparent that eukaryotic cells and complex organ systems cannot survive without the synergistic complex interactions of competent enteric bacteria and evolutionarily fashioned mitochondria.

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