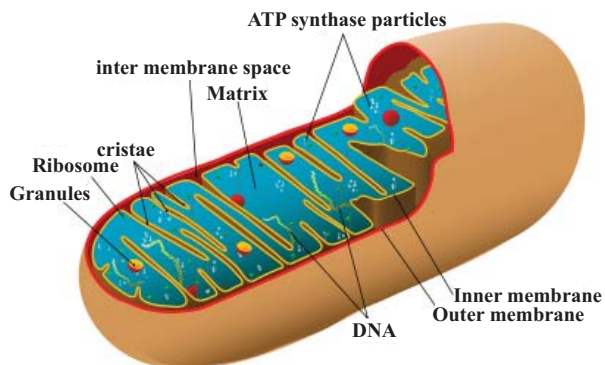


MITOCHONDRIA: MAINTAINING THE POWER PLANT

The Mitochondria. Even the name itself emanates power, centralized activity and importance - and this exudation is not misplaced. The most common metaphors used to describe the mitochondria are the 'powerplants' or the 'furnaces' of the cell. Indeed, mitochondria provide the energy a cell needs to move, divide, replicate, contract, secrete byproducts, and anything else that requires motion and the fuel energy to make it possible. Mitochondria are bacteria-sized organelles - thousands are located inside the membrane of each cell, occupying about one-fifth of its volume and lying adjacent to its nucleus.¹ Their shape can vary greatly depending on the cell type, and like the nucleus each mitochondrion is surrounded by a double-membrane composed of outer and inner segments. While the outer membrane is relatively smooth, the inner membrane is condensed with folds called cristae, and it is on these cristae that Adenosine Triphosphate (ATP) - the primary fuel of life - is produced. The cristae significantly expand the surface area of each mitochondrion, thereby increasing its cellular respiratory capacity and the ensuing production of ATP. The space within the cristae and the inner membrane is called the matrix, which contains a densely concentrated mixture of several hundred enzymes, ribosomes and DNA precursors. This is indicative of mitochondria's unique level of genetic self-sufficiency, which some scientists argue dates back to a time in evolution when the mitochondria independently sustained themselves outside the cell wall entirely!



The Vicious Cycle

The impressive capacity of the mitochondria to perform their primary function of converting organic materials into cellular energy in the form of ATP cannot be understated. That capacity, however, does not remain constant and is dependent on outside variables, such as diet, lifestyle and age. In fact, it would not be inaccurate to view the state of mitochondria as reflective microcosms of the state of the living organism as a whole.

The Mitochondrial Theory of Aging:

There are several theories of aging, each one identifying and then revolving around one particular biochemical pathway. Examples of pathways these theories depend on include glycation, free radical generation, and methylation, to name a few. Predictably, there is a significant degree of juxtaposition among all of these theories. One theory, however, is the Mitochondrial Decline Theory, or the Mitochondrial Theory of Aging. This theory is closely related to the well-established Free Radical Theory of Aging and has in fact been described by scholars as a 'maturation' of that theory.

This is because the Mitochondrial Theory of Aging begins with the premise that the cellular respiratory process (for which mitochondria are chiefly responsible) results in the production of reactive oxygen species (ROS). This is a vicious catch-22, especially in light of the fact that simultaneously increased mitochondrial activity and proliferation is almost universally associated with health-enhancing metabolic ameliorations. These include (but are no means limited to) an increased basal metabolic rate (BMR) and improved insulin sensitivity, two states themselves identified as panoramic links to the prevention of a myriad of health disorders. However, the greater the simultaneous activity and proliferation of the mitochondria, the more free radicals they generate. Paradoxically, an inefficient mitochondrion generates even more free radicals than an efficient one, since more fuel (in the form of glucose, amino acids and fatty acids) is required for each mitochondrion to produce the same amount of ATP. This results in an increased ratio of ROS-to-ATP production. To complicate matters further, mitochondrial DNA (mtDNA) differs from the DNA of the nucleus and other organelles in that mtDNA has no enzymatic defense against oxidative stressors, self-generated or not.² In-vivo studies have provided evidence for the Mitochondrial Theory of Aging so conclusive that one leading researcher summarized it this way: "It is generally accepted that oxidative mitochondrial decay is a major contributor to aging."³



Table 1: Non-genetic Strategies to Improve Mitochondrial Dysfunction⁴

Strategy	Theoretical Basis	Example
1. Enzyme Bypass	Provide energy beyond the site of the enzyme defect	Succinate, Co-Enzyme Q10
2. Anti-oxidants	Reduce free radical damage to cell structures	Vitamin E, C, lipoic acid
3. Alternative energy	Use an anaerobic system not requiring mitochondria	Creatine Monohydrate
4. Reduce lactate	Reduce acidosis, more energy into the mitochondria	Dichloroacetate, thiamine
5. Strength exercise	Improve strength, reduce number of mutant mtDNA	Weights, isometrics
6. Endurance exercise	Improve endurance, reduce cardiovascular risks	Jogging, cycling, walking
7. Nucleotide precursors	Prevent depletion of nucleotide pool (for DNA synthesis)	Triacetyluridine
8. Vasodilation	Prevent vascular spasm in MELAS stroke	L-arginine

Power Plant Maintenance - Upgrading With Cocktails

If the function of mitochondria sounds relatively straightforward (at least on a macro-level), then their aforementioned vulnerability reveals a contrasting complexity when the discussion turns to maintenance and enhancement. The process of addressing the elusive prerequisites to mitochondrial health is so intricate that entire professional medical societies have been established exclusively for its study. These include the Mitochondrial Research Society (Buffalo, N.Y.), the Mitochondrial Physiology Network (Innsbruck, Austria), and the United Mitochondrial Disease Foundation (Pittsburgh, PA), among others.

The cumulative efforts of the scientific community have resulted in some measure of fundamental consensus in the design of a protocol to address the challenges posed by an aging and/or dysfunctional mitochondrion. A review of the studies aimed at this goal has produced the following collection of pharmacological, nutritional and exercise treatment strategies - combinations of which have become known as 'mitochondrial cocktails':

1) Enzyme Bypass: The theory here is to circumvent a defect along the mitochondrial Electron Transport Chain, which is a series of inter and intra-cellular reactions that produce ATP. This chain is initiated when electrons are transferred to a lipid-soluble carrier called a ubiquinone, which in turn crosses the cellular membrane. The supplemental form of ubiquinone is Co-Enzyme Q10 (Co-Q10), and studies have shown that it can expedite the Complex II phase of the Electron Transport Chain by up to 200%.⁵ This is the phase where additional electrons are funneled into the ubiquinone by the enzyme succinate dehydrogenase.

2) Anti-oxidants: The universal anti-oxidant/free radical dichotomy certainly has mitochondrial applications as well, but the vulnerability of mtDNA alters the circumstances. Conventional anti-oxidants such as vitamins C and E are certainly useful, but the ideal mitochondrial anti-oxidant appears to be α-lipoic acid, or simply lipoic acid (preferably composed of the R(+)- enantiomer - see Advances October 2001 or Vol.3; Issue 1). Lipoic acid is metabolized to its active form, diHydro-lipoic acid (DHLA) inside the mitochondrion itself by the enzyme known as pyruvate dehydrogenase complex (PDH). This process, (and equally importantly, the dynamics of this process) produces intense biological activity, including the regeneration and recycling of vitamins C and E.⁶ Lipoic acid not only displays an intramitochondrial anti-oxidant capability, but also an intracellular and extracellular one as well, and this capability is effective in both aqueous and lipophilic environments.⁷ Indeed, the biological potency of lipoic acid is such that it has become one of the most heavily studied antioxidants in the scientific community, with the result being the development of more advanced variants of this ubiquitous compound.

3) Alternative Energy: This tactic involves the maximal utilization of a source of ATP that does not require any mitochondrial participation, thus augmenting overall ATP production without burdening dysfunctional or aging mitochondria. One way of doing this involves the supplementation of creatine monohydrate for conversion to phosphocreatine (which in turn regenerates ATP) by cytoplasmic creatine kinase enzymes. Studies have in fact confirmed creatine monohydrate's effectiveness as an alternative energy source of this kind.⁸ However, other

alternative (and highly promising) sources of ATP originating outside the mitochondria have also been isolated in recent years - not the least of which is exogenous ATP itself. The ATP molecule has been replicated in the laboratory through scientific fermentation, and numerous clinical human studies have already demonstrated its ability to augment ATP pools.⁹

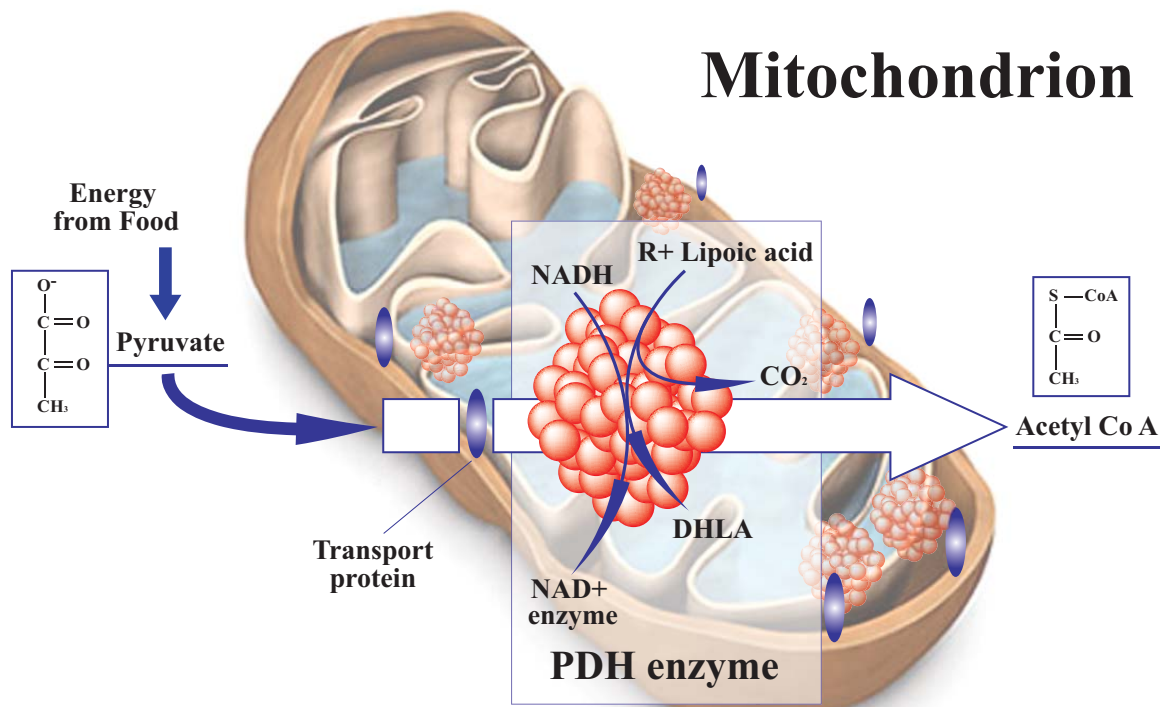
4) Reduce Lactate: Lactic acidosis is the condition whereupon the mitochondria use glucose for energy in the absence of adequate amounts of oxygen, and this cellular hypoxia is linked to mutations in mtDNA.¹⁰ The strategy here is to stimulate the enzyme pyruvate dehydrogenase - which is responsible for directing pyruvate into the mitochondria and away from lactate production. This can be done with the drug dichloroacetate as well as with vitamin B1 supplementation.¹¹ The latter option has been made even more appealing by the development of benfotiamine, a lipid-soluble thiamin that is nearly 5 times more bioavailable than conventional thiamin.¹²

5) Strength Exercise: Studies have shown that resistance training reduces oxidative damage to all DNA as well as 'significantly increasing' the activity of Complex IV of the Electron Transport Chain.¹³

6) Endurance Exercise: Extensive human studies conclusively point to the ability of endurance exercise to improve the activity and efficiency of the mitochondria. For example, one Australian study among obese adults revealed that endurance training increased mitochondrial fatty acid oxidation by 120%.¹⁴

7) Nucleotide Precursors: Nucleotides are the structural units of DNA and RNA - including mtDNA and mtRNA. As mitochondrial dysfunction is closely associated with the depletion of nucleotides, maintaining a healthy nucleotide pool is paramount. Triacetylluridine, a chemoprotective drug that is a precursor of uridine (an RNA nucleotide), is believed to be capable of this. Naturally-derived uridine supplements have been studied for their ability to improve mitochondrial function in patients with HIV.¹⁵ The supplement D-ribose, itself a structural unit of uridine, has been shown to reduce symptoms of fibromyalgia and chronic fatigue syndrome (both closely identified with mitochondrial dysfunction) by 30%.¹⁶

8) Vasodilation: Vasodilation (the widening of the blood vessels due to relaxation of smooth muscle in the vessel wall) is linked to the mitochondria via the production of nitric oxide. The mitochondria are primary targets of nitric oxide, and even small amounts can regulate ATP synthesis.¹⁷ MELAS (or mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) is a mitochondrial disorder caused by mutations in the mtDNA of endothelial cells that lead to their dysfunction. As its name implies, lactic acid buildup and stroke-like seizures are among the most common symptoms of MELAS, and supplementation with L-arginine, a nitric oxide donor, has been shown to ameliorate such symptoms in MELAS patients.¹⁸ Other nitric oxide enhancers include citrulline malate and the highly efficient *Gynostemma pentaphyllum*.¹⁹



NAD⁺/NADH: All the Difference A Letter Makes

A central facet of mitochondrial health revolves around the NAD⁺/NADH relationship. This is the process whereupon nicotinamide adenine dinucleotide is converted from its oxidized form (NAD⁺) to its reduced form, NADH; with the 'H' representing a hydrogen atom. This hydrogen atom is appropriated by the mitochondrial pyruvate dehydrogenase enzyme (PDH) along with the R(+)-enantiomer of lipoic acid to create dihydrolipoic acid (DHLA). An increasing central principle to mitochondrial (and overall) health is the importance of maintaining a favourable ratio of NAD⁺ to NADH, and there are a number of reasons for this.

Firstly, if there is insufficient R(+)-lipoic acid present to make use of the excess hydrogen atoms, then they are greeted by a mitochondrial PDH enzyme that cannot make use of them. The result is that these atoms eventually become superoxide radicals from inside the mitochondrion itself.²⁰ Secondly, the reduced form of nicotinamide adenine dinucleotide (NAD⁺) is the form that is readily available to the mitochondria as an energy source. Thirdly, a low NAD⁺/NADH ratio has been linked to diabetes, ischemia conditions, and metabolic syndrome, all of which in turn have strong ties to mitochondrial dysfunction.²¹

A metaphor for the NAD⁺/NADH ratio could be the revolutions per minute (RPM) of a car engine. If vehicle A requires its engine revving at 6,000 rpm to travel at 100km/hr while vehicle B requires 4,500 rpm for the same speed, then vehicle B is the more efficient machine.

Interventions known to produce a favourable NAD⁺/NADH ratio include R(+)- lipoic acid, carnosine, 3-carboxy-3-oxopropanoic acid, and the practice known as Calorie Restriction (CR).²² No 'mitochondrial cocktail' would be complete without something to address this central relationship.

As we have seen, the optimum maintenance of the mitochondria, the powerplant of the cell (and by extension of life itself) requires an approach that is both multifaceted and flexible. The importance of flexibility is due to the fact that research in this area is both extensive and ongoing, and new developments have to be incorporated into an intervention regimen that can already be quite complex. Examples of these new developments include such innovations as the isolation of the active enantiomer of lipoic acid [R(+)- lipoic acid], a Krebs's Cycle intermediate such as 3-carboxy-3-oxopropanoic acid, and a bioactive sirtuin activator such as trans-resveratrol.²³ These form an exciting new class of compounds known as 'calorie restriction mimetics', so named for their ability to emulate many of the

health benefits of a calorie-restricted diet, for which the mitochondria are of central importance..

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