

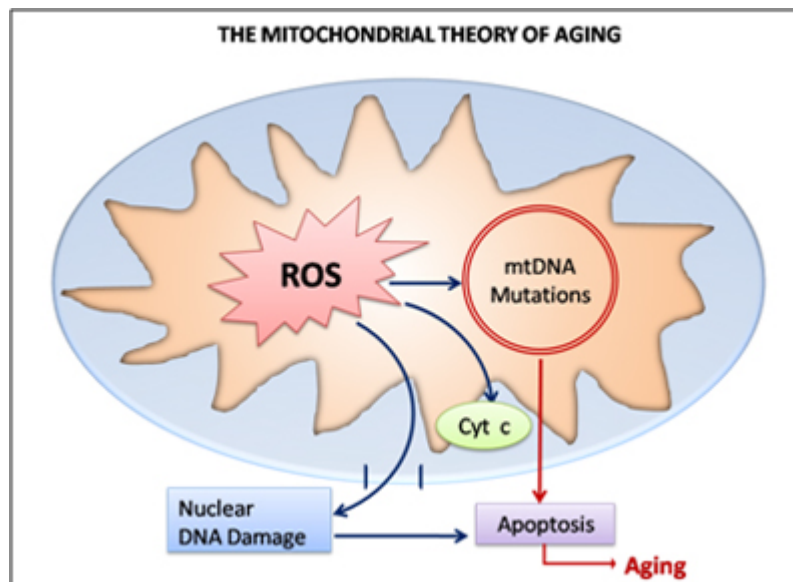
Reactive Oxygen Species, Mitochondrial Dysfunction Disease, and Aging

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As a functional medicine practitioner and instructor, my fundamental belief of how dysfunction and disease can be prevented is the basis of care that I provide to my patients and the passion that drives my lectures. My most recent research, of which I am sharing here, involved the relationship between ROS, mitochondrial dysfunction, and aging.

The primary role of the mitochondria is to generate energy in the form of ATP. The electron transport chain (respiratory chain) and oxidative phosphorylation are the pathways in which energy is produced. These reactions occur along the inner mitochondria. During the transfer of electrons from one complex to another, electrons can escape, producing reactive oxygen species (ROS). A high level of ROS and a low level of antioxidants result in oxidative stress, which cause damage to the mitochondria and surrounding tissue.

Aside from energy production, the mitochondria also participate in initiating and executing both apoptosis and necrotic cell death, as well as maintaining calcium and iron homeostasis. "Apoptosis" is a term for programmed cell death. Necrotic cell death is a form of traumatic cell death that results from acute cellular injury. Apoptosis differs from necrotic cell death in the fact that it does not damage the organism during the disposal of cellular debris. Apoptosis is a genetically controlled form of cell death essential for normal embryonic development and for the maintenance of tissue homeostasis in the adult. Normal homeostasis requires getting rid of diseased cells for the benefit of the whole organism. The target of choice for apoptosis and necrotic cell death is the mitochondria, since is it the source of energy production. (See figure 1)



Cardiolipin, a phospholipid found almost exclusively in the mitochondrial membranes of the respiratory chain has been found to be involved with execution of apoptosis. Cardiolipin appears to support (stabilize) the structural integrity of Complex III (cytochrome bc1), Complex IV (Cytochrome c oxidase) and Complex V (ATP synthase). Cardiolipin consists of four polyunsaturated linoleic acid chains (omega 6) that are subject to peroxidation by reactive oxygen species (ROS). This leads to the release of cytochrome c from the inner mitochondrial membrane to the intermembrane space and eventually into the cytoplasm, where it is recognized to initiate apoptosis. Research suggests that oxidative stress can cause premature cell death by this mechanism.

Unlike other organelles in the cell, the mitochondria contain DNA, which is inherited mainly from the mother. Damage to the mitochondrial DNA (mtDNA) can lead to loss of expression of mitochondrial polypeptides, subsequent decrease in electron transport and increased generation of reactive oxygen species, loss of mitochondrial membrane potential, and release of signals for cell death (apoptosis). MtDNA damage represents an important target for intervention and as a biomarker for many diseases. Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making transfer RNA and ribosomal RNA for proteins synthesis. MtDNA is prone to non-inherited (acquired) mutations and inherited mutations. MtDNA damage by oxidative stress can lead to lethal injury through the loss of electron transport, mitochondrial membrane potential and ATP generation. Somatic mutations have been reported in some forms of cancer, including breast, colon, stomach, liver, and kidney, as well as leukemia and lymphoma. *The major reason for mitochondrial disease appears to be reactive oxygen species (ROS).*

Other endogenous sources of ROS production, aside from the mitochondria, consists of enzyme oxidation, tissue ischemia, molecular auto-oxidation, and certain elements, such as iron and copper. Exogenous sources of free radicals that cause oxidative stress include medications (certain antibiotics, diabetic medications, antineoplastics, and anti-inflammatory), tobacco smoke, and radiation (UV, X-ray, and gamma-ray). All of these sources can lead to mitochondrial damage, leading to aging and premature death.

Signs and symptoms of mitochondrial disease are usually dependent upon what organ systems are involved and can vary from mild to severe. Onset of disease is at any age. The most affected tissues are post-mitotic (terminally differentiated) tissues. The brain, muscles, nerves, retinas and kidney are all post-mitotic tissues, making them more susceptible to mitochondrial disease. Their susceptibility is based on the fact that they have a high demand for energy and their diseased cells cannot be replaced.

Typically, diagnosing mitochondrial dysfunction and mitochondrial cytopathy is difficult due to the considerable variation in clinical presentation. There are no pathognomonic signs or symptoms. Functional medicine practitioners are well suited to suspect and/or recognize mitochondrial dysfunction and disease based on their overall training and, in particular, of energy production and oxidative stress.

The key to suspecting mitochondrial dysfunction or disease has its basis in obtaining a comprehensive history, including nutritional and environmental, and a comprehensive examination (including body composition analysis). And it must be noted that a considerable amount of medications can induce mitochondrial damage. Mitochondrial disease should be considered when: three or more organ systems are involved, the clinical presentation is atypical, there is abnormal or slow response to treatment, and/or the patient has recurrent setbacks. Assessment for mitochondrial disease requires a combination of clinical observations and laboratory testing. From a functional medicine perspective, the most sensitive and specific test to assess for mitochondrial dysfunctions is the urinary organic acid test, along with basic blood chemistries and CBC analysis.

ORGAN SYSTEM	POSSIBLE SIGNS, SYMPTOMS, AND DISEASE ^{1,2}
Muscles	Hypotonia, weakness, cramping, muscle pain, ptosis
Brain	Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke, and stroke-like events
Nerves	Neuropathic pain and weakness (which may be intermittent), acute and chronic inflammatory demyelinating polyneuropathy, absent DTR's, neuropathic gastrointestinal problems (GERD, constipation, bowel pseudo-obstruction, paresis), fainting, absent or excessive sweating, dysautonomia (aberrant temperature regulation)
Kidneys	Proximal renal tubular dysfunction (Fanconi syndrome), may result in loss of protein, magnesium, phosphorous, calcium, and other electrolytes
Heart	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia, gluconeogenic defects, non-alcoholic liver failure
Eyes	Optic neuropathy, ophthalmoplegia, acquired strabismus and retinitis pigmentosa
Ears	Sensory-neural hearing loss, aminoglycoside sensitivity
Pancreas and other glands	Diabetes and exocrine pancreatic failure, parathyroid failure (low serum calcium), hypothyroidism
Systemic	Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger

To date, there is no single treatment for mitochondrial disease. Given the fact that the major attribute for mitochondrial dysfunction is reactive oxygen species and the concomitant damage, it is reasonable to consider nutritional therapy; in particular antioxidants. You must always consider the biochemical uniqueness of the patient when prescribing therapy. Key treatment strategies are: elimination of exogenous free radicals, stress reduction, diet therapy, prescribing of appropriate vitamins, supplements, and cofactors, as indicated by functional medicine testing. (Caution on iron supplementation—Iron can generate free radicals, which can increase oxidative stress. Always perform a blood test to assess for iron status prior to supplementation on all patients, regardless of dysfunction or disease), and avoidance of physiological stress.



Dr. Wayne Sodano has over 26 years of combined private practice and teaching experience in functional medicine under the paradigm of natural internal medicine. He is a diplomate of the American Board of Chiropractic Internists in which he is a former instructor and is noted for his past radio appearances and current lectures on various functional medicine topics that include Celiac Disease, malignant diseases, AIDS, gastrointestinal disorders, and nutrient and toxic elements. Dr. Sodano's lecture topics are continually expanding and may be found on www.functionalmedicineuniversity.com. Want to learn more about functional medicine and the proven clinical benefit to your patients? Get your Downloadable FREE 12 Case Studies at www.Clinical-Rounds.com.

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