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Mitochondrial dysfunction and molecular pathways of disease

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Abstract

Since the first mitochondrial dysfunction was described in the 1960s, the medicine has advanced in its understanding the role mitochondria play in health, disease, and aging. A wide range of seemingly unrelated disorders, such as schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes, hepatitis C, and primary biliary cirrhosis, have underlying pathophysiological mechanisms in common, namely reactive oxygen species (ROS) production, the accumulation of mitochondrial DNA (mtDNA) damage, resulting in mitochondrial dysfunction. Antioxidant therapies hold promise for improving mitochondrial performance. Physicians seeking systematic treatments for their patients might consider testing urinary organic acids to determine how best to treat them. If in the next 50 years advances in mitochondrial treatments match the immense increase in knowledge about mitochondrial function that has occurred in the last 50 years, mitochondrial diseases and dysfunction will largely be a medical triumph.

Keywords: Mitochondria; Antioxidant; L-carnitine; Coenzyme Q10; Lipoic acid; Thioctic acid; Schizophrenia; Bipolar disease; Dementia; Alzheimer's disease; Epilepsy; Migraine headache; Stroke; Neuropathic pain; Parkinson's disease; Ataxia; Transient ischemic attack; Cardiomyopathy; Coronary artery disease; Chronic fatigue syndrome; Fibromyalgia; Retinitis pigmentosa; Diabetes; Hepatitis C; Primary biliary cirrhosis; Electron; Transport chain; Kreb's cycle

Mitochondria are the powerhouses of our cells. They are responsible for generating energy as an adenosine triphosphate (ATP) and heat and are involved in the apoptosis-signaling pathway. Current theory holds that mitochondria are the descendants of aerobic bacteria that colonized an ancient prokaryote between 1 and 3 billion years ago (Spees et al., 2006; DiMauro and Schon, 2003; Wallace, 2005). This allowed for the evolution of the first eukaryotic cell capable of aerobic respiration, a necessary precursor to the evolution of multicellular organisms (Spees et al., 2006). Supporting this theory is the observation that mitochondria are the only other subcellular structure aside from the nucleus to contain DNA. However, unlike nuclear DNA, mitochondrial DNA (mtDNA) are not protected by histones (Croteau and Bohr, 1997). Nuclear DNA wraps around histones, which then physically shield the DNA from damaging free radicals (Milligan et al., 1993) and are also required to repair double-stranded DNA breaks (Celeste et al., 2003). Since mtDNA lacks the structural protection of histones and their repair mechanisms, they are quite susceptible to damage.

The first mitochondrial disease was described by Luft and colleagues in 1962, when a euthyroid 35-year-old female presented with myopathy, excessive perspiration, heat intolerance, polydipsia with polyuria, and a basal metabolic rate 180% of normal (Luft et al., 1962). The patient suffered from an uncoupling of oxidative phosphorylation (ox-phos). Ox-phos is the major cellular energy-producing pathway. Energy, in the form of ATP, is produced in the mitochondria through a series of reactions in which electrons liberated from the reducing substrates nicotine adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) are delivered to O_2 via a chain of respiratory proton (H^+) pumps (Brookes et al., 2004). The uncoupling of ox-phos leads to the generation of heat without generating ATP, which was the dysfunction underlying this patient's presentation. To compensate, her mitochondria enlarged and multiplied, which was evident in a histological examination of muscle biopsies.

Since this first documented case, mitochondrial dysfunction has been implicated in nearly all pathologic and toxicologic conditions (Aw and Jones, 1989). (These conditions are outlined

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in Tables 1–3.) The conditions include sarcopenia and nonalcoholic steatohepatitis; acquired diseases such as diabetes and atherosclerosis; neurodegenerative diseases such as Parkinson's and Alzheimer's diseases; and inherited diseases, collectively called mitochondrial cytopathies.

However, since symptoms vary from case to case, age of onset, and rate of progression, mitochondrial dysfunction can be difficult to diagnose when it first appears. According to Cohen, who wrote a July 2001 article in the *Cleveland Clinic Journal of Medicine*, "The early phase can be mild and may not resemble any known mitochondrial disease. In addition, symptoms such as fatigue, muscle pain, shortness of breath, and abdominal pain can easily be mistaken for collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness" (Cohen and Gold, 2001).

Mitochondria structure and function

Cellular energy requirements control how many mitochondria are in each cell. A single somatic cell can contain from 200 to 2000 mitochondria (Veltri et al., 1990; Gray, 1989), while human germ cells such as spermatozoa contain a fixed number of 16 mitochondria and oocytes have up to 100,000 (Szewczyk and Wojtczak, 2002). The largest number of mitochondria is found in the most metabolically active cells, such as skeletal and cardiac muscle and the liver and brain. Mitochondria are found in every human cell except mature erythrocytes (Cohen and Gold, 2001).

Mitochondria produce more than 90% of our cellular energy by ox-phos (Chance et al., 1979). Energy production is the result of two closely coordinated metabolic processes—the tricarboxylic acid (TCA) cycle, also known as the Kreb's or citric acid cycle, and the electron transport chain (ETC). The TCA cycle converts carbohydrates and fats into some ATP, but its major job is producing the coenzymes NADH and FADH so that they, too, are entered into the ETC.

The overall pathway for the TCA cycle is as follows: catabolism of glucose in the cytosol produces 2 molecules of pyruvate, which pass through the mitochondrion's double membrane to enter the TCA cycle. As the pyruvate molecules pass through the membranes, they encounter two enzymes, pyruvate carboxylase and pyruvate dehydrogenase (PDH). Although PDH is referred to as one enzyme, it is actually a complex of 3 separate enzymes—pyruvate dehydrogenase, dihydrolipoyl transacetylase, and dihydrolipoyl dehydrogenase. The PDH complex requires a variety of coenzymes and substrates for its function—coenzyme A (CoA), which is derived from pantothenic acid (vitamin B5); NAD^+, which contains niacin (vitamin B3); FAD^+, which contains riboflavin (vitamin B2); lipoic acid; and thiamin pyrophosphate (TPP), which, as the name indicates, contains thiamin (vitamin B1).

Table 1
Signs, symptoms, and diseases associated with mitochondrial dysfunction (Cohen and Gold, 2001)

Organ system	Possible symptom or disease
Muscles	Hypotonia, weakness, cramping, muscle pain, ptosis, opthalmoplegia
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 deep tendon reflexes, neuropathic gastrointestinal problems (gastroesophageal reflux, constipation, bowel pseudoobstruction), fainting, absent or excessive sweating, aberrant temperature regulation
Kidneys	Proximal renal tubular dysfunction (Fanconi syndrome); possible loss of protein (amino acids), magnesium, phosphorus, calcium, and other electrolytes
Heart	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia, gluconeogenic defects, nonalcoholic liver failure
Eyes	Optic neuropathy and retinitis pigmentosa
Ears	Sensorineural hearing loss, aminoglycoside sensitivity
Pancreas	Diabetes and exocrine pancreatic failure
Systemic	Failure to gain weight, short stature, fatigue, and respiratory problems including intermittent air hunger

Table 2
Acquired conditions in which mitochondrial dysfunction has been implicated

Diabetes (Wallace, 2005; Fosslien, 2001; West, 2000)
Huntington's disease (Stavrovskaya and Kristal, 2005)
Cancer (Wallace, 2005), including hepatitis-C virus-associated hepatocarcinogenesis (Koike, 2005)
Alzheimer's disease (Stavrovskaya and Kristal, 2005)
Parkinson's disease (Stavrovskaya and Kristal, 2005)
Bipolar disorder (Stork and Renshaw, 2005; Fattal et al., 2006)
Schizophrenia (Fattal et al., 2006)
Aging and senescence (Wallace, 2005; Savitha et al., 2005; Skulachev and Longo, 2005; Corral-Debrinski et al., 1992; Ames et al., 1993)
Anxiety disorders (Einat et al., 2005)
Nonalcoholic steatohepatitis (Lieber et al., 2004)
Cardiovascular disease (Fosslien, 2001), including atherosclerosis (Puddu et al., 2005)
Sarcopenia (Bua et al., 2002)
Exercise intolerance (Conley et al., 2000)
Fatigue, including chronic fatigue syndrome (Fulle et al., 2000; Buist, 1989), fibromyalgia (Park et al., 2000; Yunus et al., 1988), and myofascial pain (Yunus et al., 1988)

Table 3
Inherited conditions in which mitochondrial dysfunction has been implicated (Cohen and Gold, 2001)

Kearns–Sayre syndrome (KSS)—external ophthalmoplegia, cardiac conduction defects, and sensorineural hearing loss
Leber hereditary optic neuropathy (LHON)—visual loss in young adulthood
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS)—varying degrees of cognitive impairment and dementia, lactic acidosis, strokes, and transient ischemic attacks
Myoclonic epilepsy and ragged-red fibers (MERRF)—progressive myoclonic epilepsy, clumps of diseased mitochondria accumulate in the subsarcolemmal region of the muscle fiber
Leigh syndrome subacute sclerosing encephalopathy—seizures, altered states of consciousness, dementia, ventilatory failure
Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP)—dementia, in addition to the symptoms described in the acronym
Myoneurogenic gastrointestinal encephalopathy (MNGIE)—gastroinstestinal pseudoobstruction, neuropathy