



# MITOCHONDRIA AND AGING

An introduction to aging science brought to you by the  
American Federation for Aging Research

## WHAT ARE MITOCHONDRIA?

Mitochondria are tiny cellular bodies or organelles, and are among the most complex structures within the cell. They have both an outer and inner membrane. Most of the energy-producing reactions occur at the inner membrane, which is made of lipids (fats) studded with proteins. Anything that interferes with the function of this structure can undermine the ability of the mitochondria to produce energy. Mitochondria also contain a small loop of DNA.

### Mitochondrial DNA

Mitochondria are the only components of cells, apart from the nucleus, to possess DNA. Mitochondrial DNA is much shorter than nuclear DNA, but no less important. Most mitochondrial proteins have their origin in the cell's nuclear DNA; these proteins are imported into the mitochondria. But a number of proteins essential to energy production come from mitochon-

drial DNA, and damage to this DNA can cripple the ability of the mitochondrion to produce energy.

### Bacteria in disguise?

The fact that they have their own membranes and their own DNA and that they divide and reproduce themselves independently from the rest of the cells have made mitochondria the subject of much speculation by scientists. It is now widely believed that mitochondria are descended from small bacteria-like organisms that, early in evolution, invaded a nucleated cell. Gradually, this primordial cell developed in such a way that the mitochondria took over the task of producing cellular energy, while the nucleated host assumed the other duties that would maintain the health and function of the mitochondria.

### What do mitochondria do?

Mitochondria are the cell's energy factories. They oxidize—in essence they “burn”—biological fuels such as lipids, proteins and fats. They then harvest the energy

stored in such fuels and eventually convert it to adenosine triphosphate (ATP), the substance needed to power many cellular processes.

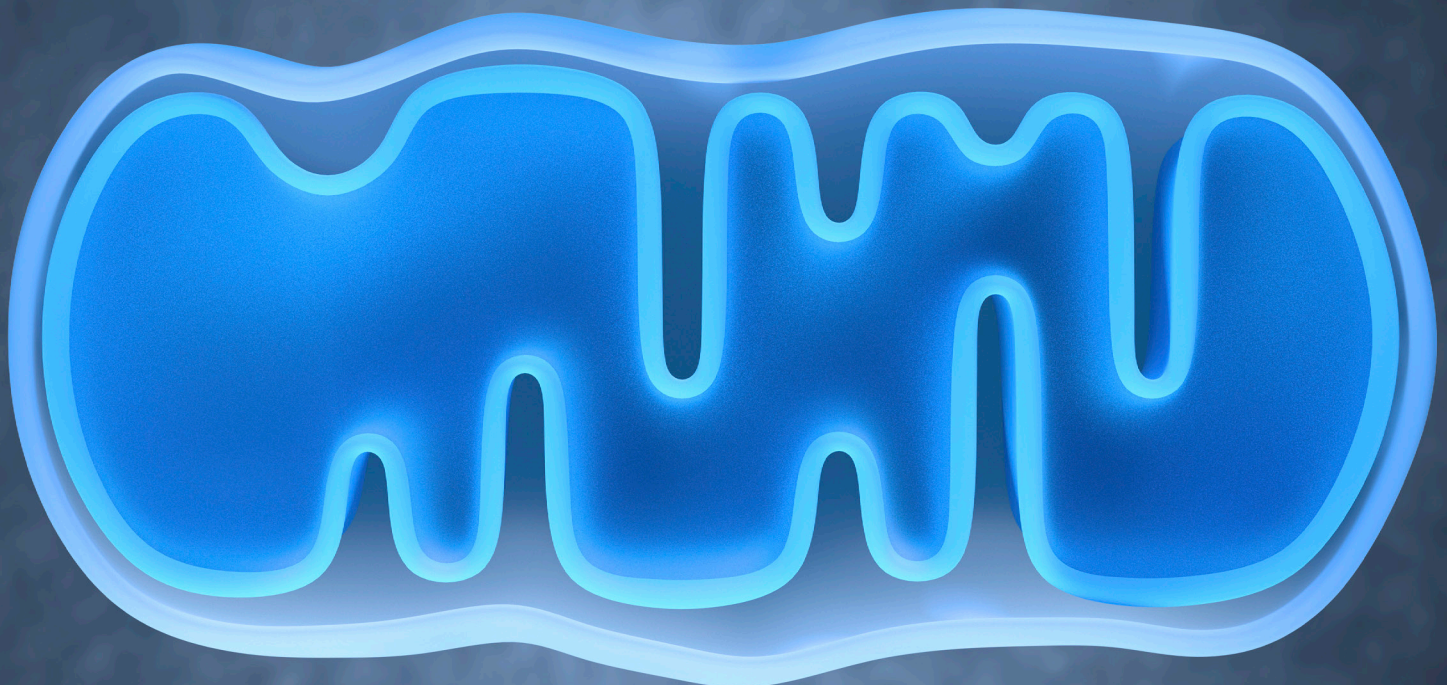
## THE ROLE OF MITOCHONDRIA IN AGING

### Oxidative damage

Among the byproducts of mitochondrial energy production are “reactive oxygen species” that include hydrogen peroxide—the same hydrogen peroxide used as an antiseptic and hair bleach. (In fact, the bleaching action of hydrogen peroxide is visible evidence of its oxidative power.) Many of these reactive oxygen species are free radicals. The free radicals include superoxide and the deadly hydroxyl radical (the same type of free radical that is produced in nuclear explosions). Oxygen-free radicals, unless they are quickly neutralized by anti-oxidants, can cause considerable damage to the membranes of mitochondria and to mitochondrial DNA. Scientists have studied the connection among mitochondria,

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oxidative stress and aging in fruit flies by housing the flies in an environment of 100% oxygen. The elevated oxygen levels cause the mitochondrial membranes to crimp in swirled patterns, which in turn decreases the life span of the insects from two months to about a week.

The injury caused by free radicals initiates a self-perpetuating cycle in which oxidative damage impairs mitochondrial function, which results in the generation of even greater amounts of oxygen-free radicals. Over time, the affected mitochondria become so inefficient they are unable to generate sufficient energy to meet cellular demands. This is why mitochondria from the cells of older individuals tend to be less efficient than those from the cells of younger people.

Recent research suggests that certain signaling molecules can slow the age-related decline of mitochondrial function. Pharmacologist Emilio Clementi of the San Raffaele Institute in Milan, Italy, and colleagues discovered that nitric oxide (NO) enhances mitochondrial production. The finding lends support to the mitochondrial theory of aging, which says that damaged mitochondria increase with age and are responsible for the physical changes of aging. If signaling molecules such as NO can boost mitochondrial supplies, then researchers may have ways of reducing the deleterious effects of mitochondrial damage in the elderly and in people with diseases such as diabetes.

Mitochondria appear, then, to be an obvious focus of study for researchers who study aging. Their role as energy producers makes them absolutely crucial to the life

of the cell. But they also produce threateningly large quantities of oxygen-free radicals. As the source of these toxic products, mitochondria are also their first potential victims. Their proximity to the free radicals they produce, combined with their exceedingly intricate structure, makes them particularly vulnerable to oxidative injury over time.

### **Mitochondrial DNA: An easy target**

Mitochondrial DNA is not as well protected as nuclear DNA, which is coated with proteins. The “naked” mitochondrial DNA becomes an easy target for rogue reactive oxygen species. In a study in *Circulation Research*, Scott Ballinger and colleagues at the University of Texas Medical Branch in Galveston found that when cultured animal cells were exposed to various types of oxygen free radicals, their mitochondrial DNA was more severely damaged than their nuclear DNA. Another study found that mitochondrial DNA damage was more extensive and persisted longer than nuclear DNA damage in human cells following oxidative stress. In general as cells age, the number of gaps and errors in their mitochondrial DNA tends to increase, and oxidant exposure is the likely cause. Controlling oxidative damage, therefore, appears to be one strategy for defeating some of the effects of aging.

A team led by Dr. Simon Melov of the Buck Center for Research in Aging in Novato, California, has developed a method for detecting mitochondrial DNA mutations. Using this assay on aging human brain cells, they found a mixed array of rearranged DNAs. The technique should have wider

applications, as scientists seek to pinpoint defects and mutations in mitochondrial DNA that might be the result of oxidative damage.

Similar genetic techniques have already proved successful in locating “hot-spots” in mitochondrial DNA—regions where defects and mutations tend to cluster. Dr. Giuseppe Attardi and his research team at the California Institute of Technology reported in the journal PNAS that mutations were not widely distributed in mitochondrial DNA, but appeared to be clustered in so-called “control” regions of the DNA that regulate its replication. One or more mutations appeared in an individual only at an advanced age. Some mutations appeared in more than one individual. Most strikingly, a DNA sequence rearrangement was found in a generally high proportion of mitochondrial DNA molecules in individuals over 65 years of age, though it was absent in younger individuals.

### **Mitochondrial factors: Cardiolipin, Carnitine, and CoQ**

As the body ages, we absorb nutrients less efficiently, and this can affect the efficiency of mitochondrial function. Cardiolipin is a component of the energy-producing process that is found almost exclusively in mitochondria. Cardiolipin levels naturally decline with age. Lipid peroxidation, a type of oxidant damage more common in older cells, leads to a decrease in cardiolipin. Cardiolipin itself can suffer the effects of lipid peroxidation, and the progressive accumulation of crippled cardiolipin molecules is yet another way in which oxidant damage can jeopardize the efficiency of energy production.

Carnitine, an amino acid, is also important to mitochondrial metabolism because it helps chaperone fatty acids into the mitochondria, where they can be metabolized. Carnitine deficiency leads to an inability to harvest the energy stored in fatty acids and to a build-up of fatty intermediates that can prove toxic to cells. Again mitochondria from older cells tend to contain less carnitine. Carnitine and cardiolipin form complexes in the membranes of mitochondria, protecting them. Certain medications, including the cancer drug adriamycin, target carnitine as part of their action, and administration of the drug L-carnitine can reverse some of the damaging effects of those drugs, while permitting them to do their necessary work in the body.

Coenzyme Q10, also known as CoQ10 or ubiquinone, is another factor necessary for energy production. It is available in the diet and it can be manufactured from simpler precursors. CoQ10 deficiency can affect brain and nerve function, and aging skeletal muscle cell mitochondria contain less of this important factor than do mitochondria from younger cells.

### **Controlling mitochondrial damage**

The assertion that mitochondrial damage and disruption contribute to aging and a number of diseases we associate with growing older, has gained wide acceptance among researchers. While our knowledge of the mechanisms that contribute to age-related mitochondrial damage is by no means complete, a fair amount is known about the generation of renegade oxygen free radicals—the compounds that indiscriminately damage components of the

mitochondria. As a result of that understanding, current research on mitochondria and aging has tended to focus on several interrelated areas:

- Minimizing the generation of compounds toxic to mitochondria
- Neutralizing and protecting mitochondria from oxidants that are formed
- Repairing mitochondrial damage once it has occurred

There are a variety of substances in the body that serve to control damage to mitochondria. These include antioxidants, the enzyme SOD (superoxide dismutase), and uncoupling proteins, or UCPs. DNA repair mechanisms also play a role. Scientists are now seeking ways to improve the efficacy of these compounds or processes to reduce the cellular damage associated with mitochondrial damage.

### **Antioxidants**

A number of naturally occurring compounds have antioxidant activity; they can scavenge and neutralize the potentially damaging oxidative compounds. Glutathione is one such antioxidant found in mitochondria. When glutathione is artificially depleted from cells, oxidative damage increases. The level of glutathione in mitochondria might be even more important than the level of glutathione in the rest of the cell. Mitochondrial glutathione levels diminish more with age than do the levels in the rest of the cell. This decline seems to make mitochondria more susceptible to oxidative damage.

Ascorbic acid, or vitamin C, is another naturally occurring antioxidant with protective powers. In aged cells, the activity of certain enzymes decreases in

mitochondria. But in one study adding ascorbate to aged cells in a growth medium—in effect, “feeding” the cells vitamin C—reduced the rate of loss of these enzymes. Vitamin E, or tocopherol, is a third antioxidant known to help prevent the mitochondrial oxidative damage. Research has shown that overproduction of mitochondrial oxidants, with subsequent membrane damage, is observed in vitamin E-deficient cells.

### **Superoxide dismutase**

Enzymes can also serve as antioxidants. The antioxidant enzyme called “superoxide dismutase” (SOD) helps defang superoxide ions, which are an especially dangerous type of oxidant molecule. The importance of SOD in protecting mitochondria from oxidant damage was convincingly demonstrated in a study of animals genetically manipulated to produce half the normal amount of SOD. Increased oxidative damage was observed in the deficient mitochondria, along with alterations in their mitochondrial function. A study published in the journal *Investigative Ophthalmology and Visual Science* looked at mice that were bred to be deficient in SOD. They were found to develop progressive thinning of the inner layers of their retinas as the result of having defective mitochondria.

### **Uncoupling Proteins (UCPs)**

When a mitochondrion turns food into fuel, it churns out reactive oxygen species (ROS) that can damage the membrane of the organelle. Uncoupling proteins diminish ROS formation by creating leaks in the mitochondrial membrane, which decreases the proton gradient that develops during cellular respiration. In essence, UCPs act to turn down

the heat on energy production, thereby limiting the production of harmful oxidants.

To investigate whether boosting UCPs extends life, Yih-Woei Fridell introduced the gene for a particular human UCP—UCP2—into fruit fly neurons. When the scientists turned on the gene in adult flies (by feeding the drug RU-486 to the flies), females lived almost 30 percent longer than they did without UCP2. Males lived about 11 percent longer. The cells of the flies also contained 40 percent less of the oxidant hydrogen peroxide and 32 percent less of a particular oxidized lipid. The work was the first demonstration that boosting UCP activity in the adult nervous system extends life span.

### DNA repair

Scientists have known for a long time that nuclear DNA has an elaborate collection of enzymes that proofread and correct mistakes and gaps in the nucleic acid sequence. For many years, mitochondria were assumed to not be as fortunately endowed. However, mitochondria are now known to have the ability to repair some errors in their DNA. Preserving, and perhaps stimulating, this activity might be one means of preventing age-related deterioration in mitochondrial DNA.

### THE ROLE OF MITOCHONDRIA IN AGE-RELATED DISEASE

The first disease-causing mutations in mitochondrial DNA were reported in 1988; today researchers have identified

more than 50 such mutations. In addition to mitochondrial DNA damage, diseases can also originate from oxidant damage to proteins and lipids in the mitochondria itself. Some of these illnesses caused by either or both of these pathways are ones we commonly associate with aging.

### Mitochondria and neurodegenerative diseases

Mutations in mitochondrial DNA may play a role in the progressive

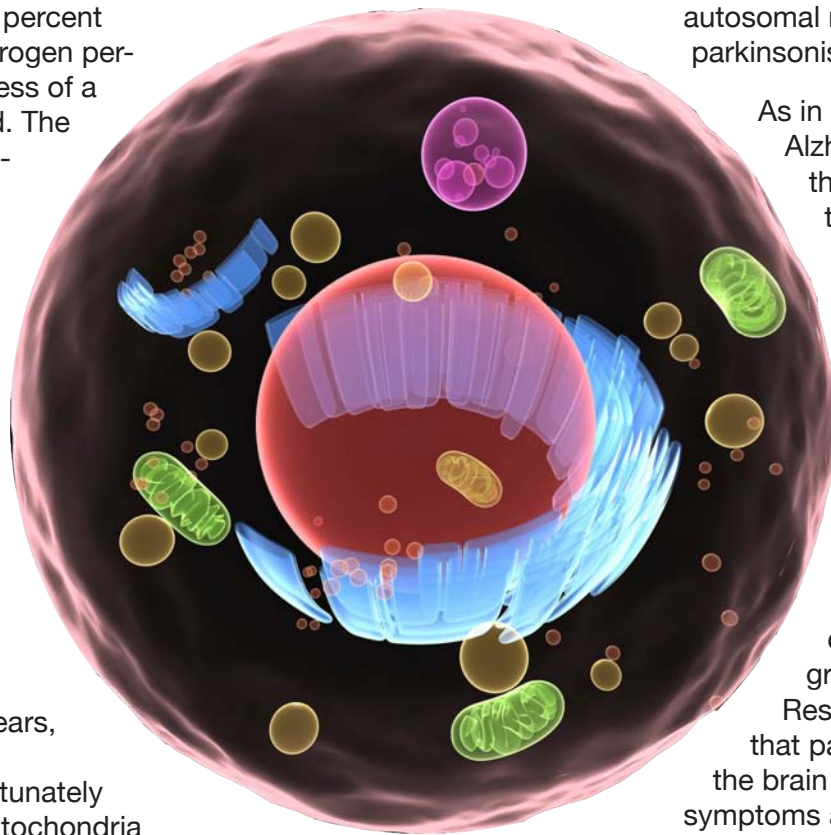
role in mitochondrial integrity. Parkin-deficient mice have fewer proteins involved in mitochondrial function and demonstrate a

delayed rate of weight gain consistent with broad metabolic abnormalities and reduced mitochondrial function. As many as 50 percent of patients with early-onset Parkinson's disease harbor mutations in the parkin gene, and a range of mutations in this gene have been shown to cause a form of PD called autosomal recessive juvenile parkinsonism.

As in Parkinson's disease, Alzheimer's patients suffer the loss of neurons, but the losses are more diffuse. They take place in large areas of the brain and are concentrated in the lobes of the brain that control some of the higher intellectual functions. One characteristic of Alzheimer's disease is the accumulation of beta amyloid aggregates, or plaques.

Research now suggests that pathologic changes in the brain occur years before symptoms are evident. For example, amyloid precursor proteins (APP) may show up long before the onset of Alzheimer's. Although APP is necessary for certain cell functions—neuronal trophism, cell adhesion, neuronal migration, neurite outgrowth, synapse formation and plasticity, and cell-to-cell signaling—higher than normal levels of this protein may lead to the development of amyloid plaques over time.

The pathology seen in Alzheimer's patients is connected to



symptoms of late-onset diseases. Mitochondrial dysfunction has been associated with Parkinson's,

Alzheimer's and Huntington's disease, all diseases of degeneration within the brain. All three seem apparently to involve defects in cellular energy production and cellular degeneration, consistent with defective mitochondria.

The parkin gene (also known as PARK2) is also thought to play



Animals are likely to serve as living laboratories for the testing of new antioxidant and gene therapies that reverse or neutralize oxidant damage.

mitochondrial metabolism in brain cells. Researchers at the Oregon Health & Science Institute (OHSI) identified a series of genes responsible for mitochondrial metabolism. By studying a mouse model, OHSI scientists were able to show that the over-expression of certain genes heightened mitochondrial activity, even before amyloid plaques were present in the animals' brains. As the disease progressed, the genes worked even harder, trying to compensate for the damage caused by the plaques. Ultimately, however, the genes couldn't keep up with the progression of the disease.

#### **Mitochondria and heart disease**

Dilated cardiomyopathy is a serious heart condition that is age-related. Often referred to as "enlarged heart," its telltale sign is a thickening of the muscular walls of the heart, particularly the walls of the left ventricle, the chamber that carries the burden of pumping blood into the general circulation. In cardiomyopathy, the ventricle becomes stiff and loses its ability to pump blood effectively, a serious condition known as heart failure. Heart muscle is metabolically very active, making it especially sensitive to mitochondrial abnormalities. A study of patients with cardiomyopathy found that older patients were more likely to have multiple defects in

mitochondrial enzymes, and they were also more likely to have defects in their mitochondrial DNA.

It may be possible, however, to optimize mitochondrial energy production in heart cells. A Johns Hopkins-led research team identified an ion channel on the membranes of mitochondria that, when activated, improves the heart's overall strength. Called mitoKCa, the newly found channel allows potassium ions to flow into the mitochondria and mitigate the effects of calcium, which can cause heart cells to die after a heart attack. The researchers also found that they could stimulate the opening of the mitoKCa channel by administering certain proteins

to rabbit hearts. These potassium channel openers seemed to offer protection during a heart attack, with treated rabbit hearts displaying only half the number of damaged cells as untreated hearts.

### **Mitochondria and diabetes**

The risk of type 2 (late-onset) diabetes increases with age and with obesity. One feature of type 2 diabetes is insulin resistance—the inability of tissues to respond to normal levels of insulin. In some individuals, insulin secretion can be affected as well. Certain mutations in mitochondrial DNA are associated with decreased production of insulin by the pancreas. Further, skeletal muscle uses a great deal of oxygen, and insulin keeps its metabolism under tight control. Abnormalities resulting from mutations in mitochondrial DNA associated with aging are thought to contribute to some instances of insulin resistance in muscle. In fact, it has been proposed that the progressive increase in the incidence of type 2 diabetes with age parallels the “normal” aging pattern, which is associated with increased injury to mitochondrial DNA and decreased energy production.

Work published by scientists from the University of Coimbra in Portugal looked at the effect of

diabetes on mitochondria in the brains and livers of rats. More oxidative damage was seen in the brains of diabetic rats than in control rats. Interestingly, the liver cells of the diabetic rats were less susceptible to oxidative damage, because the rats’ liver cells accumulated higher levels of coenzyme Q and alpha-tocopherol, both of which serve to protect mitochondria against oxidative damage.

### **HOW DO SCIENTISTS STUDY MITOCHONDRIA AND AGING?**

As in so many other areas of clinical and biological research, advances in genomics (the study of genes), proteomics (the study of proteins), and recombinant DNA techniques are increasingly being applied to the study of mitochondria and their role in aging. Scientists are already compiling databases of genes found in mitochondrial DNA, as well as the proteins associated with those genes. MitoProteome is a publicly accessible database that lists all proteins coded for by mitochondrial DNA in heart cells. This database joins MITOP, an earlier attempt at identifying human mitochondrial genes and proteins that contains over 340 unique entries.

Additionally, scientists have developed animal models in which nuclear genes coding for

antioxidant enzymes active in mitochondria have been inactivated. They also developed mice lacking superoxide dismutase. The animals show increased oxidant levels and a vulnerability to illnesses similar to human neurodegenerative diseases. In fact, this animal model was developed in order to study the relationship between oxidants and neurodegenerative diseases. The animals are likely to serve as living laboratories for the testing of new antioxidant and gene therapies that reverse or neutralize oxidant damage.

The study of mitochondrial dysfunction and its relationship to aging is still a relatively young area of investigation in biology. Mitochondria, walled off by their double membrane, present obstacles to genetic and other forms of manipulation. These problems are already being addressed, and it is likely that the DNA and internal machinery of mitochondria will one day be manipulated with ease. Mitochondrial decay is not likely to be stopped anytime soon, but scientists appear confident that the process can be slowed, and along with it, the process of aging and the development of a number of age-related diseases.

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