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## REPORT

### **Are Mutations In Mitochondrial DNA A Cause Of Aging In Humans?**

In the 1960s, nuclear physicists such as Leo Szilard (who helped develop the atomic bomb) and radiation biologists such as Howard Curtis of Brookhaven National Laboratory held the theory that aging is caused by random mutations in nuclear DNA. This theory was popular because of the excitement caused by Watson and Crick's discovery of the structure of DNA, because of the realization that DNA is the blueprint for life, and because radiation produces damaging mutations in DNA.

Subsequent research has shown that DNA repair systems are highly efficient in nuclear DNA and that, as a result, it is difficult to find enough age-related mutations in nuclear DNA to support the theory that such mutations are a major cause of aging.

#### **DENHAM HARMAN'S THEORY OF AGING**

However, another theory of aging proposed in the 1960s by Dr. Denham Harman of the University of Nebraska, which was ignored at the time, may prove to have greater validity. Dr. Harman claimed that the reason the antioxidants he fed to laboratory mice failed to extend maximum lifespan was because they failed to penetrate the mitochondria--the power plants within the cells--where oxygen combines with nutrients to generate the energy required to maintain our life functions.

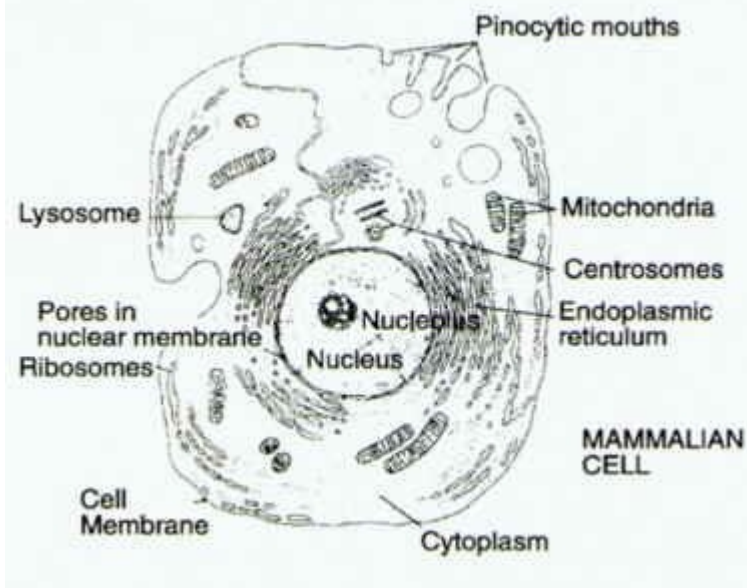
Dr. Harman feels that getting antioxidants into mitochondria is critical because of the vast number of free radical reactions produced in these organelles, which literally explode with the kind of dynamic chain-crackling chemical activity that Harman believes is a major cause of aging.

#### **THE DNA IN MITOCHONDRIA**

Mitochondria are unique among intracellular organelles in mammalian cells because they contain their own DNA, which forms the proteins involved in oxidative phosphorylation--the chemical process by which energy is generated. Mitochondrial DNA (mtDNA) does not bind to histone proteins (as does nuclear DNA), and is replicated rapidly by DNA polymerase gamma without proof reading or an efficient repair system. Since each mitochondrion has two or three copies of its mtDNA, there are several thousand such copies in every cell.

The human mitochondrial genome is very small and essentially encodes only genes involved in energy production. It contains the structural genes for seven proteins of complex I of the respiratory chain, a single subunit protein of complex III, three subunits of complex IV and two subunits of ATP synthase (complex V). The rest of the mtDNA codes for the transfer RNAs involved in mitochondrial protein synthesis. Given the small size of the mitochondrial genome, a mutation of human mtDNA is almost certain to involve a functionally important region of the genome.

It is now generally accepted that mtDNA is continuously exposed to heavy free radical activity including semiquinone radicals and reactive oxygen species. It also is known that the rate of mutation in mtDNA is much higher than in nuclear nDNA, that mtDNA mutations accumulate during the entire life of the individual, and that the rate of mtDNA mutations increases with advancing age.



### MITOCHONDRIAL DNA MUTATIONS AND THE AGING PROCESS

Recent findings about the age related mutation rate in mtDNA has led several scientists to elaborate on Dr. Harman's theory of aging. One of them is biochemist Anthony W. Linnane of Monash University in Australia who has proposed that:

"Random mutations occur in the pool of mtDNA molecules present in a cell throughout life. In addition, segregation of mtDNA molecules from this pool results in tissue bioenergy mosaics. Progressive depletion of energy production by mitochondrial oxidative phosphorylation is associated with the gradual decline of the physiological and biochemical performance of organs, significantly contributing to the aging process and ultimately to death. "

A nother theorist, who's studied the role of mtDNA mutations in the diseases of energy metabolism, is molecular geneticist Douglas C. Wallace of Emory University School of Medicine in Atlanta, who has focused his attention on oxidative phosphorylation (OXPHOS), the primary energy-generating pathway in mitochondria. Dr. Wallace proposes that:

"An individual's inherited OXPHOS genotype interacts with lifelong acquired somatic mtDNA mutations to define the energetic capacity of tissues and organs. The inherited genotype defines the initial energetic capability of the individual, while the accumulated somatic mutations erode this capacity throughout life until the energy output of the cells falls below the minimum energetic threshold necessary for normal tissue and organ function. "....Thus, aging and the common degenerative diseases are envisioned to result from the same process, energetic decline. The nature of the symptoms and the age of onset are defined by the inherited array of energy gene alleles, but the onset of symptoms and subsequent progression of the disease are determined by the accumulation of somatic mutations. "

### TISSUE BIOENERGY MOSAICS

These versions of the role of mtDNA in aging both postulate that the major cause of the mutations in mtDNA is the intense degree of free radical activity generated during energy production within the mitochondria. As the mutations accumulate, the amount of energy produced within the cell declines until, in some cases, the cell dies. This process, in turn, leads to the deterioration of organs, organ systems, and the entire organism.

Dr. Linnane has focused on the development of Tissue Bioenergy Mosaics as what, he believes, may be a critical step in the aging process. As he explains it:

"The random accumulation of mtDNA mutations with age will result in an array of cells within given tissues or organs, which will produce a tissue bioenergy mosaic...with cells ranging from fully bioenergetically competent to severely impaired. These cells, depending upon the severity of

the bioenergetic impairment, will continue to function adequately or, if they fall below a critical minimum bioenergetic threshold, will cease to function and die. The bioenergetic threshold will vary from one tissue or organ to another. Cell survival will also depend upon the extent of the energy demand placed on it any one time. Thus, metabolic demand accompanying severe exercise, emotional stress, infection or other physiological traumas may generate energy demands beyond the capacity of the cell, with catastrophic consequences for that cell. "

T issue Bioenergy Mosaics are detectable by staining for cytochrome c oxidase and other respiratory enzymes to determine the bioenergetic activity within cells. Evidence of the existence of bioenergy mosaics was revealed in a study of human hearts from subjects of widely differing ages. In a survey of 140 cardiac specimens, it was found that heart cells from young subjects were evenly and intensely stained, whereas heart cells from older people were unevenly stained--with some cells weakly stained and others completely unstained. It was found that the incidence of poorly stained and unstained heart cells increased with advancing age.

### **WHAT CELLS ARE MOST SUSCEPTIBLE TO BIOENERGY DEPLETION?**

Different individuals age at different rates, and the tissues within individuals age at different rates. The cells that are most susceptible to mitochondrial bioenergy depletion with advancing age are brain, skeletal muscle, and cardiac muscle cells all of which have an exceptionally high need for oxygen and, as a result, are highly dependent upon mitochondrial oxidative phosphorylation as a source of adenosine triphosphate (ATP) for their energy needs. (Other tissues, which contain relatively few mitochondria, depend to a greater extent on glycolysis as a source of ATP for energy production).

### **EFFECT OF DEPLETING MITOCHONDRIAL ATP**

ATP is the energy generating chemical within the mitochondria. It is needed for the synthesis of macromolecules essential for specific physiological functions within cells. The progressive accumulation of damage to the mitochondrial genome during a person's lifetime causes a decline in the entire chain of biochemical events involved in the production of energy which, in turn, depletes the vitality of the organism.

Scientists have discovered that there are more than ten different kinds of age related mutational damage in mtDNA in the tissues of aged individuals, none of whom were suffering from any serious diseases. This suggests that this type of damage occurs in normally aging tissue and that it may be one of the causes of the aging process.

### **AGE ASSOCIATED MITOCHONDRIAL DAMAGE IN HUMAN HEARTS**

A recent study by scientists at the University of Nagoya in Japan, the results of which were published in the journal *Molecular and Cellular Biochemistry*, showed an exponential increase in the incidence of mutational mtDNA in human hearts with advancing age, with a marked acceleration of these mutations in the hearts of subjects over the age of 80.

The Japanese scientists concluded that mutations in mtDNA are involved in the decline in cardiac function with advancing age, that they play an important role in heart failure in aging persons, and that cardiac drugs such as digitalis, catecholamines and phosphodiesterase inhibitors, which are effective in improving cardiac function in young people, cannot be expected to work in the elderly. Their final conclusion is that: "Protection of mtDNA against oxidative damage is of primary importance in preventing the age-associated decline in cardiac performance. "

### **AGE ASSOCIATED MITOCHONDRIAL DAMAGE IN HUMAN BRAINS**

Scientists at the Massachusetts Institute Of Technology (MIT) have published findings (in *NeuroReport*) that there are "easily quantifiable levels" of a specific damaging mutation (the 4977 kb deletion) in mtDNA in non-dividing brain cells (neurons) in individuals more than 60 years old, but not in younger individuals or fetuses. They found no greater rate of mutations in the brains of individuals with Alzheimer's disease than in controls. The MIT scientists concluded that:

"Our findings and those of others underscore the similarity in a basic biochemical process of normal brain aging and Alzheimer's disease the down regulation of ATP production in neurons and other non-dividing cells; these findings by us and others provide a rational explanation for the late onset of these conditions. "

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