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Mitochondria DNA aging and repair

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Mitochondria are the power plant of the cell; it is here that the cell produces ATP to drive cellular processes. Mitochondria contain the electron transport chain which is a significant source of reactive oxygen species that damages mitochondrial DNA. As the mitochondria regenerates, the mitochondrial DNA is continuously exposed to damaging agents. The older the cells are, the more reactive oxygen species are present in the mitochondrial DNA. Through the study of damage causing agents affecting mitochondrial DNA, researchers have concluded that mitochondrial DNA contains all the enzymes necessary for base excision repair. This review focuses on the experimental evidences that support mitochondrial dysfunction as a result of aging, as well as current knowledge of mitochondrial DNA damage and repair.

Introduction

The electron transport chain lies within the mitochondrion to create ATP to drive cellular processes. 90% of the oxygen used by the electron transport chain is consumed by the mitochondria for respiration. However, a small percentage is converted to superoxide anion radicals that form hydrogen peroxide that decompose to noxious hydroxyl radicals throughout the cell. This process harms essential macromolecules, including the mtDNA (N. Druzhyna et al). Mitochondria are necessary for the supply of ATP, therefore the continuous production of reactive oxygen species (ROS) is unavoidable. Research has shown that continuous damage to mitochondria lead to mutations that accumulate with age (B. Mandavilli et al).

Initial observations showed that mitochondria lack the ability to repair their DNA. It was previously believed that mtDNA that have undergone a substantial amount of damage will fall off and be replaced by newly generated mtDNA, that has be copied from undamaged genomes (N. Druzhyna et al). New research studies show the long term effects damage has on mitochondria with age, and the mechanisms mitochondria contains that allow for self-repair. This review will focus on the experimental evidences that support mitochondrial dysfunction in aging, as well as the current knowledge of mtDNA damage and repair.

Mitochondrial Damage

Because mtDNA is in close proximity with the electron transport chain, it is prone to oxidative damage. Oxidative damage may be in the form of base modifications, abasic sites and various other types of lesions (N. Druzhyna et al). The free-radical and non-radical oxidants generated inside the cell from the electron transport chain are damaging to mtDNA bases, an example of this is 8-oxo-2'-deoxyguanosine. This mutation is more susceptible to reactive oxygen bases than the native base (D. Cline et al). It is found in the mtDNA of Alzheimer's patient's brains and elderly adults. Reactive oxygen species are also especially damaging to abasic sites. Because the brain in a mitochondrian rich site, it contains the greatest amount of abasic sites. Recent studies have found that these sites are predominant forms of mtDNA damage caused by hydrogen peroxide (D. Cline et al).

There are multiple theories that pertain to endogenous mtDNA damage. However, there is also damage done to the mitochondrial DNA caused by environmentally induced factors. Chemicals in the environment, metabolites of dietary components, drugs in clinical therapies, and radiation from sunlight or medical procedures are external sources of DNA damage that will not be discussed in this review.

Mitochondrial Aging

The negative effects reactive oxygen species (ROS) have on mtDNA leads to mutations in mtDNA that cause

human disease and aging. Human mtDNA encodes 13 polypeptides of the electron transport system, 2rRNAs and 22 tRNAs (B. Mandavilli et al). Therefore, mutation of this gene will lead to a loss of one of the essential proteins needed to generate ATP, and decreased energy production. Results from recent studies show that mtDNA mutations accumulate in both aged humans and Alzheimer's patients, which further supports the hypothesis that the accumulation of mutations in mtDNA plays an important role in aging.

Studies have shown that mtDNA accumulates oxidative damage in an age-dependent manner in skeletal muscle, cardiac muscle, the brain and the liver (N. Druzhyna et al). This also depends on the life span on the animal, for example, slower maturing animals show less amounts of the 8-oxo-2'-deoxyguanosine in mtDNA than rapidly maturing ones. This large amount of 8-oxo-2'-deoxyguanosine will lead to mutations, including deletions, duplications, and point mutations (D. Cline et al). The most common, closely studied mutation associated with mtDNA mutations, is the 4977-bp, also called the "common deletion". This mutation normally affects those with mitochondrial disease and begins occurring in patients' mid-thirties and accumulates with age. However results show that the proportions of mutated genes hardly exceeds 1%, to explain how such a small percentage of mutations can be functionally relevant to aging is still unknown (B. Mandavilli et al).

Mitochondrial Repair

Mitochondria possess several mechanisms for genetic maintenance including base excision repair (BER). BER is responsible for the removal of DNA bases altered by oxidation, alkylation, or deamination, and the repair of abasic sites in both nucleic DNA and mtDNA (B. Mandavilli et al.). The graph below shows a comparison of base excision repair genes between mice and humans.

Gene identified in various species involved in mitochondrial base excision repair

Gene		
	Mouse Genome	Human Genome
APE	X	X
OGGI	X	X
OGG2		X
DNA Ligase III	X	X
Mut Y		X

The repair of 8-oxyguanine is a common example of base excision repair. It is initiated by the attack of OGGI resulting in a damaged base. An OGGI-associated lyase activity leads to a cleavage at the 3' end. AP endonuclease then breaks the phosphodiester bond 5' leading to one base gap. This gap is filled by DNA poly y, and the newly created nucleotide repair patch is sealed by DNA ligase III.

Discussion

The mitochondrial genome is susceptible to more reactive oxygen species than nuclear DNA because of its involvement in the electron transport system. Mitochondria deal with damage to the mtDNA caused by reactive oxygen species through DNA repair. Based on the previous example mitochondria have the ability to repair damages through base excision repair, a strategy also used by nuclear DNA. Understanding the mtDNA ability to repair DNA is one step closer to understanding the process of human aging and disease progression.

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