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Introduction to the Evolutionary Metabolic Medicine Based on Mitochondrial Dysfunction

Mini Review

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Abstract

Mitochondrion is a microorganism exists in all eukaryotic cell. All the metabolic activities in eukaryotic cells are regulated in mitochondria. Nearly 97 percent of human and primate diseases are related to the dysfunction and inheritances related to the mitochondria such as Cancer, Diabetes, Multiple Sclerosis, Alzheimer's and Parkinson's Disease. Even diseases caused by viruses, bacteria and many parasites changes the metabolic state of the human tissue cells such as AIDS, Ebola, Hepatitis, Herpes and etc. The main causes of these diseases is the increasing in the inflammation and the amount of Reactive Oxygen Species or Reactive Nitrogen Species in human cells. This mini review study introduces a new branch of medicine which is related to the mitochondrial dysfunction and metabolic changes in eukaryotic cells.

Keywords: *Evolutionary Metabolic Medicine; Mitochondrial Dysfunction; Mitochondrion*

Introduction

Evolution of the Mitochondria

The endosymbiotic hypothesis for the origin of mitochondria (and chloroplasts) suggests that mitochondria are descended from specialized bacteria (probably purple non-sulfur bacteria) that somehow survived endocytosis by another species of prokaryote or some other cell type, and became incorporated into the cytoplasm [12].

Eukaryotic Cell Respiration

In eukaryotic cells, the respiration process goes through aerobic and anaerobic. The aerobic respiration mainly happens in mitochondrion which requires oxygen for creating Adenosine 3-Phosphate (ATP) [1]. Despite consuming protein, carbohydrates and fats as reactants, it is the preferred method of pyruvate breakdown in glycolysis and requires that pyruvate enter the mitochondria in order to be fully oxidized by the Krebs cycle. The products of this process are carbon dioxide and water, but the energy transferred is used to break bonds in ADP as the third phosphate group is added to form ATP (adenosine triphosphate), by substrate-level phosphorylation, NADH and 2FADH2 [Baily, Regina, Cellular Respiration].

The simplified equation is mentioned below:

The potential of NADH and FADH2 is converted to more ATP through an electron transport chain with oxygen which is the terminal electron acceptor. Most of the ATP produced by aerobic cellular respiration is produced by oxidative phosphorylation [3]. This works by the energy released in the consumption of pyruvate to create a chemiosmosis potential by pumping protons across the cell

membrane [2]. This potential is then used to drive ATP synthase and produce ATP from ADP and a phosphate group. By going through the respiration process formula, 38 ATP molecules can be made per oxidized glucose molecule during cellular respiration. Which is, 2 from glycolysis, 2 from the Krebs cycle, and about 34 from the electron transport system. But, this maximum yield is never reached since the losses due to leaky membranes as well as the cost of moving pyruvate and ADP into the mitochondrial matrix, and current estimates range around 29 to 30 ATP per glucose [3].

Aerobic metabolism is almost 15 times more efficient than anaerobic metabolism which yields 2 molecules ATP per 1 molecule glucose [4]. Glycolysis is a metabolic pathway that happens in the cytosol of cells in all living organisms. This pathway can function with or without the presence of oxygen. In humans, aerobic conditions produce pyruvate and anaerobic conditions produce Lactic acid. In aerobic conditions, the process converts one molecule of glucose into two molecules of pyruvic acid, generating energy in the form of two molecules of ATP. Four molecules of ATP per glucose are actually produced; however, two are consumed as part of the preparatory phase [5]. The initial phosphorylation of glucose is required to increase the reactivity in order for the molecule to be cleaved into two pyruvate molecules by the enzyme aldolase. During the pay-off phase of glycolysis, four phosphate groups are transferred to ADP by substrate-level phosphorylation to make four ATP, and two NADH are produced when the pyruvate are oxidized [6].

Glucose + 2 NAD+ + 2 Pi + 2 ADP → 2 pyruvates + 2 NADH + 2 ATP + 2 H+ + 2 H_2O + heat

Starting with glucose, 1 ATP is used to donate a phosphate to glucose to produce glucose 6phosphate. Glycogen can be converted into glucose 6-phosphate as well with the help of glycogen phosphorylase. During energy metabolism, glucose 6-phosphate becomes fructose 6-phosphate. An additional ATP is used to phosphorylate fructose 6-phosphate into fructose 1,6-disphosphate by the help of phosphofructokinase [7]. Fructose 1,6-diphosphate then splits into two phosphorylated molecules with three carbon chains which later degrades into pyruvate. Glycolysis can be translated as sugar splitting [8].

Oxidative phosphorylation

In eukaryotes, oxidative phosphorylation occurs in the mitochondrial cristae. It comprises the electron transport chain that establishes a proton gradient (chemiosmosis potential) across the boundary of inner membrane by oxidizing the NADH produced from the Krebs cycle. ATP is synthesized by the ATP synthase enzyme when the chemiosmosis gradient is used to drive the phosphorylation of ADP. The electrons are finally transferred to exogenous oxygen and, with the addition of two protons, water is formed [9].

Reactive oxygen species

Reactive oxygen species (ROS) are chemically reactive chemicals containing oxygen. Examples include: peroxides, superoxide, hydroxyl radical, and singlet oxygen [10].

In biology, ROS are formed as a natural by-product of the normal metabolism of oxygen, and have important roles in cell signaling and homeostasis [11]. However; during times of environmental stress that means, UV or heat exposure, ROS levels can increase highly [12]. This may result in significant damage to cell structures. Cumulatively, this is known as oxidative stress. ROS are also generated by exogenous sources such as ionizing radiation [13].

Endogenous ROS

ROS are produced intracellularly through several mechanisms and depending on the cell and tissue types, the major sources being the professional producers of ROS: NADPH oxidase (NOX) complexes in cell membranes, mitochondria, peroxisomes, and endoplasmic reticulum [14]. Mitochondria convert energy into a usable form for the cell, adenosine triphosphate (ATP) [15]. The process in which ATP is produced, called oxidative phosphorylation, includes the transport of protons across the inner mitochondrial membrane by the means of the electron transport chain. In the electron transport chain, electrons are passed through a series of proteins by means of oxidation/reduction reactions, with each acceptor protein along the chain having a greater reduction potential than the previous. The last destina-

tion for an electron through this chain is an oxygen molecule. In normal conditions, the oxygen is reduced to produce water, however; in around 0.1% to 2% of electrons passing through the chain, this number derives from studies in isolated mitochondria, though the exact rate in live organisms is yet to be fully agreed on, oxygen is instead prematurely and incompletely reduced to give the superoxide radical, most well documented for Complex I and Complex III [16,18]. Superoxide is not particularly reactive by itself, but can inactivate specific enzymes or initiate lipid peroxidation in its protonated form, hydro-peroxyl HO•2. The pK_a of hydro-peroxyl is 4.8. Therefore; at physiological pH, the majority will exist as superoxide anion [17].

If too much damage is present in mitochondria, a cell goes into apoptosis state or programmed cell death. Bcl-2 proteins are layered on the surface of the mitochondria, detect damage, and activate a class of proteins called Bax, which punch holes in the mitochondrial membrane, causing cytochrome C to leak out [19]. This cytochrome C binds into Apaf-1, or apoptotic protease activating factor-1, which is free-floating in the cell cytoplasm. Using energy from the ATPs in the mitochondrion, the Apaf-1 and cytochrome C bind together to form apoptosomes. The apoptosomes bind into and activate caspase-9, another free-floating protein. The caspase-9 then cleaves the proteins of the mitochondrial membrane, causing it to break down and start a chain reaction of protein denaturation and at last, phagocytosis of the cell [20].

Another type of reactive oxygen species is singlet oxygen, which is produced as a byproduct of photosynthesis in plants for instance. In the presence light and oxygen, photosensitizers like chlorophyll, may convert triplet oxygen to singlet oxygen [4]:

Singlet oxygen is highly reactive, specifically with organic compounds that contain double bonds. The resulting damage caused by singlet oxygen reduces the photosynthetic efficiency of chloroplasts. In plants exposed to excess light, the increased production of singlet oxygen can result in cell death [8]. Several substances like carotenoids and tocopherols, contained in chloroplasts quench singlet oxygen and protect against its toxic behaviors. In addition to direct toxicity, singlet oxygen acts as a signaling molecule [11]. Oxidized products of beta-carotene arising from the presence of singlet oxygen act as second messengers that can either protect against singlet oxygen induced toxicity or cause programmed cell death. Levels of Jasmonate play a key role in the decision between cell acclimation or cell death in response to elevated levels of this reactive oxygen species [20].

Oxidative damage

In aerobic organisms, the energy needed to fuel the biological functions is produced in the mitochondria by means of the electron transport chain. In addition to energy, reactive oxygen species with the potential to cause cellular damage are produced. ROS can damage lipid, DNA, RNA, and proteins, which theoretically, contributes to the physiology of aging. ROS are produced as a normal byproduct of cellular metabolism. particularly, one main contributor to oxidative damage is hydrogen peroxide (H_2O_2), which is converted from superoxide that leaks from the mitochondria. Catalase and superoxide dismutase ameliorate the damaging effects of hydrogen peroxide and superoxide, by converting these compounds into oxygen and hydrogen peroxide which is later converted to water, resulting in the production of benign molecules [27]. However, this conversion is not 100 percent efficient, and residual peroxides persist in the cell. While ROS are produced as a byproduct of normal cellular functioning, excessive amounts can cause deleterious effects [21].

Memory capabilities decline with age, evident in human degenerative diseases such as Alzheimer's disease, which is accompanied by an accumulation of oxidative damage [26]. Current research studies show that the accumulation of ROS can decrease an organism fitness, since oxidative damage is a contributor to senescence. particularly, the accumulation of oxidative damage may lead to cognitive dysfunction, as concluded in a study, in which, old rats were given mitochondrial metabolites and then given cognitive tests. Outcomes demonstrated that the rats performed better after receiving the metabolites, suggesting that the metabolites reduced oxidative damage and improved mitochondrial functioning [22].

Accumulating oxidative damage can then affect the efficiency of mitochondria and further increase the rate of ROS production [23]. The accumulation of oxidative damage and its implications for aging, depends on the special tissue type where the damage is happening. Additional experimental outcomes suggest that oxidative damage is responsible for age-related decrease in brain functioning. Older gerbils were found to have higher levels of oxidized protein in comparison to younger gerbils [24]. Treatment of old and young mice with a spin trapping compound caused a decline in the level of oxidized proteins in older gerbils, but did not have an effect on younger gerbils. Additionally, older gerbils performed cognitive tasks better during treatment, but ceased functional capacity when treatment was discontinued, caused oxidized protein levels to incline. This led researchers to conclude that oxidation of cellular proteins is mainly important for brain functioning [25].

Causes of Cellular Damage

There are many things that can damage a cell and its mitochondria. This includes oxygen deprivation, nutritional imbalances, physical trauma, toxic chemicals, allergic reactions, radiation, infections, parasites and more. Lack of essential fatty acids directly damages cell membranes because cell membranes are made of these lipids. When the essential fatty acids are missing from the diets, cell have no choice but to substitute inappropriate fat into their structure resulting in type 2 diabetes and cancer. If the cellular damage involves mitochondria, thereby interfering with production of ATP, then this can cause significance damage to the cell because ATP is needed for important cellular processes such as membrane transport, lipogenesis and protein synthesis. With damaged mitochondria, for it is very survival the cell has no choice but to revert to the more primitive system of anaerobic respiration that is the characteristic of the cancer cells. Sometimes the damage is reversible, in which case the cell can be healed. Sometimes, the damage is irreversible, and a way must be found to destroy the cell. Also the causes of harm to the cells must be removed to prevent repeated damage or damage to additional cells. We suggest for the prevention of the mitochondrial damage the one should focus on the nutritional basis in their lives and digest vitamin K2, Coenzyme Q-10, Alpha Lipoic Acid, Acetyl-L-Carnitine for their mitochondrial health. [S. Zaminpira, S. Niknamian, The Prime Cause, Prevention and Treatment of Cancer, 2017, page 268].

Conclusion

From this mini review we have come to the conclusion that the mitochondrial dysfunction disorder is the cause of the most important diseases in the world. Our researches on several diseases which have been mentioned above shows that the mitochondrial dysfunction is the prime cause of these diseases. The inflammation or basically the increase in the amount of ROS and RNS in the cells causes the mitochondrial damages and the specialists should go through the evolutionary aspect of the cell's metabolism and dysfunctions to find the best treatment. Therefore; we introduce a new branch of medical field which focuses on the evolutionary aspects of the mitochondrial metabolism disorders which we call Evolutionary Metabolic Medicine (EMM).

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