MITOCHONDRIAL CARBON STRESS AND OXIDATIVE STRESS: IMPLICATIONS FOR HUMAN HEALTH

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Received on : xx-xx-xxxx
Accepted on : xx-xx-xxxx

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ABSTRACT

A vital component of cellular redox equilibrium, mitochondria also play a crucial role in the synthesis of energy within cells. Disturbances in the metabolism of carbon inside the mitochondria may cause malfunction and oxidative stress, which in turn may contribute to the etiology of a number of human diseases. This is supported by newly emerging research. The interaction of oxidative stress and mitochondrial carbon stress is examined in this review, with particular attention on how these effects affect human health. We go over the processes that underlie oxidative stress caused by mitochondrial carbon stress and its consequences for various physiological processes such as aging, cancer, metabolic disorders, and neurodegenerative illnesses. We also highlight prospective therapeutic approaches that focus on redox balance and mitochondrial function in order to lessen the harmful effects of oxidative stress and mitochondrial carbon stress on human health.

KEYWORDS: Mitochondria, Carbon metabolism, Oxidative stress, Human health, Disease.

INTRODUCTION

Oxidative stress is the state of the body linked to an increased production of reactive oxygen species (ROS). It suggests an imbalance between the defense antioxidant systems and the generation and build-up of ROS (1). Low-level ROS are physiologically important in intracellular signaling pathways (2), but when they are created in excess, they become one of the primary agents of tissue and cell damage. The latter comes from direct damage to biological structures such nucleic acids, lipids, and proteins (1, 3).

While exogenous oxidative stress can be brought on by external stressors such ionizing or X-ray radiation, UV, pollution, cigarette smoke, heavy metals, and some medications, endogenous ROS are produced as byproducts of oxygen metabolism (4). Chronic inflammatory responses in the organism worsen oxidative stress and increase ROS production (5). The superoxide anion (O_2^-) and the hydroxyl radical (OH), which are extremely unstable species with unpaired electrons and capable of starting oxidation and producing further ROS such as hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl), are the most reactive free radicals (4).

The mitochondria are the primary source of free radicals within the cell. Apart from their principal function of ATP generation, mitochondria also aid in the manufacture of lipids, hemes, purines, amino acids, and steroidogenesis (6, 7). They also govern cell division, thermogenesis, and programmed cell death in addition to maintaining intracellular Ca^{2+} homeostasis (6, 8). Reactive oxygen species (ROS) are produced and stored by mitochondria during the strong oxidative metabolism. Approximately 1-2 percent of the molecular oxygen that cells take up during normal respiration is transformed to ROS. Actually, most free radicals and superoxide anion are byproducts of respiration in the mitochondria, produced during electron flow in complexes I, II, and III of the mitochondrial electron transfer chain (9, 10).

It has been calculated that the concentration of O_2^- in the mitochondrial matrix is five to ten times higher than that of the cytosol or nucleus (11). Hypoxia, nutritional availability, cytokines, or modifications in mitochondrial membrane potential are stimuli that cause oxidative stress in mitochondria (6,12). When reactive oxygen species (ROS) are produced in excess or when mitochondrial antioxidant defenses are compromised, damage to biomolecules (DNA, proteins, and lipids) by ROS can impair mitochondrial function and trigger cell death by releasing pro-

apoptotic proteins from the inner membrane space of the mitochondria. Therefore, a wide range of illnesses have been linked to mitochondrial oxidative stress.

Mitochondrial Carbon Stress and Oxidative Stress

Traits of Carbon Metabolism Disturbances

To preserve cellular energy homeostasis and redox equilibrium, mitochondrial carbon metabolism is strictly controlled. Mitochondrial activity can be disrupted and carbon stress in the mitochondria can result from dysregulation of carbon metabolism, including changes in glucose and lipid metabolism. For example, an excessive intake of nutrients, such as those found in diets heavy in fat or sugar, might exceed the capacity of the mitochondria, leading to the build-up of metabolites that damage the mitochondria (13).

Consequences for Oxidative Stress

Oxidative stress can be brought on by mitochondrial carbon stress in a number of ways. Excess ROS are produced during mitochondrial respiration, especially when there are too many nutrients present or when there is mitochondrial malfunction. This is one method. ROS can harm lipids, proteins, and DNA, which are components of the mitochondria, worsening mitochondrial dysfunction and compromising cellular function. The cellular NAD+/NADH ratio can also be changed by disruptions in carbon metabolism, which can impact redox-sensitive enzyme performance and exacerbate oxidative stress (14-15).

Because of their shared functions in cellular metabolism and equilibrium, oxidative stress and mitochondrial carbon stress are related. The synthesis of energy, biosynthesis, and redox balance are all aspects of cellular metabolism that are primarily controlled by mitochondria. Oxidative stress can arise from an imbalance in cellular redox status caused by dysregulation of mitochondrial carbon metabolism. On the other hand, oxidative stress has the potential to worsen mitochondrial dysfunction even further, resulting in a vicious cycle of damage and malfunction in cells.

Mitochondrial Dysfunction: Changes in nutritional availability or metabolic flux, for example, might cause imbalances in the way that the mitochondria metabolize carbon. Because of this malfunction, the electron transport chain is disrupted, which results in electron leakage and the production of reactive oxygen species (ROS) as byproducts.

Generation of ROS: One of the main places where cells produce ROS is the mitochondria. Excessive reactive oxygen species (ROS), such as superoxide anion (O2−) and hydrogen peroxide (H2O2), are produced by dysfunctional mitochondria and are linked to oxidative stress.

Oxidative Damage: When mitochondrial malfunction results in the production of reactive oxygen species (ROS), it can harm proteins, lipids, and DNA, which aggravates cellular stress and further impairs mitochondrial performance.

Effects on the Cellular Systems:

Energy Metabolism: By compromising oxidative phosphorylation, mitochondrial carbon stress impairs energy metabolism. This results in a reduction in ATP synthesis and the loss of cellular energy.
Redox Balance: By overpowering antioxidant defense systems, oxidative stress upsets the redox balance of cells, causing biomolecule oxidation and cellular damage.

Cellular Signaling: Cell destiny and function can be affected by modulating cellular signaling pathways involved in apoptosis, inflammation, and cell proliferation. This can be achieved by both mitochondrial carbon stress and oxidative stress (16). Carbon stress in the mitochondria is caused by: Numerous things, including as nutritional imbalances, environmental pollutants, genetic abnormalities, and metabolic dysregulation, can lead to mitochondrial carbon stress.

Metabolic Dysregulation: Impaired nutrition uptake and energy generation can result from malfunctioning mitochondrial carbon metabolism-related enzymes or pathways, which can exacerbate mitochondrial carbon stress.

Carbon stress can be made worse by diseases like diabetes, obesity, or metabolic syndrome, which is characterized by dysregulated lipid and glucose metabolism. These conditions can also impair mitochondrial function (17) .

Imbalances in the Nutrient Supply: The carbon metabolism of the mitochondria can be hampered by deficiencies in the nutrients, such as glucose, fatty acids, amino acids, vitamins, and minerals, that are necessary for mitochondrial function. Overconsumption of specific nutrients, such as diets heavy in fat or carbs, can cause carbon stress by overloading the mitochondria (18) .

Environmental Toxins: Exposure to industrial chemicals, pesticides, heavy metals, and air pollutants can cause oxidative stress, which can then lead to mitochondrial carbon stress. These toxins can also disrupt mitochondrial function. Toxins from the environment can interfere with mitochondrial biogenesis and dynamics, damage the integrity of the mitochondrial membrane, and alter the activity of the electron transport chain in the mitochondria (19).

Genetic Mutations: Genes encoding proteins or mitochondrial enzymes involved in carbon metabolism can be mutated either inheritedly or acquiredly, which can impair mitochondrial function and increase the risk of carbon stress. Mutations in nuclear DNA, mitochondrial DNA, or epigenetic modifications can affect substrate usage, metabolic control, or mitochondrial oxidative phosphorylation (20). These elements may work alone or in concert to cause mitochondrial carbon stress, which can result in oxidative damage, cellular malfunction, and the emergence of different illnesses. To lessen the detrimental consequences of mitochondrial carbon stress on cellular health and organismal physiology, preventive and therapeutic measures aimed at comprehending the underlying mechanisms and risk factors linked to this phenomenon are essential.

Mechanisms for reducing carbon stress in mitochondria: In order to mitigate mitochondrial carbon stress, one must activate cellular pathways that decrease metabolic load, promote mitochondrial function, and lessen oxidative stress. The following are a few strategies used by organisms to combat an excessive carbon load inside mitochondria.

Pathways for Mitochondrial Quality Control: Mitophagy: The process of selectively breaking down malfunctioning or damaged mitochondria by autophagy aids in the preservation of mitochondrial quality and the removal of carbon stressors. Numerous factors, such as PINK1/Parkin signaling and mitophagy receptor proteins like BNIP3 and FUNDC1, govern mitophagy.

Mitochondrial Biogenesis: The process of stimulating the creation of new mitochondria increases the cellular ability to produce energy and lessens the load on already-existing mitochondria. Important modulators of mitochondrial biogenesis are PGC-1α and NRF1, transcriptional coactivators.

Pathways of Metabolic Adaptation:

Activation of AMPK: The enzyme known as AMP-activated protein kinase, or AMPK, detects the level of energy within cells and initiates processes related to energy synthesis and metabolic adaptability. In order to reduce carbon stress, AMPK activation increases fatty acid oxidation, inhibits energy-consuming activities, and stimulates mitochondrial biogenesis.

Sirtuin Activation: Sirtuins, in particular SIRT1 and SIRT3, control metabolism, oxidative stress response, and mitochondrial function. By enhancing antioxidant defenses, improving mitochondrial function, and promoting mitochondrial biogenesis, sirtuin activation helps to mitigate the effects of carbon stress.

Redox Signaling Pathways:

Nrf2 Pathway: The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) controls the expression of genes involved in detoxification and antioxidant defense. The Nrf2 pathway is activated, which reduces carbon stress by scavenging reactive oxygen species (ROS), strengthening cellular antioxidant defenses, and guarding against damage brought on by oxidative stress.

Transcription Factors for FOXO: The transcription factors known as forkhead box O (FOXO) control genes related to metabolism, lifespan, and cellular stress response. By enhancing antioxidant defenses, modulating metabolic pathways, and promoting mitochondrial biogenesis, the activation of FOXO factors helps to mitigate the effects of carbon stress.

Pathways for Sensing Nutrients:

mTOR Inhibition: A nutrient-sensitive kinase that controls cell division, metabolism, and autophagy is known as the mechanistic target of rapamycin, or mTOR. By promoting autophagy induction, mitochondrial quality control, and metabolic adaptability, inhibition of mTOR signaling helps to reduce carbon stress.

GCN2 Activation: General control nonderepressible 2 (GCN2) kinase senses amino acid availability and regulates cellular responses to nutrient stress. GCN2 activation promotes autophagy, enhances mitochondrial function, and maintains cellular homeostasis under conditions of carbon stress.

Growth Factor and Hormonal Signaling: Insulin/IGF-1 Signaling: Growth, stress reactions, metabolism, and insulin-like growth factor 1 (IGF-1) signaling pathways are all regulated. Insulin/IGF-1 signaling modulation affects metabolic adaptability, mitochondrial function, and cellular resistance to carbon stress. (21-23) By enhancing cellular stress resistance, restoring mitochondrial function, and lessening the damaging effects of mitochondrial carbon stress on cell health and organismal physiology, activation of these pathways can aid.

Effect on the Health of Humans

Mitochondrial carbon stress can have a major negative impact on cell health and play a role in the onset and progression of a number of illnesses, such as metabolic syndrome and neurodegenerative diseases.

Reduced Energy Production: The main organelles in cells that produce energy through oxidative phosphorylation are the mitochondria. When mitochondrial metabolism is disturbed by carbon

stress, cellular energy is depleted and ATP generation is reduced. Deficits in energy can lead to tissue malfunction and impair cellular processes, especially in organs with high energy requirements including the heart, brain, and muscles (24).

Damage to Cells and Oxidative Stress:

Reactive oxygen species (ROS) are produced in greater quantities when mitochondrial carbon metabolism is dysregulated, as this leads to the buildup of metabolic intermediates and electron leakage from the electron transport chain. Overproduction of ROS damages proteins, lipids, and DNA by overpowering the antioxidant defenses of the cell. This process is known as oxidative stress. Oxidative damage has a role in the pathophysiology of many diseases by inducing cellular malfunction, inflammation, and apoptosis (25).

Cancer

Cancer is characterized by altered metabolism, with tumor cells displaying altered mitochondrial metabolism and increased glycolysis to facilitate their fast growth. The formation and progression of cancer are significantly impacted by mitochondrial dysfunction and oxidative stress, which affect the survival, proliferation, and metastasis of tumor cells. Therapy approaches for cancer treatment that focuses on redox signaling networks and mitochondrial metabolism may be promising.

Neurodegenerative Disorders:

The etiology of neurodegenerative illnesses, including amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease, is linked to mitochondrial dysfunction and oxidative stress. Neurodegeneration progresses due to a combination of neuroinflammation, loss of synapses, and accumulation of damaged mitochondria and poor energy metabolism (26). Free radicals harm mitochondria in Alzheimer's disease, which may lead to a buildup of amyloid β. Parkinson's disease is characterized by damage to dopamine-producing neurons' mitochondria brought on by oxidative stress. Oxidative stress and mitochondrial damage are also present in multiple sclerosis and ALS. The pathogenesis of schizophrenia is linked to oxidative stress, and patients with the disorder have lower levels of antioxidants. Research points to intricate processes including neuroinflammation, mitochondrial bioenergetic disturbance, and redox dysregulation.

Neurodevelopmental Disorders: Prenatal exposure to toxins during oxidative stress has been related to autism. Inflammatory mechanisms that cause oxidative stress and mitochondrial damage, which exacerbates cellular damage, lead to impaired brain development. There is potential for lowering autistic behaviors using antioxidant therapy.

Kidney and Lung Diseases: Oxidative stress and inflammation in the mitochondria are factors in chronic illnesses such as COPD and CKD. ROS aggravate airway inflammation and cellular damage in COPD, but they also contribute to kidney injury and inflammation in CKD.

Cardiovascular Diseases (CVDs): ROS-induced endothelial dysfunction and inflammation exacerbate atherosclerosis and heart failure. In CVD patients, oxidative stress markers are increased, which contributes to the pathophysiology and advancement of the disease (27).

Metabolic syndrome: which includes obesity, insulin resistance, dyslipidemia, and hypertension, is primarily caused by dysregulated mitochondrial metabolism and oxidative stress. Mitochondrial failure in adipose tissue, liver, and skeletal muscle inhibits food metabolism, resulting in insulin resistance and dyslipidemia. Excessive ROS production causes inflammation, adipocyte malfunction, and endothelial dysfunction, which exacerbates metabolic problems (28).

Obesity, type 2 diabetes, and nonalcoholic fatty liver disease are all associated with dysregulated glucose and lipid metabolism, as well as mitochondrial dysfunction and oxidative stress. Mitochondrial carbon stress-induced oxidative damage causes insulin resistance, inflammation, and organ malfunction, indicating a relationship between metabolic diseases and mitochondrial dysfunction. Autoimmune diseases, such as type 1 diabetes and multiple sclerosis, are influenced by reactive oxygen species. Oxidative stress and inflammation cause tissue damage and disease progression (27).

Aging

Mitochondrial malfunction and oxidative stress are typical signs of aging. The accumulation of mitochondrial DNA mutations, poor mitochondrial quality control, and dysregulated redox signaling all contribute to age-related declines in cellular performance and tissue homeostasis. Mitochondrial carbon stress-induced oxidative damage may hasten the aging process and increase vulnerability to age-related illnesses.

Enhanced oxidative stress is caused by increased reactive oxygen species, overpowering antioxidant defences, mtDNA damage, and mitochondrial malfunction. This can then result in inflammation, apoptosis, damage to cells and biomolecules, and other processes that lead to a variety of diseases. Showed in figure below (26).

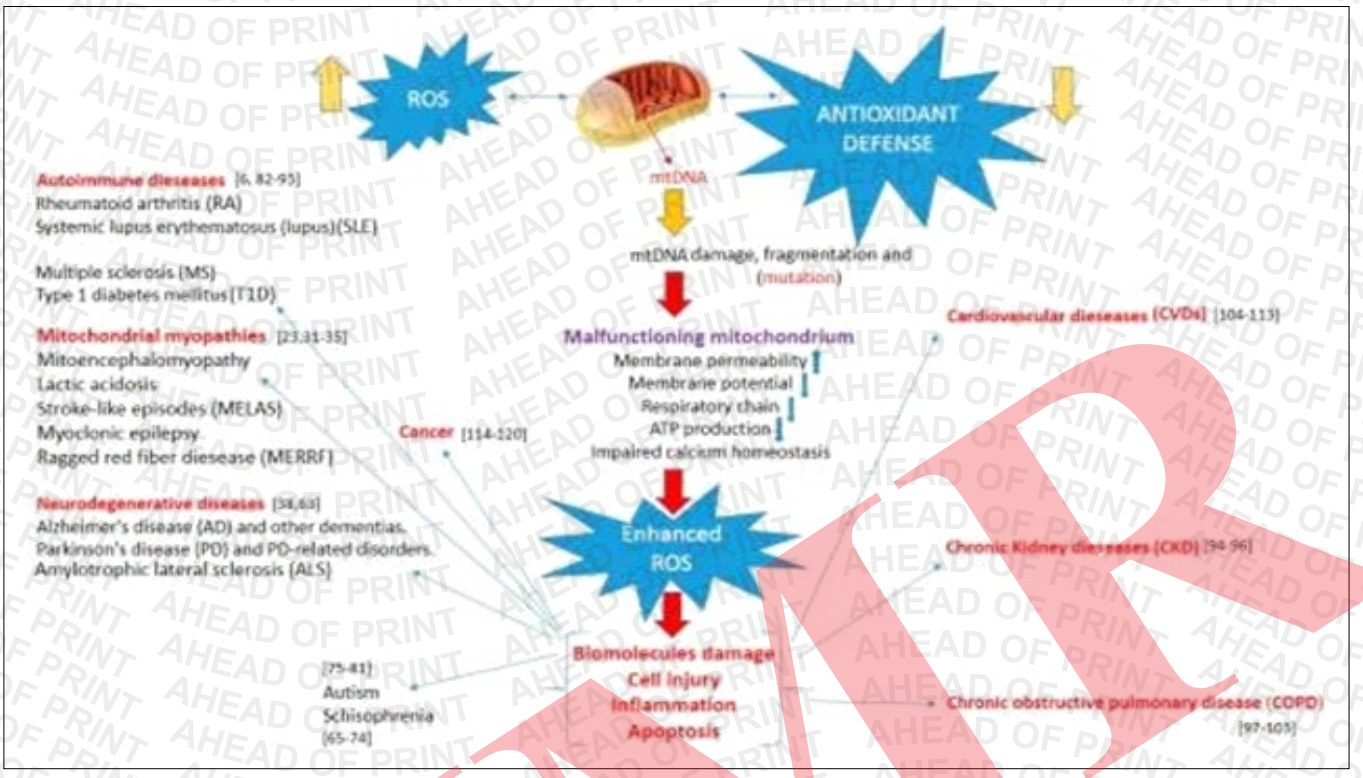

Fig. 1: Displays every Disease Entity Caused by Damage to the Mitochondria

Therapeutic Strategies

Therapeutic approaches that target mitochondrial function and redox balance hold promise for disease prevention and therapy, given the prominent role that oxidative stress and mitochondrial malfunction play in human diseases. Numerous strategies have demonstrated positive outcomes in preclinical and clinical investigations, including calorie restriction, exercise, pharmaceutical drugs that target mitochondrial metabolism, and antioxidants. However, more investigation is required to clarify the precise mechanisms underlying oxidative stress caused by mitochondrial carbon stress and to create focused treatments to lessen its harmful effects on human health.

Dietary Interventions: Caloric Restriction (CR): Research has demonstrated the benefits of CR on cellular stress resistance, oxidative stress reduction, and mitochondrial function. Mitigating mitochondrial carbon stress, CR increases autophagy, boosts mitochondrial biogenesis, and boosts metabolic efficiency. (29)

Medication-Based Therapies:

Resveratrol: A naturally occurring polyphenol present in red grapes and berries, resveratrol activates AMPK and sirtuins, resulting in better energy metabolism, increased mitochondrial biogenesis, and decreased oxidative stress. It has the potential to reduce carbon stress in the mitochondria and postpone age-related illnesses (29).

Changes in Lifestyle:

Exercise: Studies have demonstrated that regular exercise training increases mitochondrial biogenesis, lowers oxidative stress, and improves mitochondrial function. Exercises that increase mitochondrial adaptation, such as aerobic and resistance training, improve metabolic health and lower carbon stress in the mitochondria. (30)

Other Therapeutic Modalities:

Mitochondrial Peptides: Recent studies indicate that human in and MOTS-c, two examples of mitochondrial peptides, have cytoprotective and metabolic regulating qualities. Potential therapeutic effects for alleviating mitochondrial carbon stress may result from these peptides' targeting of mitochondria, modulation of mitochondrial activity, and conferred resilience to cellular stress. (31)

Oxidative Stress Therapeutics

Antioxidants with Enzymes:

The essential endogenous antioxidants known as superoxide dismutase (SOD) catalyze the conversion

of superoxide radicals into oxygen and hydrogen peroxide. Mn porphyrin and GC4419 are two examples of SOD mimetics that have been created to increase efficacy and show promise in the treatment of joint ailments, cancer, and inflammation.(32) Glutathione Peroxidases (GPx): Enzymes that degrade hydrogen peroxide into water and are dependent on selenium; may find use in the treatment of cancer. Decreased GPx levels are linked to the advancement of some diseases, such as colorectal cancer.(33)

Non-Enzymatic Antioxidants:

Intracellular antioxidant glutathione (GSH) is essential for maintaining redox equilibrium. Many diseases begin and worsen as a result of reduced GSH levels, and changing GSH concentrations can change how cells react to oxidative damage.

Uric Acid: Antioxidant qualities are demonstrated by uric acid, especially in neurological disorders such as multiple sclerosis and Parkinson's disease. Chronic increase, however, could be dangerous, and research on its antioxidant function is currently ongoing.

Bilirubin: A byproduct of hemoglobin disintegration, bilirubin has antioxidant properties that can protect against hydrogen peroxide and peroxyl radicals. In vivo, bilirubin has demonstrated antitumor efficacy against hepatocellular and colon cancer.

Melatonin: Known to control mood and sleep, melatonin also preserves the ratio of antioxidants to oxidants. It has demonstrated encouraging antioxidant effects in neurodegenerative illnesses by upregulating the expression and activity of antioxidant enzymes like SOD and GPx..(34-41)

Vitamins and Minerals:

Vitamins C and D are necessary nutrients that have antioxidant qualities that boost immunity and lessen oxidative damage. They might be able to stop a lot of illnesses. Zinc and selenium are trace minerals that function as antioxidants, boosting immunity and lowering oxidative stress.

Lactoferrin: Antioxidant protein that strengthens immunity and lessens damage caused by oxidative stress (42-43).

Antioxidants provide therapeutic potential in reducing oxidative stress-related diseases and promoting general health. These novel therapeutic approaches hold promise for preventing or ameliorating mitochondrial carbon stress, thereby promoting cellular health and resilience against age-related diseases. To completely comprehend their modes of action and maximize their therapeutic applications, more study is necessary.

CONCLUSION

The pathophysiology of several human diseases, including as aging, cancer, metabolic disorders, and neurological diseases, is largely dependent on mitochondrial carbon stress-induced oxidative stress. Developing effective therapeutic solutions to combat these disorders requires an understanding of the mechanisms by which disruptions in mitochondrial carbon metabolism lead to oxidative stress. Researchers may find novel ways to support healthy aging and fight age-related disorders by targeting mitochondrial malfunction and oxidative stress. To further understand the underlying mechanisms and tailor therapeutic techniques for clinical use, more research is necessary. To enhance human health and lifespan, future studies should concentrate on uncovering new intervention targets and applying these discoveries to clinical settings.

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How to cite this article:
Anwar S., Naziya S., Sharma P. Mitochondrial Carbon Stress And Oxidative Stress: Implications For Human Health Era J. Med. Res. 2024; 11(1): 1-8.