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Review Paper

Mitochondrial Abnormalities and Pathways of Cancer

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Abstract

Mitochondrial DNA (mtDNA) depletes mainly through damaged induced by DNA replication/reading errors and reactive oxygen species (ROS). Endothelial dysfunction (ED) is a result of increased oxidative stress, resulting from electron leakage in the biochemical reactions that occur in mitochondria, and leading to inhibition of nitric oxide (NO) production from endothelial nitric oxide synthase (eNOS). Dysfunction of eNOS leads to development of multiple forms of cancers. An increased reactive oxygen species (ROS) production causes mtDNA damage contributing to ED and accelerated ageing. This review explores an insight into mechanisms of mitochondrial dysfunction in cancer.

Keywords: Cancer, endothelial nitric oxide synthase, glycation end products, mitochondrial dysfunction, reactive oxygen species.

Introduction

Cancer is a complex disease that can spread to every cell, tissue and organ of the human body. Development of cancer includes various factors such as biological, environmental and molecular events and is undoubtedly distinctive and different for each individual patient. However, all cancers have certain similar mechanisms like self-sufficiency in growth factors, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, ability to invade and metastasize[1]. One of the hallmarks of cancer is mitochondrial dysfunction. Mitochondrial DNA (mtDNA) depletes mainly through damaged induced by DNA replication/reading errors and reactive oxygen species (ROS). The impaired mitochondria send a signal to damaged mtDNA to either stimulate repair or destroy mechanism. If the signals are not generated by damaged mitochondria, then the damage goes unrepaired[2].

Several researches have sought to understand the mechanism of this metabolic switch and how energy metabolism is reprogrammed during cancer. Hence it hypothesized as; cancer could be caused by accumulative mitochondrial damage, reduced mitochondrial function, leading ultimately to a compensatory shift in metabolism that drives cellular proliferation. If this hypothesis is correct, it follows that proper mitochondrial function is crucial for the balance between cell division and cell growth. Furthermore, some forms of cancer could be prevented or treated if mitochondrial function and the signals for mitochondrial damage were better understood.

Mitochondrial Dysfunction

Mitochondrial dysfunction is linked to many molecular pathways in cell division, which are controlled by energy production leading to several types of cancer. Moreover, mitochondria does numerous functions like degradation, fission, fusion, signaling and synthesis. It also comprises its own DNA encoding energy generating proteins. In the early 19th century, Otto Warburg who first hypothesized that the link between mitochondrial dysfunction and cancer and he observed that an increased rates of aerobic glycolysis in a variety of tumor cell types[3]. A single cell comprises about 1000 mitochondria and each mitochondrion contains in between 1-10 copies of mtDNA. Therefore, the damage to single mitochondria has negligible effect on overall function. However, if mtDNA damage accumulates, for example, with age then the mitochondria function and energy production will decline. Fortunately, cells can generate energy independent of mitochondria by glycolysis, though less effective, glycolysis provides sufficient energy for the cell to survive.

Mitochondrial (mt) DNA damage, respiratory chain dysfunction and reactive oxygen species (ROS) production contribute to one theory of ageing by forming a vicious cycle that leads to a decline in mitochondrial function. The accumulation of oxidative mtDNA damage is believed to be part of the normal ageing process in human and animal[4].

These include inflammatory molecules, oxidants and antioxidants, mitogens, angiotensin II, high glucose, nitric oxide, advanced glycation end products (AGEs) and mitochondrial function. These factors thereby influence senescence through two different paths i.e. by modifying the levels of cellular oxidative stress and by altering telomerase activity. Oxidative stress plays a key role in inducing senescence. ROS produced through intracellular or extracellular sources accelerates senescence development. Telomeres are

extremely vulnerable to oxidative damage. ROS have the ability to induce senescence by telomerase independent mechanisms thereby they lead to genomic DNA and mitochondrial damage[5].

Mitochondria as the Source of ROS Production

Probably in almost all cells ROS is produced continuously, by reduction of molecular oxygen through the electron transport chain leading to the production of superoxide, which is then dismutated into hydrogen peroxide[6]. The production of ROS depends on the metabolic state of mitochondria. mtDNA is damaged by ROS as are other redox sensitive components present in the organelle. This hinders the normal functions of mitochondria[7]. ROS generated through mitochondria are vital for signaling pathways that contribute to cardiovascular pathologies. Epidermal growth factor (EGF), angiotensin II, transforming growth factor (TGF)-β and tumor necrosis factors (TNF)-α can efficiently modulate mitochondrial ROS (figure 2). Cellular proliferation can be stimulated by mitochondrial ROS in cancer which in turn leads to the accumulation of mtDNA damage. The resultant ROS then cause uncontrolled activation of proliferative signaling pathways[8]. ROS play a major role in pathophysiological diseases such as ageing and neurodegenerative disorders. They also cause cardiovascular diseases like keshan disease (selenium deficiency), atherosclerosis, and Adriamycin cardio toxicity.

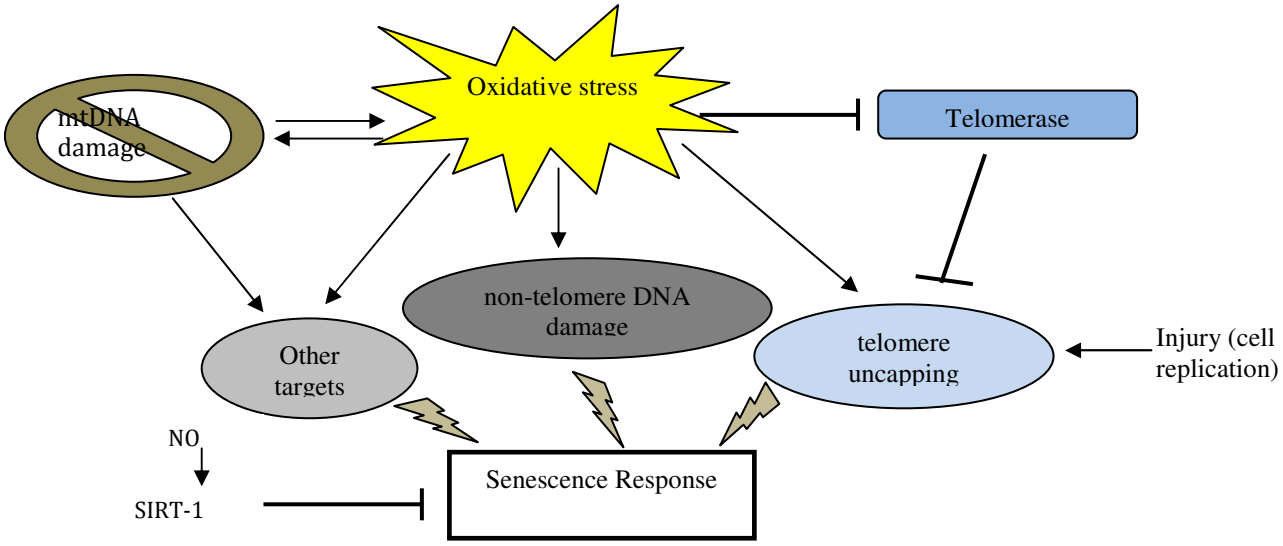

Figure-1

Adapted from Erusalimsky, 2009. In this diagram shows various factors, which induce senescence

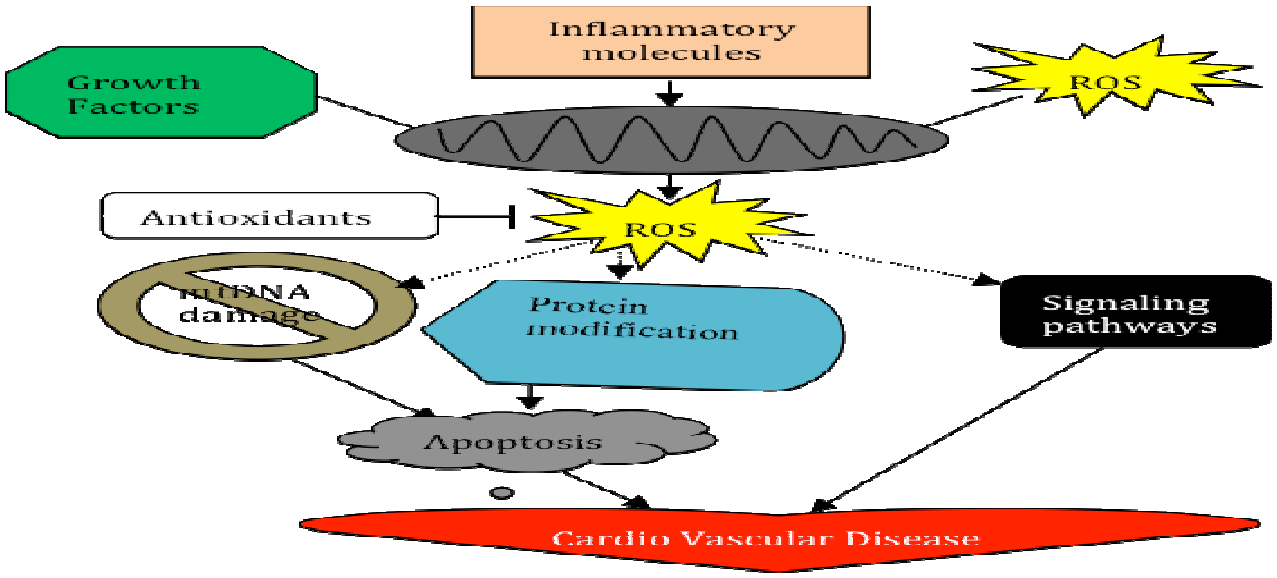

Figure-2

Overview of mitochondrial redox signalling pathways

Figure 2: Adapted from Gutierrez 2006. This figure shows the overview of mitochondrial redox signaling pathways. Mitochondria respond to extracellular, cytosolic ROS as well as growth factors and inflammatory responses. They further respond by producing ROS, which promotes cell death or oxidative stress through mtDNA damage, protein modification and bioenergetics dysfunction leading to cardiovascular diseases.

Mitochondrial targets of ROS

Oxidative stress plays a major role in stimulating the induction of senescence. Intracellular sources of ROS are mitochondria, plasma membrane oxidases and commonly NADPH oxidases. This leads to accelerated senescence, and in turn damages the mitochondria[9, 10]. Mitochondria are targeted by prolonged and severe oxidative stress. The mtDNA, proteins and lipids lose their normal function due to oxidative modifications in mitochondria. ROS inhibits various enzymes such as α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, aconitase, and complexes I, II and III. The inhibition of oxidative phosphorylation (OXPHOS) takes place due to oxidative inactivation of mitochondrial DNA polymerase γ which also slows down the mtDNA replication[11]. ROS produced through intracellular or extracellular sources accelerates senescence development. Telomeres are extremely vulnerable to oxidative damage. ROS have the ability to induce senescence by telomerase independent mechanisms thereby they lead to genomic DNA and mitochondrial damage.

Damage to mitochondrial macromolecules

Mitochondrial lipids, enzymes and DNA may be damaged by ROS, which leads to mitochondrial dysfunction. Other causes of mitochondrial dysfunction are free cholesterol, oxidized low-density lipoprotein and glycated lipoprotein. Modifications in mtDNA take place due to its close proximity to ROS and also due to lack of histone proteins, which act as a protective shield from oxidative damage. In mtDNA increased mutations take place due to relative lack of base excision repair[12, 13]. The endoplasmic reticulum (ER) is a major Ca^{2+} store in endothelial cells. Ca^{2+} plays a key role in regulating several mitochondrial enzymes. Thus an increase in Ca^{2+} is directly proportional to increase in mitochondrial ATP production in endothelial cells[13, 14] (figure 3).

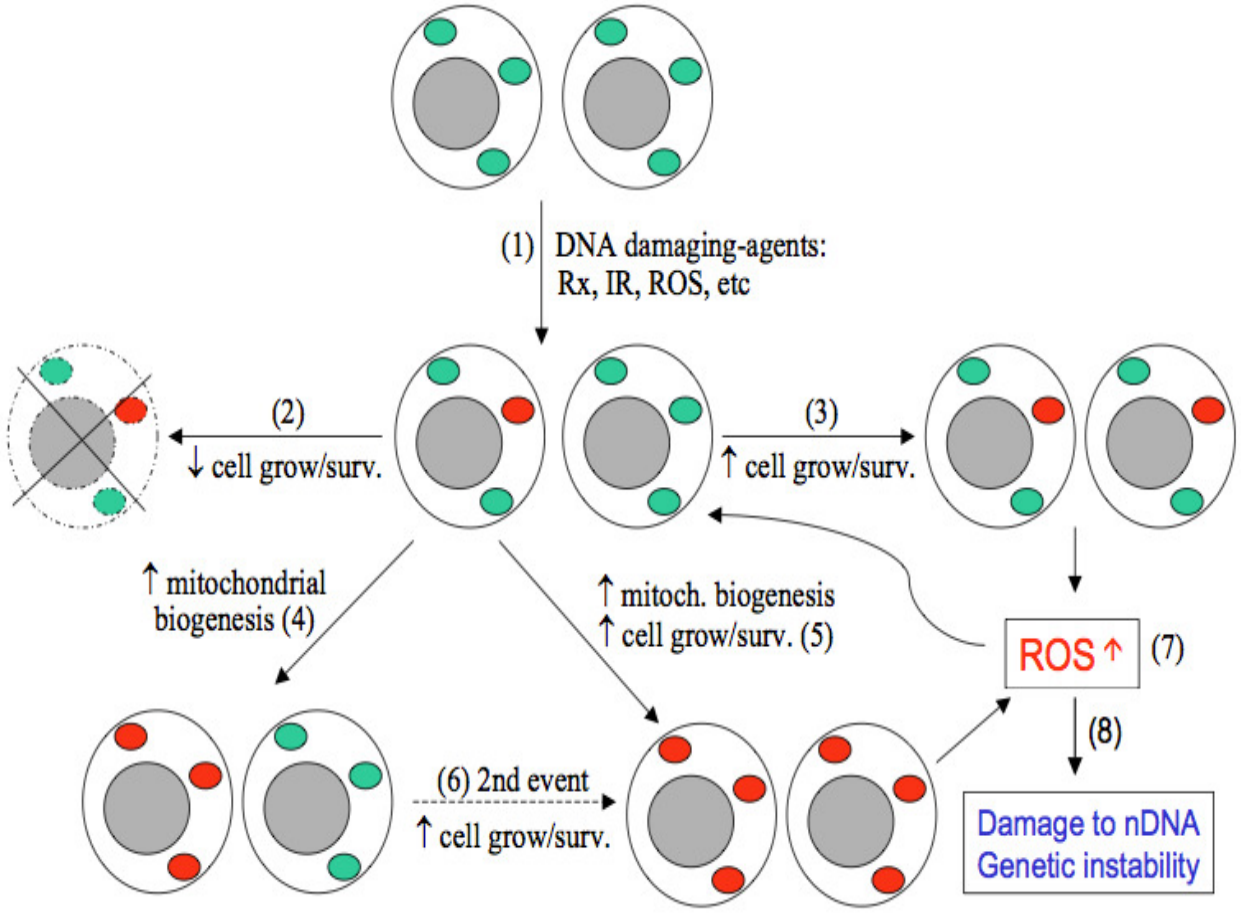

Figure-3
Somatic mtDNA mutation

Mutations in cells

mtDNA mutations have been stated in a variety of cancers, such as blood, brain, breast, colon, eye, kidney and liver[15-17]. Mutations spotted in mtDNA are basically point mutations, to deletions and duplications. Most tumors contain homoplasmic (100% pure) mutant mtDNA because of the clone nature of cancers.

Table-1
Mitochondrial DNA mutation in cancer

Mitochondrial DNA mutation in cancer	
Cancer	**Ref.**
Brain	3
Breast	4
Colon	5
Gastric	6
Liver	7
Leukemia	8
Lung	9
Salivary	10
Thyroid	11

The abundance and homoplasmic nature of mitochondria make mtDNA a definitive molecular marker of cancer[18]. Definitely, mutant mtDNA in tumour cells is reported to be 220 times as abundant as a mutated nuclear marker. Additionally, a new research study on mtDNA from patients with bladder, lung, head and neck cancers has highlighted that mutated mtDNA is readily measurable in urine, blood and saliva samples from these patients. Hence, mtDNA mutation might prove to be an extremely useful biomarker for the detection of many cancers[19]. Ongoing research on DNA repair genes involved in maintaining the genetic integrity of the mitochondrial genome combined with further study. A summary of mtDNA mutations in various tumors is presented in figure 4[15].

Table-2
Mitochondrial diseases

Mitochondrial Diseases	
Tissue/Organ affected	Clinical Condition
Blood	Pearson syndrome
Brain	Ataxia
Colon	Pseudo-obstruction
Eye	Retinopathy
Heart	Cardiomyopathy
Inner ear	Sensorineural hearing loss
Kidney	Glomerulopathy
Liver	Hepatopathy
Skeletal muscle	Neuropathy

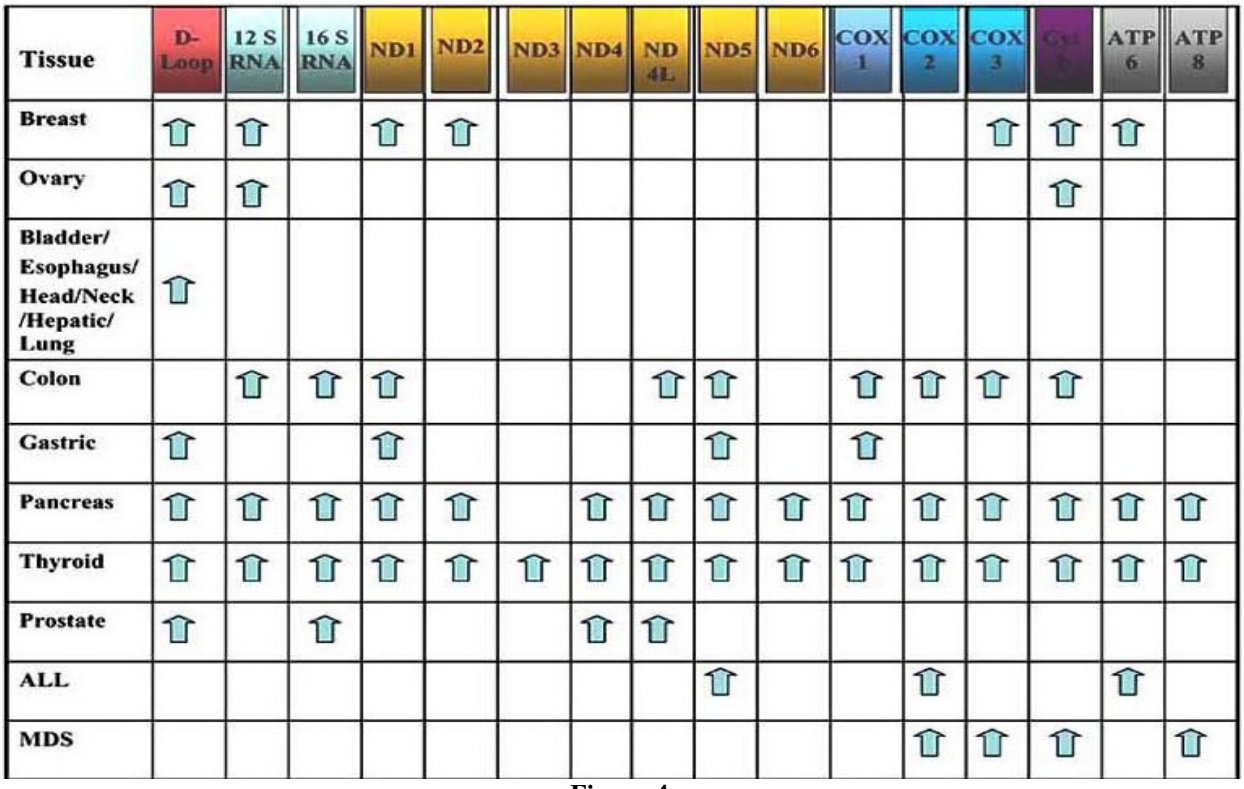

Figure-4
mtDNA mutations found in various tumours examined (Adapted from Modica-Napolitano et al., 2007). Arrows indicate the coding and non-coding (D-loop) region of mtDNA mutated in tumours

Mitochondrial functions regulate the endothelial Nitric oxide synthase (eNOS)

Three distinct cellular isoforms of NOS have been identified: the endothelial (eNOS), neuronal (nNOS) and inducible (iNOS), all three isoforms can in fact be regulated by transcriptional and post-transcriptional mechanisms and are constitutively expressed in certain tissues. eNOS is attached to the outer mitochondrial membrane in neurons and endothelial cells which indicates that mitochondria might regulate NOS activity and, conversely, that eNOS might regulate mitochondrial function [20,21]. NO regulates mitochondrial function by binding to cytochrome *c* oxidase, the terminal enzyme in the electron-transport chain. It competes with O_2, inhibiting the activity of the enzyme[22, 23] and thus negatively regulating mitochondrial oxidative phosphorylation. Finally, the recent finding that mitochondria have a form of NOS themselves is consistent with the idea that NO regulates mitochondrial functions directly[24, 25]. Sangam S.R. et al., demonstrated that mtDNA depletion/repletion caused by some of the carcinogens such as ethidium bromide (EtBr), dideoxycytidine (DDC) and dideoxyinosine (DDI) affects the eNOS expression in human umbilical vein endothelial cells (HUVECs) and could leads to endothelial dysfunction[26].

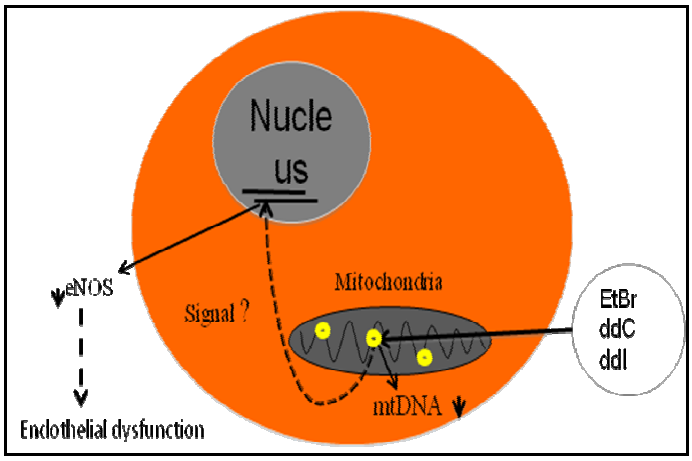

Figure-5
How does mtDNA depletion affect eNOS expression

Programmed cell death (Apoptosis)

Apoptosis, one form of programmed cell death, is a naturally occurring phenomenon in which a cell is directed towards its death. It occurs by intrinsic and extrinsic pathways. The extrinsic pathway is initiated by ligation of death receptors present on the cell by extrinsic ligands (eg - FasL/Fas receptor ligation). The intrinsic pathway is initiated by signals from inside the cell. It depends upon the release of cytochrome c from mitochondria, along with other molecules like apoptotic inducing factor (AIF), Smac/DIABLO, HtrA2/Omi. In this pathway, the proapoptotic Bcl-2 proteins interact with truncated Bid (tBid), which is a result of activation of Bid by caspase 8 and forms heterodimers, which are then translocated into the mitochondria. This leads to opening of the mitochondrial permeability transition port (mPTP), and helps in release of cytochrome c. This cytochrome c combines with apoptotic protease activating factor 1 (APAF), procaspase 9 and dATP to form an apoptosome, which converts procaspase 9 to caspase 9. Thus leads to apoptosis via caspase 3 activation[27, 28].

Conclusion

This review concludes that the depletion and/or repletion of mitochondrial DNA (mtDNA) regulate the eNOs expression. This obviously shows the significant role of mtDNA dysfunction in ageing process of endothelial cells of blood vessels and constitutes a novel pathway of mtDNA genes involving intimately with endothelial cells and thus pertaining to maintenance of vascular homeostasis.

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