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ROLE OF MITOCHONDRIA IN CANCER

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ABSTRACT

Mitochondria is an important organelle of the body. The role of mitochondria in the body is to produce energy in the form of ATP. Mitochondria have their DNA that participates in coding certain enzymes which involve in oxidative phosphorylation. Mutation of any other genetic variation in mitochondrial DNA leads to dysfunction of mitochondrial DNA (mt DNA) which contributes to many types of cancer. Observations made during the last few decades revealed that a variety of disorders including cancer and different neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis, have a mitochondrial origin. Disturbance of mitochondrial critical functions, such as ATP production, calcium buffering capacity, and excessive production of reactive oxygen species (ROS), can be potentially implicated in disease pathogenesis. In this article we explained the role of mitochondria behind the adenosine triphosphate production and also simultaneous production of (ROS) which causes mtDNA damage, leads to many types of cancers. In this article, we also explained what strategy we may use to minimize the production of ROS or free radical to reduce oxidative damage and another way which may be used to destroy dysfunctional mitochondria and accomplish healthy copy of the genome.

Key words: Mitochondria, mitochondrial DNA (mt DNA), Reactive oxygen species (ROS), Cancer

INTRODUCTION

There are very essential changes in cell physiology that normally might dictate malignant transformation: self-sufficiency in growth signals, sustained angiogenesis, insensitivity to growth-inhibitory (antigrowth) signals, limitless replicative potential, evasion of apoptosis and tissue invasion and metastasis (Hanahan and Weinberg 2000). Additionally, much evidence demonstrates that one of the unique qualities of tumor cells, they dependent on glycolysis for adenosine triphosphate (ATP) generation. Cancer cells generate their ATP through glycolysis still in aerobic conditions, Otto Warburg found this phenomenon in 1926 (Gogvadze, Zhivotovsky et al. 2010).There was an association between glycolytic ATP generation and violence of the tumor cells (Simonnet, Alazard et al. 2002). The universal characteristics of malignant cells are 'aerobic glycolysis' that was presumed by Warburg and he also proposed that impaired mitochondrial metabolism leads to cancer. Warburg hypothesized that cancer cells could be removed through the inhibition of mitochondrial oxphos (e.g. by average doses of ionizing radiation), which would reduce the action of these organelles lower than threshold level critical for cell survival and mitochondria in normal cells would yet be able to generate ATP. But further research challenged this and shows that

tumor cell's mitochondria do respire and generate ATP energy (Weinhouse 1976). Currently, for the visualization of tumors by positron emission tomography, the extensive glucose utilization by malignant cells is broadly used to highlight the significance of Warburg's observation. Nowadays the finding of tumor suppressor genes, finding of oncogenes, and other recent research in tumor biology shifted the attention of cancer researchers away from studies of energy metabolism to other areas. Mitochondria activities are not restricted to only ATP generation but it also produces ROS which participates in many physiological processes. But excessive ROS production might be harmful to the cell. In the process of apoptosis, mitochondria are essential for the control of intracellular Ca2+ homeostasis. Obviously, all these functions of mitochondria are crucial for tumor cell physiology, development, growth and survival. This review is dedicated to the important role of mitochondrial impairment in cancer.

MITOCHONDRIA

Mitochondria is a unique organelle in many other organelles because it has a unique property to produce energy in the form of ATP no other organelle has this type of property so mitochondria are called the powerhouse of the body. Cells have a high need for energy and they depend on mitochondria for it. Mitochondria metabolize oxygen to generate high amounts of energy. In contrast, mitochondria of tumor cells are defective in their ability to metabolize (O_2) oxygen (Wallace 2012).

PROCESS OF ENERGY PRODUCTION

Normally, mitochondria complete their task of generating energy, by using three important foodstuffs which are Fatty acids, Carbohydrates, and Protein. Mitochondria uses 95% of oxygen which we breathe to oxidize foodstuffs in the respiratory chain where food is burned. By using a series of enzymes encoded in their DNA. The cells them self can break down glucose without an oxygen requirement, called glycolysis. This process occurs in the cytoplasm of the cell outside the mitochondria.The breakdown of food occurs mainly in three steps. First, fuel breakdown occurs in cytoplasm then breakdown food is oxidized in Kreb cycle and at last by using four enzyme complexes or carriers (I, II, III, and IV) in electron transport chain Figure.1 (ETC) or chemically called oxidative phosphorylation (oxphos).In this process electrons (hydrogen ions) extracted from food are transferred from one complex to another complex in a redox process to a final stage IV where energy (ATP) is produced(Solaini, Sgarbi et al. 2011).

This is the first stage of fuel breakdown, fatty acids, carbohydrates, and proteins from food are broken down into their individual molecular components and used for energy production. Oxygen (O_2) is used by mitochondria as fuel to oxidize foods in the oxphos chain (Alberts, Johnson et al. 2002). Several important molecules are needed to run the Krebs cycle, like all the enzymes and other substrates. In the process of food digestion first glucose (from sugar), enters into the cell using some special molecule in the membrane called "glucose transporters". Glucose converts into pyruvate in multi-steps through the process of glycolysis. Pyruvate then transported from the cytosol into the mitochondria. Pyruvate then converted into acetyl COA, by a soluble multienzyme pyruvate dehydrogenase complex. In this energy-rich form, the molecule is fully oxidized to carbon dioxide (CO2)by reactions of the citric acid cycle or Krebs cycle(Lodish, Berk et al. 2000).

It is very necessary to continue the breakdown process of the citric acid cycle inside the mitochondria. Carbon and hydrogen, the best fuels, are released during the process of the Krebs cycle. These carbon molecules are used to make more CO_2that together with hydrogen

ions (H+) is take up by NAD and FAD. The CO_2 is a form of toxic waste in the body. This is quickly removed by red blood cells and hydrogen ions along with their partner electrons reach the terminal respiratory enzyme complex cytochrome oxidase to combine with oxygen to make water (H_2O). The electrons obtained in the oxidation of acetyl COA are a couple with oxaloacetate to make citric acid. Then citric acid gets oxidized to succinic acid, then succinate is converted to fumaric acid than malic acid and back to oxaloacetate. The electrons released during the oxidation are then transferred into the third stage of the "electron transport chain" with four major respiratory enzyme complexes that are-

A. Complex I NADH dehydrogenase
B. Complex II succinate dehydrogenase
C. Complex III cytochrome C – reductase
D. Complex IV Cytochrome oxidase a/a 3

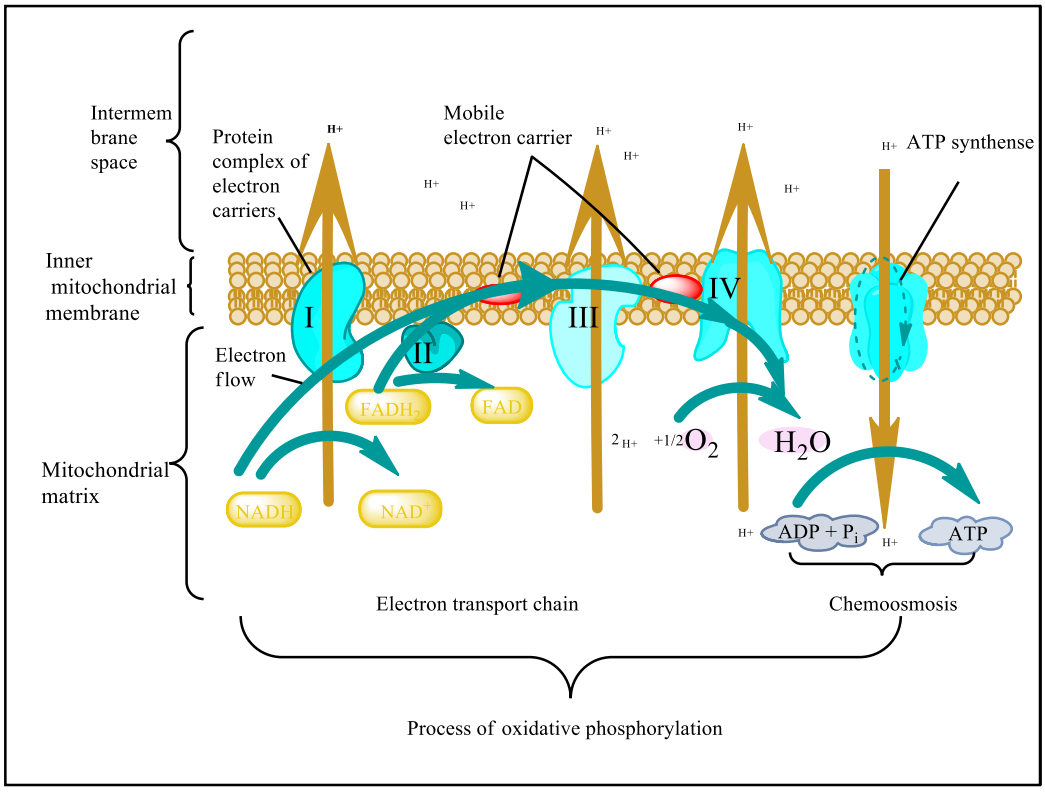

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Figure.1Mitochondrial energy metabolism.

This process is based on oxidation-reduction potential. Electrons are transported across the inner mitochondrial membrane to the final cytochrome oxidase complex a/a3 (complex IV). From here it passes them to molecular oxygen and combines with protons, generating energy in the form of ATP. Then the synthesis of ATP is done by complex V. The mitochondrial enzyme ATP synthase and energy stocked can be transported to cells where it is needed. This ATP is utilized in the various purpose of the cell such as growth, development, and differentiation.

Another mechanism that occurs in the mitochondria is fatty acid oxidation. The enzymes of the beta-oxidation pathway are also present in the mitochondrial matrix. Some enzymes of the gluconeogenesis and urea cycle are found in the mitochondrial matrix. Cytosolic NAD which is required for the substrate-level phosphorylation step in glycolysis is regenerate by mitochondria. Mitochondria are also maintained the intracellular homeostasis of inorganic ions such as phosphate and calcium. Many studies demonstrate that mitochondria play an important role in the series of intracellular events that lead to apoptosis (Zamzami, Susin et al. 1996).

MITOCHONDRIAL LINKWITH CANCER

Now a day researchers are interested to develop anti-cancer drug targeting to mitochondria because in many studies researchers found that mitochondria have a link with cancer. In tumor cells, many metabolic pathways altered which occurs only in mitochondria. Metabolic alterations that are related to mitochondrial function have been documented in tumor cells are increased rate of gluconeogenesis (Lundholm, Edstrom et al. 1982), increased lactic acid production and reduced pyruvateoxidation (Mazurek, Boschek et al. 1997), increased glutaminolytic activity(Mazurek, Boschek et al. 1997), and reduced fatty acid oxidation(Ockner, Kaikaus et al. 1993).

MITOCHONDRIAL DNA

Normally all mammalian cells have about 1000 mitochondria and up to 10,000 copies of mitochondrial DNA (mtDNA).The mitochondrial genome is double-helical a 16.6 kb, closed-circular molecule. Two rRNAs, 22 tRNAs, and 13 polypeptides are encoded by mitochondria Figure.2 (Baysal 2006). Mitochondria have seven, one, three, and five subunits of respiratory enzyme Complex I NADH dehydrogenase, Complex III cytochrome C – reductase, Complex IV Cytochrome oxidase a/a 3,and complex V respectively. Other mitochondrial proteins, among those participating in the replication, transcription, and translation of mitochondrial DNA, are encoded by nuclear genes, then a specific transport system targeted to these proteins to mitochondrion by a specific transport system(Schatz 1996). Mitochondrial genes show maternal inheritance means that they are inherited from the female, this is probably because the number of mtDNA copies in the egg is normally 103-fold higher than that present in the sperm (Song, Ballard et al. 2014).

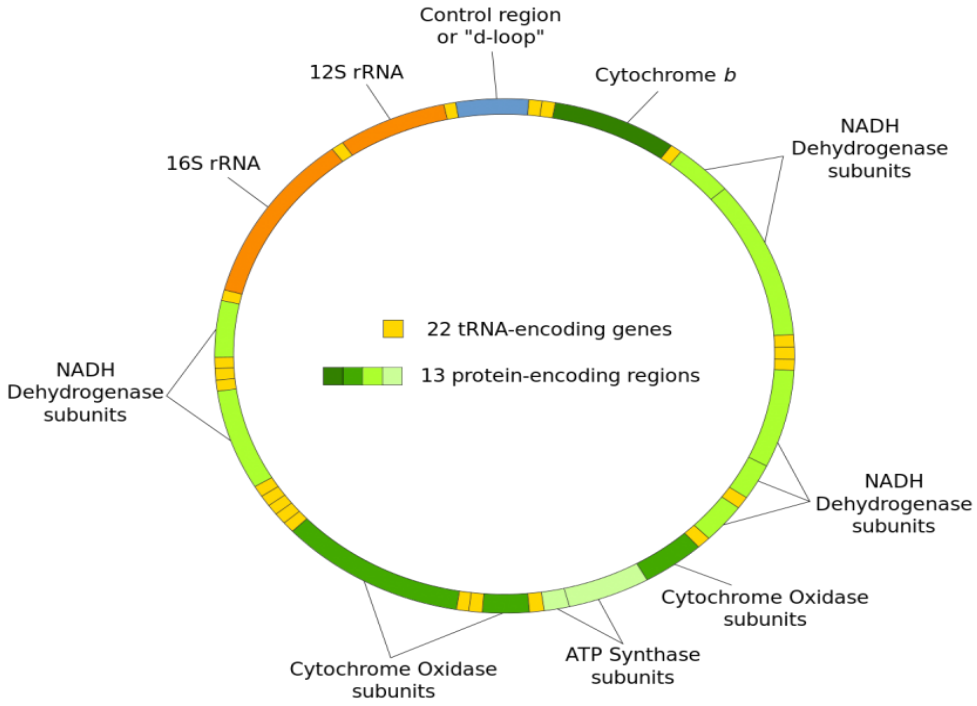

Figure.2 Structure of mitochondrial DNA

By derivative work: Shanel (talk) Mitochondrial DNA de.svg: translation by Knopfkind; layout by jhc (Mitochondrial DNA de.svg) [GFDL (http://www.gnu.org/copyleft/fdl.html) or CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0/)], via Wikimedia Commons

MITOCHONDRIAL DNA IS MORE VULNERABLE TO MUTATION THEN NUCLEAR DNA

Mammalian mitochondrial DNA (mtDNA) represents approximately less than 1% of total cellular DNA. Its gene products are required for normal cellular function. Nuclear DNA has defensive histones and introns but mtDNA does not have defensive histones and intron are vulnerable to ROS generated by oxidative phosphorylation. Additionally, the replication of mtDNA is highly error prone (Kunkel and Loeb 1981, Shay and Werbin 1987, Singh 2004).

The mutations in mtDNA are about tenfold greater compared to nuclear DNA(Grossman and Shoubridge 1996). Normally all mitochondria have identical DNA sequences into a single cell are called homoplasmic, when differences in mtDNA sequences into the same cell, happens it is called heteroplasmy. This may happen due to de novo or “somatic” mutations in cells. When a minimum threshold of heteroplasmy has been reached mitochondrial pathologies arise. This threshold value is different for different tissue types and it is based on the energy status of a cell.

MITOCHONDRIA AND CANCER

ALTERATIONS OCCURS AT METABOLIC LEVEL

The specifically mitochondrial bioenergetic function associated with metabolic aberrations has been observed in cancer cells. These comprise differences between normal and tumor cells regarding, rate of electron transport and anion transport, preference for respiratory substrates, and also the capacity to accumulate and retain calcium(Pedersen 1978). There are activities of some enzymes participating in the procedure of oxidative phosphorylation that is

decreased in malignant versus normal cells. For example, in hepatocellular carcinoma, the measured maximal velocity of ATPase activity in isolated mitochondria(Pedersen and Morris 1974)and submitochondrial particles(Capuano, Guerrieri et al. 1997)is lower than in normal liver cells. In cellular homogenate and the mitochondrial samples from cultured human carcinoma cell lines, the activity of cytochrome c oxidase is less than that calculated in the control epithelial cell line (Modica-Napolitano and Singh 2002). Decreased activity of mitochondrial cytochrome c oxidase has been documented in biopsies of human colonic adenocarcinoma compared to normal colon mucosa (Sun, Sepkowitz et al. 1981), and in cultured rat HC252, hepatoma cells compared with non-neoplastic liver cells(Sun and Cederbaum 1980).In certain hepatoma compared to normal liver cells the adenine nucleotide exchange purpose of adenine nucleotide translocase (ANT) and the reactivity of (ANT) enzyme to bongkrekic acid (Chan and Barbour 1983) are also decreased in mitochondria. The membrane potential of mitochondrial is higher in carcinoma cells than in normal epithelial cells(Johnson, Walsh et al. 1981, Summerhayes, Lampidis et al. 1982).It is very important to note that despite the large number of metabolic alterations identified, undoubtedly none of these is common to all tumor cells because of the number of differences in the molecular constitution of the mitochondrial inner membrane among the normal and tumor cells have also been found. Alterations in the level of gene expression of cytochrome c oxidase also decrease this enzyme's specific activity in tumor cells. In colonic biopsies of carcinoma versus normal mucosa samples collected from humans, the mean level of expression of the mtDNA encoded subunit COX III was shown to be minimum(Heerdt, Halsey et al. 1990). In addition alterations in gene expression between normal and tumor cells comprise the anti-apoptotic oncogenes encoding Bcl-XL and Bcl-2, and genes encoding the PBR-linked protein Prax-1and the peripheral benzodiazepin receptor (PBR), and mitochondrial creatine kinase (Kroemer 1997, Reed 1997). The lower expression of BAX a pro apoptotic, inner mitochondrial membrane protein also found in cancer cell lines (Nishikawa, Oshitani et al. 2005).

ALTERATION OCCURS AT GENETIC LEVEL CHANGES

The mitochondrial genome, known to be a mutational "hot spot" in human cancer particularly the displacement loop (or D-loop) region. The D-loop is a triple-stranded and non-coding region of mtDNA. In humans, the 16,569 base pairs of mitochondrial DNA encode for only 37 genes (Anderson, Bankier et al. 1981) and houses cis-regulatory elements that are required for replication and transcription. Somatic mutations in the region of the D-loop region have been documented in uterine serous carcinoma (Pejovic, Ladner et al. 2004). hepatocellular carcinoma(Tamori, Nishiguchi et al. 2004), melanoma (Takeuchi, Fujimoto et al. 2004),gastric cancer(Zhao, Yang et al. 2005), colorectal cancer(Lievre, Chapusot et al. 2005),breast cancer(Tan, Bai et al. 2002), and ovarian cancer (Liu, Shi et al. 2001). These studies suggest that mutations in the D-loop region of mitochondrial DNA maybe take part in the carcinogenesis of human cancers.

Apart from D-loop region mutations, some other mutations like deletions, point mutations, insertions, and duplications are also found in the mitochondrial genome. These mutations have been documented in a variety of human cancers such as thyroid, ovarian, liver, lung, salivary, colon, and prostate cancer(Clayton and Vinograd 1967, Boultwood, Fidler et al. 1996). For example, insertion of a 40 bp sequence confined in the COX I gene found to be particular for renal cell oncocytoma (Welter, Dooley et al. 1989).and a deletion mutation resulting in the loss of mitochondrial DNA into the NADH dehydrogenase subunit III is related to renal carcinoma (FIGURE.3)(Selvanayagam and Rajaraman 1996). In renal cell carcinoma, the co-occurrence of somatic and germ-line mitochondrial DNA mutations has

also been reported (Sangkhathat, Kusafuka et al. 2005). In human cancer, tumor-specific changes in mitochondrial DNA copy number have been documented. For example, the mtDNA content was found to be increased in primary tumors of head and neck squamous cell carcinoma (Canter, Kallianpur et al. 2005)and the histopathologic rank was found to be an increase in premalignant and malignant head and neck lesions (Mandelker, Yamashita et al. 2005). Mitochondrial DNA copy number was revealed to increase conversely, it was also reported that mitochondrial DNA content is decreased in 80% of breast tumors compared to normal controls cells. Additionally, one current study exploring mitochondrial DNA copy number, in the number of cancers, both increases, and decreases in mitochondrial DNA content associate to controls were discovered for each type of cancer (Liu, Shi et al. 2001).Hence , the actual mitochondrial DNA copy number in specific cancers might depend upon the particular site of mutation, which means that mutations caused in the D-loop region, which regulate mitochondrial DNA replication, would be predicted to result in lowering its copy number. Conversely, mitochondrial DNA mutations in genes encoding oxphos proteins might be probable to increase in mitochondrial DNA copy number. It has been hypothesized that this response might happen due to compensatory response to mitochondrial dysfunction (Kim, Lee et al. 2004).

Tissue	D-Loop	12 S RNA	16 S RNA	ND1	ND2	ND3	ND4	ND 4L	ND5	ND6	COX 1	COX 2	COX 3	Cyt b	ATP 6	ATP 8
Breast	⇧	⇧		⇧	⇧								⇧	⇧	⇧	
Ovary	⇧	⇧												⇧		
Bladder/ Esophagus/ Head/Neck /Hepatic/ Lung	⇧															
Colon		⇧	⇧	⇧				⇧	⇧		⇧	⇧	⇧	⇧		
Gastric	⇧			⇧					⇧		⇧					
Pancreas	⇧	⇧	⇧	⇧	⇧		⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧
Thyroid	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧
Prostate	⇧		⇧				⇧	⇧								
ALL									⇧			⇧			⇧	
MDS												⇧	⇧	⇧		⇧

FIGURE. 3. mtDNA mutations found in different types of tumors investigated, Arrows point out the coding and non-coding (D -loop) regions of mtDNA mutated in tumors. (Modica-Napolitano, Kulawiec et al. 2007)

MITOCHONDRIAL BIOENERGETICS IN TUMOR CELLS

PRODUCTION OF ENERGY

It is very necessary to generate a huge amount of ATP for energy and also for the synthesis of biomolecules required for the cells such as nucleotides, lipids, and proteins, required for cancer cell's rapid proliferation.

RATE OF GLYCOLYSIS INCREASED IN TUMOR CELLS

Cancer cells use glucose for many reasons (Kroemer and Pouyssegur 2008).First, it enables cells to use the extracellular nutrient, glucose to generate an adequate amount of ATP. The total yield of ATP per glucose molecule consumed is low. However, the study suggests that if the process of glycolysis is high enough, the total percentage of ATP generated from glycolysis can go greater then that of that generated from oxphos (Guppy, Greiner et al. 1993).

Second, in the anaerobic glycolysis, tumor cells may tune themselves to conditions of various oxygen concentrations (because of variable hemodynamics of distant blood vessels) that would be very toxic for cells that depend on oxphos to synthesize cellular ATP (Pouyssegur, Dayan et al. 2006).

In third, the process of anaerobic glycolysis, tumor cells produce lactic acid which creates a favorable acidic condition, essential for tumor cell invasion(Swietach, Vaughan-Jones et al. 2007).Fourth, and very necessary, for biosynthetic pathways, tumor cells utilize intermediates of the glycolytic pathway. Hence, tumors can metabolize glucose via the pentose phosphate pathway (PPP) to generate NADPH that can take part in the synthesis of fatty acid and together with ribose 5-phosphate, to synthesis of nucleotide from de novo pathway(DeBerardinis, Lum et al. 2008). Long-chain fatty acids synthesize from acetyl-CoA, malonyl-CoA and NADPH by fatty acid synthase, it’s activity is up regulated in a lot of tumor cells and contrary to normal cells, de novo fatty acid synthesis also take place at higher rates in cancer cells (Kuhajda 2000). Besides, tumor cells utilize intermediates of the glycolytic pathway for synthesis of glycogen, lipid, and alanine and malate (Gatenby and Gillies 2004).

WARBERG EFFECT

Cancer cells consume glucose at a higher rate and produce lactate, not carbon dioxide (CO2) Otto Warburg has been the first to observed(Warburg 1956). This observation suggests that tumors use less of the highly efficient oxphos and use glycolysis for ATP production. This shift happens even when, there was adequate oxygen available to provide mitochondrial energy metabolism and so, this event has been known as “aerobic glycolysis” or the “Warburg effect”. While the enhanced rate of glycolysis is a maincharacteristic of tumorigenicity. Global ATP concentration and adenylate energy charge change a little bit in cancer cells versus normal cells have shown by the number of bioenergetics measurements (Brizel, Schroeder et al. 2001). It is suggesting that mitochondrial metabolism is not essentially shut down. Otto Warburg first hypothesized that an increased rate of glycolysis under normal oxygen conditions arose from a deficiency in the mechanism of oxidative phosphorylation in mitochondria (Warburg 1956).Many studies have shown that alteration in

the mitochondrial energy metabolism in tumor cells as the number of mitochondria decreases, changes in mitochondrial ultra structure, and composition of the oxphosprotein in the respiratory chain activity and occurrence of somatic mutations mtDNA(Polyak, Li et al. 1998, Isidoro, Casado et al. 2005). Interestingly, it has been described in the AMPK pathway mediate the up regulation of glycolysis and the related attenuation in the oxphos in two human cancer cell lines (Wu, Neilson et al. 2007).

Though, these studies show no reliable pattern and do not explain the hypothesis of Warburg. Furthermore, several studies have demonstrated that mitochondrial energy metabolism is not changed in all cancer cells(Zu and Guppy 2004). Consequently, several mechanisms in cancer cells for increased glycolysis have been reported. Nowadays further research in molecular biology and biochemical proof representing those oncogenes most likely take part in the mechanisms which run the switch to anaerobic glycolysis.

HIF-1 ACTIVATION AND SUPPRESSION OF MITOCHONDRIAL ACTIVITY

HIF-1α, which is stabilized and functional at lower oxygen consumption, increases the rate of glycolysis by increasing the glycolytic enzymes and glucose transporters (Semenza, Jiang et al. 1996). Recent studies demonstrate that HIF-1 suppresses mitochondrial function in cancer cells, suggesting that it altered the reciprocal relationship between the process of glycolysis and oxidative phosphorylation.

The switch among two processes, glycolysis and oxphos is regulated by the corresponding activities of two important enzymes, pyruvate dehydrogenase (PDH) and lactatedehydrogenase (LDH). Pyruvate dehydrogenase kinase 1 (PDK1) regulated the activity of pyruvate dehydrogenase (PDH). HIF-1 was found to stimulate Pyruvate dehydrogenase kinase 1(PDK1) and in that way, it inactivatespyruvate dehydrogenase (PDH) the enzyme help in the conversion of pyruvate into acetyl-CoA as a result, it suppresses the citric acid cycle(Kim, Tchernyshyov et al. 2006, Papandreou, Cairns et al. 2006) and the process of mitochondrial respiration(Kim, Tchernyshyov et al. 2006).The enzyme lactate dehydrogenaseA is encoded by the gene which stimulates by the HIF-1. This enzyme converts pyruvate into lactate (Semenza, Jiang et al. 1996). This result would further diminish the use of pyruvate by mitochondria, inhibiting the mitochondrial respiration. HIF-1 can also alter the expression of cytochrome oxidase, under hypoxic conditions; the composition of COX subunit is altered to optimize its activity. The expression of the COX4–2 subunit is enhanced, whereas the COX4–1 subunit, which optimizes COX activity under normal aerobic conditions, is degraded by a mitochondrial protease known as LON,(Fukuda, Zhang et al. 2007).

Consequently, some other mechanisms for the increased glycolysis in tumor cells have been recognized and molecular and biochemical confirmation signifying that oncogenes underlie the process that drives the switch to anaerobic glycolysis particularly by stabilization of HIF-1α (Almeida, Moncada et al. 2004, Elstrom, Bauer et al. 2004).Therefore, oncogenes, for example, Ras or Myc have been trigger glycolysis by induction of glucose transporters and glycolytic enzymes phosphorfructokinase or hexokinase (Dang and Semenza 1999).Fascinatingly, it has been looked like that the above displayed cancer-geneidea is completely in tune with the Warburg effect but, most likely, with oncogenes as the result cause metabolic alterations(Ramanathan, Wang et al. 2005). In contrast to oncogenes, the induction of the tumor suppressor gene p53 cause diminishes the level of glycolysis and a raise in oxidative phosphorylation (Bensaad, Tsuruta et al. 2006). Therefore, the loss of p53,the tumor suppressor can enhance the glycolytic flux in cancer cells(Levine and Oren

2009).Several studies have shown that ROS are involved in the induction of HIF and stabilize it under hypoxic conditions(Brunelle, Bell et al. 2005, Guzy, Hoyos et al. 2005).Fascinatingly, ROS also appears to act downstream of some oncogenes to stabilize HIF under the condition of normoxia, leading to activation of HIF and the support tumorigenesis (Gao, Zhang et al. 2007).Recently, it has been shown that some mitochondrial proteins can be tumor suppressors whose modification indirectly induce anaerobic glycolysis,four genes are concerned with it, SDHD and SDHC, and the fumarase gene FH, the succinate dehydrogenase (SDH) genes (Gottlieb and Tomlinson 2005).

ROS DAMAGE

Oxygen is very essential for the survival of the living organism and forms the basis of cellular respiration. But oxygen (O_2) in the form of free radical serves as a molecule that causes oxidative stress(Stamati, Mudera et al. 2011). When free radicals produced in a large amount to the human body these state is caused by a deleterious effect on the life cycle of living cells (Bensaad, Tsuruta et al. 2006). So this oxidative stress is the origin of many age-related diseases such as Alzheimer's and Parkinson's, cancer and aging. When the ratio of oxidative stress generators like free radicals and the antioxidants get imbalance, then cell suffers from oxidative cellular stress(Liguori, Russo et al. 2018). Reactive oxygen species (ROS) include Singlet oxygen, hydroxyl radicals, superoxide, hydrogen peroxide, hydroperoxyl radicals, and ozone, etc(Halliwell and Cross 1994). The hypoxic environment of proliferating tumor cells provides a facility for ROS production. However, in hypoxia conditions, when electron transport complexes are in the reduced state, the ROS level can also be enhanced(Guzy and Schumacker 2006). Consequently, under hypoxic circumstances and in particular, after normalization of oxygen (O_2) supply, production of ROS in cancer cells can be enhanced to level that might leads to damage fundamental biomolecules such as mitochondrial DNA, lipid and protein. This might trigger a dangerous cycle (hypoxia, ROS generation, mitochondrial DNA (mtDNA) mutations, failure of the mitochondrial respiratory chain, etc), this series of events damaging mitochondrial structure and function, causing a shift to glycolytic ATP generation.

ROS DETOXIFICATION IN CELL

Under normal physiological conditions of cells, the intracellular levels of ROS are continuously maintained by some special types of enzymes known as an antioxidant enzyme like superoxide dismutase, catalase, Peroxiredoxins, etc. Some other non-enzymetic molecules also serve as a ROS scavenger like glutathione, flavonoids, and vitamins A, C, and E, to prevent cells from damage caused by ROS(Nita and Grzybowski 2016). Superoxide dismutases (SODs) are a type of metalloenzymes that catalyze the dismutation of superoxide anion to oxygen (O_2) and hydrogen peroxide (H_2O_2). Superoxide dismutases utilize metal ions such as copper (Cu2), zinc(Zn2), manganese (Mn2),or iron (Fe2) as cofactors(Younus 2018). The various types of SOD enzymes are present in various compartments of the cell and are highly specific in controlling associated biological processes(Copin, Gasche et al. 2000).The decomposition of H_2O_2 to water and oxygen facilitates by Catalase. The localization of catalase in most eukaryotes is in the peroxisomes and cytosol (Glorieux and Calderon 2017).These enzymes play a major role in the detoxification of ROS.

In cancer cells increased levels of ROS can result from mitochondrial impaired, enhanced cellular receptor signaling, high metabolic activity, oncogene action, increased activity of oxidases, peroxisome action, thymidine phosphorylase and lipoxygenases or during cross-talk between infiltrating immune cells(Storz 2005).

MAJOR SIGNALING PATHWAYS IN CANCER REGULATED BY ROS

In various types of cancer a number of ROS-sensitive signaling pathways are elevated where they participate in cell growth, proliferation, differentiation, glucose metabolism, cell survival, and inflammation process(Kumari, Badana et al. 2018). ROS, mainly(H_2O_2), can serve as a second messengers in cellular signaling (Di Marzo, Chisci et al. 2018). H_2O_2 controls the protein activity by reversible oxidation of its targets involving receptor tyrosine kinases, proteintyrosine kinases, protein tyrosine phosphatases, and transcription factors (Truong and Carroll 2013).

ROS-MEDIATED CONTROL OF THE MAPK/ERK1/2 PATHWAY

In cancer, the MAPK (mitogen-activated protein kinase)/Erk1/2 (extracellular-regulated kinase 1/2) pathway is activated by growth factors and K-ras. It was functionally associated with enhanced cell growth (Khavari and Rinn, 2007; Roberts and Der, 2007). For instance, in human breast cancer cells, Erk1/2 activated through (H_2O_2) generated as a by product through the metabolism of estrogen, enhances cell proliferation (Aggarwal, Tuli et al. 2019).

For instance, Ras is known as an upstream activator for Erk1/2. It can be activated directly through oxidative modification at its cysteine 118 residue, leading to the inhibition of GDP/GTP exchange (Mitchell, Hobbs et al. 2013). It was shown that increased Erk1/2 activity in ovarian cancer cells in the presence of the elevated concentration of endogenous ROS consequences from sustained ubiquitination and loss of endogenous MKP3 (mitogen-activated protein kinase phosphatase 3), a phosphatase that negatively-regulates Erk1/2 activity (Chan, Liu et al. 2008).In Addition to its effects on cell growth, it was also shown in multiple cancers types like ovarian cancer, breast cancer, melanoma, and leukemia that the activation of Erk1/2 through ROS anchorage-independent growth, motility and increases cell survival. While a Participation of ROS-activated Erk1/2 signalling in cell growth is well established (Roberts and Der 2007).The ability of ROS to control cancer cell survival appears to be cell-type definite (Rygiel, Mertens et al. 2008). For instance, MCF-7 and MDA-MB-435 breast cancer cells when treated with ROS inhibitor or scavengers or that support apoptosis and cell adhesion by targeting Erk1/2 or its upstream kinase MEK (mitogen-activated protein kinase) (Ostrakhovitch and Cherian 2005).

OXIDATIVE STRESS REGULATES THE PI3K/AKT PATHWAY

Akt or protein kinase B; PKB mediates cell survival by phosphorylation and inactivation of its substrates such as the pro-apoptotic proteins Bad, Bax, Bim, or FOXO transcription factors that take part in apoptosis which leads to cell death(Bonni, Brunet et al. 1999, Zhang, Tang et al. 2011). In breast cancer, ROS production during estrogen metabolism or many other potential mammary carcinogens was shown to activate thePI3K/Akt signaling pathway (Park, Na et al. 2009, Zhang, Tang et al. 2011). Hydrogen peroxide (H_2O_2) produced by epithelial growth factor (EGF) in human ovarian cancer cells activates Akt and p70 S6K1, a substrate of Akt that regulates protein synthesis process (Liu, Hu et al. 2006). Furthermore, the inhibition of ROS by ROS scavenger in the human pancreatic tumor cell line Panc-1 reduced the levels of phosphorylated (active) Akt and induced apoptosis (Subramani, Gonzalez et al. 2016).The activity Of AKT is firmly controlled by a signaling cascade that includes the kinases PDK-1(3'-phosphoinositide-dependent kinase-1), mTOR andPI3K as well as the phosphatase PTEN (phosphatise and tensin homolog deleted on chromosome 10). PDK-1 and mTOR control Akt activating phosphorylations at S473 and T308, whereas PI3K generatesphosphatidylinositol-3,4,5-triphosphate (PIP3), which serves as a membrane anchor(Storz and Toker 2002). PTEN serves as a negative regulator of the PIP3 level and thus decreases Akt activity (Ogg and Ruvkun.,1998;Sun et al.,1999). Study shows that

treating cells with exogenous hydrogen peroxideleads to activation of Akt and PDK-1(Higaki, Mikami et al. 2008). It is observed that PTEN is reversibly inactivated by (H_2O_2) (Lee, Yang et al. 2002). Loss of PTEN increases basal levels of hydrogen peroxide (H_2O_2) and superoxide due to a reduction in the expression of several antioxidant enzymes such ascopper/zinc superoxide dismutase and peroxiredoxins (Basseres and Baldwin 2006). This reveals a constant Akt activation through increase ROS production due to depletion of PTEN but also activation of its upstream kinases mediated by oxidative stress.

REGULATION OF THE IKK/NF-KB PATHWAY BY ROS

In various cancers types, the transcription factor known as NF-κB is uncoupled from its usual state of regulation and demonstrates increased activity (Biswas, Shi et al. 2004). Recent studies have recognized a pivotal role for NF-κB in the regulation of cell cycle and proliferation, tumor cell survival, cellular adhesion, and development of drug resistance in cancer cells during therapy(Ahmed, Cao et al. 2006, Bourguignon, Spevak et al. 2009).NF-κB serves as a redox-regulated sensor for oxidative stress (Li and Karin 1999)and low doses of (H_2O_2) activated it(Schreck, Albermann et al. 1992). In inactive, state NF-κB is inflexibly bound to IκB, its inhibitor that sequesters the transcription factor in the cytosol (Beg, Finco et al. 1993, Bonizzi, Bebien et al. 2004). The canonical activation of NF-κB is mediated by the NF-κB-inducing kinase (NIK) and the IκB kinase (IKK) complex, consisting of IKKα, IKKβ, and NEMO. Upon its activation by cytokines for example TNFα or IL-1, NIK phosphorylates and activates its downstream targets, the kinases IKKα and IKKβ (Bergmann, Hart et al. 1998). Active IKKs phosphorylate IκB and this process leads to its subsequent ubiquitination and proteasomal degradation (Singh, Darnay et al. 1996, Ghoda, Lin et al. 1997). Degradation of IκB translocates NF-κB to the nucleus, where it acts as a transcription factor to provoke the expression ofanti-inflammatory genes and anti-apoptotic genes (Liu, Zhang et al. 2017). Oxidative stress activates NF-κB by distinct signaling pathways (Janssen-Heininger, Poynter et al. 2000).

INVOLVEMENT OF MITOCHONDRIA IN CELL DEATH

In both normal and cancer cells, mitochondria not only participate in cellular ATP production but also play vital life-supporting roles in cellular homeostasis as well as ROS production, calcium signaling, and amino acid production (cataplerosis).ATP formation and cataplerosis are synchronized during the shared Krebs cycle in the mitochondria. To preserve the integrity of mitochondria due to cataplerosis, the entry of biosynthesis intermediates (anaplerosis) is therefore required. Glutamine was found to be an essential factor in this (Kovacevic and McGivan 1983). In Contrast to normal cells, in cancer cells, glutamine becomes a major substrate for the development and proliferation of cells (Bustamante and Pedersen 1977).

Mitochondria also play a central role in the intrinsic pathway of apoptosis. In response to several different stimuli that result in the permeabilization of the outer mitochondrial membrane (OMM), mitochondria release the number of soluble proteins from their intermembrane space to the cytosol that can activate cellular apoptotic programs (Saelens, Festjens et al. 2004). These critical and lethal functions are connected to a few important components of the mitochondrial bioenergetic metabolism, like cytochrome c, cardiolipin, ROS production, and membrane permeability.

A soluble nuclear-encoded protein of mitochondria known as Cytochrome c works as a single electron shuttle from the complex III to the complex IV of the electron transport chain. Though when cytochrome c is released into the cytosol, from mitochondria it takes part in the construction of the apoptosome and the progression programmed cell death(Wang 2001).

Normally most of the cytochrome c lies within the cristae, which are supposed to form anobstacle against its diffusion into the intermembrane space of mitochondria. In this context, the release of cytochrome c through mitochondria would require two mainsteps during the process of apoptosis. The first step needs an early remodeling of cristae configuration (Sun, Williams et al. 2007) which would need an expansion of the narrow tubular cristae junction, building the cytochrome cristae pool releasable after its relocation in the intermembrane space(Scorrano, Ashiya et al. 2002). Studies show that cristae remodeling is connected with the disassembly of the Optic Atrophy 1 (OPA1) oligomer (Frezza, Cipolat et al. 2006).This oligomer is essential for an adequate amount of cytochrome c to be released for the process of the cascade of apoptosis(Yamaguchi, Lartigue et al. 2008). This hypothesis is also supported by information that a definite threshold of released cytochrome c must be passed to activate caspases and induce apoptosis (Clayton, Clark et al. 2005). The second step is which need for cytocrome c release is Bcl-2 family proteins that regulate the oligomerization of pro-apoptotic protein Bax/Bak in the outer membrane of mitochondria, firmly regulate the movement of cytocrome c across the outer membrane(Kluck, Bossy-Wetzel et al. 1997).This results in construction of apoptosis-induced channel(Dejean, Ryu et al. 2010).

Moreover, in this way of cytochrome c release, the mitochondrial permeability transition pore (mPTP) is another way that plays a critical role in cell death following necrosis and ischemic injury(Halestrap 2009). mPTP mostly assembled at the contact sites of mitochondrial inner and outer membranes, it opens a large pore with low ion selectivity that enhances the permeability of the inner mitochondrial membrane (Kinnally, Peixoto et al. 2011). The important activators of mPTP opening are the mitochondrial ROS, calcium, and phosphate (Halestrap 2009). At the time of apoptotic cell death, m PTP might participate in the amplification loop that essential forcytochrome cexciting calcium mobilization through the endoplasmic reticulum (Boehning, Patterson et al. 2003). Therefore as apoptosis is stimulated, the construction of mitochondrial apoptosis-induced channel releases cytochrome c that might connect to and ease the calcium-dependent inactivation of inositol (Hanahan and Weinberg 2000) triphosphate receptors, allow to leave calcium through the endoplasmic reticulum. Calcium would then stimulate the mPTP, as a result, mitochondrial swelling occurs, this leads to disruption of the outer mitochondrial membrane which in turn leads to cytochrome c release from intermembrane space(Boehning, Patterson et al. 2003). s

MITOCHONDRIA AS A CLINICAL MARKER FOR CANCER

The homoplasmic nature of mtDNA and it's abundance make it an attractive molecular marker for cancer (Kirches 2017).Undoubtedly, it has been revealed that the presence of mutant mtDNA in cancer cells to be 220 times more than the mutated nuclear DNA marker(Chatterjee, Dasgupta et al. 2011). Mutant mtDNA is simply detectable in blood, urine, and saliva samples collected from patients with, bladder, neck, head, and lung cancers. mtDNA mutations have been used as clonal markers in breast cancer (Sultana, Rahman et al. 2012)and hepatocellular carcinoma(Nomoto, Yamashita et al. 2002). It is expected that 1,000different proteins comprise mitochondria. A new approach in proteomic technologies has made possible the quantitative analysis of protein expressed in mitochondria. The mitochondrial proteomic database has newly been documented by the National Institutes of Standards and Technology(Gulcicek, Colangelo et al. 2005). The help of mitochondrial protein profiles through new research efforts in normal and cancer cells will lead to the identification of markers fora clinical finding of cancer that may provide an understanding of how differential protein expression might affect the proportion of the disease(Cho 2007).A recent study showed that mitochondrial biomarkers also help in the prediction of tumor progression and poor overall survival in gastric cancers (Sotgia and Lisanti 2017).

MITOCHONDRIA AS A TARGET IN TUMOR CELLS FOR CANCER THERAPY

Even if the main contribution of mitochondrial energy metabolism remains controversial in cancer cells, the participation of mitochondria in cancer cell proliferation persists. For instance, the down regulation of some mitochondrial protein linked with disease detection (Cuezva, Krajewska et al. 2002, Isidoro, Casado et al. 2005). For that reason, mitochondria appear to be a promising therapeutic target for cancer treatment. It is essential to target pathways that found to differ between tumor cells and normal cells since the energy metabolism of tumors and the host cells rely on the same essential pathways for ATP. Amongst the potential therapeutic pathway targets in mitochondria that could put off-tumor progression was glutaminase or aminotransferases, enzymes that permit glutamine to trigger the Krebs cycle to make sure anaplerosis. Certainly, inhibiting aminotransferases by aminooxyacetic acid inhibitsxenograft tumor growth of MDA-MB-231 breast cancer cells (Thornburg, Nelson et al. 2008). Fatty acid synthesis which takes place in mitochondria is another important target for the treatment of cancer cells. Hence, blocking the fatty acid oxidation by etomoxir is seems to provoke cell death in human glioblastoma cells by diminishing NADH production, increase ROS generation, and reduce the generation of ATP(Pike, Smift et al. 2011).Additionally, the growth of human ovarian cancer cells in SCID mice was noticeably diminished by blocking the activity of fatty acid synthase (Wang 2001). Dichloroacetate indirectly triggers mitochondrial ATP formation by blocking pyruvate dehydrogenase kinase (PDK) and therefore activating pyruvate dehydrogenase (PDH)(Gudi, Bowker-Kinley et al. 1995). Dichloroacetate has been reducing in vivo and in vitro tumor cell growth(Chen, Cairns et al. 2009).In recent times, it was examined that blocking of MCT-1 results in the interruption of the metabolic symbiosis between oxygenated tumor cells and hypoxicby preventing the ability of aerobic cells to utilize lactate for oxidative phosphorylation and enforce them to utilize glucose instead of lactate. As a result, hypoxic tumor cells are deprived of glucose and died. This growth retardation of tumor cell and make available the rest of the cell (positioned at the neighborhood of blood vessels) susceptible to radiotherapy (Sonveaux, Vegran et al. 2008).To date, therapy targeting the intrinsic apoptosis pathway of mitochondria is one of the most exciting areas of cancer research and it's treatment. In this point ofview, mPTP is also a becoming target of selection. It was shown that lonidamine, a putative adenine nucleotide translocator (ANT), one of the major components of (mPTP) ligand, applies a cytostatic effect on tumor growth and survival in Phase II clinical study(Oudard, Carpentier et al. 2003). Furthermore, clodronate that serves as

a competitive ANT inhibitor has newly been seeming to get better the overall survival of patients suffering from primary breast cancer(Diel, Jaschke et al. 2008). To induce apoptosis in tumor cells, it is believable to therapeutically initiate mitochondrial outer membrane permeabilization (mPTP) through targeting mitochondrial membranes(Debatin, Poncet et al. 2002). The involvement of mitochondrial ROS in tumorigenic pathways demonstrates that the inhibition of ROS generation in mitochondria may be a useful strategy for cancer treatment. By using antioxidants such as quercetin, curcumin, vitamin C, and vitamin B, targeted particularly to mitochondria could signify a very fascinating approach toward cancer therapy(Mut-Salud, Alvarez et al. 2016, Forni, Facchiano et al. 2019).

The mtDNA also serves as a therapeutic target for cancer. Several discrete differences in mtDNA structure and function among normal cells and tumor cells provide the probable clinical use of mitochondria not only as markers for the diagnosis of cancer but also as targets for the new and site-specific anti-cancer drug for cancer treatment(Rowe, Weissig et al. 2001, Verschoor, Ungard et al. 2013).

Mitochondrial membrane potential plays an important role in the chemotherapeutic approach, which uses delocalized lipophilic cations (DLCs) that aggregate selectively in carcinoma cells in response to raised membrane potential. Some of these compounds have found to be effective in carcinoma cell killing *in* vivo and *in vitro*(Anderson, Wood et al. 1993). Some DLCs have been employed in photo chemotherapy (PCT), an investigational type of cancer treatment implicating light activation of a photo reactive drug or photosensitizer, that is selectively taken up or preserved by tumor cells (Weiss, Wong et al. 1987, Agostinis, Berg et al. 2011). The use of PCT as a form of treatment for neoplasms of the lung, brain, breast, or any other tissue available to light transmitted either by the body surface or internally through fiber-optic endoscopes. Cationic photosensitizers are principally capable as strong PCT agents. Similar to other DLCs, these compounds are aggregated by the cells into mitochondria in response to –inside negative trans membrane potentials and are hence, selectively accumulatein the mitochondria of tumor cells. By the use of localized photo irradiation, the photosensitizer can be transformed into a more reactive and toxic species, increasing theselective toxicity to tumor cells and providing a highly specific way to kill tumor cells without harm to normal cells of the body. Many efforts are being made to develop mitochondrially targeted drug and DNA delivery systems. A study has been demonstrated that by attaching mitochondriotropic residues to thesurface of liposomesmitochondria-specificconventional liposomes can be accomplished (Ellerby, Arap et al. 1999). Another recent study suggests that targeting mitochondria in the therapy of cancer could offer a foundation for selective anti-cancer activity (Rozanov, Cheltsov et al. 2019).

The long-term therapeutic objective of this type of research in the field of cancer biology is to someday successfully create mitochondria-specific vehicles that will potentially deliver drugs or mtDNA into the organelle to eliminatedysfunctional mitochondria or restore mitochondria with functional copies of the genome.

CONCLUSION

Mitochondria play a critical role in most of the important processes of energy metabolism in the body.Thus impairment of mitochondrial function or dysfunction of mt DNA leads to many neurological disorders and cancer development. For all those reasons mitochondria serve as a promising target for cancer therapy. Furthermore, besides particularly target mitochondria, targeting the anaerobic glycolysis, for example, hexokinase and oncogenes will significantly contribute to these anti-cancer therapies. Studies have shown that all types of

cancer cells illustrate a high glycolytic flux but not all have diminished mitochondrial oxidative phosphorylation. For that reason, contrary to Warburg theory, not all tumor cells rely on glycolysis for ATP and the increased glycolysis is not the outcome of altered oxidative phosphorylation in all tumor cells. However, mitochondria stay in the middle of critical physiological processes in tumor cells and play a vital role in the progression of tumors.

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REFERENCES

Aggarwal, V., H. S. Tuli, A. Varol, F. Thakral, M. B. Yerer, K. Sak, M. Varol, A. Jain, M. A. Khan and G. Sethi (2019). "Role of Reactive Oxygen Species in Cancer Progression: Molecular Mechanisms and Recent Advancements." Biomolecules9(11).

Agostinis, P., K. Berg, K. A. Cengel, T. H. Foster, A. W. Girotti, S. O. Gollnick, S. M. Hahn, M. R. Hamblin, A. Juzeniene, D. Kessel, M. Korbelik, J. Moan, P. Mroz, D. Nowis, J. Piette, B. C. Wilson and J. Golab (2011). "Photodynamic therapy of cancer: an update." CA Cancer J Clin61(4): 250-281.

Ahmed, K. M., N. Cao and J. J. Li (2006). "HER-2 and NF-kappaB as the targets for therapy-resistant breast cancer." Anticancer Res26(6B): 4235-4243.

Alberts, B., A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter (2002). How cells obtain energy from food. Molecular Biology of the Cell. 4th edition, Garland Science.

Almeida, A., S. Moncada and J. P. Bolanos (2004). "Nitric oxide switches on glycolysis through the AMP protein kinase and 6-phosphofructo-2-kinase pathway." Nat Cell Biol6(1): 45-51.

Anderson, S., A. T. Bankier, B. G. Barrell, M. H. de Bruijn, A. R. Coulson, J. Drouin, I. C. Eperon, D. P. Nierlich, B. A. Roe, F. Sanger, P. H. Schreier, A. J. Smith, R. Staden and I. G. Young (1981). "Sequence and organization of the human mitochondrial genome." Nature290(5806): 457-465.

Anderson, W. M., J. M. Wood and A. C. Anderson (1993). "Inhibition of mitochondrial and Paracoccus denitrificans NADH-ubiquinone reductase by oxacarbocyanine dyes. A structure-activity study." Biochem Pharmacol45(10): 2115-2122.

Basseres, D. S. and A. S. Baldwin (2006). "Nuclear factor-kappaB and inhibitor of kappaB kinase pathways in oncogenic initiation and progression." Oncogene25(51): 6817-6830.

Baysal, B. E. (2006). "Role of mitochondrial mutations in cancer." Endocr Pathol17(3): 203-212.

Beg, A. A., T. S. Finco, P. V. Nantermet and A. S. Baldwin, Jr. (1993). "Tumor necrosis factor and interleukin-1 lead to phosphorylation and loss of I kappa B alpha: a mechanism for NF-kappa B activation." Mol Cell Biol13(6): 3301-3310.

Bensaad, K., A. Tsuruta, M. A. Selak, M. N. Vidal, K. Nakano, R. Bartrons, E. Gottlieb and K. H. Vousden (2006). "TIGAR, a p53-inducible regulator of glycolysis and apoptosis." Cell126(1): 107-120.

Bergmann, M., L. Hart, M. Lindsay, P. J. Barnes and R. Newton (1998). "IkappaBalpha degradation and nuclear factor-kappaB DNA binding are insufficient for interleukin-1beta and tumor necrosis factor-alpha-induced kappaB-dependent transcription. Requirement for an additional activation pathway." J Biol Chem273(12): 6607-6610.

Biswas, D. K., Q. Shi, S. Baily, I. Strickland, S. Ghosh, A. B. Pardee and J. D. Iglehart (2004). "NF-kappa B activation in human breast cancer specimens and its role in cell proliferation and apoptosis." Proc Natl Acad Sci U S A101(27): 10137-10142.

Boehning, D., R. L. Patterson, L. Sedaghat, N. O. Glebova, T. Kurosaki and S. H. Snyder (2003). "Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis." Nat Cell Biol5(12): 1051-1061.
Bonizzi, G., M. Bebien, D. C. Otero, K. E. Johnson-Vroom, Y. Cao, D. Vu, A. G. Jegga, B. J. Aronow, G. Ghosh, R. C. Rickert and M. Karin (2004). "Activation of IKKalpha target genes depends on recognition of specific kappaB binding sites by RelB:p52 dimers." EMBO J23(21): 4202-4210.
Bonni, A., A. Brunet, A. E. West, S. R. Datta, M. A. Takasu and M. E. Greenberg (1999). "Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms." Science286(5443): 1358-1362.
Boultwood, J., C. Fidler, K. I. Mills, P. M. Frodsham, R. Kusec, A. Gaiger, R. E. Gale, D. C. Linch, T. J. Littlewood, P. A. Moss and J. S. Wainscoat (1996). "Amplification of mitochondrial DNA in acute myeloid leukaemia." Br J Haematol95(2): 426-431.
Bourguignon, L. Y., C. C. Spevak, G. Wong, W. Xia and E. Gilad (2009). "Hyaluronan-CD44 interaction with protein kinase C(epsilon) promotes oncogenic signaling by the stem cell marker Nanog and the Production of microRNA-21, leading to down-regulation of the tumor suppressor protein PDCD4, anti-apoptosis, and chemotherapy resistance in breast tumor cells." J Biol Chem284(39): 26533-26546.
Brizel, D. M., T. Schroeder, R. L. Scher, S. Walenta, R. W. Clough, M. W. Dewhirst and W. Mueller-Klieser (2001). "Elevated tumor lactate concentrations predict for an increased risk of metastases in head-and-neck cancer." Int J Radiat Oncol Biol Phys51(2): 349-353.
Brunelle, J. K., E. L. Bell, N. M. Quesada, K. Vercauteren, V. Tiranti, M. Zeviani, R. C. Scarpulla and N. S. Chandel (2005). "Oxygen sensing requires mitochondrial ROS but not oxidative phosphorylation." Cell Metab1(6): 409-414.
Bustamante, E. and P. L. Pedersen (1977). "High aerobic glycolysis of rat hepatoma cells in culture: role of mitochondrial hexokinase." Proc Natl Acad Sci U S A74(9): 3735-3739.
Canter, J. A., A. R. Kallianpur, F. F. Parl and R. C. Millikan (2005). "Mitochondrial DNA G10398A polymorphism and invasive breast cancer in African-American women." Cancer Res65(17): 8028-8033.
Capuano, F., F. Guerrieri and S. Papa (1997). "Oxidative phosphorylation enzymes in normal and neoplastic cell growth." J Bioenerg Biomembr29(4): 379-384.
Chan, D. W., V. W. Liu, G. S. Tsao, K. M. Yao, T. Furukawa, K. K. Chan and H. Y. Ngan (2008). "Loss of MKP3 mediated by oxidative stress enhances tumorigenicity and chemoresistance of ovarian cancer cells." Carcinogenesis29(9): 1742-1750.
Chan, S. H. and R. L. Barbour (1983). "Adenine nucleotide transport in hepatoma mitochondria. Characterization of factors influencing the kinetics of ADP and ATP uptake." Biochim Biophys Acta723(1): 104-113.
Chatterjee, A., S. Dasgupta and D. Sidransky (2011). "Mitochondrial subversion in cancer." Cancer Prev Res (Phila)4(5): 638-654.
Chen, Y., R. Cairns, I. Papandreou, A. Koong and N. C. Denko (2009). "Oxygen consumption can regulate the growth of tumors, a new perspective on the Warburg effect." PLoS One4(9): e7033.
Cho, W. C. (2007). "Contribution of oncoproteomics to cancer biomarker discovery." Mol Cancer6: 25.
Clayton, D. A. and J. Vinograd (1967). "Circular dimer and catenate forms of mitochondrial DNA in human leukaemic leucocytes." Nature216(5116): 652-657.
Clayton, R., J. B. Clark and M. Sharpe (2005). "Cytochrome c release from rat brain mitochondria is proportional to the mitochondrial functional deficit: implications for apoptosis and neurodegenerative disease." J Neurochem92(4): 840-849.

Copin, J. C., Y. Gasche and P. H. Chan (2000). "Overexpression of copper/zinc superoxide dismutase does not prevent neonatal lethality in mutant mice that lack manganese superoxide dismutase." Free Radic Biol Med28(10): 1571-1576.
Cuezva, J. M., M. Krajewska, M. L. de Heredia, S. Krajewski, G. Santamaria, H. Kim, J. M. Zapata, H. Marusawa, M. Chamorro and J. C. Reed (2002). "The bioenergetic signature of cancer: a marker of tumor progression." Cancer Res62(22): 6674-6681.
Dang, C. V. and G. L. Semenza (1999). "Oncogenic alterations of metabolism." Trends Biochem Sci24(2): 68-72.
Debatin, K. M., D. Poncet and G. Kroemer (2002). "Chemotherapy: targeting the mitochondrial cell death pathway." Oncogene21(57): 8786-8803.
DeBerardinis, R. J., J. J. Lum, G. Hatzivassiliou and C. B. Thompson (2008). "The biology of cancer: metabolic reprogramming fuels cell growth and proliferation." Cell Metab7(1): 11-20.
Dejean, L. M., S. Y. Ryu, S. Martinez-Caballero, O. Teijido, P. M. Peixoto and K. W. Kinnally (2010). "MAC and Bcl-2 family proteins conspire in a deadly plot." Biochim Biophys Acta1797(6-7): 1231-1238.
Di Marzo, N., E. Chisci and R. Giovannoni (2018). "The Role of Hydrogen Peroxide in Redox-Dependent Signaling: Homeostatic and Pathological Responses in Mammalian Cells." Cells7(10).
Diel, I. J., A. Jaschke, E. F. Solomayer, C. Gollan, G. Bastert, C. Sohn and F. Schuetz (2008). "Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up." Ann Oncol19(12): 2007-2011.
Ellerby, H. M., W. Arap, L. M. Ellerby, R. Kain, R. Andrusiak, G. D. Rio, S. Krajewski, C. R. Lombardo, R. Rao, E. Ruoslahti, D. E. Bredesen and R. Pasqualini (1999). "Anti-cancer activity of targeted pro-apoptotic peptides." Nat Med5(9): 1032-1038.
Elstrom, R. L., D. E. Bauer, M. Buzzai, R. Karnauskas, M. H. Harris, D. R. Plas, H. Zhuang, R. M. Cinalli, A. Alavi, C. M. Rudin and C. B. Thompson (2004). "Akt stimulates aerobic glycolysis in cancer cells." Cancer Res64(11): 3892-3899.
Forni, C., F. Facchiano, M. Bartoli, S. Pieretti, A. Facchiano, D. D'Arcangelo, S. Norelli, G. Valle, R. Nisini, S. Beninati, C. Tabolacci and R. N. Jadeja (2019). "Beneficial Role of Phytochemicals on Oxidative Stress and Age-Related Diseases." Biomed Res Int2019: 8748253.
Frezza, C., S. Cipolat, O. Martins de Brito, M. Micaroni, G. V. Beznoussenko, T. Rudka, D. Bartoli, R. S. Polishuck, N. N. Danial, B. De Strooper and L. Scorrano (2006). "OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion." Cell126(1): 177-189.
Fukuda, R., H. Zhang, J. W. Kim, L. Shimoda, C. V. Dang and G. L. Semenza (2007). "HIF-1 regulates cytochrome oxidase subunits to optimize efficiency of respiration in hypoxic cells." Cell129(1): 111-122.
Gao, P., H. Zhang, R. Dinavahi, F. Li, Y. Xiang, V. Raman, Z. M. Bhujwalla, D. W. Felsher, L. Cheng, J. Pevsner, L. A. Lee, G. L. Semenza and C. V. Dang (2007). "HIF-dependent antitumorigenic effect of antioxidants in vivo." Cancer Cell12(3): 230-238.
Gatenby, R. A. and R. J. Gillies (2004). "Why do cancers have high aerobic glycolysis?" Nat Rev Cancer4(11): 891-899.
Ghoda, L., X. Lin and W. C. Greene (1997). "The 90-kDa ribosomal S6 kinase (pp90rsk) phosphorylates the N-terminal regulatory domain of IkappaBalpha and stimulates its degradation in vitro." J Biol Chem272(34): 21281-21288.

Glorieux, C. and P. B. Calderon (2017). "Catalase, a remarkable enzyme: targeting the oldest antioxidant enzyme to find a new cancer treatment approach." Biol Chem398(10): 1095-1108.
Gogvadze, V., B. Zhivotovsky and S. Orrenius (2010). "The Warburg effect and mitochondrial stability in cancer cells." Molecular aspects of medicine31(1): 60-74.
Gottlieb, E. and I. P. Tomlinson (2005). "Mitochondrial tumour suppressors: a genetic and biochemical update." Nat Rev Cancer5(11): 857-866.
Grossman, L. I. and E. A. Shoubridge (1996). "Mitochondrial genetics and human disease." Bioessays18(12): 983-991.
Gudi, R., M. M. Bowker-Kinley, N. Y. Kedishvili, Y. Zhao and K. M. Popov (1995). "Diversity of the pyruvate dehydrogenase kinase gene family in humans." J Biol Chem270(48): 28989-28994.
Gulcicek, E. E., C. M. Colangelo, W. McMurray, K. Stone, K. Williams, T. Wu, H. Zhao, H. Spratt, A. Kurosky and B. Wu (2005). "Proteomics and the analysis of proteomic data: an overview of current protein-profiling technologies." Curr Protoc BioinformaticsChapter 13: Unit 13 11.
Guppy, M., E. Greiner and K. Brand (1993). "The role of the Crabtree effect and an endogenous fuel in the energy metabolism of resting and proliferating thymocytes." Eur J Biochem212(1): 95-99.
Guzy, R. D., B. Hoyos, E. Robin, H. Chen, L. Liu, K. D. Mansfield, M. C. Simon, U. Hammerling and P. T. Schumacker (2005). "Mitochondrial complex III is required for hypoxia-induced ROS production and cellular oxygen sensing." Cell Metab1(6): 401-408.
Guzy, R. D. and P. T. Schumacker (2006). "Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia." Exp Physiol91(5): 807-819.
Halestrap, A. P. (2009). "What is the mitochondrial permeability transition pore?" J Mol Cell Cardiol46(6): 821-831.
Halliwell, B. and C. E. Cross (1994). "Oxygen-derived species: their relation to human disease and environmental stress." Environ Health Perspect102 Suppl 10: 5-12.
Hanahan, D. and R. A. Weinberg (2000). "The hallmarks of cancer." Cell100(1): 57-70.
Heerdt, B. G., H. K. Halsey, M. Lipkin and L. H. Augenlicht (1990). "Expression of mitochondrial cytochrome c oxidase in human colonic cell differentiation, transformation, and risk for colonic cancer." Cancer Res50(5): 1596-1600.
Higaki, Y., T. Mikami, N. Fujii, M. F. Hirshman, K. Koyama, T. Seino, K. Tanaka and L. J. Goodyear (2008). "Oxidative stress stimulates skeletal muscle glucose uptake through a phosphatidylinositol 3-kinase-dependent pathway." Am J Physiol Endocrinol Metab294(5): E889-897.
Isidoro, A., E. Casado, A. Redondo, P. Acebo, E. Espinosa, A. M. Alonso, P. Cejas, D. Hardisson, J. A. Fresno Vara, C. Belda-Iniesta, M. Gonzalez-Baron and J. M. Cuezva (2005). "Breast carcinomas fulfill the Warburg hypothesis and provide metabolic markers of cancer prognosis." Carcinogenesis26(12): 2095-2104.
Janssen-Heininger, Y. M., M. E. Poynter and P. A. Baeuerle (2000). "Recent advances towards understanding redox mechanisms in the activation of nuclear factor kappaB." Free Radic Biol Med28(9): 1317-1327.
Johnson, L. V., M. L. Walsh, B. J. Bockus and L. B. Chen (1981). "Monitoring of relative mitochondrial membrane potential in living cells by fluorescence microscopy." J Cell Biol88(3): 526-535.
Kim, I. Y., D. H. Lee, D. K. Lee, W. J. Kim, M. M. Kim, R. A. Morton, S. P. Lerner and S. J. Kim (2004). "Restoration of bone morphogenetic protein receptor type II expression leads to

a decreased rate of tumor growth in bladder transitional cell carcinoma cell line TSU-Pr1." Cancer Res64(20): 7355-7360.
Kim, J. W., I. Tchernyshyov, G. L. Semenza and C. V. Dang (2006). "HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia." Cell Metab3(3): 177-185.
Kinnally, K. W., P. M. Peixoto, S. Y. Ryu and L. M. Dejean (2011). "Is mPTP the gatekeeper for necrosis, apoptosis, or both?" Biochim Biophys Acta1813(4): 616-622.
Kirches, E. (2017). "MtDNA As a Cancer Marker: A Finally Closed Chapter?" Curr Genomics18(3): 255-267.
Kluck, R. M., E. Bossy-Wetzel, D. R. Green and D. D. Newmeyer (1997). "The release of cytochrome c from mitochondria: a primary site for Bcl-2 regulation of apoptosis." Science275(5303): 1132-1136.
Kovacevic, Z. and J. D. McGivan (1983). "Mitochondrial metabolism of glutamine and glutamate and its physiological significance." Physiol Rev63(2): 547-605.
Kroemer, G. (1997). "The proto-oncogene Bcl-2 and its role in regulating apoptosis." Nat Med3(6): 614-620.
Kroemer, G. and J. Pouyssegur (2008). "Tumor cell metabolism: cancer's Achilles' heel." Cancer Cell13(6): 472-482.
Kuhajda, F. P. (2000). "Fatty-acid synthase and human cancer: new perspectives on its role in tumor biology." Nutrition16(3): 202-208.
Kumari, S., A. K. Badana, M. M. G, S. G and R. Malla (2018). "Reactive Oxygen Species: A Key Constituent in Cancer Survival." Biomark Insights13: 1177271918755391.
Kunkel, T. A. and L. A. Loeb (1981). "Fidelity of mammalian DNA polymerases." Science213(4509): 765-767.
Lee, S. R., K. S. Yang, J. Kwon, C. Lee, W. Jeong and S. G. Rhee (2002). "Reversible inactivation of the tumor suppressor PTEN by H2O2." J Biol Chem277(23): 20336-20342.
Levine, A. J. and M. Oren (2009). "The first 30 years of p53: growing ever more complex." Nat Rev Cancer9(10): 749-758.
Li, N. and M. Karin (1999). "Is NF-kappaB the sensor of oxidative stress?" FASEB J13(10): 1137-1143.
Lievre, A., C. Chapusot, A. M. Bouvier, F. Zinzindohoue, F. Piard, P. Roignot, L. Arnould, P. Beaune, J. Faivre and P. Laurent-Puig (2005). "Clinical value of mitochondrial mutations in colorectal cancer." J Clin Oncol23(15): 3517-3525.
Liguori, I., G. Russo, F. Curcio, G. Bulli, L. Aran, D. Della-Morte, G. Gargiulo, G. Testa, F. Cacciatore, D. Bonaduce and P. Abete (2018). "Oxidative stress, aging, and diseases." Clin Interv Aging13: 757-772.
Liu, L. Z., X. W. Hu, C. Xia, J. He, Q. Zhou, X. Shi, J. Fang and B. H. Jiang (2006). "Reactive oxygen species regulate epidermal growth factor-induced vascular endothelial growth factor and hypoxia-inducible factor-1alpha expression through activation of AKT and P70S6K1 in human ovarian cancer cells." Free Radic Biol Med41(10): 1521-1533.
Liu, T., L. Zhang, D. Joo and S.-C. Sun (2017). "NF-κB signaling in inflammation." Signal transduction and targeted therapy2(1): 1-9.
Liu, V. W., H. H. Shi, A. N. Cheung, P. M. Chiu, T. W. Leung, P. Nagley, L. C. Wong and H. Y. Ngan (2001). "High incidence of somatic mitochondrial DNA mutations in human ovarian carcinomas." Cancer Res61(16): 5998-6001.
Lodish, H., A. Berk, S. L. Zipursky, P. Matsudaira, D. Baltimore and J. Darnell (2000). Oxidation of glucose and fatty acids to CO2. Molecular Cell Biology. 4th edition, WH Freeman.

Lundholm, K., S. Edstrom, I. Karlberg, L. Ekman and T. Schersten (1982). "Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients." Cancer50(6): 1142-1150.
Mandelker, D. L., K. Yamashita, Y. Tokumaru, K. Mimori, D. L. Howard, Y. Tanaka, A. L. Carvalho, W. W. Jiang, H. L. Park, M. S. Kim, M. Osada, M. Mori and D. Sidransky (2005). "PGP9.5 promoter methylation is an independent prognostic factor for esophageal squamous cell carcinoma." Cancer Res65(11): 4963-4968.
Mazurek, S., C. B. Boschek and E. Eigenbrodt (1997). "The role of phosphometabolites in cell proliferation, energy metabolism, and tumor therapy." J Bioenerg Biomembr29(4): 315-330.
Mitchell, L., G. A. Hobbs, A. Aghajanian and S. L. Campbell (2013). "Redox regulation of Ras and Rho GTPases: mechanism and function." Antioxid Redox Signal18(3): 250-258.
Modica-Napolitano, J. S., M. Kulawiec and K. K. Singh (2007). "Mitochondria and human cancer." Curr Mol Med7(1): 121-131.
Modica-Napolitano, J. S. and K. K. Singh (2002). "Mitochondria as targets for detection and treatment of cancer." Expert Rev Mol Med4(9): 1-19.
Mut-Salud, N., P. J. Alvarez, J. M. Garrido, E. Carrasco, A. Aranega and F. Rodriguez-Serrano (2016). "Antioxidant Intake and Antitumor Therapy: Toward Nutritional Recommendations for Optimal Results." Oxid Med Cell Longev2016: 6719534.
Nishikawa, M., N. Oshitani, T. Matsumoto, T. Nishigami, T. Arakawa and M. Inoue (2005). "Accumulation of mitochondrial DNA mutation with colorectal carcinogenesis in ulcerative colitis." Br J Cancer93(3): 331-337.
Nita, M. and A. Grzybowski (2016). "The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults." Oxid Med Cell Longev2016: 3164734.
Nomoto, S., K. Yamashita, K. Koshikawa, A. Nakao and D. Sidransky (2002). "Mitochondrial D-loop mutations as clonal markers in multicentric hepatocellular carcinoma and plasma." Clin Cancer Res8(2): 481-487.
Ockner, R. K., R. M. Kaikaus and N. M. Bass (1993). "Fatty-acid metabolism and the pathogenesis of hepatocellular carcinoma: review and hypothesis." Hepatology18(3): 669-676.
Ostrakhovitch, E. A. and M. G. Cherian (2005). "Inhibition of extracellular signal regulated kinase (ERK) leads to apoptosis inducing factor (AIF) mediated apoptosis in epithelial breast cancer cells: the lack of effect of ERK in p53 mediated copper induced apoptosis." J Cell Biochem95(6): 1120-1134.
Oudard, S., A. Carpentier, E. Banu, F. Fauchon, D. Celerier, M. F. Poupon, B. Dutrillaux, J. M. Andrieu and J. Y. Delattre (2003). "Phase II study of lonidamine and diazepam in the treatment of recurrent glioblastoma multiforme." J Neurooncol63(1): 81-86.
Papandreou, I., R. A. Cairns, L. Fontana, A. L. Lim and N. C. Denko (2006). "HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption." Cell Metab3(3): 187-197.
Park, S. A., H. K. Na, E. H. Kim, Y. N. Cha and Y. J. Surh (2009). "4-hydroxyestradiol induces anchorage-independent growth of human mammary epithelial cells via activation of IkappaB kinase: potential role of reactive oxygen species." Cancer Res69(6): 2416-2424.
Pedersen, P. L. (1978). "Tumor mitochondria and the bioenergetics of cancer cells." Prog Exp Tumor Res22: 190-274.
Pedersen, P. L. and H. P. Morris (1974). "Uncoupler-stimulated adenosine triphosphatase activity. Deficiency in intact mitochondria from Morris hepatomas and ascites tumor cells." J Biol Chem249(11): 3327-3334.

Pejovic, T., D. Ladner, M. Intengan, K. Zheng, T. Fairchild, D. Dillon, S. Easley, D. Dillon, D. Marchetti, P. Schwartz, S. Lele, J. Costa and K. Odunsi (2004). "Somatic D-loop mitochondrial DNA mutations are frequent in uterine serous carcinoma." Eur J Cancer40(16): 2519-2524.
Pike, L. S., A. L. Smift, N. J. Croteau, D. A. Ferrick and M. Wu (2011). "Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells." Biochim Biophys Acta1807(6): 726-734.
Polyak, K., Y. Li, H. Zhu, C. Lengauer, J. K. Willson, S. D. Markowitz, M. A. Trush, K. W. Kinzler and B. Vogelstein (1998). "Somatic mutations of the mitochondrial genome in human colorectal tumours." Nat Genet20(3): 291-293.
Pouyssegur, J., F. Dayan and N. M. Mazure (2006). "Hypoxia signalling in cancer and approaches to enforce tumour regression." Nature441(7092): 437-443.
Ramanathan, A., C. Wang and S. L. Schreiber (2005). "Perturbational profiling of a cell-line model of tumorigenesis by using metabolic measurements." Proc Natl Acad Sci U S A102(17): 5992-5997.
Reed, J. C. (1997). "Double identity for proteins of the Bcl-2 family." Nature387(6635): 773-776.
Roberts, P. J. and C. J. Der (2007). "Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer." Oncogene26(22): 3291-3310.
Rowe, T. C., V. Weissig and J. W. Lawrence (2001). "Mitochondrial DNA metabolism targeting drugs." Adv Drug Deliv Rev49(1-2): 175-187.
Rozanov, D., A. Cheltsov, A. Nilsen, C. Boniface, I. Forquer, J. Korkola, J. Gray, J. Tyner, C. E. Tognon, G. B. Mills and P. Spellman (2019). "Targeting mitochondria in cancer therapy could provide a basis for the selective anti-cancer activity." PLoS One14(3): e0205623.
Rygiel, T. P., A. E. Mertens, K. Strumane, R. van der Kammen and J. G. Collard (2008). "The Rac activator Tiam1 prevents keratinocyte apoptosis by controlling ROS-mediated ERK phosphorylation." J Cell Sci121(Pt 8): 1183-1192.
Saelens, X., N. Festjens, L. Vande Walle, M. van Gurp, G. van Loo and P. Vandenabeele (2004). "Toxic proteins released from mitochondria in cell death." Oncogene23(16): 2861-2874.
Sangkhathat, S., T. Kusafuka, A. Yoneda, S. Kuroda, Y. Tanaka, N. Sakai and M. Fukuzawa (2005). "Renal cell carcinoma in a pediatric patient with an inherited mitochondrial mutation." Pediatr Surg Int21(9): 745-748.
Schatz, G. (1996). "The protein import system of mitochondria." J Biol Chem271(50): 31763-31766.
Schreck, R., K. Albermann and P. A. Baeuerle (1992). "Nuclear factor kappa B: an oxidative stress-responsive transcription factor of eukaryotic cells (a review)." Free Radic Res Commun17(4): 221-237.
Scorrano, L., M. Ashiya, K. Buttle, S. Weiler, S. A. Oakes, C. A. Mannella and S. J. Korsmeyer (2002). "A distinct pathway remodels mitochondrial cristae and mobilizes cytochrome c during apoptosis." Dev Cell2(1): 55-67.
Selvanayagam, P. and S. Rajaraman (1996). "Detection of mitochondrial genome depletion by a novel cDNA in renal cell carcinoma." Lab Invest74(3): 592-599.
Semenza, G. L., B. H. Jiang, S. W. Leung, R. Passantino, J. P. Concordet, P. Maire and A. Giallongo (1996). "Hypoxia response elements in the aldolase A, enolase 1, and lactate dehydrogenase A gene promoters contain essential binding sites for hypoxia-inducible factor 1." J Biol Chem271(51): 32529-32537.
Shay, J. W. and H. Werbin (1987). "Are mitochondrial DNA mutations involved in the carcinogenic process?" Mutat Res186(2): 149-160.

Simonnet, H., N. Alazard, K. Pfeiffer, C. Gallou, C. Beroud, J. Demont, R. Bouvier, H. Schagger and C. Godinot (2002). "Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma." Carcinogenesis23(5): 759-768.
Singh, K. K. (2004). "Mitochondria damage checkpoint in apoptosis and genome stability." FEMS Yeast Research5(2): 127-132.
Singh, S., B. G. Darnay and B. B. Aggarwal (1996). "Site-specific tyrosine phosphorylation of IkappaBalpha negatively regulates its inducible phosphorylation and degradation." J Biol Chem271(49): 31049-31054.
Solaini, G., G. Sgarbi and A. Baracca (2011). "Oxidative phosphorylation in cancer cells." Biochimica et Biophysica Acta (BBA)-Bioenergetics1807(6): 534-542.
Song, W. H., J. W. Ballard, Y. J. Yi and P. Sutovsky (2014). "Regulation of mitochondrial genome inheritance by autophagy and ubiquitin-proteasome system: implications for health, fitness, and fertility." Biomed Res Int2014: 981867.
Sonveaux, P., F. Vegran, T. Schroeder, M. C. Wergin, J. Verrax, Z. N. Rabbani, C. J. De Saedeleer, K. M. Kennedy, C. Diepart, B. F. Jordan, M. J. Kelley, B. Gallez, M. L. Wahl, O. Feron and M. W. Dewhirst (2008). "Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice." J Clin Invest118(12): 3930-3942.
Sotgia, F. and M. P. Lisanti (2017). "Mitochondrial biomarkers predict tumor progression and poor overall survival in gastric cancers: Companion diagnostics for personalized medicine." Oncotarget8(40): 67117-67128.
Stamati, K., V. Mudera and U. Cheema (2011). "Evolution of oxygen utilization in multicellular organisms and implications for cell signalling in tissue engineering." J Tissue Eng2(1): 2041731411432365.
Storz, P. (2005). "Reactive oxygen species in tumor progression." Front Biosci10: 1881-1896.
Storz, P. and A. Toker (2002). "3'-phosphoinositide-dependent kinase-1 (PDK-1) in PI 3-kinase signaling." Front Biosci7: d886-902.
Subramani, R., E. Gonzalez, A. Arumugam, S. Nandy, V. Gonzalez, J. Medel, F. Camacho, A. Ortega, S. Bonkoungou, M. Narayan, A. Dwivedi and R. Lakshmanaswamy (2016). "Nimbolide inhibits pancreatic cancer growth and metastasis through ROS-mediated apoptosis and inhibition of epithelial-to-mesenchymal transition." Sci Rep6: 19819.
Sultana, G. N., A. Rahman, A. D. Shahinuzzaman, R. A. Begum and C. F. Hossain (2012). "Mitochondrial DNA mutations---candidate biomarkers for breast cancer diagnosis in Bangladesh." Chin J Cancer31(9): 449-454.
Summerhayes, I. C., T. J. Lampidis, S. D. Bernal, J. J. Nadakavukaren, K. K. Nadakavukaren, E. L. Shepherd and L. B. Chen (1982). "Unusual retention of rhodamine 123 by mitochondria in muscle and carcinoma cells." Proc Natl Acad Sci U S A79(17): 5292-5296.
Sun, A. S. and A. I. Cederbaum (1980). "Oxidoreductase activities in normal rat liver, tumor-bearing rat liver, and hepatoma HC-252." Cancer Res40(12): 4677-4681.
Sun, A. S., K. Sepkowitz and S. A. Geller (1981). "A study of some mitochondrial and peroxisomal enzymes in human colonic adenocarcinoma." Lab Invest44(1): 13-17.
Sun, M. G., J. Williams, C. Munoz-Pinedo, G. A. Perkins, J. M. Brown, M. H. Ellisman, D. R. Green and T. G. Frey (2007). "Correlated three-dimensional light and electron microscopy reveals transformation of mitochondria during apoptosis." Nat Cell Biol9(9): 1057-1065.
Swietach, P., R. D. Vaughan-Jones and A. L. Harris (2007). "Regulation of tumor pH and the role of carbonic anhydrase 9." Cancer Metastasis Rev26(2): 299-310.
Takeuchi, H., A. Fujimoto and D. S. Hoon (2004). "Detection of mitochondrial DNA alterations in plasma of malignant melanoma patients." Ann N Y Acad Sci1022: 50-54.

Tamori, A., S. Nishiguchi, M. Nishikawa, S. Kubo, N. Koh, K. Hirohashi, S. Shiomi and M. Inoue (2004). "Correlation between clinical characteristics and mitochondrial D-loop DNA mutations in hepatocellular carcinoma." J Gastroenterol39(11): 1063-1068.
Tan, D. J., R. K. Bai and L. J. Wong (2002). "Comprehensive scanning of somatic mitochondrial DNA mutations in breast cancer." Cancer Res62(4): 972-976.
Thornburg, J. M., K. K. Nelson, B. F. Clem, A. N. Lane, S. Arumugam, A. Simmons, J. W. Eaton, S. Telang and J. Chesney (2008). "Targeting aspartate aminotransferase in breast cancer." Breast Cancer Res10(5): R84.
Truong, T. H. and K. S. Carroll (2013). "Redox regulation of protein kinases." Crit Rev Biochem Mol Biol48(4): 332-356.
Verschoor, M. L., R. Ungard, A. Harbottle, J. P. Jakupciak, R. L. Parr and G. Singh (2013). "Mitochondria and cancer: past, present, and future." Biomed Res Int2013: 612369.
Wallace, D. C. (2012). "Mitochondria and cancer." Nat Rev Cancer12(10): 685-698.
Wang, X. (2001). "The expanding role of mitochondria in apoptosis." Genes Dev15(22): 2922-2933.
Warburg, O. (1956). "On respiratory impairment in cancer cells." Science124(3215): 269-270.
Weinhouse, S. (1976). "The Warburg hypothesis fifty years later." Z Krebsforsch Klin Onkol Cancer Res Clin Oncol87(2): 115-126.
Weiss, M. J., J. R. Wong, C. S. Ha, R. Bleday, R. R. Salem, G. D. Steele, Jr. and L. B. Chen (1987). "Dequalinium, a topical antimicrobial agent, displays anticarcinoma activity based on selective mitochondrial accumulation." Proc Natl Acad Sci U S A84(15): 5444-5448.
Welter, C., S. Dooley and N. Blin (1989). "A rapid protocol for the purification of mitochondrial DNA suitable for studying restriction fragment length polymorphisms." Gene83(1): 169-172.
Wu, M., A. Neilson, A. L. Swift, R. Moran, J. Tamagnine, D. Parslow, S. Armistead, K. Lemire, J. Orrell, J. Teich, S. Chomicz and D. A. Ferrick (2007). "Multiparameter metabolic analysis reveals a close link between attenuated mitochondrial bioenergetic function and enhanced glycolysis dependency in human tumor cells." Am J Physiol Cell Physiol292(1): C125-136.
Yamaguchi, R., L. Lartigue, G. Perkins, R. T. Scott, A. Dixit, Y. Kushnareva, T. Kuwana, M. H. Ellisman and D. D. Newmeyer (2008). "Opa1-mediated cristae opening is Bax/Bak and BH3 dependent, required for apoptosis, and independent of Bak oligomerization." Mol Cell31(4): 557-569.
Younus, H. (2018). "Therapeutic potentials of superoxide dismutase." Int J Health Sci (Qassim)12(3): 88-93.
Zamzami, N., S. A. Susin, P. Marchetti, T. Hirsch, I. Gomez-Monterrey, M. Castedo and G. Kroemer (1996). "Mitochondrial control of nuclear apoptosis." J Exp Med183(4): 1533-1544.
Zhang, X., N. Tang, T. J. Hadden and A. K. Rishi (2011). "Akt, FoxO and regulation of apoptosis." Biochimica et Biophysica Acta (BBA)-Molecular Cell Research1813(11): 1978-1986.
Zhao, Y. B., H. Y. Yang, X. W. Zhang and G. Y. Chen (2005). "Mutation in D-loop region of mitochondrial DNA in gastric cancer and its significance." World J Gastroenterol11(21): 3304-3306.
Zu, X. L. and M. Guppy (2004). "Cancer metabolism: facts, fantasy, and fiction." Biochem Biophys Res Commun313(3): 459-465.