Targeting Mitochondria as a Novel Disease-Modifying Therapeutic Strategy in Cancer

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Abstract

Mitochondria are important for the metabolism of energy, regulation of apoptosis and cell signaling. Overproduction of reactive oxidation species (ROS) in mitochondria is one of the indications of cancer cells; moreover, this boosts the proliferation of cancerous cells by causing genomic instability and altering gene expressions. Mitochondrial and nuclear DNA mutations, caused by oxidative damage which impairs the mechanism of oxidative phosphorylation, can lead to more mitochondrial ROS output, genome instability, and the development of the cancer. Classic approach to target mitochondria of cancerous cells with novel-targeted therapeutics helps in targeting the mitochondrial apoptotic proteins and changing energy metabolism. Key benefit of selective drug delivery is it reduces the toxicity of drug and increases specificity. Better understanding of mitochondrial role in tumor growth will help to design more therapeutic agents with better selectivity.

Keywords

Mitochondria · Cancer · ROS · Mitochondrial medicine · Bioenergetic therapy · Targeted drug delivery

Abbreviations

AMPK	AMP kinase
ATP	Adenosine triphosphate
CoQ	Coenzyme Q
COX	Cytochrome oxidase
DM	Diabetes mellitus
ERR	Estrogen-related receptors
ETC	Electron transport chain
FAD	Flavin adenine dinucleotide
GPx	Glutathione peroxidase
GSH	Glutathione
HVR	Hyper variable region
IP3	Inositol triphosphate
MetS	Metabolic syndrome
MitoQ	Mitochondria-targeted quinone
mtDNA	Mitochondrial DNA
mTOR	Mammalian target of rapamycin
NCR	Noncoding Region
OXPHOS	Oxidative phosphorylation

PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellitus
TCA	Tricarboxylic acid
TNF-α	Tumor necrosis factor-α

Introduction

Globally cancer has become a major health threat of human race. Cancer was responsible for 9.6 million deaths in 2018 around the globe and it is considered as the second leading cause of death worldwide. The prevalence and mortality rate are higher in low- and middle-income countries. Improved health care infrastructure may have improved this situation in the developed world. As per the world health organization, the most common types of cancers which accounts for the millions of deaths across the world are lung cancer which causes 2.09 million cases followed by breast cancer which also causes 2.09 million cases; colorectal cancer which causes 1.80 million cases; prostate cancer which causes 1.28 million cases; skin cancer (non-melanoma) which causes 1.04 million cases; and stomach cancer which causes 1.03 million cases. On the other side types of cancer which cause the majority of deaths are lung cancer with 1.76 million deaths followed by colorectal cancer 8,62,000 deaths and stomach, liver, and breast cancer with 7,83,000, 7,82,000, and 6,27,000 deaths each year, respectively. Cancer is a multifactorial disease in which both the genetic and environmental factors interplay prominent role in their pathogenesis in many parts of the body. Apart from hundreds of susceptibility genes, the life style related modifiable risk determinants included obesity, smoking, tobacco, unhealthy diet, infections, sedentary life style, etc. (de Martel et al. 2020).

In eukaryotic cells, mitochondria is responsible for various major changes. First, mitochondria are the main production site of ATP to meet the cells' bio-energy needs. Several sources of carbon, including glycolysis, produced pyruvates, glutamines, and fatty acids, are used to produce ATP. Some carbon sources help in producing NADH and $FADH_2$ equivalents by entering in the tricarboxylic acid cycle (TCA), which further transfers their electron to the electron transport chain via inner mitochondrial membrane (Weinberg and Chandel 2015). Emerging evidence has also shown that mitochondria play an important role in cell signaling regulation, either by functioning as a scaffold for protein-protein interactions or by controlling the intracellular levels of messengers (Ca^{2+} or ROS). In addition to that with mitochondria, copious quantities of reactive oxygen (ROS) species have been released to facilitate damage to DNA and genetic instability (Ames et al. 1993). The idea is taken from two well-established observations. First, in 1920s, it was suggested that in presence of oxygen, cancer cells can easily take up glucose and can emit lactate in good quantities (Koppenol et al. 2011). The above-mentioned

statement is referred as Warburg effect or aerobic glycolysis. This observation has led a theory that mitochondria are impaired in tumors so that the key metabolic pathway for the proliferation of cancer cells is glycolysis (Warburg 1956). Secondly, tumors also produce high mitochondrial ROS to invoke genetic instability and eventually tumors (Cross et al. 1987). It was then accepted that mitochondrial dysfunction is one of the characteristics of cancer cells.

Etiology of Cancer

Tobacco

Several different types have been developed over the long history of tobacco production. Both combustible and nonsmoking items are included. Combustible products are cigarettes, cigars, bidi, chutta, and kretek. Cigarettes and cigars use separate blended tobacco formulations. The specific type of tobacco mixture can affect the content of nicotine and carcinogen and therefore affect smoke toxicity. The most popular form of tobacco is cigarettes in the USA. 36.5 million adults smoke cigarettes in the USA (Office on Smoking and Health NCfCDPaHP). Lung cancer has an estimated 1.59 million deaths annually, contributing to lung mortality worldwide (Stewart and Wild 2014). Lung cancer is widespread in the low and middle-income countries (LMIC) with an estimated 18 million new cases per year (Cancer IAfRo 2016). Lung cancer is more prevalent in men than in women despite tobacco use trends in men and women, particularly among women in high-income countries (HICs), where lung cancer rates are high, particularly women in LMICs, where cases of lung cancer are growing. In the USA, lung cancer deaths have exceeded the deaths from breast cancer, the most common cause of fatality in females, with also higher cases of breast cancer. After mass production and marketing of cigarettes, lung cancer was declared a global disease as 100 years ago it was regarded as a rare disease (Proctor 2012).

Mainly the smoke produced from tobacco contains hydrocarbons such as polycyclic aromatic hydrocarbons which mainly are benzo-[a]-pyrene (Bap) and derivatives of nicotine which are N-nitroso-nor-nicotine and each of them are responsible for the mutations in genes such as p53 and k-ras that eventually cause lung cancer in experimental animals (Hecht 2008). In the first step, tobacco carcinogens are bound to cellular DNA, resulting in the activation of oncogene by point mutations, translocations, and amplifications. It was noted that the genes which were responsible for igniting lung carcinoma belong to ras family and erb family. Furthermore, in only 30% of NSCLC cancer cell lines and tumors, K-ras mutation was found; however, in SCLC there was no mutation. Another important role played by Ras gene is that it encodes the proteins which helps in signal transmission which sends signals within cell (cell membrane to nucleus). Usually, proteins activation takes place through epidermal growth factor which is connected to its growth factor (Warren and Cummings 2013). Early development of lung cancer can be influenced by her-2/neu (a family member of the erb oncogenes family). Its output is a GFR similar to

that of the receptor for the epidermal growth factor (EGFR). Besides, Her2 code sends continued proliferative communications to the nucleus for excessive amounts of anomalous GFRs. Although Her-2-neu is not a significant factor in SCLC, at least 30% of adenocarcinoma and squamous cell carcinoma of the lungs are over-expressed. Enhanced her-2/new oncogene appears to work in an animal model when mammalian carcinoma is initiated (Hecht 2003).

Environmental Carcinogens

Individuals in low-income countries or developing-countries are more exposed to environmental carcinogens and the level of exposure is still unclear; however, the estimated values are very alarming and some well-known environmental pollutants are aflatoxin, radon, air pollution and hydrocarbons (Wynder and Weisburger 1977). Consequences of other pollutants such as metals (nickel, cadmium) and various other man-made pollutants are very difficult to ration because there is no data of individuals affected by these pollutants. Economic progress leading to development (in towns and industries) in Africa, for instance, is contributing to increased exposure to emerging environmental health threats in Africa (Matos and de Lustig 1978). The projected costs of pesticide toxicity only in sub-Saharan Africa surpass the average yearly amount of development assistance related to health in overseas countries-as the UN Environment Program reports emphasized, while the involvement of chemical exposures to cancer is not established. This is almost universal exposure to diesel exhaust – pollution listed by the International Agency for Research on Cancer, (IARC) as a human carcinogen (group 1) (Donato and Raffetti 2014). Exposure to diesel generators from residential areas is a major risk for many low-HDI countries. Lung cancer can also be caused due to exposure to radon as radon is considered as a residential pollutant (Gubetta and Costa 1978). In some parts of the world, it was reported that skin cancer was caused due to excessive acquaintance to sunlight, sunlight is considered as an influential environmental carcinogen. In several European countries, the incidence of melanoma has risen consistently across all ages. Strategies to reduce sunlight among different ages provide major prevention evidence, as evidenced, for example, in the SunSmart community-wide program in Australia (Loomis et al. 2018).

Diet, Obesity, and Physical Activity

The risk of breast (postmenopausal), colorectal, endometrial, prostate, esophageal, and pancreatic cancers are due to obesity. The hepatic, upper aerodigestive channel, breast, and colorectal cancer are linked with alcohol. Colorectal cancer has been linked with the intake of red and processed meats and a diet low in nutrients (Grosso et al. 2017). Lower physical movement is a key risk factor for colon, breast, and endometrial cancers, both indirectly due to its BMI effects, and specifically due to other causes, only partially understood. The World Cancer Research Fund and the

American Institute for Cancer Research (WCRF/AIRC) have published evidence-based preventive guidelines that are small, physically active, avoid energy-dense foods, eat various fruits, vegetables, whole grains, and pulses and reduce the consumption of alcohol, and the guidelines were correlated with reducing overall levels of cancer risk (5%), with larger reductions for colorectal (12%) and stomach (16%) cancers (Xu and Peterson 2019). WCRF/AICR guidelines are periodically updated based on emerging evidence – ecological proof suggests a modest contribution to the total burden of cancer, especially those of smoking-associated and digestive tract cancers, while fruit and vegetables are high in the WCRF classification (Nencioni et al. 2018). Despite this advancement and a gigantic body of research published in recent decades, the general commitment of diet and sustenance to disease is ill-defined. To meet the remarkable requirement for evidence-based guidance, a few territories may be tended to in a new way. The section may need enhancement for strategies for searching the correct diet plan such as surfing the internet or using mobile applications made for this purpose; the mechanism through which diet and nutrients affects cancer pathway was diagnosed with molecular genetics tools; gut microbiota and genome of the host on how they react to certain nutrients and dietary patterns; and accepting the dietary pattern and healthy lifestyle for better health (Chajès and Romieu 2014). Diet is one aspect of cancer research in which the new strategies for molecular science empower inventive methodologies, remarkably in connecting of exposures to epigenetic changes – that is, practical and possibly reversible changes in gene expression interceded by systems, for example, histone acetylation, CpG island methylation, or microRNAs. These and other rapid advances in the comprehension of the mechanism of carcinogenesis, and the related innovations (alleged omics) to concentrate such procedures, guarantee new methodologies for cancer epidemiology (Mentella et al. 2019).

Mitochondrion-Structural Components and Functions

Structure of Mitochondria

Mitochondria are double-membrane organelles in the cytoplasm that are fundamental for the life and the death of the cells. Most of the time mitochondria are transferred maternally; however, in odd circumstances they may be transferred paternally (Reddy and Beal 2005). Mitochondria are essential as they contribute to the routine of many cellular functions which include the production of ATP, free-radical scavenging, intercellular calcium regulation, the release of protein that activates caspase family of proteases, and changes in the potential of cells (reduction-oxidation) (Reddy 2006, 2008). The mitochondrial structural components mainly consist of two membranes the outer and inner membrane made of proteins and phospholipid bilayers. The main characteristic feature of outer membrane is that it is permeable and molecules with less than 10,000 Daltons weight can pass through it and allows movement between inner membrane and cytosol. The inner membrane, on the other hand, is highly invaginated and folded into a structure called cristae to

increase the surface area of the membrane greatly. Moreover, the inner membrane is highly resistant to ionic flow; it also houses the electron transport chain and mitochondrial matrix. Moreover, tricarboxylic acid cycle (TCA) and fatty acid oxidation takes place in mitochondrial matrix (Bhatti et al. 2017).

Mitochondria contain its own compact mitochondrial DNA (mtDNA) and some RNA contents. The constituents that make the mitochondria are proteins and some molecules which originate in the cell nucleus. However, 37 genes are present in the human mitochondrial genome, 13 of which generate some of the machinery of the ETC. Major difference between nuclear DNA and Mitochondrial DNA (mtDNA) is that mtDNA lacks the DNA repair mechanisms and that's why it is susceptible to mutations. MAM (mitochondria-associated ER membrane) is a mechanism through which communication between the endoplasmic reticulum (ER) and mitochondria takes place (Vance 2014). Studies demonstrate that in MAM the mitochondria and ER are present and they are separated by only 10–25 nm and joined by protein complexes, which takes approximately 20% of the mitochondrial outer membrane (de Brito and Scorrano 2010) (Fig. 1).

Mitochondrial DNA

The mitochondrial DNA (mtDNA) weighs 10^7daltons with 16,595 base pairs and is circular in nature with double-stranded formation (Anderson et al. 1981). Proteins associated with mitochondrial DNA are structured in nucleoids located near the mitochondrial membrane of the mitochondrial matrix (Garcia et al. 2017). In the inner mitochondrial matrix, mtDNA encodes for the 13 polypeptides of the oxidative phosphorylation complex (OXPHOS). To produce ATP via OXPHOS, this requires all complexes (complex I–V) and subunits; subunits are required from only complex

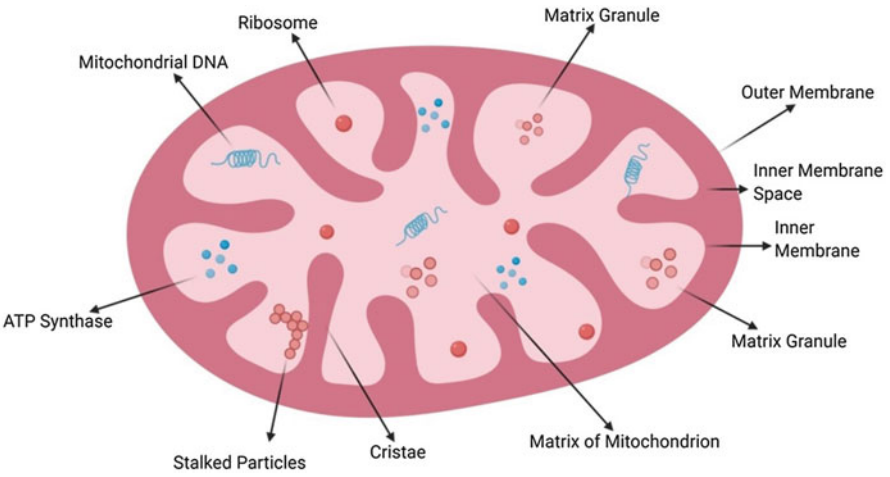


Fig. 1 Structural components of a mitochondrion

I (7 subunits), complex III (1 subunit), complex IV (3 subunits), and complex V (2 subunits) (Garcia et al. 2017). However, nuclear genome encodes the various mitochondrial proteins which are then translocated in inner and outer membrane of mitochondria. Additionally, mitochondrial DNA helps in translation of mitochondria via encoding 22 transfer RNAs and 2 ribosomal RNAs. In comparison to genomic DNA, mtDNA has no histones and is maternally inherited while there has been recent evidence for a paternal heritage.

The mtDNA has double strand formation with one heavy (H) and one light (L) strand, main component of heavy strand are guanine nucleotides, and light strand is composed of cytosine; furthermore, it owes 1.1 kb of control region with promoter of heavy and light strand and the heavy strand is considered as the origin of replication (OH). On the other side of the mtDNA chain, the L-strand origin of replication (OL) is located inside a group of five tRNA genes (Lang et al. 1999). The NCR is the preferred polymorphic site within the mtDNA with few documented polymorphisms in both HVR regions in the NCR. In the mtDNA, the NCR serves a regulatory role that takes care of transcription and translation. The NCR serves a regulated function. In addition, the mtDNA control region includes the origin of replication of a strand and the region of transcription of both strands. The area control can also be viewed as a position of the mtDNA displacement loop. The D-loop also has three DNA strands consisting of a light strand, a heavy strand, and a heavy partially replicated strand, which are linking hydrogen with a light string. Replication of the D-loop initiates of mtDNA containing the transcripts of the promoters (Sun and St John 2016).

Functions of Mitochondria

To produce ATP, two processes integrate: the tricarboxylic acid cycle (TCA) in mitochondrial matrix and oxidative phosphorylation (OXPHOS) in inner mitochondrial membrane. Fatty acids and pyruvate are transported through the cytoplasm to the mitochondria by the membrane-bound permeases. CO_2 and the reduced electron carrier NADH and $FADH_2$ are yielded in the process by oxidizing the acetyl-CoA in several steps. The coenzymes act as an electron source that has to be translocated to inner membrane via respiratory chain, in a process that results in ATP production. The electrons in the electron transportation chain (ETC) are crossed between four complexes (I-IV) by a series of donors and acceptors that comprising a variety of electron carriers, including cytochromes, to transmit electrons from one complex into another. Water formation takes place in the last reaction which is catalyzed by complex IV; in this reaction, transfer of electron from reduced cytochrome c to molecular oxygen takes place. A recent study showed that protons would return to the mitochondrial matrix under some conditions without contributing to the ATP synthesis. This procedure is called a proton leak or mitochondrial leakage and is caused by the ease of diffusion through the mitochondrial matrix. The whole process is moderated by a proton channel called thermogenin (Mozo et al. 2005). Moreover, the process results in the unhardened potential energy being released as heat from the electrochemical gradient of the proton (Voet et al. 2006).

Electron Transport Chain in Mitochondria

Electron transport chain (ETC) is a stepwise process of synthesis of ATP which takes place in the inner mitochondrial membrane via a series of transfer of electron through large protein complex which is also present in the inner mitochondrial membrane. In the whole process, oxygen is consumed and an electrochemical gradient is formed that helps in the generation of ATP. ETC consists of enzyme/transmembrane protein complexes which are complex I–V named as NADH CoQ reductase, succinate CoQ reductase, ubiquinol cytochrome c reductase, cytochrome c oxidase and ATP synthase. Complex I–IV are the individual redox-active complexes which guide the electrons to the final acceptor – oxygen to form water. The composition of these protein complexes varies tremendously. Complex I consists of more than 40 proteins and it receives an electron from NADH, on the other hand, complex II consists of only 4. Complex I, III, and IV exist as a super complex (Guo et al. 2018).

The process mainly involves the conversion of redox energy stored as NADH (Nicotinamide Adenine Dinucleotide) and $FADH_2$ (Flavin Adenine Dinucleotide) into chemical energy in the form of ATP. Electrons from both flow through the four complexes and are ultimately passed to oxygen (1/2 O_2). The energy released during the reduction of molecular oxygen to water is used for the pumping of protons out across the inner mitochondrial membrane, which creates an electro-gradient potential or proton motive force; this force is used for ATP production via F_1F_0 ATP synthase (complex V) (Herst et al. 2017). F_1-F_0-ATP synthase (complex V) constitutes of 22 subunits and it is considered as an enzyme complex. In addition, complex V also helps the proton by providing it a passage to re-enter the matrix and re-establish equilibrium. The conditions in which the ETC works properly requires activation of enzymes via cofactors and enzymes production via nutrition fulfillment.

Reactive Oxygen Species in Mitochondria

Mitochondrion is the birth place of reactive oxygen species, also known as mitochondrial reactive oxygen species (mtROS). The ETC, which is located in the inner mitochondrial membrane, is the place where ROS generation takes place during oxidative phosphorylation (OXPHOS). Furthermore, in ETC leakage of electron takes place in complex I and III which converts oxygen to superoxide. The ROS have the ability to produce other reactive species by interacting with specific biomolecules. Exogenous and endogenous ROS are also active and mediate by various stresses or signaling such as growth factors and amino acid, oxidative and ER stresses, or immunity signaling in several biological processes (Yang et al. 2016).

Generation of free radicals takes place during ROS formation, some common examples of free radicals are oxygen radicals ($O_2^{\cdot\cdot}$), superoxide ($O_2^{\bullet-}$), hydroxyl ($OH^{\cdot}$), and nitrogen oxide ($NO_2^{\cdot}$). Some other nonradical species such as hypochlorous acid (HOCl), ozone (O_3), hydrogen peroxide (H_2O_2), organic peroxides (ROOH), aldehydes (HCOR), singlet oxygen ($^1O_2$) are considered in this category as there are chances they might generate free radicals in living organisms. Molecular

oxygen (dioxygen) has a special electronic configuration and is a radical itself. Superoxide anion radical ($O_2^{\bullet -}$) is formed by the addition of one electron to dioxygen and can be produced either by activation of oxygen through physical irradiation or by metabolic processes; this superoxide anion is known as "primary" ROS. Interaction of this radical with other molecules results in the formation of "secondary" ROS. Superoxide radical's generation takes place at two chief sites: Complex I and complex III which are NADH dehydrogenase and ubiquinone cytochrome c reductase, respectively. The electrons are transferred from complex I or II to coenzyme Q and result in the formation of ubiquinol (QH_2), the reduced form of CoQ; this QH_2 reproduces CoQ through an unstable intermediate semiquinone anion ($^{\cdot}Q^{-}$) in the Q-cycle. The semiquinone anion quickly transfers the electrons to oxygen which further leads to the formation of superoxide radical. The production of ROS increases with an increase in the metabolic rate. Hydrogen peroxide (H_2O_2) is formed by superoxide anion, and the reaction is catalyzed by superoxide dismutase (SOD), furthermore, reduced by glutathione peroxidase and catalase enzymes (Phaniendra et al. 2015). By reducing complexes such as cytochrome-c and ferric-ethylene diaminetetraacetic acid (Fe^{+}-EDTA) with the help of superoxide, in which Fe^{+3} is converted to Fe^{+2}, it can also solve the purpose of oxidizing agent. The reactions between free radicals and superoxide radicals can form extremely reactive species such as peroxynitrite ($ONOO^{-}$); these species are deadly as they easily react with CO_2 to form other lethal species such as peroxynitrous acid and peroxo-carboxylate. ($ONOO^{-}$) can oxidize tyrosine and methionine residues in proteins and DNA to nitroguanidine. Peroxidase enzymes catalyze the hydrogen peroxide reactions, which generate, among other species, hypochloric acid (HOCl) and singlet oxygen ($^1O_2$). Additionally as hypochloric acid is a prevailing species, it is involved in reactions such as chlorination and oxidation (Breitenbach et al. 2014).

To maintain the low ROS steady-state level, antioxidants are used by the cells; oxidative stress occurs due to an imbalance between the formation of ROS and antioxidant defense mechanisms. Numerous endogenic enzymes are involved in antioxidant defense mechanism such as thioredoxin reductase, glutathione reductase (GR), catalase (CAT), Cu-Zn SOD (SOD1), Mn-SOD (SOD2), and extracellular SOD (SOD3); various dietary supplements such as vitamins A, C, E, zinc, folic acid, and flavonoids are involved, furthermore, some circulating biomolecules such as coenzyme Q10, uric acid, pyruvate, and albumin are also involved (Annesley and Fisher 2019). The findings indicate that elevated oxidative stress can have a significant effect on cancer pathology (Fig. 2).

Mitochondrial Dysfunction

Mutations that destroy bioenergetic system enzymes, as well as mutations on mtDNA, have been found in cancer cells. Within certain tumor cells, Mitochondrial mutations have been described: mtDNA control region variants have endometrial or cervical cancer (Zhai et al. 2011); mtDNA cytochrome c Oxidase Subunit 1 (CO1) nucleotide variant has been associated with breast cancer (Canter et al. 2005) risk

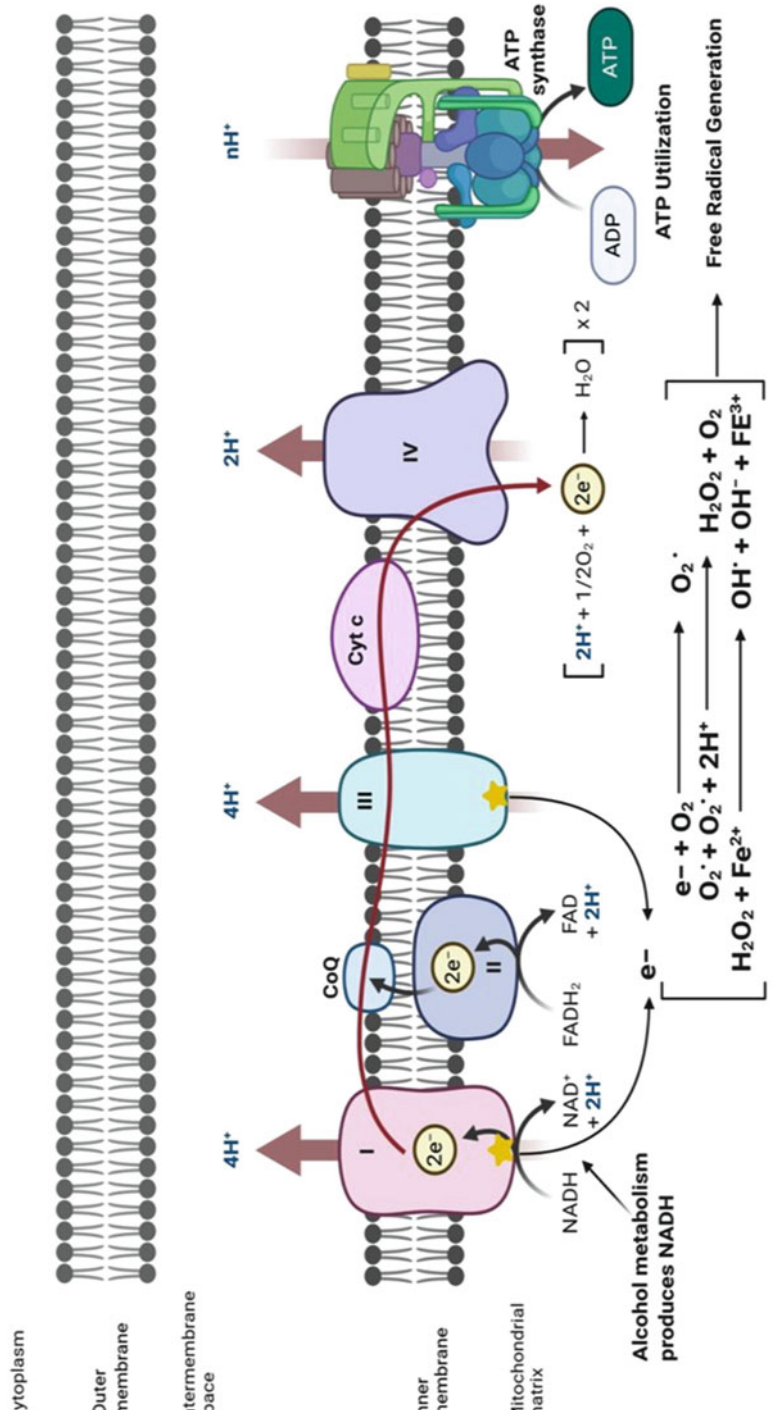


Fig. 2 Generation of free radicals in the mitochondria through the electron transport chain

within NADH dehydrogenase Subunit 3 complex I (ND3). Most mutations of the mitochondrial enzyme result in a loss of enzyme functionality which results in maintaining the equilibrium hypoxia-inducible factor 1α (HIF-1α). Moreover, HIF-1α is a type of transcription factor when stabilized it get transferred into the nucleus and it changes the energy metabolism from oxidative to glycolytic (Wallace et al. 2010). Reduction of SDH (succinate dehydrogenase is protein complex which is present in inner mitochondrial membrane and its main function is to oxidize succinate to fumarate and transfer a pair of electrons to coenzyme Q10) levels-up the inhibition of mitochondria and cytosolic succinate levels which in turn inhibits prolyl hydroxylases which are dependent on α-ketoglutarate and moreover, it stabilizes the HIF-1α. In paragangliomas and pheochromocytomas, mutations leading to loss of SDH function have been reported (Bardella et al. 2011). The HIF-1α transcription factor can also be regulated by the hydratase (FH) gene. FH transforms fumarate to malate and the lack of FH function leads to higher fumarate and succinate concentrations. Like succinate, fumarate was also hypothesized for inhibiting PHDs and stabilizing HIF1α (Adam et al. 2011). Multiple leiomyomata of the cutaneous and uterine skin are aggressive types of renal cell cancer are linked to homozygous null mutations in the FH gene (Picaud et al. 2011). In another mitochondrial enzyme family, isocitrate dehydrogenase (IDH), mutations that lead to IDH1 and IDH2 are recognized as a result of energy shifts in tumor cells. The wild form of the enzymes allows isocitrate to be converted to α-ketoglutarate, while αketoglutarate is reduced by the mutants in R (-)-2-hydroxyglutarate (R)-2HG). The WNT gene (Turcan et al. 2012) is one of the genes being targeted. Moreover, activation of OXPHOS gene expression and mitochondrial biogenesis is controlled by Wnt signaling. Finally, mutations in mtDNA are evident to contribute to mitochondrial dysfunction that also leads to changes in the expression of nuclear genes, a process called retrograde signaling (Wallace 2012). This mechanism possibly helps tumor cells to respond to the high metabolism and to facilitate tumor progression.

Therapeutic Targets in Cancer Pathology

An ideal target is simply the one that ultimately helps to eliminate the cancerous cells with a high therapeutic index and broad therapeutic window. This depends on the selectivity of the pharmacokinetically favorable compound and the quotient of the dominance of the trait against the regular physiological function of the target (Tan et al. 2016). Radiotherapy and surgery are the most common and effective treatments for nonmetastatic cancers, while for metastatic cancers, chemotherapy, biological therapies, and hormone therapies are in use. Due to several reasons such as the effect of chemotherapy on normal cells which have rapid proliferation rates, the toxicity of the agents and development of multidrug resistance led to the discovery of new targeted treatments that aim to block specific biologic transduction pathways or cancer proteins (Perez-Herrero and Fernandez-Medarde 2015). The new targeted therapy involves modulation of apoptosis, molecules that obstruct tumor growth, cell cycle protein, signaling molecules, and growth factors. Moreover, the new targeted therapy methods are: (a) *monoclonal antibodies:* the unique feature of it is that it

binds with exact cancer protein in such a way that immune system can recognize and kill them, or else it can simply stick to it to restrict the signals from growth factor receptors overexpressed in tumors; (b) *small molecules inhibitors*, they simply block the signaling pathway involved in abnormal growth example of such inhibitors is tyrosine kinase; (c) *antiapoptotic molecules*; or (d) *blockers* of tumoral neo-angiogenesis (Lee et al. 2018). An example of a monoclonal antibody is bevacizumab: a humanized monoclonal antibody with a circulatory system target (VEGF-A), and an example of a small molecule can be imatinib: a tyrosine kinase inhibitor. After finding a possible therapeutic agent, the difficult task is to find a potential target. The efficiency of the drug can be tested via experimental models by finding a linkage between proposed target and therapeutic target and its mode of action (Padma 2015). Gene therapy and cancer vaccines are at times considered as targeted therapies as they obstruct the growth of specific cancer cells.

Additional methods often allow use different approaches such as monoclonal antibodies or peptide ligands or chemical linker to conjugate drugs on them to deliver cytotoxic drugs to molecular targets which are overexpressed on tumor cells, another method of adding cytotoxic drug is via nanocarriers that can target the tumor more effectively because of their permeability and retention effect; moreover, to avoid multidrug resistance, targeting drugs are conjugated on the surface of nanocarriers which can actively target the tumor sites. For treatment of acute myeloid leukemia, a drug named Gemtuzuman (Mylotarg®; Wyeth, CT, USA) which has a CD-33 specific monoclonal antibody which is coupled with calicheamicin chemotherapy for better results. Researchers are now working on developing two types of nano materials one is antibody-coated lipid and another is lipid based for anticancer study (Fay and Scott 2011).

There are certain limitations of the targeted therapies. Since this method works by inhibiting particular biomarkers vital for cancer development, the treatment is only efficient in patients with tumors that express the particular biomarker (Lee et al. 2018). In most of the cases, traditional chemotherapy is done apart from some cases where targeted therapy is used. Use of monoclonal antibodies makes targeted therapy a costly option (Gerber 2008). The chief side effects of these therapies are diarrhea and liver disorders (high level of liver enzymes and hepatitis), others being high blood pressure, skin problems, problems in blood clotting. Currently there are more than 800 drugs are under clinical trials but only a few will make it through and launches in market. The major problems that why a few drugs are present in the market is shortage of biomarkers, complication of cancer regulatory mechanisms, sensitivity of drug, drug resistance, drug testing platforms, and strict laws are the reasons that there is a scarceness of drugs in market.

Mitochondrial Medicine in Cancer

Mitochondria perform a controlled regulation of several functions in healthy cells to maintain the cycle of growth – death. In tumor cells, however, the dysregulation of mitochondrial metabolism occurs to meet the higher metabolic requirement of rapidly proliferating cells (Wisnovsky et al. 2016). The distinctions between cancer

cell mitochondria and normal cells include a variety of functional changes, such as mtDNA mutation leading to inhibition of OXPHOS and therefore, respiration deficiency, generation of ATP, mtDNA mutation encoded mitochondrial enzymes such as isocitrate dehydrogenase1 (IDH1), isocitrate dehydrogenase 2IDH2, and succinate dehydrogenase (SDH) (Parker and Metallo 2015). And physical changes, for example, in mitochondria basicity are high in mitochondrial lumen as well as high membrane potential in mitochondrial cancer cells. Mitochondria mediated inhibition of apoptosis and evasion of cell death is considered as a characteristic of cancer. ROS generation by mitochondria is very much needed for cell signaling. However, ROS leads to neoplastic transformation when apoptosis is inhibited in the case of cancer. Besides, to support cancerous cell for their survival in severe tumor conditions, like hypoxia and nutrient depletion, mitochondria provide alteration in various pathways through up- or downregulation (Wallace 2012). Compared to their natural counterparts, dysregulated mitochondrial metabolism of cancerous cells is advantageous for targeted drugs which targets mitochondria in cancer, while focusing on other aspects of cancer mitochondria (Rin Jean et al. 2014). Benefit of targeted therapeutic agents is that it acts directly on mitochondria and will eliminate the cancer cells because the drug molecules are designed in such a way that it will act on cell's center point, that's why engineered mitochondrial targeted drugs have gained so much importance in cancer treatment.

Medicines that decrease the number of mitochondrial DNA copies, or inhibit replication, target mitochondrial DNA. The DNA polymerase gamma, important for the replication of mitochondrial DNA, was inhibited by vitamin K3 (menadione) (Sasaki et al. 2008). Parkinsonian toxin 1-methyl-4-phenyl pyridinium is responsible for destabilizing the mtDNA structure by decreasing its copy number (Umeda et al. 2000). Another point which can be considered for targeted therapy is deregulated production of ROS in mitochondria during cancer. However, human trials were not successful because they did not inhibit the ROS formed by mitochondria (Bjelakovic and Gluud 2007).

The protein family Bcl-2 is made up of both pro- and antisurvival factors (Youle and Strasser 2008). In the absence of survival factors, cell death is favored. A domain that interacts with Bax/Bak proteins is used to attack the tumors by mimic medicaments attacking the domains of BH3 of these proteins (Youle and Strasser 2008). Drugs including mitochondrial changes in cancers such as ABT-263, Gossypol, antimycin A, or alpha-tocopheryl succinates are some examples of family targeting of mitochondrial cell deaths due to interaction with the BH3 region (Kang et al. 2010). Given that generation of ATP is essential for normal cells and tumor cells, bioenergetic mitochondrial targeting drugs need to be specifically targeted at tumor cells. Poorly perfused tumors that produce ATP (Rumsey et al. 1990), a suitable target for drugs that inhibit ATP development as only in these poorly perfused tumors can it cause cell death. It is thought that in diabetic patients metformin (antidiabetic drug) can be used to increase ATP production without destroying normal cells and tissues. Moreover, metformin helps in lowering the hepatic gluconeogenesis which in turn lowers the insulin levels (Bailey and Turner 1996). Adding to it metformin has proven to be effective on cancerous cells. It works by inhibiting

the growth of insulin-dependent tumors which in turn lowers the blood glucose and insulin levels. It works on the complex I of mitochondria (Owen et al. 2000). It also impairs glycolysis by reducing enzyme hexokinase 2 activity, which is an essential enzyme for glycolysis (Salani et al. 2013). Hence, it is believed that metformin decreases the glucose supply to prevent tumor growth upon acting on complex I and thus reducing mitochondrial ATP production. However, clinical trials are still under review to check mode of action of drug. Phenformin is a similar drug as metformin which is composed of biguanide that attacks the mitochondrial complex I. Phenformin has shown better results in breast cancer than metformin because of its higher affinity with mitochondria (Birsoy et al. 2014).

One type of drugs that has also tried to inhibit ATP production is VLX600, an inhibitor of the ETC. This drug has been shown to reduce tumor growth in colon cancer (Zhang et al. 2014) at experimental levels. The translation of mitochondrial protein is geared towards some drugs such as tigecycline which reduce the expression of 13 ETC subunits. Furthermore, the medication hampers the ATP production in leukemic cells, which eventually kills the cancerous cells (Skrtić et al. 2011). Medicines such as Gamitrinib that are engineered to accumulate in mitochondria and reduce HSP90 and ATPase 1, thereby reducing mitochondrial generation, target mitochondrial chaperones such heat shock protein. Another way to deal with mitochondrial cancer is to develop medications that target biosynthetic pathways. Glutamine-dependent tumors are mainly caused by Myc and Kras (Gaglio et al. 2011). These tumors can be treated by the use of glutaminase inhibitors that use glutamine to start the tricarboxylic acid cycle in their reaction. Inhibitors of glutaminase, such as bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide) or 968 compounds already attenuate tumor development (Le et al. 2012). Mitophagy also makes raw materials for the TCA cycle of the mitochondria. Several autophagy inhibitors are being investigated, and chloroquine is one of those medications. Studies have suggested that targeting mitophagy directly is a better idea for trials because autophagy drugs are toxic in nature. Moreover, there are many protein-specific inhibitors such as hexokinase inhibitors VDAC and ANT inhibitors which are mitochondria-related and are being used to target mitochondria in cancers (Ben Sahra et al. 2010).

Bioenergetic Therapy in Cancer

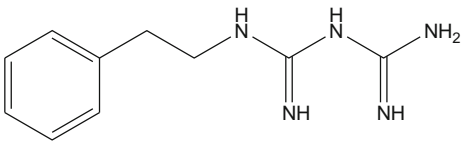
One of the major contributing factors from mitochondria, particularly from the malfunctioning or dysfunctioning ones to cancer, is excessive production of ROS. The fact that mitochondria are closely involved in the development of cancer allows them to be a good target for anticancer therapy. Studies have suggested that there are three major reasons which can be considered as a plus in targeting the production of mitochondrial ATP as a therapeutic strategy to cure cancer. Firstly, the center part of various jellied tumor is poorly enriched and exists in low glucose and oxygen as well as nutrient-poor conditions, and thus, many of them do not have adequate glucose but have enough oxygen to produce mitochondrial ATP. As a consequence, a drug

blocking mitochondrial ATP generation in these tumors would cause cell death. Second, the tumor subsets that have a high reliance on OXPHOS for ATP are inclined towards drugs that hamper the ATP generation of mitochondria because of collapsed glycolytic compensation. The third reason is disturbing the production of ATP would be synergistic towards the treatment that helps in lowering glycolysis, the best example is the inhibitors of P13K pathway (Weinberg and Chandel 2015). Several mitochondria-targeted agents may specifically bind to normal cellular components, and this is believed to be an in vivo problem. An obstacle to enhance the therapeutic effectiveness and decrease the sideeffects of mitochondria-targeted drugs is the selective and high-concentration delivery of these agents at tumor sites, and for this purpose, several efficient transport methods have been described (Zhang et al. 2011). Metformin (1,1-dimethylbiguanide) is a widely used drug used for the treatment of patients with type 2 diabetes mellitus and can be used as an anticancer agent that targets mitochondrial ATP production without inducing toxicity in normal tissues. Some experimental studies have confirmed a better sensitivity to chemotherapy in a range of cancer cell lines treated with metformin (Morales and Morris 2015). The drug causes a decline in blood glucose and, as a result, fluctuation in insulin levels (in cancer cells insulin is a kind of mitogen) as well as the hindrance in the function of mitochondrial electron transport chain especially in complex 1 to decrease the growth of tumor. Phenformin drug, an alternative to metformin, is comparatively more lipid-soluble and less polar, thus exhibits a higher affinity for mitochondrial membranes as well as a greater antineoplastic activity. In a study, it was observed that an ETC inhibitor named VLX600 remarkably decreased the tumor growth and interestingly showed antitumor property for cancerous cells where the rate of cancerous cells production was very high and which developed a bioenergetic need that cannot be fulfilled by glycolysis (Zhang et al. 2014). However, intervention at the mitochondrial level may prove to be beneficial for the maintenance of mitochondrial health that may influence psychological and psychiatric disorders (Murphy and Hartley 2018).

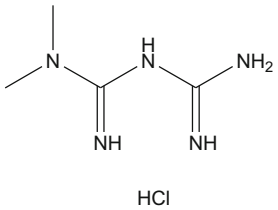
Figure 3 shows the structures of some of the possible therapeutic drugs used in mitochondrial bioenergetics.

Conclusion and Future Perspective

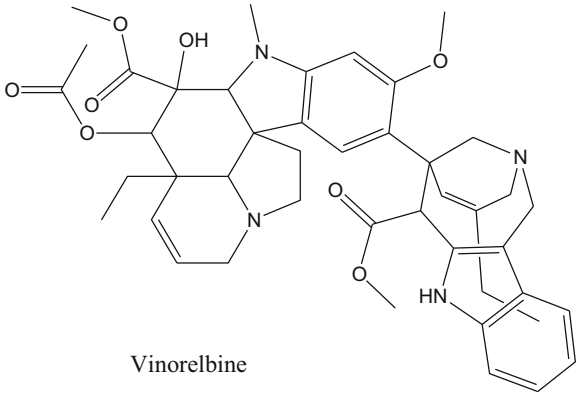
Mitochondrial dysfunction is known to be a common major issue in a broad range of metabolic, degenerative, cancer, and aging diseases; however, for years, therapies have been used to target only the symptoms. Scientists around the globe have been working rigorously on developing drugs and specific molecules that target and protect mitochondria and neurons against the toxic nature of protein mutation and aging. Moreover, maintaining the bioenergetic flux is also very important. Bioenergetic medicine has the capabilities to change the present situation of drugs but the long-term benefits are to be seen, but developing and nurturing this field seems worth pursuing. In addition to this, many clinical trials are in progress and many therapeutic options are being considered. Although traditionally neglected in tumorigenesis,



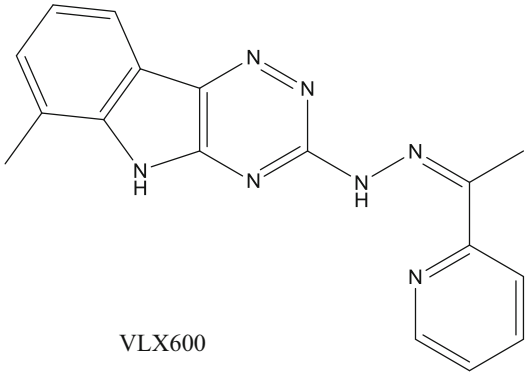
Phenformin



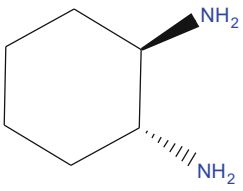
Metformin

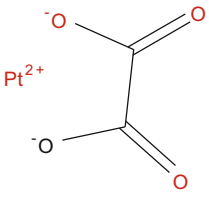


Vinorelbine

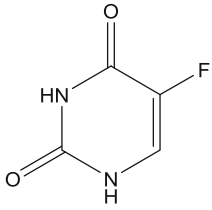


VLX600





Oxaliplatin



5-fluorouracil

Fig. 3 Anticancer agents targeting mitochondria

the production of mitochondrial energy is needed for many types of cancer and strong evidence suggests that its dysregulation may be a valuable clinical target. How mitochondrial malfunction may influence mental processes is currently unclear, and it also raises the question that manipulation at mitochondrial level can trigger psychological and psychiatric disorders.

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