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REVIEW ARTICLE

Differentiating Compromised Mitochondria of Lung Cancer Cells from Mitochondria in Healthy Cells

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Abstract

Mitochondria are double-walled organelles that generate energy in the form of ATP. ATP is an energy-rich compound and a driver of fundamental cell functions. Mitochondria-oriented studies help design advanced therapies to target lung cancer. Lung cancer is the leading cause of cancer incidences and death globally. Various studies have supported that mitochondrial function is disrupting cancerous cells. Mitochondrial dysfunctions lead to dysregulated ATP synthesis, disturbed respiratory chain, unbalanced mitochondrial fission or fusion, disturbed cellular redox homeostasis, dysregulated apoptosis, and interfered non-smooth intracellular calcium signaling. Dysfunction mitochondria are associated with cancer cell proliferation, metastasis, and death. In this review, we have tried to elaborate on how normal cell mitochondria function differently from the mitochondria of lung cancer cells. It includes various targets such as mitochondrial proteins and related pathways, along with new drug molecules like Militarin analog-1, Dihydromyricetin, and papuamine. As mitochondrial metabolism is associated with the proliferation and metastasis of lung cancer cells, finding interlinks between malfunctioning mitochondria and the process of lung cancer can promote the development of new treatments.

Abbreviations

OXPHOS: Oxidative Phosphorylation; ATP: Adenosine Triphosphate; ETC: Electron Transport Chain; Mtdna: Mitochondrial Deoxyribonucleic Acid; NSCLC: Non-Small Cell Lung Cancer; ROS: Reactive Oxygen Species

Introduction

Mitochondria

Mitochondria are precious organelles that are known to be cellular "powerhouses" [1]. They produce energy from the food we consume [1]. When 10 million billion mitochondria throughout our bodies work together, the bulk of the ATP is generated for our cells [1]. Every day, mitochondria produce nearly fifty kilograms of Adenosine Triphosphate [ATP] [2]. As per Nick Lane, an English biochemist and writer, "Gram per gram, even when sitting comfortably, you are converting 10,000 times more energy than

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the sun every second" [2]. Specialty and uniqueness lie in the fact that mitochondria contain their DNA, which is very similar to bacterial DNA [3]. This makes them entirely different from other cellular organelles [3]. These organelles are responsible for a remarkable set of cellular functions, for example; generating ATP via oxidative phosphorylation, maintaining cellular redox homeostasis, regulating apoptosis, and intracellular calcium signaling [4-6]. The health of mitochondria is mandatory for the proper functioning of the human body.

Various studies in the past era are based on somatic mutation theory but recent studies are openly challenging this with a perspective that cancer can be a mitochondria-based metabolic disease i.e. supporting mitochondrial metabolic theory [7,8]. A compelling example is the rarity of cancer in chimpanzees or primitive humans. But, cancer is common in humans, why? Diet and lifestyle rather than genetic mutations can be an answer [9,10]. Even in the presence of sufficient oxygen, cancer cells can undergo fermentation to produce lactate and this process is known as aerobic fermentation. It is an indicator of respiratory insufficiency and a characteristic of cancer cells [11-13]. Lactate and succinate production are a key metabolic feature found in a cancer cell [13,14]. Increase in lactate and succinate makes the tumor environment acidic leading to an increase in angiogenesis [15]. Although lactate has its role in cancer progression glucose and glutamine are considered a major source of energy required for cancer growth [16]. Dysfunctional mitochondria can be considered as the fifth cancer hallmark [5]. Hence, we bring forth this literature review by connecting dots to explain how mitochondrial malfunctioning is associated with deadly diseases such as Lung cancer.

Historical facts about mitochondria

Around 1.6 billion years ago, mitochondria were understood to have originated by endocytosis because of their resemblance to α-proteobacteria [17]. It is evident from an evolutionary pattern that there is a close homology of bacterial and mitochondrial respiratory chain complexes [17]. 'Old' bacterial and 'new' eukaryotic-derived proteins together formed mitochondrial proteome [18]. Studies have explicitly shown an evolutionary relationship between mitochondrial translational machinery and bacteria [19]. For example; mutants of *Caenorhabditis elegans* have contributed to understanding the role of mitochondria in ATP synthesis by tricarboxylic acid cycle and oxidative phosphorylation [20]. Due to the distinct DNA code in their genetic system, they can be differentiated from their bacterial ancestors and their eukaryotic hosts [17]. Recently, mitochondrial similarities and differences from bacterial ribosomes have been determined by Single-Particle Electron Cryomicroscopy [cryo-EM] [21].

In 1865, Swiss physiologist and anatomist Albert von Kolliker observed granular structures in the cells of muscle tissue [22]. In 1870 Eduard Friedrich Wilhelm Pflüger explained that a process known as respiration takes place in cells [23,24]. Later in 1898, based on shape it was named "Mitochondrion" by Carl Benda. This term is the fusion of "mitos", thread, and "chondros", grain [25]. About a century later, the cycle of reactions taking place in mitochondria like the Krebs cycle was discovered by Sir Hans Adolf Krebs, a Nobel prize winner [26]. It helped in the interpretation of the citric acid cycle's role in the intermediate metabolism [27]. In the early 1910s, Kingsbury's postulation revealed that respiration takes place in "mitochondria," [23,24]. David Keilin in 1925 identified pigments and called them cytochromes. Decades back, observations set by Charles MacMunn assisted Keilin with these identifications. Further, It helped various researchers like Warburg, and Hartree to explore and learn more about important concepts like the "respiratory chain," and related enzymes like "dehydrogenases", Warburg's oxygen-reducing respiratory enzyme (The Atmungsferment) [23,27]. Between the late 1920s and the early 1940s, various key aspects of aerobic metabolism came forth, for example, the discovery of ATP by Lohmann in 1929 [28].

In 1931, Warburg demonstrated the nature of the cytochromes and the mode of action of the respiratory enzyme [29]. In 1946, succinoxidase and cytochrome oxidase in an isolated mitochondrion was illustrated by Albert Claude [30]. In the early 1950s, Palade and Sjostrand revealed a detailed structure of mitochondria as a double-membrane structure with curvy twisted cristae through electron micrographs [31]. In 1978, Mitchell received a Nobel Prize for his chemiosmotic theory about the anisotropic arrangement of components which play a role in ATP synthesis within the proton's impermeable inner mitochondrial membrane so electrons transferring and protons expelling across the membrane can be done by complexes. It helped set a base for a meticulous understanding of the processes of OXPHOS [3]. In 1981, the MRC Laboratory of Molecular

Biology in Cambridge found the sequence of the human mitochondrial genome [32]. In 1998, the first study on mitochondrial proteomics was published. In 2003, comprehensive research studies explaining mitochondrial proteome by Albert Sickmann, Eric Lander/Matthias Mann, and Steven Taylor were published. In 2016, Khacho and colleagues brought forth the fact that change in mitochondrial shape is a key regulator of neural stem cell fate [33].

In the current scenario, mitochondria-oriented studies help devise new therapies to target lung cancer. A simple explanation of why these discrete organelles are is targeted that they lead a vast array of functions central to cellular life, death, and differentiation U[34,35]. ndoubtedly, mitochondrial function is disrupted in cancerous cells. Even treatment with pharmacological compounds such as chemotherapeutics and antiviral drugs is incompletely safe for the mitochondria of healthy cells [36-38]. Hence, today researchers are making tremendous efforts to learn more about mitochondrial biology so it can be safely targeted to cure various mitochondrial-based diseases especially, lung cancer.

Structure and function of mitochondria in a healthy cell

Mitochondria are organelles with double membranes [39]. This double-membrane system separates mitochondria from the cytoplasm [40] and itself is separated by inner membrane space [41]. Various features of mitochondria play a role in fusing, importing proteins, organizing, and maintaining membrane composition along with membrane potential [42,43]. The detailed internal features of mitochondria can be observed by electron microscopy only [44]. The tubular network formed by mitochondria in a cell keeps on dividing and fusing constantly with the help of numerous dynamin-related GTPases [45,46]. When mitochondria are isolated from the cell, fragments are formed after network disintegration which then undergoes spontaneous resealing [47]. Even in isolation, these dynamic organelles [48] are competent for respiration and ATP synthesis [47].

ATP is an energy-rich compound [49] and a driver of fundamental cell functions such as protein folding and degradation, maintaining a tightly regulated interface with other subcellular compartments, building force required for cell division [50,51]. Mitochondria play a role in producing ATP via OXPHOS and are also called cell powerhouses [52]. Different parts of mitochondria include outer and inner membranes, inner membrane space, cristae, and matrix [19,39,51,53,54].

The outer membrane plays a role in defining the overall shape and forms to control molecule permeation along with the separation of mitochondria from cytoplasm [39]. It allows permeation to molecules with a weight less than 6000 Daltons [41] by forming large aqueous channels through lipid bilayer [55] along with the help of porin [55], a pore-forming membrane transport protein like voltage-dependent anion channel VDAC [40]. Inner membrane space empowers ATP synthesis by maintaining a pH gradient by receiving actively transported H+ ions from the mitochondrial matrix [50]. In aerobic cells, the Inner membrane is the site of ATP synthesis employing oxidative phosphorylation and generates around 32-34 ATP per glucose molecule [19,50]. In a healthy cell, 2 molecules of ATP per glucose molecule, are generated by glycolysis, and 2 ATP are generated by the Citric Acid cycle.

The presence of densely packed hydrophobic combinations like double phospholipid cardiolipin makes the inner membrane highly impermeable to most ions and large molecules [50,53]. Upon translation, products of mitochondrial ribosomes like hydrophobic membrane protein subunits are integrated into the inner membrane [56]. It has a high electronegative environment of potential -140 to -180 mV generated by protein complexes of the Electron Transport Chain [ETC] [50]. ETC is located in the inner membrane with proximity to the mitochondrial matrix [57]. It has five complexes: complex I: ubiquinone oxidoreductase, complex II: succinate dehydrogenase, complex III: ubiquinol–cytochrome c oxidoreductase [or cytochrome bc1 complex], complex IV: cytochrome c oxidase, and complex V: ATP synthase [52]. These complexes help in ATP synthesis via oxidative phosphorylation [52]. Electron transporters ubiquinone and cytochrome c also play a crucial role in the mammalian mitochondrial Electron Transport Chain [ETC] [57]. Various pathways involved in energy production in a healthy cell are shown in this paper (Figure 1).

The inner membrane divides into the inner boundary membrane and the cristae [51]. The inner boundary membrane contains carrier proteins that assist in transporting ions, ATP, and ADP between the cytoplasm and the matrix [58]. Cristae are cisternal invaginations [59] of inner membrane

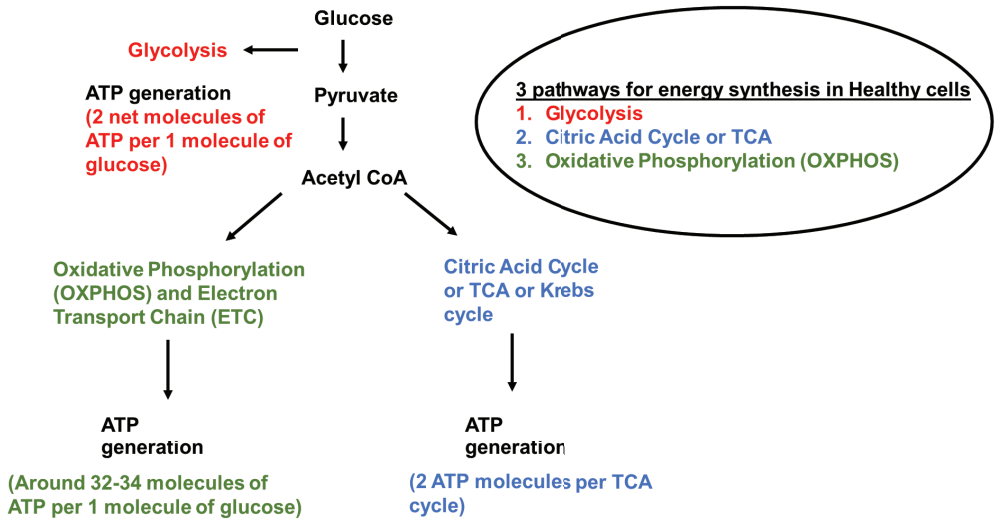

Figure 1 Pathways for energy production in a healthy cell.

disk-like lamellar, tubular, or bag-like extensions of inner boundary membrane [44,59] which were first discovered by electron microscopy of plastic-embedded cells and tissues [31,60]. Several important processes like Mitochondrial energy conversion take place in cristae [51]. Dimerization or multimerization of ATP synthase complexes helps in the stabilization of these mitochondrial features [59]. The most prominent protein complex present in the cristae is mitochondrial F1-Fo ATP synthase [61]. ATP synthase helps in ATP synthesis by rotatory catalysis [61]. Within the cristae membrane, ATP synthase-assisted ATP generation takes place which is driven by a shallow proton gradient between the inter-membrane space [pH 7.2-7.4] and the matrix [pH 7.9-8] [51].

Cristae with numerous folds extend into the interior of mitochondria to form a Mitochondrial matrix [41]. It is surrounded by an inner membrane [54] and has a high protein density of up to 500 mg/ml [62,63]. Proteins have to pass through the outer membrane, intermembrane space, and inner membrane to get into the matrix [62,63]. DNA replication, transcription, protein biosynthesis, and numerous enzymatic reactions take place in this part of mitochondria [64]. The genetic code in animal mitochondria is slightly modified compared to the universal code [65]. Mammalian mitochondria have their genome with 16,000 base pairs of DNAs encoding 2 rRNAs, 22 tRNAs, and 13 polypeptides organized [65]. It contains a distinct set of ribosomes with 28S small subunits and 39S large subunits [66] as well as a small amount of endogenous DNA (mtDNA) [67]. Mitochondrial DNA [mtDNA] can be found in high copy numbers (103-104 copies per cell) in cells [55]. 13 essential subunits of the oxidative phosphorylation machinery are encoded by endogenous DNA, which undergoes transcription and translation [68]. rRNA and tRNA molecules are important parts of translational machinery [68]. In mammalian mitochondria, tRNAs can be differentiated from canonical tRNAs. They are generally shorter than other tRNAs. They don't have conserved or semi-conserved nucleotides. Conserved or semi-conserved nucleotides help in creating an L-shaped tertiary structure of eukaryotic cytoplasmic tRNAs. Characteristics of mitochondria in a healthy cell are explained in this paper (Figure 2).

Mitochondria in lung cancer

Cancer: Cancer is the leading cause of premature death in 57 countries [69]. In 2023, 1,958,310 new cases of cancer and 609,820 death cases due to cancer were projected by the American Cancer Society [70]. As per Global demographic characteristics, in the year 2025, a rise in new cancer cases can exceed more than 20 million [71] and may reach 24 million by 2035 [72]. In the United States, more than 7 million people were infected with COVID-19 by the end of September 2020 [73,74]. The Coronavirus disease 2019 [COVID-19] caused alarming states around the world [75]. As per studies, screenings for breast, colon, prostate, and lung cancers were decreased by 85%, 75%, 74%, and 56%, respectively, especially when COVID-19 was at its peak [76]. Hence, cancer patients experienced huge challenges in accessing care which led to an increase in case numbers [76]. Cancer is a death-

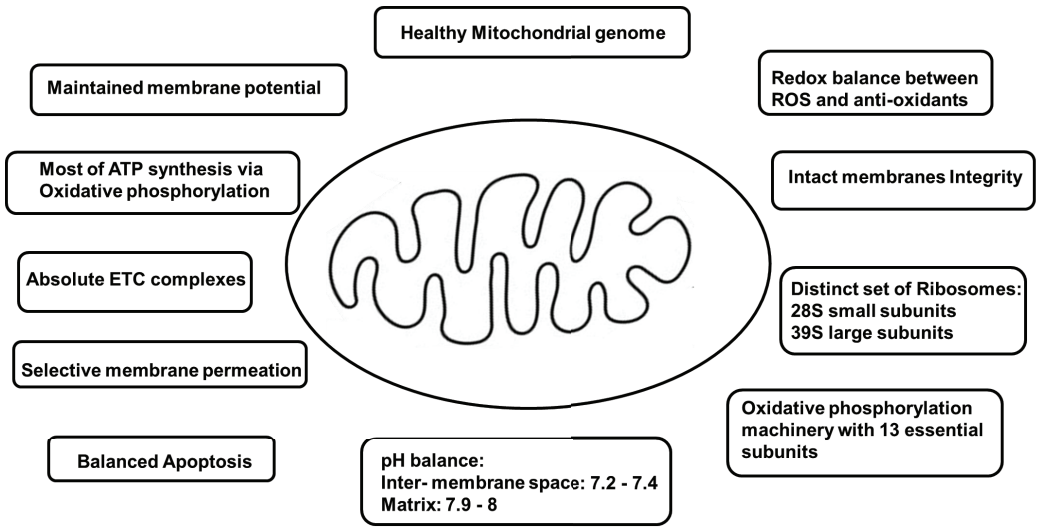

Figure 2 Characteristics of mitochondria in a healthy cell.

causing disease and researchers are investing their tremendous efforts in the search for a cure with minimal adverse effects [77].

Lung cancer: Lung cancer is the leading cause of cancer incidences and mortality globally [78,79]. Based on the origin, lung cancer can be Small-Cell Lung (SCLC) and Non-Small-Cell Lung Cancers (NSCLC) [80]. Neuroendocrine cancers such as Small Cell Carcinoma (SCLC), Squamous Cell Carcinoma (SCC), adenocarcinoma, Large Cell Neuroendocrine Carcinoma (LCNEC), and carcinoid are some most common types of lung cancer [80]. The second most common cancer in males is lung cancer with an estimated 1,369,000 cases [81,82]. The risk of diagnosis in males is 3.8% whereas in females it is 1.77% [81,82]. North America, Northern and Western Europe have the highest incidences in females whereas eastern, central, and western Africa have the lowest cases in both males and females [83]. As per Torre, et al. [84] in the US, for lung cancer diagnosis in both males and females, the average age is 70 years old. Young non-smoker females of age 20-46 years have been diagnosed with NSCLC, more advanced adenocarcinoma [85]. In the US, it is considered as main cause of death in women over 59 years old and in men over 40 years old.

Both genetic and non-genetic factors are responsible for lung cancer [86–89]. Smoking has been stated as the principal cause of lung cancer [72]. It comprises more than 80% of lung cancer cases [81]. In the South African population, male marijuana smokers are found with a 2.4 times increased risk of lung cancer [90]. Exposure to carcinogens like asbestos accounts for 5-10% of global lung cancer cases [91]. Exposure to natural gas like radon or metals like uranium can increase the risk of squamous cell carcinoma of the lungs [92–94]. As per IACR, people working with arsenic are subjected to cancer of the lungs [90,95]. Chronic Obstructive Pulmonary Disease (COPD) [96], tuberculosis [97], HIV [98–100], inflammation and cellular damage [97], and air pollution [101] are causative agents of lung cancer.

According to Genome-Wide Association Studies (GWAS), variants in different chromosomal regions can result in a higher risk of lung cancer [102]. For example: 15q25–26 loci,5p15 locus, and 6p21 locus. 15q25–26 loci can increase nicotine dependence [88], the 5p15 locus includes a gene for the Telomerase Reverse Transcriptase (TERT) [102], and the 6p21 locus regulates G-protein signaling and chances of lung cancer [103]. To get properly treated, prognosis is very important as it is strongly associated with the stage of Lung cancer [104]. According to the U.S. Preventive Services Task Force, low-dose computed tomography [CT] screening is suggested for patients with high risk of Lung cancer [105]. Various new molecules are under laboratory testing with a solo focus on targeting mitochondrial metabolic pathways to combat cancer. Taking current lung cancer statistics into consideration, there is a huge necessity to bring these results to the clinical level. Based on our literature search, there are very few clinical studies targeting mitochondrial metabolism in lung cancer (Table 1).

Dysfunctional mitochondria in lung cancer

As mentioned in previous sections, mitochondria play a huge role in ATP production at the cellular level in all organs like lungs. According to various studies, whether the energy level is too high or too low, both are associated with detrimental effects on cell viability [106]. In a cell, a low level of ATP can induce necrosis or apoptosis and a high level can disturb membrane pumping with survival inhibition [106]. Irregular changes in ETC, mtDNA, and proton motive gradient of the inner membrane can result in mitochondrial impairment [106,107]. ATP production is affected by mitochondrial dysfunction. Mitochondria in various cancers for instance, lung cancer are structurally and functionally irregular and are not capable of producing normal levels of cellular energy [108–117]. Uncoordinated mitochondrial function can lead to dysregulation in oncogenes and tumor suppressor genes, for example, regulation and expression of p53 [118–120]. Malfunctional mitochondria can amplify cytoplasmic calcium levels, irregular iron-sulfur complexes, and reactive oxygen species and can lead to genome mutability [121-127]. p53 is a tumor suppressor [128]. Its suppression or its disability can downregulate hypoxia-induced apoptosis, ETC dysfunction, and dysregulated oncogenic signaling pathways [129], thus, supporting cancer cell proliferation and survival [129-132]. Any alteration in mitochondrial energy homeostasis, uncontrolled rise in ROS level, radiation, mutagens, and carcinogens can lead to cardiolipin abnormalities [113]. An increase in ROS levels is related to abnormal genome stability, disturbed tumor suppressor gene function, and uncontrolled excess cell proliferation [121,133]. Cardiolipin works closely with proteins of ETC and is the only lipid produced in mitochondria. Abnormal cardiolipin composition and quantity can alter OXPHOS by hindering the uptake of ADP [134-138]. Cancer cells have abnormal cardiolipin content leading to dysregulated ETC [114]. OXPHOS has been shown to have a critical effect on the energy metabolism of lung cancer cells [139,140]. Some mitochondrial characteristics in a cancer cell are shown in this paper (Figure 3).

In the 1920s, Otto Warburg observed, that cancer cells produced ATP by undergoing a high level of glycolysis rather than mitochondria-mediated oxidative phosphorylation, and this condition was termed as "Warburg effect." [141]. Even oxygen-rich conditions can't prevent it and hence, this phenomenon was called "aerobic glycolysis" [11,12]. In many types of cancer including lung cancer, an increase in glucose uptake to produce ATP leads to enhanced synthesis of DNA, protein, nucleic acids, and amino acids, an increase in mtDNA mutations resulting in mitochondrial dysfunction and related somatic mutations [142–145]. Aerobic glycolysis or aerobic fermentation or Warburg effect, along with the Glutaminolysis pathway and mitochondrial substrate-level phosphorylation provide supplements for the rapid proliferation of cancer cells as they contribute to the production of biomass precursors, such as nucleotides, amino acids, and lipids [146]. Different pathways involved in energy production in a cancer cell are clearly explained in this paper (Figure 4).

Dysfunctional Mitochondria produce ATP through aerobic glycolysis and produce 16-fold less ATP than OXPHOS [147]. The disbalance of OXPHOS and aerobic glycolysis leads to cytoplasmic accumulation of mitochondrial metabolites with a side effect known as hypoxia [148]. Hypoxia has a proliferative effect on lung cancer because it induces the enlargement of mitochondria and apoptotic resistance [149]. Hypoxia-Inducible Transcription Factor (HIF-1α) helps cells adapt to stress conditions by synthesizing 70 hypoxia-related factors [150]. HIF-1α has been

Table 1: Clinical studies targeting mitochondria in lung cancer.

Treatment	Cancer Type	Stage	Phase	Study Type	ClinicalTrials.gov ID
Targeting Mitochondrial Metabolism with Papaverine in Combination With Chemoradiation	Non-Small Cell Lung Cancer	Stage 1 1-11 1	Phase 1	Interventional	NCT05136846
Targeting Mitochondrial System using Radiofrequency Ablation	Non-small Cell Lung Cancer	Early stage	Not applicable	Interventional	NCT03840408
Dose Escalation Study of ME-344 in Patients With Refractory Solid Tumors	Non-small Cell Lung Cancer	Locally advanced or metastatic cancer	Phase 1	Interventional	NCT01544322

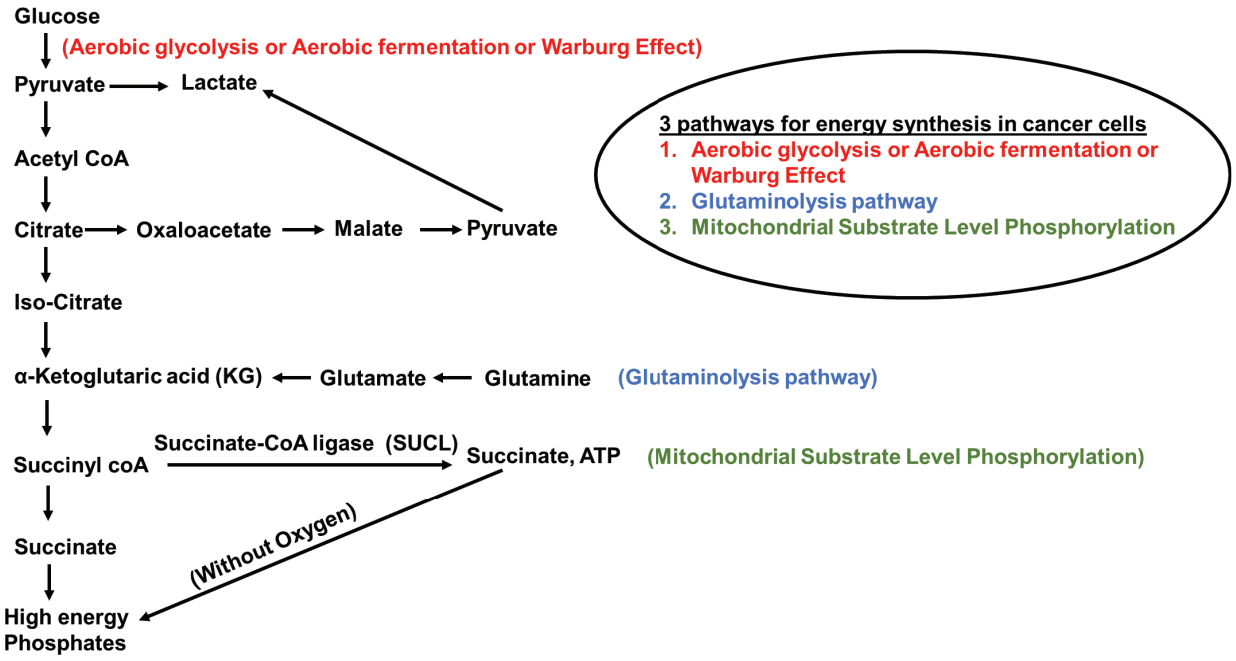

Figure 4 Pathways for energy production in a cancer cell.

shown to regulate glycolytic conversion leading to low ATP yields in cancer [116,151-153]. Various targets associated with mitochondrial dysfunction in a lung cancer cell are clearly illustrated (Figure 5).

In the study conducted by Yoon, et al. [154], the regulation of c-Jun N-Terminal Kinase (JNK) and p38 Mitogen-Activated Protein Kinase (MAPK) is important in combating lung cancer. They used a Militarin analog-1 to study apoptotic mechanisms against human lung cancer cell lines like A549 lung cancer cells and Bronchial Epithelial Cell Line (BEAS-2B). They found inhibition of ROS generation and JNK/p38 MAPK with enhanced DNA fragmentation, nuclear condensation, mitochondrial membrane permeabilization, cytochrome c release, activation of caspase-9/-3, cleavage of poly (ADP ribose) polymerase, leading to apoptosis in Lung cancer cell lines [154]. Mitochondrial dysfunction in patients with lung-centered disorders like COPD is prone to metastatic lung cancer development [155]. mtDNA repairing mechanism in such patients is defective because of low levels of sirtuin-1 [156]. A hypoxic environment further enhances the potential risk of metastasis due to boosted epithelial-mesenchymal transition factors [96]. Factors like activation of NLRP3 inflammasome [157] and chronic tissue inflammation can damage mitochondria, promoting the growth of lung cancer [158,159]. Cellular mitochondria of the trachea, bronchi, and bronchioles have been implicated in lung cancer [160]. In the study conducted by Kao, et al. [161] Dihydromyricetin, a medicinal flavonoid obtained from Ampelopsis grossedentata has a selective cytotoxic effect against NSCLC cells. It acts by activating caspase-9/-7/-3, increasing intracellular peroxide, inducing poly [ADP-ribose] polymerase (PARP) cleavage in A549 and H1975 cells, activating extracellular signal-regulated kinase (ERK)1/2 and c-Jun N-terminal kinase (JNK)1/2. Thus, it induces mitochondrion-derived apoptosis in human NSCLC cells. According to this study, a combination of Dihydromyricetin along with ERK and JNK inhibitors can prove beneficial in preventing NSCLC proliferation [161].

Barrett AG, et al. [162], have shown that targeting mitochondria can be an effective strategy to manage cancer. They used a pentacyclic alkaloidal compound called papuamine which is derived from marine sources like *Haliclona* sp to target mitochondria in NSCLC. Not only was mitochondrial membrane potential lost but also intracellular ATP production was inhibited. It induced apoptosis and inhibited NSCLC cell viability [163]. TIM-4 is a type I membrane protein and stands for T-cell immunoglobulin and mucin domain-containing molecule [140,164]. It plays an important role in clearing apoptotic cells and prevents autoimmunity. It is highly expressed in human and mouse macrophages and dendritic cells [165,166]. TIM-4 is found to be highly expressed in

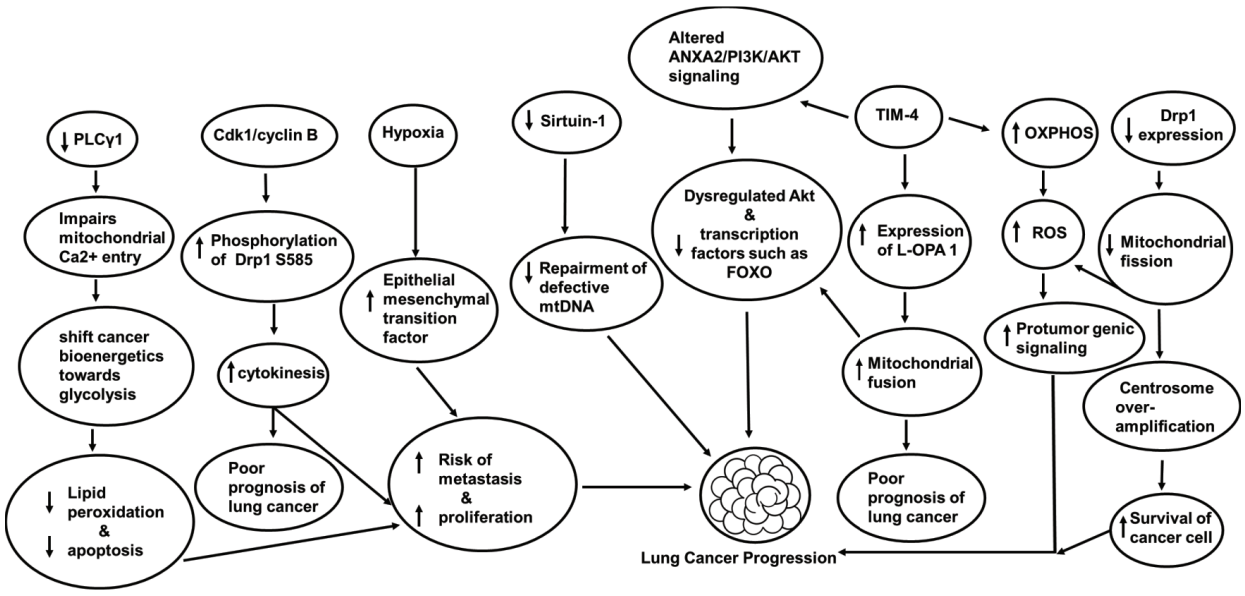

Figure 5 Mitochondrial-associated dysfunctional targets in lung cancer progression.

lung cancer [166]. According to the study conducted by Wang, et al. [167], TIM-4 promotes OXPHOS level and mitochondrial function of lung cancer cells. It upregulates the expression of protein L-OPA1[The unprocessed, N-terminal transmembrane anchored and is the long form of OPA1], and thus regulates mitochondrial morphology and kinetic balance of lung cancer cells. It is involved in the ANXA2/PI3K/AKT signaling pathway [167]. Dysregulation in Akt (acute transforming retrovirus thymoma protein kinase) [168] and inhibition of transcription factors such as forkhead box subfamily O (FOXO) [128] is associated with lung cancer progression [169]. In the study conducted by Saliakoura, et al. [170], PLCγ1 plays a crucial role in lung cancer. On suppression, it impairs Ca2+ entry into the mitochondria and switches cancer bioenergetics towards glycolysis which prevents lipid peroxidation and increases cancer cell proliferation by opposing apoptosis. They found in KRAS-mutant human lung adenocarcinoma cancer cell lines PLCγ1 is poorly expressed during hypoxia with lower patient survival.

When two mitochondria join together, it is termed mitochondrial fusion and when separated into two, is known as mitochondrial fission [171]. Mitofusins (MFN1 and MFN2) and Optic Atrophy 1 (OPA1) are fusion proteins and DRP1, FIS1, MFF, MiD49, and MiD51 are fission proteins [171]. Accumulation of fission proteins on the mitochondrial membrane mediates apoptosis [172]. Silencing Mitofusins 1 and 2 can promote apoptotic cell death [173]. In a study focusing on lung cancer [NSCLC], the expression of a spliced isoform of Mfn1 is found to be upregulated at the mRNA level and is associated with suppressed apoptosis in NSCLC cells [174]. On initiation of apoptosis, Drp1 is recruited to the outer mitochondrial membrane from the cytoplasm [175-178]. Downregulation of Drp1 is shown to lower cytochrome c release, mitochondrial fragmentation, caspase activation, and apoptosis [175,179-180]. On initiation of apoptosis, Drp1 is recruited to the outer mitochondrial membrane from the cytoplasm [175-178]. Prohibitins are inner mitochondrial membrane proteins that play a role in regulating cell cycle and apoptosis [181].

Opa1 works in association with prohibitins (PHB1/2) to regulate cell proliferation [181]. Loss of Opa1 can lead to spontaneous apoptosis [182]. Higher expression of Opa1 has been shown in lung adenocarcinoma cells and is associated with poor prognosis [183]. Based on studies, reduced Drp1 protein expression has been noted in adenocarcinoma alveolar epithelial cells, an NSCLC model, promoting mitochondrial phenotypes elongation, with limited fission and apoptosis [184]. Inhibition of mitochondrial fission can result in mitochondrial dysfunction, loss of mtDNA, elevated ROS, depleted ATP levels [185], cell cycle modification, centrosome overamplification, chromosomal instability, and increased survival of cancer cells [186]. Based on these studies, targeting mitochondrial fission machinery can produce positive outcomes in lung cancer

management [55]. Cyclin-dependent kinase 1 [Cdk1]/cyclin B plays an important role in cytokinesis as it allows equal distribution of mitochondria in daughter cells by phosphorylating Drp1 S585 [187], [188]. According to studies cyclin B1 is overly expressed non-small cell lung cancer and is associated with poor prognosis [188]. Inhibiting cyclin-dependent kinases could be used as a therapeutic target in controlling metastatic lung cancer [189,190].

ROS is mentioned in the majority of studies included in this review. Without ROS, studying mitochondrial metabolism in lung cancer can be considered Incomplete. Why? It's because Mitochondria and ROS are very closely associated. Around 90% of intracellular ROS are produced in mitochondria during OXPHOS [191]. The production of ROS can promote tumor growth and progression [192]. In comparison to normal cells, cancer cells generate ROS in larger quantities [193]. ROS can lead to mutations in mtDNA, lower the capacity for DNA "proofreading" [194], increased leakage of electrons leading to dysfunctional ETC, oncogenic transformation, cancer progression, genetic mutations in the mitochondrial genome, and alteration in transport chain signaling pathways [195]. ROS can itself act as a signal to promote protumor genic signaling, facilitate proliferation, adaptation to hypoxia, and survival of cancer cells [196]. That's why ROS are known for their dual role in promoting cancer progression [121]. Mitochondrial complexes I, II, and III subunits generate ROS such as toxic superoxide anion radicals [O2-·], and Hydrogen Peroxide (H_2O_2). Lack of anti-oxidant action like depleted GSH levels, may create an imbalance between production and neutralization leading to oxidative stress in a cell [191]. Mutation of complex I alters its interaction with complex III generating an incorrect number of electrons resulting in ROS overproduction. That's why, the complex I subunit is of significant target for inhibiting tumor progression and metastasis [197]. As per published scientific literature, complex I appear to be altered frequently in lung cancer, especially in the non-smoker population [198]. Song, et al. [199] have shown that targeting ROS downstream effectors such as JNK and p38MAPK and ROS/MAPK signaling pathway might induce cytotoxicity in cancer cells.

Primary processes such as mitochondrial biogenesis, mitochondrial dynamics, mitophagy, mitochondrial regulation of mtDNA, and mitochondrial unfolded protein response, are involved in the maintenance of mitochondrial quality control [200]. We already discussed mitochondrial dynamics above and here we are elaborating another crucial companion required to maintain mitochondrial quality control. key regulators of mitochondrial biogenesis such as Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 alpha (PGC-1α) are upregulated in lung cancer. PGC-1α promotes metastasis by enhancing oxidative phosphorylation, mitochondrial biogenesis, and oxygen consumption [201]. Deacetylation of PGC-1α by Sirtuin-1 can affect mitochondrial function and biogenesis and is involved in hypoxia-induced chemoresistance in non-small cell lung cancer [202]. Oncogenic pathways like MAPK/ERK and PI3K/AKT/mTOR are upregulated in lung cancer and associated with the regulation of mitochondrial function and biogenesis [203]. Mitophagy is a type of macro autophagy that is essential for removing damaged, excess, or old mitochondria [204]. It has many roles in cancer progression and carcinogenesis. It can be PINK1/PRKN-dependent and PTEN-induced putative kinase 1 (PINK1)/ parkin RBR E3 ubiquitin-protein ligase (PRKN)-independent [205]. Mitophagy targets damaged or dysfunctional mitochondria for degradation to maintain cellular integrity and health. It helps in maintaining the quality and functionality of mitochondria [206]. Mitophagy can act as a tumor promoter or suppressor [207]. Mitophagy mediated by Caveolin-1 (Cav-1)/Parkin can contribute to the resistance of non-small cell lung cancer [208]. In the adaptation to chemotherapy drug treatment, mitophagy acts as a cytoprotectant [209]. Downregulation of Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) can make cav-1-knockdown A549 cells more sensitive toward drugs such as cisplatin [210]. Overexpression of Apurinic Endonuclease 1 (APE1) has been reported to induce Parkin-mediated mitophagy in A549 cells. knockdown of APE1 can promote cell apoptosis and restore the sensitivity of cancer cells toward drugs like cisplatin [209]. Mitochondrial transcription factor A (TFAM], a 25-kDa nDNA-encoded protein [211] is involved in mitochondrial biogenesis [211]. It can translocate into mitochondria and bind to mtDNA, thus important for the maintenance of mtDNA [212]. Mitochondrial quality control proteins such as the dimeric form of DRP1, Sirtuin 3, and BCL2/adenovirus e1B 19 kDa protein-interacting protein 3(BNIP3) determine the integrity level of mitochondria. These could be used to separate patients with lung cancer into high- and low-risk groups [213]

Mitochondria are autonomous [214] and may attain various shapes based on their cellular states such as tubular under normal conditions, round during apoptosis, swollen and distended during necrosis, elongated during autophagy, donut-shaped mediated by mitochondrial calcium [215]. Leucine zipper EF-hand-containing transmembrane protein-1 (LETM1) is an anchoring protein that is involved in mitochondrial morphology, cell viability, and ion homeostasis. Overexpression of LETM1 and mitochondrial fragmentation has been shown in lung cancer cells [216]. Sideroflexin1 (SFXN1) is a potential prognostic biomarker for lung adenocarcinoma. Its high expression is correlated with advanced clinical stage, larger tumor size, expression of multiple immunomodulators, immune cell infiltration [natural killer cells, dendritic cells, activated CD8 + T cells, macrophages], and positive lymph node metastasis [217]. In lung adenocarcinoma, transmembrane protein 70, flavoprotein 2, and NADH dehydrogenase [ubiquinone] act as protective factors. NAD-dependent protein deacetylase sirtuin-5 serves as a protective factor in lung squamous cell carcinoma. NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8 acts as a protective factor in small-cell lung cancer [218]. MitomiRs are regulators of various mitochondrial processes and are an important contributor to the pathogenesis and progression of lung cancer. Expression of mitochondrial proteins along with controlling the functional activity of mitochondria is regulated by a class of microRNA called a MitomiR. MicroRNAs are non-coding RNA molecules. They regulate various mitochondrial activity and mitochondrial genes involved in carcinogenesis processes. These are exported into the cytosol after being encoded in the nuclear genome. These can be derived from mitochondrial DNA and can be located in mitochondria [219]. Levofloxacin has been reported to inhibit mitochondrial respiration and reduce ATP production by inhibiting activities of mitochondrial electron transport chain complexes I and III. It can inhibit proliferation and induce apoptosis in various lung cancer cell lines [220].

Conclusion

Mitochondrial metabolism is closely related to the proliferation and metastasis of lung cancer. Factors like excessive ROS production, dysfunctional mitochondrial metabolism, disbalance in the anti-oxidant system, and alteration in mitochondrial DNA play a crucial role in the progression of lung cancer. Thus, we found different cross-connections between malfunctional mitochondria and the growth of lung cancer. Emerging research facts state cancer is a metabolic disease. To conclude, a research renaissance is required to switch our focus from understanding cancer as a genetic disease to cancer as a mitochondrial metabolic disease with mitochondria as a potential target in the inhibition of lung cancer.

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