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The Bioenergetic Role of Mitochondria in Lung Cancer

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<http://dx.doi.org/10.5772/67238>

Abstract

In 1920s, Otto Warburg made the observation that cancer cells utilize significantly more glucose than normal, healthy cells, which led him to believe that cancer cells relied on glycolysis more than healthy cells. However, many subsequent studies have shown that glucose is not only necessary for glycolysis but also for oxidative phosphorylation and production of building blocks for the synthesis of other molecules. There are many challenges associated with studying and treating lung cancer, and there is a diverse set of metabolic factors influencing the tumorigenesis and metastasis of lung cancer. Lung cancer cells rely heavily on mitochondrial respiration, and several studies have shown that inhibiting mitochondrial function is an effective method to combat lung cancer. Several agents have been used to inhibit mitochondrial function, including cycloamine and metformin. Further, more research has noted increased levels of heme flux and function as critical to intensified oxygen consumption and accompanying amplified pathogenesis and progression of lung cancer. The upregulation of mitochondrial DNA and biogenesis genes are also correlated with lung cancer. In this chapter, we will cover these recent and emerging topics in lung cancer bioenergetics research.

Keywords: heme, mitochondrial respiration, respiration genes, oxidative fuels, glutamine, cycloamine

1. Introduction

Cells perform a variety of diverse functions and processes, all of which require some form of cellular energy. The general currency of cellular energy exists as adenosine triphosphate, a high energy molecule created by two main bioenergetic pathways: glycolysis and oxidative phosphorylation.

Glycolysis, which translates to “sweet splitting,” is the process of breaking down a substrate, usually glucose, through a series of steps to produce two ATP molecules. This process does not require oxygen, and it is sometimes referred to as anaerobic respiration. To begin the process, glucose transporters allow glucose uptake into the cell [1]. Hexokinase then phosphorylates glucose, which becomes glucose-6-phosphate. Glucose-6-phosphate isomerase is an enzyme that catalyzes the reversible isomerization of glucose-6-phosphate and fructose-6-phosphate which follow the pentose phosphate pathway that produces nucleotides and NADPH, or the glycolytic pathway to make lactate. Fructose-6-phosphate undergoes a reaction facilitated by phosphofructokinase-1 to become fructose-1,6 bisphosphate, which then becomes glyceraldehyde-3-phosphate for glycolysis or dihydroxyacetone phosphate to help create lipids. Glyceraldehyde-3-phosphate becomes glycerate-2-phosphate by glyceraldehyde-3-phosphate dehydrogenase. Glycerate-2-phosphate becomes phosphoenol pyruvate via enolase. To produce the two ATP of glycolysis, pyruvate kinase catalyzes the conversion of phosphoenol pyruvate into pyruvate (see **Figure 1**). Finally, pyruvate is converted to lactate, a process which is mediated by the enzyme lactate dehydrogenase-A. This process generates NAD^+ from NADH. The production of NAD^+ allows the process of glycolysis to be cyclical.

Figure 1. Cells use lipids, glutamine, protein, and glucose in order to gain energy. Many of these substrates, including those produced by glycolysis eventually lead into the tricarboxylic acid (TCA) cycle. The steps involved in ATP synthesis or consumption are marked in red. Those involved in utilization or production of GTP are marked in pink, while NAD^+ /NADH and FAD/FADH_2 are in blue. The numbers of ATP/GTP and $\text{NADH}/\text{FADH}_2$ produced by glycolysis and by the tricarboxylic acid cycle are indicated.

Oxidative phosphorylation has many more steps than glycolysis, and it requires oxygen. Oxidative phosphorylation creates significantly more ATP per substrate molecule than does glycolysis. It is a slower process, and it is made possible by mitochondrial respiratory chain complexes.

Mitochondria are the site of oxidative phosphorylation (see **Figure 2**). Mitochondria are present in many diverse types of cells in eukaryotes, and they are capable of producing large quantities of energy. The respiratory chain complexes in mitochondria are responsible for facilitating the reactions associated with oxidative phosphorylation. Consequently, the unique bioenergetics of cancer suggests altered mitochondria. Indeed, some genes have been found to be mutated in mitochondria (see **Figure 2**).

Figure 2. Mitochondrial and heme function in cellular bioenergetics. Bioenergetic fuels, including glucose, glutamine, and fatty acids, can generate metabolites that feed into the tricarboxylic acid (TCA) cycle. Through oxidative phosphorylation, NADH and FADH₂ generated from the tricarboxylic acid cycle can be used to generate a large amount of ATP. Heme is a central molecule in mitochondrial function and oxidative phosphorylation. Heme can be taken up from the extracellular space via heme transporters HRG1 and HCP1. Heme is also synthesized in mitochondria in most mammalian cells. Heme serves as a prosthetic group or cofactor for many enzymes in Complexes II–IV. In non-small cell lung cancer cells, it has been shown that heme flux and function are intensified to support enhanced oxidative phosphorylation.

The process of oxidative phosphorylation requires several protein complexes, named Complex I–V, all of which are partly coded by mitochondrial DNA with the exception of Complex II [2]. Within the inner membrane of the mitochondria, there are electron carriers that are critical for mitochondrial respiration. Importantly, up to 2% of electrons cycling through the electron transport chain can escape the process, and this creates reactive oxygen species, or ROS [3]. These ROS can cause significant damage to mitochondrial DNA.

Pyruvate is transported into the mitochondria or transformed into lactate and nicotinamide adenine dinucleotide (NAD) by lactate dehydrogenase (LDH). Direct transport of pyruvate into the mitochondria across the outer mitochondrial membrane, intermembrane space, and inner mitochondrial membrane is facilitated by mitochondrial pyruvate carrier (MPC). Mitochondrial pyruvate carrier also facilitates the removal of hydroxide from the mitochondria. Once within the mitochondrial matrix, pyruvate is converted to acetyl coenzyme A (acetyl CoA) via pyruvate dehydrogenase catalysis. Acetyl CoA enters the tricarboxylic acid cycle, and succinate is formed via organic acid oxidation. NADH contains electrons that go through the electron transport chain (ETC), which consists of mitochondrial Complexes I–IV (see **Figure 2**). Complex I, alternatively called NADH dehydrogenase or NADH ubiquinone oxidoreductase, marks the beginning of the electron transport chain and is also the largest of the five mitochondrial complexes [4]. From Complex I, the electron transport chain brings electrons toward coenzyme Q through the inner mitochondrial membrane. Alternatively, electrons can skip Complex I entirely. The transport of these electrons is mediated by flavin-containing enzyme complexes and they also reach coenzyme Q via this alternative pathway [5]. From coenzyme Q, electrons are transferred to Complex III. Yet another pathway to coenzyme Q is possible via Complex II. Succinate is reduced and the electrons from the reduction of succinate are taken to coenzyme Q and Complex III. Complex III and cytochrome c shift electrons to Complex IV. The movement of electrons over the inner mitochondrial matrix by Complexes I, III, and IV creates a proton gradient. This causes protons to enter the mitochondrial matrix, a process allowed by Complex V, ATP synthase (V), and causes the production of ATP (see **Figure 2**). Taken together, Complexes I–V facilitate oxidative phosphorylation and can create up to 36 mol of ATP per mol glucose. ROS created via oxidative phosphorylation can be used to regenerate NAD^+ . It is important to note that many cancer cells prefer glutamine as opposed to glucose [6]. This may be because cancer mimics the effects of starvation on the body. During starvation, the body utilizes amino acids from a pool of amino acids, and then breaks down skeletal muscle to replenish the pool of amino acids. One of the major amino acids consumed in this process is glutamine, the very same amino acid substrate which many cancer cells are remarkably adept at converting for energy. Many glycolytic molecules are considerably upregulated in cancer, including hexokinase II, glucose transporters, pyruvate kinase, and lactate dehydrogenase-A [1]. These molecules serve as targets for chemotherapy drugs. In the same way, many oxidative phosphorylation enzymes and molecules are differentially regulated in cancer.

2. Unique clinical problems of lung cancer

Lung cancer screening with low-dose computer tomography has proven to be effective in significantly reducing mortality of lung cancer patients through detection of nonsymptomatic patients at early stages [7]. These early stage patients are typically treated with surgical or radiological procedures followed by periodical surveillance with radiographic imaging. Although these curative treatments have been successful in saving many of these patients from lung cancer, 30–60% of the patients are predicted to present with local or distant recurrences (mostly within 5 years, but some beyond the first 5 year period) [8]. This is a unique problem for lung cancer that limits overall survival rates in these patients to less than 60% despite early detection, as compared with greater than 95% in the case of early stage prostate or breast cancers [9].

If these patients can be accurately identified at the time of initial treatment, adding appropriate adjuvant therapy to their initial treatment plan may significantly increase their survival rates. However, adjuvant chemotherapy on Stages I–III non-small cell lung cancer (NSCLC) patients showed only marginal 5-year overall survival benefits of less than 6% in meta-analyses of recent clinical trials [10, 11]. Neither epidermal growth factor receptor-targeting therapy nor immunotherapy showed significant benefits in adjuvant settings for early stage NSCLC patients [12, 13]. Thus, no methods are currently available to effectively treat these patients. However, several recent experiments strongly suggest that targeting mitochondria will yield effective strategies to treat lung cancer patients in the future [14–18].

3. Lung cancer cells are extremely susceptible to inhibitors of mitochondria

Several studies have suggested that inhibiting mitochondrial function makes drug-resistant tumors more sensitive to treatment [14–16, 18]. When oxidative phosphorylation was suppressed, cancer became less able to proliferate in an anchorage-independent manner [14]. This drastically limits the tumorigenic capacity of cancer cells. Because mitochondria are crucial for the electron transport chain and therefore oxidative phosphorylation, two processes which are especially prominent in cancer cells, inhibiting mitochondrial function essentially starves the cancer cell of ATP, affecting processes such as growth and metastasis of tumors. However, because healthy cells have drastically lower levels of oxidative phosphorylation and often significantly lower energy requirements, healthy cells are not as strongly impacted as cancer cells and can maintain functionality. Consequently, when the mitochondria of tumor cells are tampered with to inhibit oxidative phosphorylation, these tumor cells become significantly more susceptible to cytotoxic drugs [16, 19]. Agents such as cyclopamine tartrate, a water-soluble derivative of a molecule found in corn lilies [20]; metformin, an antidiabetic drug [18]; BAY 87-2243, a lead structure [15]; and microRNA-126, a microRNA [21] have shown potential to interfere with normal mitochondrial function in cancer cells. These molecules interact with various aspects of mitochondrial function, such as interfering with Hedgehog signaling and inhibiting Complex I. Cyclopamine tartrate functions by inhibiting Hedgehog signaling [20]. Cyclopamine was the first chemical found which effectively inhibited Hedgehog signaling. Cyclopamine tartrate is an analog of cyclopamine, but it is more soluble in water than cyclopamine. The mechanism by which cyclopamine and cyclopamine tartrate work has been studied extensively. Smoothened (SMO) is a G protein-coupled receptor. SMO is responsible for facilitating Hedgehog signaling. Cyclopamine tartrate inhibits SMO, thereby inhibiting Hedgehog signaling. In NSCLC HCC4017 cells, studies have demonstrated intensified oxygen consumption compared to benign HBEC cells from the same patient [20]. Low levels of glucose also contribute to higher oxygen consumption rates, and low levels of glutamine lower oxygen consumption rates. Low levels of glucose also encourage NSCLC cells to utilize glutamine, and low levels of glutamine contribute to increased glucose consumption. Although NSCLC cell lines have varying levels of sensitivity to cyclopamine tartrate, this agent can be used to induce apoptosis by targeting these aerobic respiration pathways. Further, Cyclopamine tartrate helps generate ROS, which disturb the mitochondria in

tumor cells. Cyclopamine tartrate can cause mitochondrial fission and fragmentation in several types of NSCLC cells, including H1299, A549, and H460 cells. Consequently, cyclopamine tartrate reduces mitochondrial respiration. Metformin has been used for years to combat Type II diabetes, but as of 2001, scientists were only beginning to take note of the anticancer properties of the drug in mammals [22]. Scientists also noticed that those individuals taking metformin for diabetes had lower overall rates of cancer. Recently, researchers have shed some light onto the mechanism of metformin. Metformin inhibits mitochondrial Complex I by reducing oxygen consumption in the presence of malate and pyruvate, which create NADH as a substrate for Complex I [23]. Metformin has also been reported to interrupt the tricarboxylic acid cycle, the methionine cycle, and the folate cycle, as well as decrease nucleotide synthesis.

4. Enhanced heme function is important for NSCLC cells

Heme, or iron protoporphyrin IX, is notably and inextricably linked with oxygen transport, storage, and utilization. Most mammalian cells can synthesize heme *de novo*. Many cells also uptake heme via heme transporters, such as HRG1 and HCP1. Heme is important for neurogenesis, circadian rhythm, erythroid biogenesis, and pancreatic development and functions as a prosthetic group for hemoglobin, myoglobin, cytochromes, peroxidases, and catalases [24]. Heme directly regulates transcription, cell cycle, cell death, and protein synthesis [25–29]. When heme levels are too low or too high, therefore, many diverse processes are affected. There are several diseases associated with altered heme levels. These include anemia, porphyrias, Alzheimer's disease, Parkinson's disease, Type-2 diabetes, coronary heart disease, and several types of cancer including colorectal, pancreatic, and lung cancers [25, 30].

When levels of heme flux and function are increased, levels of oxygen utilization are also increased. Intensified oxygen consumption allows increased cancer cell proliferation and function [17]. Recent research suggests that non-small cell lung cancer (NSCLC) cells upregulate proteins that stimulate heme synthesis, uptake, and function. When these proteins abound, heme is significantly upregulated, and aids in lung cancer progression. Notably, affected proteins include ALAS, HRG1, HCP1, cytoglobins, and cytochromes [30].

When NSCLC cells were compared to normal cells from the same patient, studies showed that rates of heme biosynthesis were significantly raised in cancerous cells [30]. ALAS1, a rate limiting enzyme in nonerythroid heme synthesis, is higher in NSCLC cells. Succinyl acetone has been used to lower heme levels by inhibiting heme synthesis. Succinyl acetone attacks delta-aminolevulinic acid dehydratase.

5. Mitochondrial respiration and biogenesis genes are upregulated in lung tumor cells

Lung cancer often has a genetic basis. Up to 60% of lung adenocarcinoma tissues have a driver mutation. These genes include Kirsten rat sarcoma viral oncogene (KRAS), epidermal growth

factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and proto-oncogene B-Raf (BRAF) [31, 32]. In lung adenocarcinoma, the type of NSCLC most frequently found to plague nonsmokers, smoking causes a very different pathway of tumorigenesis [33]. In nonsmokers, there are four times as many differently expressed genes as in smokers [33]. This is thought to be due to the lung tumor locally evolving in nonsmokers. By contrast, in smokers the lung tumor is thought to evolve from a patch of genetically altered tissue. Furthermore, some of the genes that were found to be upregulated in smokers were upregulated more depending on how frequently the smoker smoked. Malic enzyme (ME) expression is also significantly increased in the lung tissues of smokers compared to nonsmokers [34]. The EGFR pathway is the most common signaling pathway for lung cancer, and the mutation rate of genes of the EGFR pathway reach 70–80% [32]. About 30–35% of lung adenocarcinoma genetic variation is attributable to the KRAS mutation. In NSCLC cells, 97% of KRAS mutations occur in codon 12 or 13, and by testing codon 12 for KRAS mutation in bronchoalveolar lavage, scientists can diagnose lung cancer. Some labs have identified proteins that are overexpressed significantly in lung adenocarcinomas. Particularly, ATP synthase subunit d (ATP5D) is significantly over-expressed in lung adenocarcinomas (tumor: $n = 93$, 1.155 ± 0.418 ; normal: $n = 10$, 0.663 ± 0.210 ; p value: <0.0001) [35]. Some common marker genes include neuron-specific enolase, carcinoembryonic antigen, cytokeratin 19 fragments (CYFRA 21-1), squamous cell carcinoma antigen, cancer antigen CA 125, and tissue polypeptide antigen, although no one marker gene is as efficient as multiple marker genes at predicting and diagnosing lung adenocarcinomas. Both ME and ATP-citrate lyase (ACLY) are enzymes related to aerobic glycolysis and fatty acid synthesis. They are both correlated with NSCLC cells, and ACLY tends to be more localized, whereas ME tends to signify mediastinal lymph nodes, a site of metastasis in the human body [34]. Interestingly, in young patients, overexpression of ACLY and/or ME correlated with extended survival compared to patients who did not overexpress ACLY and/or ME. However, in older patients, overexpression of ACLY and/or ME is predictive of shorter period of survival as compared to patients who do not overexpress ACLY and/or ME. It can therefore be inferred that potential rising treatments must take into consideration the age group of the afflicted patient. Mitochondrial respiration genes have also been shown to be upregulated in lung tumor cells. In lung adenocarcinoma, many genes, especially those associated with mitochondrial respiration, have been shown to be differently expressed than in healthy tissue [32]. One study noted 535 upregulated and 465 downregulated differentially expressed genes in lung adenocarcinoma comparing matched tissues of the same patients. One prominent class of upregulated genes is related to mitochondrial oxidative phosphorylation and the electron transport chain. ATP5D, UQCRC2, NDUFA2, NDUFB8, NDUFA7, NDUFA1, NDUFB1, NDUFS7, UQCR11, NDUFV1, NDUFV2, and NDUFS3 are specifically related to bioenergetic pathways including mitochondrial ATP synthesis-coupled electron transport and the electron transport chain [32]. Additionally, genes associated with mitochondrial biogenesis are specifically upregulated in circulating lung cancer cells and have been reported to be essential for their metastatic potential [36]. By studying metastatic cancers, LeBleu et al. investigated the role of peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1 α) in enhancing metastatic potential by increasing oxygen consumption, mitochondrial biogenesis, and oxidative phosphorylation rates. The effect of PGC-1 α on respiration appears to be key to allowing metastasis specifically, and does not appear to strongly affect cancer cell proliferation, epithelial-to-mesenchymal transfer, or primary tumor growth. Activating mutations in Ras guanosine nucleotide-binding

proteins result in insensitivity to GTPase-activating proteins [37]. These Ras mutations are common in human cancers [38]. Activated GTP-bound Ras family members increase glucose uptake and flux, which partly promotes the survival and proliferation of lung cancer [37]. This effect is important because it increases the capacity for energy production in lung adenocarcinoma cells. Activated Ras also increases tricarboxylic acid cycle activity and oxygen consumption, which further enables cancerous cells to produce energy and therefore increases carcinogenic and metastatic potential of cancer cells. Cytochrome c oxidase is activated by Ras [39]. Cytochrome c oxidase contains 3 mitochondrial DNA-encoded and 10 genomic DNA-encoded subunits and forms Complex IV of the electron transport chain [40]. In some types of cancer, levels of cytochrome c oxidase are significantly elevated [40, 41]. Without activated cytochrome c oxidase, A549 lung adenocarcinoma is incapable of growth [37]. Still more mutations in nuclear genes affecting mitochondrial form and function have been linked with lung cancer. Succinate dehydrogenase, including SDHB, SDHC, and SDHD genes, and isocitrate dehydrogenase, including IDH1 and IDH2 genes, code for mitochondrial components [42]. By affecting the structure of the mitochondria, these genes affect the function of the mitochondria, and consequently are associated with or considered causal to cancer. Due to the large genetic variation between lung tumor cells, or tumor heterogeneity, chemoresistance is a major problem in lung cancer treatment. Many chemicals which are effective on certain types of lung cancer are not effective on other types of lung cancer. Furthermore, individual tumors possess intratumoral heterogeneity. That is, the tumor has nonidentical cells. Therefore, while some cell types may respond favorably to treatment, other cell types may not. Consequently, over time, these cell types begin to dominate the tumor and the tumor becomes chemoresistant by acquiring genetic and epigenetic changes. This process was first proposed by Nowell as clonal evolution [43]. Understanding tumor heterogeneity and variation among NSCLC categories therefore significantly increases the ability of research to successfully unearth potential treatments and cures for lung cancer.

6. Mitochondrial DNA is correlated with lung cancer

Mitochondrial DNA is especially susceptible to reactive oxygen species because it does not have protective histones and introns [44]. Further, mitochondria lack the capacity to repair damaged mitochondrial DNA. Consequently, mitochondrial DNA mutates more frequently than other genomic DNA [45]. The instability of mitochondrial DNA can have devastating effects on the cell, including mutations and copy number alterations [2]. Both germline and somatic mitochondrial DNA defects are associated with cancer. Mitochondrial DNA is thought to be able to function as a driver or as a complementary gene mutation of carcinogenesis according to the multiple-hit model, thereby allowing increased clonogenic and/or mutagenic capacities in cancer cells [2]. To combat these mutations, mitochondria increase their copy number drastically. Some studies suggest that the number of copies of mitochondrial DNA is strongly correlated with carcinogenesis [44, 46]. This relationship has been supported by several other labs [47, 48]. This relationship has been especially noted in lung adenocarcinoma. It is important to note that some diseases have a causal effect with cancer, and may also increase mitochondrial DNA copy number. To overcome this bias due to a latent disease, mitochondrial DNA was measured in peripheral white blood cells. The results suggested that even in the absence of a causal disease, increased copy number is indicative of an increased risk of lung cancer [44]. Importantly, this connection does not hold

true for all types of cancer [47, 48]. Some cancers express lower mitochondrial copy numbers. However, in lung adenocarcinoma, the mitochondrial copy number is increased compared to controls. There is also a strong correlation between mitochondrial DNA copy number and TFAM (Transcriptional Factor A, Mitochondria) expression [48]. TFAM is a factor for transcription and replication and in nucleoids. TFAM binds to mitochondrial DNA. Significantly, the gene set responsible for controlling the tricarboxylic acid cycle and respiratory electron transport is most commonly correlated to copy number. In NSCLC cells, epithelial-to-mesenchymal transition is thought to be the critical moment defining metastatic potential [49]. It is thought that during epithelial-to-mesenchymal transition, the copy number of mitochondrial DNA is altered. In A549 cells, copy number increased from 1700 to 2800 during epithelial-to-mesenchymal transition.

7. Stromal cells in the tumor microenvironment contribute bioenergetic molecules to cancer cells

Despite the deregulation of normal metabolic processes in tumor cells and the many contributors to mitochondrial dysfunction, tumors still have remarkable capacity to perform oxidative phosphorylation. This is in part due to a phenomenon where surrounding tissues contribute fuel sources to tumor tissues [50]. A two-compartment model was proposed in 2012 to explain this process [51–53]. Glycolytic stromal cells produce L-lactate and ketone bodies which are utilized by oxidative epithelial cancer cells. The metabolites produced by these fibroblasts (see **Figure 3**) provide fuel for cancer proliferation via oxidative phosphorylation [54]. This process is thought to be mediated by pyruvate kinase isoforms. Glutamine helps to fuel this process [55–57]. It appears as though the tumor cells take advantage of the stromal cells in a form of micro-level commensalism [52].

Figure 3. Metabolic fuels for tumor cells. Cancer cells use a variety of bioenergetic substrates including glucose, glutamine, fatty acids, and ketones. Stromal cells in the tumor microenvironment can provide various oxidative fuels depending on their characteristics. Shown here are adipocytes and fibroblasts.

8. Summary

Emerging evidence increasingly shows that mitochondrial respiration is key to cancer bioenergetics. Particularly, heme is a central molecule in mitochondrial respiration. Many lines of evidence from epidemiological studies, gene expression studies of human tumor tissues, and molecular studies of cancer cell lines indicate that functions of heme and oxygen-utilizing hemoproteins are critical for tumorigenesis, particularly lung tumorigenesis. Enhanced heme flux and function is a key feature of non-small cell lung cancer cells. Consistent with these observations, many cancer cells are susceptible to inhibitors of mitochondrial function and heme biosynthesis. A better understanding of the relationships between mitochondrial and heme function with cancer bioenergetics should facilitate the development of effective strategies to treat cancers, particularly lung cancer.

Acknowledgements

Work on lung cancer in Dr. Li Zhang's lab is funded by the CPRIT Grant and the Cecil H and Ida Green Funds from the University of Texas at Dallas.

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