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Elevated Mitochondrial and Heme Function as Hallmarks for Non-Small Cell Lung Cancers

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Abstract

Many targeted therapies have been developed to treat lung cancer. Unfortunately, however statistical data over the past two decades suggest only a slight improvement in a patient's survival rate after diagnosis. Clonal evolution and tumor heterogeneity are the major obstacles in designing effective targeted treatments against cancer. To create more comprehensive treatments, emerging therapies target bioenergetic pathways of cancer cells. Like normal cells, cancer cells can generate energy only through glycolysis and oxidative phosphorylation. Notably, a number of studies have shown that many types of cancer cells rely heavily on mitochondrial respiration. Importantly, research carried out in the authors' laboratory showed that non-small cell lung cancer cells exhibit increased levels of mitochondrial and heme function. Hence, limiting heme availability interferes with bioenergetics of cancer cells. Evidently, targeting heme function may provide an effective way for treating lung cancer.

Keywords: Heme; Lung cancer; NSCLC; Mitochondrial function; Oxidative phosphorylation

Introduction

Lung cancer is the leading cause of cancer-related death in the US [1]. It is mainly divided in two types: small cell lung cancer and non-small cell lung cancer. Non-small cell lung cancer (NSCLC) constitutes about 85% of the lung cancer cases [2]. There are various targeted therapies that have recently been approved to treat lung cancer. For example, in 2013 the FDA approved erlotinib as the first-line treatment of patients with metastatic NSCLC, whose tumors had epidermal growth factor receptor (EGFR) mutations [3]. Similar to erlotinib, Iressa was also developed to treat NSCLC that contained mutations in the EGFR gene. Unfortunately, only ten percent of NSCLC cases have EGFR gene mutations [4]. In 2006 the FDA approved the labeling extension for bevacizumab in combination with paclitaxel and carboplatin for the treatment of locally advanced, recurrent, or metastatic, non-squamous, non-small cell lung cancer [5]. Spanning from 1990 to 2015, the various innovations in treatments have helped increase the survival of patients with advanced NSCLC, but this increase has only shifted average survival time from 7.1 to 11.4 months [6].

Many studies have revealed that the failure of targeted therapies is in part due to clonal evolution and tumor heterogeneity [7-9]. Clonal evolution arose from the idea that tumor cell populations are genetically unstable and that presence of carcinogens or nutritional deficiencies within the tumor can result in human malignancies being highly individual, both karyotypically and biologically [10]. Furthermore, a number of recent studies have confirmed the idea of tumor heterogeneity. For example, Ellsworth et al. found that primary carcinomas in 30 breast cancer patients were genetically heterogeneous. They also determined that metastasis is influenced by primary tumor heterogeneity and variability in the timing of dissemination [11].

Likewise, tumor cells are versatile in their ability to adapt to their environment and support their proliferation and function. It has previously been shown that tumor cells can generate ATP by metabolizing an array of substrates, including glucose, glutamine and fatty acids [12-18]. The two main pathways through which cells can generate ATP are glycolysis and oxidative phosphorylation. In 1920, Otto Warburg suggested that tumor cells metabolize glucose through glycolysis even in the presence of ample amount of oxygen the phenomenon, called "Warburg effect" [19]. Contrary to the Warburg hypothesis, a study on cultured Hela cells showed that more than half of ATP is produced from glutamine, even in high concentrations of glucose [20]. Furthermore, recent studies have confirmed that cancer cells use glutamine as a major carbon source to drive ATP production through oxidative phosphorylation [21-28].

Additionally, a study showed that a subpopulation of dormant tumor cells surviving oncogene ablation relies on oxidative phosphorylation for survival [29]. This particular study revealed that surviving cancer cells had prominent expression of genes governing mitochondrial function and a strong reliance on mitochondrial respiration, as well as a decrease in glycolysis [29]. Similarly, a study on the depletion of mtDNA in tumor cells increased their sensitivity to cytotoxic chemotherapy. Placing normal mitochondria into these mtDNA depleted cells returned their tumorigenic phenotype [30]. Mitochondria are crucial to cancer cells and inhibiting the function of mitochondria starves the cells of ATP. In 2014, a study revealed how migratory and invasive cancer cells favor mitochondrial respiration and increased ATP production [31]. Le Bleu et al. found a correlation between expression of PGC-1a, an inducer of mitochondrial biogenesis, and the formation of distant metastases. Interestingly, silencing PGC-1a in cancer cells suspended their invasiveness [31]. Evidently, many lines of evidence suggest that mitochondrial respiration is important in the progression of cancer.

Interestingly, Ras mutations which are very common in human cancers have been correlated with increase in TCA cycle activity and oxygen consumption. Telang et al. showed that introducing activated

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H-Ras into human bronchial epithelial cells increased COX activity and oxygen consumption [32]. Consequently, transfecting A549 cells with COX Vb shRNA reduced the ability of these cells to grow in soft agar. In addition to this, a study on Metformin revealed that patients with Type II diabetes taking this drug had overall lower rates of cancer [33]. Metformin has been shown to inhibit mitochondrial Complex I [34]. Andrzejewski et al. showed that Metformin induce a shift in favor of uncoupling reactions, which causes mitochondrial metabolism to become energetically inefficient [35].

Similarly, our lab has previously shown that oxygen consumption is intensified in NSCLC cells versus normal nonmalignant lung cells [36]. We used CycT and SANT1 to, effectively target G protein-coupled receptor SMO, which mediates Hedgehog signaling. Consequently, CycT and SANT1 suppressed, aerobic respiration, and the rates of oxygen consumption and cancer cell proliferation were significantly reduced [36]. CycT increases the levels of ROS which causes mitochondrial fission and fragmentation in NSCLC cells. This leads to a reduction in mitochondrial respiration.

Heme as a New Target

Heme is used as a protein-bound prosthetic group in Complex II, Complex III, and Complex IV [37]. Heme is also well known to function in the transport, storage, and utilization of oxygen [38]. It serves as prosthetic group or as a cofactor for a number of enzymes and proteins such as hemoglobin, myoglobin, cytochromes, peroxidases, and catalases, which play essential roles in oxygen utilization and metabolism [39]. Heme is critical for cytochrome c oxidase (COX-2) biogenesis and mitochondrial respiration [40]. Importantly, it has been shown that heme levels directly affect a number of physiological and disease processes in humans. A decrease in levels of heme is associated with porphyrias, anemia, and neurological disorders like Alzheimer's disease [41]. On the other hand, various epidemiological and experimental studies directly relate high heme intake to risk of heart disease, diabetes, and cancer [42]. Additionally, a meta-analysis of prospective cohort studies of colon cancer reported heme intake of 566,607 individuals and 4,734 cases of colon cancer [43]. Heme-related mechanisms have also been proposed to explain the association between red meat and the risk of cancer. For example, heme may increase the formation of endogenous N-nitroso compounds, which increases the overall mutation rate in the DNA [42]. Hence, it is likely that heme availability is linked to progression of lung cancer.

Consistent with these findings, our lab showed that NSCLC cells and tumors exhibit high levels of heme, as well as elevated enzymes required for heme synthesis, such as ALAS1. Proteins such as HCP1 and HRG1, which are crucial for the uptake of heme in cells, have also shown to be upregulated in NSCLC cells. This enables cancer cells and tumors to produce high amounts of hemoproteins, resulting in intensified oxygen consumption and cellular energy production to fuel cancer cell progression [44]. Therefore, limiting heme availability in tumor cells should interfere with the biogenesis of mitochondrial respiratory chain complexes and should suppress mitochondrial function.

In order to confirm this, our lab used succinyl acetone, an inhibitor of heme synthesis, to treat cells. We found that levels of ALAS1 were further increased in cancer cells versus normal cells. The levels of cytoglobin and cytochrome c, which are elevated in cancer cells versus normal cells, were reduced in response to the addition of succinyl acetone [45]. This also reduced oxygen consumption in NSCLC cells selectively. Furthermore, we found that lowering heme biosynthesis and uptake, like lowering mitochondrial respiration, effectively reduced oxygen consumption, cancer cell proliferation, migration, and colony formation. In contrast, lowering heme degradation does not have an effect on lung cancer cells [45]. These results show that increased heme flux and function are a key feature of NSCLC cells [46]. In summary, heme and mitochondrial function is an important factor in lung tumor development and progression and likely other cancers.

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