Elevated mitochondrial and heme function as hallmarks for Non-small cell lung cancers

Chantal Vidal, Sagar Sohoni and Li Zhang*
Department of Molecular and Cell Biology, Center for Systems Biology, University of Texas at Dallas, USA

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 survivability 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.

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. In 2013 the FDA approved erlotinib as the first-line treatment of patients with metastatic non-small cell lung cancer, 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 is 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]. LeBlu et al. found a correlation between expression of PGC-1α, an inducer of mitochondrial biogenesis, and the formation of distant metastases. Interestingly, silencing PGC-
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.

Acknowledgements

Work in the Zhang laboratory is supported by CPRIT (Cancer Prevention and Research Institute of Texas) RP160617.

References

1. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics. 2014. CA Cancer J Clin 64: 9-29. [Crossref]
2. DeSantis CE, Lin CC,Mariotto AB, Siegel RL, Stein KD, et al. (2014) Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 64: 252-271. [Crossref]
3. RP FDA (2013) Approval for Erlotinib Hydrochloride. 2013 July 3, 2013.
4. SS FDA (2015) Approves New Use of Iressa (Gefitinib) for EGFR-mutated Lung Cancer. 2015 July 20, 2010 July 18, 2016.
5. RP FDA (2014) Approval for Bevacizumab.
6. JA Roth (2015) Survival gains from first-line systemic therapy in advanced non-small cell lung cancer in the United States, 1990-2015: progress and opportunities. Presented at: World Conference on Lung Cancer, Denver, CO, USA.
7. Gerlinger M, Swanton C (2010) How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine. Br J Cancer 103: 1139-1143.
8. Graves M, Maley CC (2012) Clonal evolution in cancer. Nature 481: 306-313. [Crossref]
9. Yates LR, Campbell PJ (2012) Evolution of the cancer genome. Nat Rev Genet 13: 795-806. [Crossref]
10. Nowell PC (1976) The clonal evolution of tumor cell populations. Science 194: 23-28. [Crossref]
11. Ellsworth RE, Toro AL, Blackburn HL, Decewicz A, Deyarmin B, et al. (2015) Molecular Heterogeneity in Primary Breast Carcinomas and Axillary Lymph Node Metastases Assessed by Genomic Fingerprinting Analysis. Cancer Growth Metastasis 8: 15-24. [Crossref]
12. Zaidi N, Lupien L, Kuenzmerle NB, Kinlaw WB, Swinnen JV, et al. (2013) Lipogenesis and lipolysis: the pathways exploited by the cancer cells to acquire fatty acids. Prog Lipid Res 52: 585-589. [Crossref]
13. Menendez JA, Lupu R (2007) Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer 7: 763-777. [Crossref]
14. Price DT, Coleman RE, Liao RP, Robertson CN, Polasick TJ, et al. (2002)Comparison of [18 F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. J Urol 168: 273-280. [Crossref]
15. Liu Y, Zhuiker LS, GhesaniVNghesani (2010) Dominant uptake of fatty acid over glucose by prostate cells: a potential new diagnostic and therapeutic approach. Anticancer Res 30: 369-374. [Crossref]
16. Zha S, Ferdinandusse S, Hicks JL, Denis S, Dunn TA, et al. (2005) Peroxiosomal branched chain fatty acid beta-oxidation pathway is upregulated in prostate cancer. Prostate 63: 316-323. [Crossref]
17. Comerford SA, Huang Z, Du X, Wang Y, Cai L, et al. (2014) Acetate dependence of tumors. Cell 159: 1591-1602. [Crossref]
Vidal C (2016) Elevated mitochondrial and heme function as hallmarks for Non-small cell lung cancers

18. Mashimo T, Ichihara K, Vemireddy V, Hanatapai KJ, Singh DK, et al. (2014) Acetate is a bioenergetic substrate for human glioblastoma and brain metastases. Cell 159: 1603-1614. [Crossref]

19. Warburg O (1956) On the origin of cancer cells. Science 123: 309-314. [Crossref]

20. Reitzer LJ, Wice BM, Kennell D (1979) Evidence that glutamine, not sugar, is the major energy source for cultured HeLa cells. J Biol Chem 254: 2669-2676. [Crossref]

21. Anastasiou D, Cantley LC (2012) Breathless cancer cells get fat on glutamine. Cell Res 22: 443-446. [Crossref]

22. DeBerardinis RJ, Cheng T (2010) Q’s next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene 29: 313-324. [Crossref]

23. Ward PS, Thompson CB (2012) Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. Cancer Cell 21: 297-308. [Crossref]

24. Hensley CT, Wasti AT, DeBerardinis RJ (2013) Glutamine and cancer: cell biology, physiology, and clinical opportunities. J Clin Invest 123: 3678-3684. [Crossref]

25. Kovacevic Z, Morris HP (1972) The role of glutamine in the oxidative metabolism of malignant cells. Cancer Res 32: 326-333. [Crossref]

26. Lanks KW, Hitti IF, Chin NW (1986) Substrate utilization for lactate and energy production by heat-shocked L929 cells. J Cell Physiol 127: 451-456. [Crossref]

27. Goossens V, Grooten J, Fiers W (1996) The oxidative metabolism of glutamine. A modulator of reactive oxygen intermediate-mediated cytotoxicity of tumor necrosis factor in L929 fibrosarcoma cells. J Biol Chem 271: 192-196. [Crossref]

28. Fan J, Kamphorst JI, Mathew R, Chung MK, White E, et al. (2013) Glutamine-driven oxidative phosphorylation is a major ATP source in transformed mammalian cells in both normoxia and hypoxia. Mol Syst Biol 9: 712. [Crossref]

29. Viale A, Pettazzoni P, Lysiotis CA, Ying H, Sánchez N, et al. (2014) Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. Nature 514: 628-632. [Crossref]

30. Cavalli LR, Varella-Garcia M, Liang BC (1997) Diminished tumorigenic phenotype after depletion of mitochondrial DNA. Cell Growth Differ 8: 1189-1198. [Crossref]

31. LeBlue VS, O’Connell JT, Gonzalez Herrera KN, Wikman H, Pantel K, et al. (2014) PGC-1alpha mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis. Nat Cell Biol 16: 992-1003, 1-15. [Crossref]

32. Telang S, Nelson KK, Siew DL, Yalcin A, Thornbury JM, et al. (2012) Cytochrome c oxidase is activated by the oncoprotein Ras and is required for A549 lung adenocarcinoma growth. Mol Cancer 11: 60. [Crossref]

33. Schneider MB, Matsuzaki H, Haorah J, Ulrich A, Standop J, et al. (2001) Prevention of pancreatic cancer induction in hamsters by metformin. Gastroenterology 120: 1263-1270. [Crossref]

34. Jara JA, López-Muñoz R (2015) Metformin and cancer: Between the bioenergetic disturbances and the antifolate activity. Pharmacol Res 101: 102-108. [Crossref]

35. Andrzejewski S, Gravel SP, Pollak M, St-Pierre J (2014) Metformin directly acts on mitochondria to alter cellular bioenergetics. Cancer Metab 2: 12. [Crossref]

36. Alam MM, Sohoni S, Kalainayakan SP, Garrossian M, Zhang L (2016) Cyclopamine tartrate, an inhibitor of Hedgehog signaling, strongly interferes with mitochondrial function and suppresses aerobic respiration in lung cancer cells. BMC Cancer 16: 150. [Crossref]

37. Kim HJ, Khalimonchuk O, Smith PM, Winge DR (2012) Structure, function, and assembly of hemecenters in mitochondrial respiratory complexes. Biochim Biophys Acta 1823: 1604-1616. [Crossref]

38. Bock K W, Aldridge WN. Heme and Hemoproteins. 1978, New York Springer-Verlag Berlin Heidelberg.

39. Layer G, Reichelt J, Jahn D, Heinz DW (2010) Structure and function of enzymes in heme biosynthesis. Protein Sci 19: 1137-1161. [Crossref]

40. Fontanesi F, Soto IC, Barrientos A (2008) Cytochrome c oxidase biosynthesis: new levels of regulation. JUBMB Life 60: 557-568. [Crossref]

41. Zhang L (2011) HEME BIOLOGY: The Secret Life of Heme in Regulating Diverse Biological Processes. World Scientific.

42. Hooda J, Shah A, Zhang L (2014) Heme, an essential nutrient from dietary proteins, critically impacts diverse physiological and pathological processes. Nutrients 6: 1080-1102.

43. Bastide NM, Pierre FH, Corpet DE (2011) Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved. Cancer Prev Res (Phila) 4: 177-184. [Crossref]

44. Hooda J, Alam MM, Zhang L (2015) Evaluating the Association of Heme and Heme Metabolites with Lung Cancer Bioenergetics and Progression. Metabolomics 5:150.

45. Hooda J, Cadima D, Alam MM, Shah A, Cao TM, et al. (2013) Enhanced heme function and mitochondrial respiration promote the progression of lung cancer cells. PLoS One 8: e63402. [Crossref]

46. Alam MM, Lal S, FitzGerald KE, Zhang L (2016) A holistic view of cancer bioenergetics: mitochondrial function and respiration play fundamental roles in the development and progression of diverse tumors. Clin Transl Med 5: 3. [Crossref]

Copyright: ©2016 Vidal C. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.