European Review for Medical and Pharmacological Sciences 2017; 21 (3 Suppl): 43-46

Hypoxia associated biomarkers in lung cancer – an update

W. CUI[1], F. WU[2], L. MA[1]

[1]Cancer Biomarkers, Therapeutics and Theranostics Laboratory, Tsinghua-Berkeley Shenzhen Institute, Tsinghua University, Shenzhen, China
[2]Division of Life Science and Health, Graduate School at Shenzhen, Tsinghua University, Shenzhen, China

Abstract. – The high incidence rates of lung cancer have resulted in multiple progressions in cancer research leading to the development of novel therapeutic strategies. The three main branches of cancer research where improvements are being made are surgery, chemotherapy, and radiotherapy. These research developments have significantly improved the survival rates of cancer patients as most of these therapeutic options target specific molecules involved in cancer progression and metastasis. Experimental research has successfully identified potentially important molecules responsible for cancer progression. Further, the above molecular markers of disease are clinically approved biomolecules of significant prognostic value. The above molecular biomolecules also helped in rapid identification of subgroups of patients who need immediate emergency treatment. Hypoxia is one of such conditions where the human system is deprived of an adequate oxygen supply and requires immediate treatment. Hypoxia markers have been proved to be beneficial in the timely management of cancer. The present review is focused on the latest updates in the area of hypoxia related to markers in the prognosis of lung cancer.

Key Words:
Lung cancer, Hypoxia, Markers.

Introduction

Oxygen is vital for human metabolism and is essential for the gain of energy for the survival as well as homeostasis[1]. In growing tissue, or in tumors there is continuously changing oxygen pressure that needs proper regulation for survival. Under normal situations, most of the tissues have 2-9% of O_2 levels. On the other hand, tissue hypoxia is the situation when levels of O_2 fall below 2%[2]. Based on histological studies of lung tumors, it was observed that the necrosis was responsible for hypoxia[3]. Electrodes for precise estimation perform the hypoxia measurement but still more precision in the methodology is required[4]. Hypoxia is a cardinal phenotype of the tumor environment. Further, the low oxygen tension triggers the gene expression towards an aggressive phenotype. The aggressive phenotype is characterized by activation of key hallmarks of cancer like angiogenesis, metastasis, increased DNA replication and proliferation in both hypoxia induced factor (HIF) dependent and independent manners. Further, hypoxia is recognized as a key feature of resistance to radiotherapy. The later hypoxia-modifying studies with hyperbaric O_2 and hypoxic cell radio-sensitizers, have shown disappointing results; thus, hypoxic modification is normally not influencing clinical practice[5]. Hypoxia is also known to mediate resistance to chemotherapy via stimulation of interstitial fluid pressure (IFP)[6]. With decreasing oxygen tension, there is increased HIF1α activity causing increased production of acid. This in turn results in an increased rate of glycolysis and development of resistance to chemotherapy as well radiotherapy.

Hypoxia Induced Factor

Hypoxia induced factor (HIF) is an active heterodimer of HIFα and HIFβ. HIFα has short half-life during hypoxia and is the most studied member of HIF family. HIF1α is ubiquitously expressed and induces various genes responsible for induction of hypoxia. Its expression has been confirmed to be elevated in various tumors including lung tumors[7,8]. Further, the HIF2α isoform seems important in physiology as targeted therapy against HIF2α that leads to embryonic lethality. Despite similarities in sequence homology of HIF1α and HIF2α, they have specific tissue distributions and effects during carcinogenesis. HIF1α

Corresponding Author: Lan Ma, MD; e-mail: mppphf@163.com

expression has been observed in every tissue, but HIF2α expression is more prevalent in tissues associated systemic delivery of O_2, like lung, heart and endothelium. HIF1α uniquely stimulates the expression of many enzymes like lactate dehydrogenase 5 (LDH5) and carbonic anhydrase IX (CAIX). However, HIF2α stimulates growth factor-α (TGF-α) and erythropoietin (EPO). On the other hand, transcriptional genes like glucose transporter 1 (GLUT1) and VEGF-A are commonly up regulated by both HIF1α and HIF2α. HIF3α contribution in this area is not yet properly determined, but is rapidly induced by hypoxia in most of the tissues[9,10].

HIF Induced Gene Products

GLUT1

Sugars are an important substrate for energy production through cellular respiration. Moreover, cancer cells mainly utilize glycolysis with oxygen or even without oxygen[11]. To achieve this phenotype, an increased of sugars is essentials. Sugars are hydrophilic and need to be transported with the help of GLUTs (glucose transporters). There are several subtypes of these sugar transporters, but GLUT1 is the most studied one in this context as it is responsible for the basal glucose uptake in cancer. Further, it has been reported to be directly responsible for glucose metabolism and is induced by hypoxia[12]. All these instances confirmed it as one of the main markers for the induction of hypoxia during cancer.

CAIX

Cellular biochemistry could be significantly altered by small changes in pH and proper regulation is vital for survival and function of cells. Further, there is high intracellular production of protons (H+) in cancer cells due to rapid metabolism. So, this huge production of intracellular protons in managed by CAIX. Further, carbonic anhydrase IX (CAIX) is another evolving marker associated with hypoxia[13]. Moreover, among the molecules related to hypoxia, CAIX is the most reliable markers of hypoxia, although this is still a matter of controversy[14].

LDH5

Lactate dehydrogenase 5 (LDH5), also called LDHA, is responsible for catalyzing pyruvate to lactate with great efficiency. Furthermore, LDH5 is also associated with HIF1α and has often been reported to be overexpressed in common cancers like NSCLC[15] head and neck cancers[16], non-Hodgkin B-cell lymphomas[17] and colorectal cancers[18]. LDH5, is composed of 4 M-subunits encoded by the LDHA gene, and has role in transformation of pyruvate to lactate for ATP production under hypoxic conditions[19,20]. Moreover, LDHA regulation has been reported in a recent study to be regulated by oncogenes, like the myelocytomatosis cMyc, or microRNA, independent of HIF or hypoxia[21].

HIF Hydroxylases

The half-life of the HIFα-subunit is mainly responsible for regulation of the HIF activity that in turn, controlled by the oxygen dependent post-translational hydroxylation by HIF hydroxylases. Under normoxia, HIFα is hydroxylated by prolyl hydroxylases (PHD1, PHD2 and PHD3). Hydroxylation of the proline residues in the N-terminal area transactivation domain (N-TAD) by PHDs helps in the binding with von Hippel-Lindau (VHL) tumor suppression protein. This subsequently targets HIFα for further degradation of proteasomes by poly-ubiquitination[22]. Further, PHD2 has been observed to be the prominent regulator of HIF1α activity, probably due to its relative abundance. RNA interference against PHD2 induces stabilized HIF1α subunits whereas PHD1 and PHD3 silencing had no effect on HIF1α-stabilization. On the other hand, PHD3 has been noticed to be associated with regulation of HIF2α[23]. Moreover, these hydroxylases are known as HIF hydroxylases and serve the function of oxygen sensing in the vital cellular oxygen homeostasis[24]. PHD expression has been detected in normal human tissues, but PHDs are overexpressed in common cancers like breast, prostate and head and neck. On the other hand, a slight decrease in the expressions of PHDs was noticed in lung cancer, renal cell carcinomas and follicular lymphomas[25].

Recent non-Invasive Blood Biomarkers Associated with Hypoxia

Recent research in the field of hypoxia-associated biomarkers is focused on the use of non-invasive techniques to diminish the burden for patients. The utilization of blood-biomarkers provides non-invasive, fast and promising source of extra information that could help in disease prognosis as well as treatment response[26]. The noninvasive hypoxia markers included OPN that has been reported to be associated with tumors aggressiveness and metastatic potential[27]. Further, Cyfra

21-1, is another hypoxia marker associated with tumor load and has been identified as a prognostic factor for NSCLC[28]. Another, evolving method viz. radiomics also revealed relevant prognostic value of sophisticated image analysis related to hypoxia related prognosis of lung cancer[29]. Moreover, PET tracers are also a promising non-invasive option, which has the ability to obtain extra information related to hypoxia (18F-FMISO, Sigma-Aldrich, St. Louis, MO, USA)[30].

Conclusions

Hypoxia markers hold good potential to be utilized as established biomarkers for lung cancer diagnosis. Further, non-invasive biomarkers are currently evolving and could act as gold standard hypoxic biomarker in near future.

Conflict of interest

The authors declare no conflicts of interest.

References

1) Carvalho S, Troost EG, Bons J, Menheere P, Lambin P, Oberije C. Prognostic value of blood-biomarkers related to hypoxia, inflammation, immune response and tumour load in non-small cell lung cancer - a survival model with external validation. Radiother Oncol 2016; 119: 487-494.
2) Dai T, Hu Y, Zheng H. Hypoxia increases expression of CXC chemokine receptor 4 via activation of PI3K/Akt leading to enhanced migration of endothelial progenitor cells. Eur Rev Med Pharmacol Sci 2017; 21: 1820-1827.
3) Liu CX, Wang H, Qian XM, Lu FX, Zhuang SF, Yang MX, Wang FL, Wang YT. The effect of three dimensional coformal radiotherapy on loccaly recurrnt nasopharyngeal carcinoma and on the expressoin of succinate dehydrogeanse B. Eur Rev Med Pharmacol Sci 2016; 20: 4852-4857.
4) Helmlinger G, Yuan F, Dellian M, Jain RK. Interstitial pH and pO2 gradients in solid tumors in vivo: high-resolution measurements reveal a lack of correlation. Nat Med 1997; 3: 177-182.
5) Overgaard J. Hypoxic radiosensitization: adored and ignored. J Clin Oncol 2007; 25: 4066-4074.
6) Brahimi-Horn MC, Chiche J, Pouyssegur J. Hypoxia and cancer. J Mol Med 2007; 85: 1301-1307.
7) Talks KL, Turley H, Gatter KC, Maxwell PH, Pugh CW, Ratcliffe PJ, Harris AL. The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages. Am J Pathol 2000; 157: 411-421.
8) Zhong H, De Marzo AM, Laughner E, Lim M, Hilton DA, Zagzag D, Buechler P, Isaacs WB, Semenza GL, Simons JW. Overexpression of hypoxia-inducible factor 1α in common human cancers and their metastases. Cancer Res 1999; 59: 5830-5835.
9) Makino Y, Cao R, Cao R, Svensson K, Bertilsson G, Asman M, Tanaka H, Cao Y, Berkenstam A, Poellinger L. Inhibitory PAS domain protein is a negative regulator of hypoxia-inducible gene expression. Nature 2001; 414: 550-554.
10) Heidbreder M, Frohlich F, Johren O, Dendorfer A, Qadri F, Dominiak P. Hypoxia rapidly activates HIF-3alpha; mRNA expression. FASEB J 2003; 17: 1541-1543.
11) Warburg O. On the origin of cancer cells. Science 1956; 123: 309-314.
12) Calvo MB, Figueroa A, Pulido EG, Campelo RG, Aparicio LA. Potential role of sugar transporters in cancer and their relationship with anticancer therapy. Int J Endocrinol 2010; 2010: 205357.
13) Swietach P, Hulikova A, Vaughan-Jones RD, Harris AL. New insights into the physiological role of carbonic anhydrase IX in tumour pH regulation. Oncogene 2010; 29: 6509-6521.
14) Mayer A, Hockel M, Vaupel P. Endogenous hypoxia markers: case not proven! Adv Exp Med Biol 2008; 614: 127-136.
15) Kayser G, Kassem A, Sienel W, Schulte-Uentrop L, Mattern D, Aumann K, Stickeler E, Werner M, Passlick B, zur Hausen A. Lactate-dehydrogenase 5 is overexpressed in non-small cell lung cancer and correlates with the expression of the transketolase-like protein 1. Diagn Pathol 2010; 5: 22.
16) Koukourakis MI, Giatromanolaki A, Winter S, Leek R, Sivridis E, Harris AL. Lactate dehydrogenase 5 expression in squamous cell head and neck cancer relates to prognosis following radical or postoperative radiotherapy. Oncology 2009; 77: 285-292.
17) Giatromanolaki A, Koukourakis MI, Pezzella F, Sivridis E, Turley H, Harris AL, Gatter KC. Lactate dehydrogenase 5 expression in non-Hodgkin B-cell lymphomas is associated with hypoxia regulated proteins. Leuk Lymphoma 2008; 49: 2181-2186.
18) Koukourakis MI, Giatromanolaki A, Simopoulos C, Polychronidis A, Sivridis E. Lactate dehydrogenase 5 (LDH5) relates to up-regulated hypoxia inducible factor pathway and metastasis in colorectal cancer. Clin Exp Metastasis 2005; 22: 25-30.
19) Holbrook JJ, Liljas A, Steindel SJ, Rossman MG. Lactate dehydrogenase. In: Boyer PD, editor. The enzymes, Vol. XI, 3rd ed. New York: Academic Press, 1975; pp. 191-292.
20) Masson N, Ratcliffe PJ. Hypoxia signaling pathways in cancer metabolism: The importance of co-selecting interconnected physiological pathways. Cancer Metab 2014; 2: 3.
21) Cao Y, Guo WT, Tian S, He X, Wang XW, Liu X, Gu KL, Ma X, Huang D, Hu L, Cai Y, Zhang H1, Wang

Y, Gao P. miR-290/371-Mbd2-Myc circuit regulates glycolytic metabolism to promote pluripotency. EMBO J 2015; 34: 609-623.

22) Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, von Kriegsheim A, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH, Pugh CW, Ratcliffe PJ. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science 2001; 292: 468-472.

23) Appelhoff RJ, Tian YM, Raval RR, Turley H, Harris AL, Pugh CW, Ratcliffe PJ, Gleadle JM. Differential function of the prolyl hydroxylases PHD1, PHD2, and PHD3 in the regulation of hypoxia-inducible factor. J Biol Chem 2004; 279: 38458-38465.

24) Stolze IP, Tian YM, Appelhoff RJ. Genetic analysis of the role of the asparaginyl hydroxylase factor inhibiting hypoxia-inducible factor (FIH) in regulating hypoxia-inducible factor (HIF) transcriptional target genes [corrected]. J Biol Chem 2004; 279: 42719-42725.

25) Jokilehto T, Jaakkola PM. The role of HIF prolyl hydroxylases in tumour growth. J Cell Mol Med 2010; 14: 758-760.

26) Graves EE, Maity A, Le QT. The tumor microenvironment in non-small cell lung cancer. Semin Radiat Oncol 2010; 20: 156-163.

27) Liu Y, Gu X, Lin Q, Tian T, Shao L, Yuan C. Prognostic significance of osteopontin in patients with non-small cell lung cancer: results from a meta- analysis. Int J Clin Exp Med 2015; 8: 12765-12773.

28) Xu Y, Xu L, Qiu M, Wang J, Zhou Q, Yin R. Prognostic value of serum cytokeratin 19 fragments (Cyfra 21–1) in patients with non-small cell lung cancer. Sci Rep 2015; 5: 9444.

29) Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 2014; 5: 4006.

30) Peeters SG, Zegers CM, Lieuwes NG, van Elmpt W, Eriksson J, van Dongen GA, Dubois L, Lambin P. A comparative study of the hypoxia PET tracers [18F]HX4, [18F]FAZA, and [18F]FMISO in a preclinical tumor model. Int J Radiat Oncol Biol Phys 2015; 91: 351-359.