Hypoxia associated biomarkers in lung cancer – an update

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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. 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 O₂ levels. On the other hand, tissue hypoxia is the situation when levels of O₂ fall below 2%. Based on histological studies of lung tumors, it was observed that the necrosis was responsible for hypoxia. Electrodes for precise estimation perform the hypoxia measurement but still more precision in the methodology is required. 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 O₂ and hypoxic cell radio-sensitizers, have shown disappointing results; thus, hypoxic modification is normally not influencing clinical practice. Hypoxia is also known to mediate resistance to chemotherapy via stimulation of interstitial fluid pressure (IFP). 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. 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
expression has been observed in every tissue, but HIF2α expression is more prevalent in tissues associated with systemic delivery of O2, 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 tissues9,10.

**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 oxygen11. 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 hypoxia12. 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 hypoxia13. Moreover, among the molecules related to hypoxia, CAIX is the most reliable markers of hypoxia, although this is still a matter of controversy14.

**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 NSCLC15 head and neck cancers16, non-Hodgkin B-cell lymphomas17 and colorectal cancers18. 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 conditions19,20. 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 hypoxia21.

**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-ubiquitination22. 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 HIF2α23. Moreover, these hydroxylases are known as HIF hydroxylases and serve the function of oxygen sensing in the vital cellular oxygen homeostasis24. 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 lymphomas25.

**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 response26. The noninvasive hypoxia markers included OPN that has been reported to be associated with tumors aggressiveness and metastatic potential27. Further, Cyfra
Hypoxia associated biomarkers in lung cancer – an update

21-1, is another hypoxia marker associated with tumor load and has been identified as a prognostic factor for NSCLC. Another, evolving method is radiomics which has the ability to obtain extra information related to hypoxia (18F-FMISO, Sigma-Aldrich, St. Louis, MO, USA)10.

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


