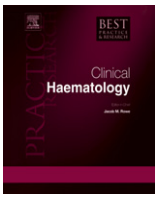
Best Practice & Research Clinical Haematology 25 (2012) 493–497

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha



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Molecular basis of polycythemic disorders due to aberrant hypoxia sensing and its relevance to acute leukemia

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Keywords:
acute leukemia forum
Beutler
cancer cell metabolism
glycolysis
hypoxia-inducible factor
HIF
HIF-1
HIF-2
HIF-3
IDH1
IDH2
isocitrate dehydrogenase
leukemia
polycythemia
tumorigenesis
von Hippel-Lindau
Warburg

The author of this lecture has been especially honored to be selected to deliver the Ernest Beutler Memorial Lecture at the Acute Leukemia Forum 2012 and to write this overview. Ernest Beutler was the pivotal influence in my introduction to academic life, and his contribution to hematology in the last 5 decades was unsurpassed. Taking a cue from Ernie's example, I have elected in the keynote speech and this brief treatise, to start with an unconventional introduction and to expand on some discoveries made in my laboratory. Then I will extend these findings to the focus of the Acute Leukemia Forum to address potentially new approaches to therapies of acute leukemias. Somatic and germline mutations of acute leukemias are unfortunately caused by arrays of somatic and germline mutations. Simultaneous targeting of so many mutations makes it not possible to efficiently target all for cure. Albeit we should be aware that we should not in the near future ignore targeted therapy of those functionally important genetic and epigenetic events that are either initiating or contributing to aggressivity of acute leukemia, as these may be ameliorated by targeted intervention against one, or even a few together, of these defined molecular lesions. Yet, leukemic cells, like other cancer cells, have the unique metabolic feature to generate energy, referred as the Warburg effect, which can potentially be targeted to suppress or even eradicate cancer.

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http://dx.doi.org/10.1016/j.beha.2012.10.014

Introduction

Normal cells in the absence of oxygen derive energy from glycolysis, and in the presence of oxygen, by more efficient citric acid cycle. This is known as the *Pasteur effect*. The Otto Warburg Nobel Prize-winning experiments in the 1920s attacked this venerable postulate, demonstrating that cancer cells even in the absence of oxygen maintain active glycolysis. This is now known as the *Warburg effect*. This was surprising, and until recently, unexplained. Hypoxia-inducible factors (HIFs) are transcription factors that control a wide range of functions connected to the way cells respond to oxygen, including metabolism and the creation of red blood cells. Clearly, upregulation of HIFs plays a central role in the Warburg effect.

Hypoxia, erythropoiesis, and polycythemia

How can the Warburg effect be linked to erythropoiesis, my principal interest? Erythroid production is largely controlled by responses of the body to hypoxia. Hypoxia leads to increased levels of master transcription factors, named hypoxia-inducible factors (HIFs). HIF-1 and HIF-2 are essential for production of the principal cytokine regulating erythropoiesis, ie, erythropoietin (EPO), but also have a direct erythropoietin-independent role in the augmentation of erythropoiesis. Seminal studies from Alan Erslev and others demonstrated the close relationship between hematocrit and EPO levels in humans and experimental animals, and also to hypoxia.

Studies of erythropoietin-producing cell lines resulted in the discovery of the oligonucleotide sequence, which is essential for hypoxic control of erythropoietin gene transcription named HRE, which subsequently led to the discovery of HIF-1 by several groups [1]. HIF-1 is a dimer subunit of alpha and beta subunits, and only the alpha subunit is hypoxia regulated. Subsequently, two other isoforms, HIF-1-alpha and HIF-2-alpha, and later HIF-3-alpha (also known as FIH) have been discovered. The seminal studies from Bill Kaelin and Peter Radcliffe's group [2] led to our concept of hypoxia sensing (Fig. 1), indicating that in the presence of oxygen, HIF-alpha subunits are rapidly degraded by first being prolyl hydroxylated by one of the proline hydroxylase enzymes. This modified alpha subunit can then interact with von Hippel-Lindau proteins, which leads to ubiquitination and rapid degradation in proteasome. In the absence of oxygen, or with deficient or abnormal proline hydroxylase of von

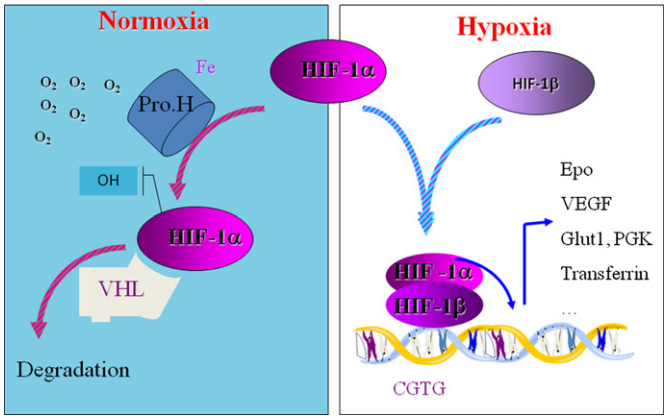

Fig. 1. Hypoxia sensing. Hypoxia sensing is the mechanism by which cells sense a decrease in oxygen and initiate an appropriate response, allowing the organism to adapt to new conditions. Hypoxia-inducible factor-1 (HIF-1) plays a crucial role in this process. The cellular level of the alpha subunit is controlled by oxygen level. Oxygen activates prolyl hydroxylase, which will hydroxylate HIF-1-alpha. This leads to the binding of a tumor suppressor, von Hippel-Lindau protein, and subsequent ubiquitination of HIF-1á. In contrast, in hypoxia, HIF-1á can associate with the beta subunit. The complex then binds to hypoxia-responsive elements within the genome, activates associated genes, and initiates or increases production of related genes that comprise EPO, VEGF, etc. VHL has been widely studied as a tumor suppressor gene and for its role in hypoxia sensing.