



Review Article

Hypoxia-inducible factor prolyl hydroxylases as targets for neuroprotection by “antioxidant” metal chelators: From ferroptosis to stroke

Rachel E. Speer^{a,b,c,1}, Saravanan S. Karuppagounder^{b,c,1}, Manuela Basso^{b,c}, Sama F. Sleiman^{b,c}, Amit Kumar^{b,c}, David Brand^{b,c}, Natalya Smirnova^{b,c}, Irina Gazaryan^{b,c}, Soah J. Khim^{b,c}, Rajiv R. Ratan^{b,c,*}

^a Graduate Program in Neuroscience, Weill Medical College of Cornell University, New York, NY 10065, USA

^b Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY 10065, USA

^c Burke Medical Research Institute, White Plains, NY 10605, USA

ARTICLE INFO

Keywords:

Metal chelators
Neurodegeneration
Hypoxia-inducible factors
Transcription
Prolyl hydroxylases
Free radicals

ABSTRACT

Neurologic conditions including stroke, Alzheimer disease, Parkinson disease, and Huntington disease are leading causes of death and long-term disability in the United States, and efforts to develop novel therapeutics for these conditions have historically had poor success in translating from bench to bedside. Hypoxia-inducible factor (HIF)-1 α mediates a broad, evolutionarily conserved, endogenous adaptive program to hypoxia, and manipulation of components of the HIF pathway is neuroprotective in a number of human neurological diseases and experimental models. In this review, we discuss molecular components of one aspect of hypoxic adaptation in detail and provide perspective on which targets within this pathway seem to be ripest for preventing and repairing neurodegeneration. Further, we highlight the role of HIF prolyl hydroxylases as emerging targets for the salutary effects of metal chelators on ferroptosis in vitro as well in animal models of neurological diseases.

© 2013 Elsevier Inc. All rights reserved.

Contents

Adaptive mechanisms to stress: combating neurodegeneration	2
Oxygen-dependent metabolism	2
Hypoxia-inducible factor	2
Oxygen-dependent degradation of HIF-1 α	3
HIF PHDs	3
Von Hippel-Lindau protein	4
The ubiquitin–proteasome degradation pathway	4
Regulation of HIF-1 α by ODD-independent mechanisms	4
Regulation of HIF-1 α activity	4
ODD-independent regulation of HIF-1 α protein stability	4
Regulation of HIF-1 α transcription and translation	5
HIF PHD inhibition as a neuroprotective strategy	5
HIF PHD inhibitors abrogate ferroptosis, a novel form of nonapoptotic death	5
Cerebral ischemia	7
Epidemiology and pathology of cerebral ischemia	7
HIF-1 α in cerebral ischemia	7
Quantitative mechanistic reporters for HIF-1 α as a surrogate for dynamically monitoring PHD activity in cells	8

* Corresponding author. Fax: (914) 597 2225.

E-mail address: rrrr2001@med.cornell.edu (R.R. Ratan).

¹ These authors contributed equally to this work.

Concluding remarks	8
Acknowledgments	8
References	8

Adaptive mechanisms to stress: combating neurodegeneration

Over the past 20 years, our laboratory has used two primary approaches to understand therapeutic strategies for preventing oxidative stress-mediated neurodegeneration. First, we have studied the endogenous mechanisms that lead to or prevent cell death induced by depletion of the antioxidant glutathione in primary neurons in vitro. Detailed biochemical analysis of this form of death, recently termed ferroptosis [1], has revealed novel redox-regulated transcriptional pathways that can compensate for persistent glutathione depletion and oxidative stress to foster cell survival [2,3]. In parallel, investigations into the mechanism of classical “antioxidants” in our in vitro model have surprisingly revealed remarkable and recurrent bias toward transcriptional adaptive mechanisms often involving more than 100 genes [4–7]. In this review, we discuss evidence from these distinct investigations and how that evidence has led us to focus our attention on an evolutionarily conserved adaptive response and its role in neuroprotection.

Oxygen-dependent metabolism

It is thought that self-replicating RNA became enclosed in a phospholipid membrane about 3.8 billion years ago, forming the basic unit of life called the cell (reviewed by [8]). These cells were able to obtain the energy required to replicate themselves and perform other necessary tasks from the sea of organic molecules from which they originated. However, such a self-limiting situation drove cells to evolve mechanisms through which they could autonomously generate, store, and use energy.

The principal pathways of energy metabolism are remarkably similar in all present-day cells, indicating that they emerged early in the process of evolution and have been conserved. For instance, all cells use ATP as the currency of energy to drive the synthesis of cell constituents and to carry out other energy-requiring activities. The mechanisms by which cells generate ATP are thought to have evolved sequentially: first glycolysis, then photosynthesis, and finally oxidative metabolism. In glycolysis, glucose is broken down to produce 2 ATP molecules. In photosynthesis, energy from the sun is harvested to produce glucose, which creates molecular oxygen (O_2) as a by-product and has caused that oxygen to become abundant in the earth's atmosphere. In oxidative metabolism, oxygen is used to break down glucose much more efficiently than in glycolysis, yielding 36 ATP molecules instead of 2.

Because of this efficiency, almost all present-day cells—including archaea, bacteria, and eukaryotic cells in humans—use oxidative reactions as their principal source of energy. For cells to rely on oxygen for metabolism, they need to be able to sense a decrease in oxygen availability—a phenomenon called hypoxia—and to then trigger a response program that helps them to cope with that decrease. One simple way to do so is to have sensor enzymes that use oxygen to inhibit the response program; when oxygen supply drops, the sensors are inhibited and the response program is then rapidly activated.

Cells as simple as bacteria express prolyl 4-hydroxylase domain-containing enzymes (PHDs) that use oxygen to add a hydroxyl group to proline residues on specific substrate proteins. This hydroxylation is a highly evolutionarily conserved sensory mechanism for oxygen;

in fact, prolyl 4-hydroxylation is the single most prevalent posttranslational modification in humans [9]. In all animal cells, even those of the simplex animal, *Trichoplax adhaerens*, one of the proteins subject to prolyl 4-hydroxylation is called hypoxia-inducible factor (HIF) [10].

Hypoxia-inducible factor

HIF was first identified as a transcriptional activator that binds to the hypoxia-response element (HRE) in the promoter region of erythropoietin and has since been shown to coordinate many evolutionarily conserved adaptive responses to hypoxia [11]. HIF target genes include VEGF, EPO, GLUT1, PFK1, BNIP3, neuroglobin, and dozens of other genes that work in concert at cellular, local tissue, and systemic levels, to restore oxygen delivery, to enhance glucose uptake and glycolysis, to reduce mitochondrial content and the rate of oxidative phosphorylation, and to regulate cell survival either by promoting adaptation or by engaging programmed cell death under prolonged or severe stress conditions. HIF-1 regulates gene expression not only by direct binding to target gene promoters at the consensus sequence (5'-RCGTG-3'), but also by counting among its targets numerous transcription factors, histone demethylases, and microRNAs that can in turn affect gene expression [69].

HIF is a heterodimer consisting of a constitutively present β subunit and a short-lived, oxygen-regulated α subunit. HIF family members are diagrammed in Fig. 1. Three α isoforms have been

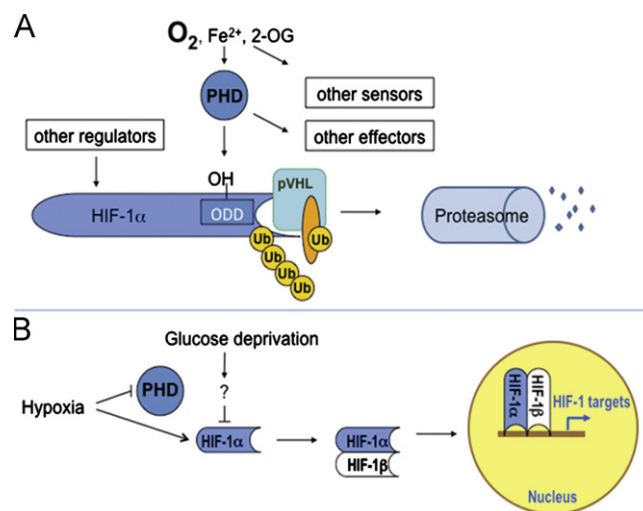


Fig. 1. Schematic of oxygen-dependent HIF-1 α regulation. (A) Under normoxic conditions, PHDs hydroxylate P564 on HIF-1 α , allowing it to be recognized by the E3 ubiquitin ligase von Hippel-Lindau protein (VHL), ubiquitinated, and targeted for proteasomal degradation. As members of a large family of iron- and 2-oxoglutarate-dependent dioxygenases, PHDs integrate multiple signals of metabolic homeostasis and are one of many such sensors; further, PHDs have HIF-independent substrates, and HIF protein levels and transcriptional activity are regulated in many PHD-independent ways. (B) Under hypoxia, PHDs are inhibited, allowing HIF-1 α to elude degradation, dimerize with its β partner in the nucleus, bind transcriptional coactivators and hypoxia-response elements in promoter regions of target genes, and enhance transcription rates. Glucose deprivation has been reported to decrease hypoxic stabilization of HIF-1 α ; the mechanisms by which this occurs are unclear.

Download English Version:

<https://daneshyari.com/en/article/8270971>

Download Persian Version:

<https://daneshyari.com/article/8270971>

[Daneshyari.com](https://daneshyari.com)