Hypoxia-Inducible Factors: From Health To Cancer

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Introduction

Hypoxia is defined as a decrease in available oxygen reaching the tissues of the body, so this condition can restrict their normal functions. It can be present in physiological conditions but also in some pathological situations (like cancer).

The hypoxia-inducible factors (HIFs) are a family of transcription factors that coordinate a cell transcriptional program in response to decreases in the environmental oxygen concentration in order to ensure cell survival.

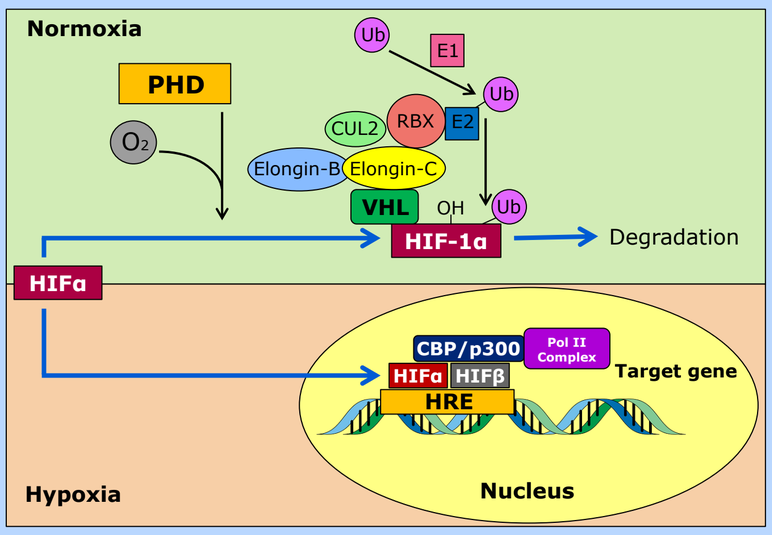


Figure 1. The HIF system. *Adapted from: Harris AL. Hypoxia—a key regulatory factor in tumour growth (2002). Nat Rev Cancer 2(1):38-47*

There are three different isoforms of HIF, called HIF-1, HIF-2 and HIF-3. Each of these isoforms contains its own α subunit and one of the constitutively active HIF-β subunit, so when the dimerization occurs HIF is stabilized in the cell and it can work as a transcription factor.

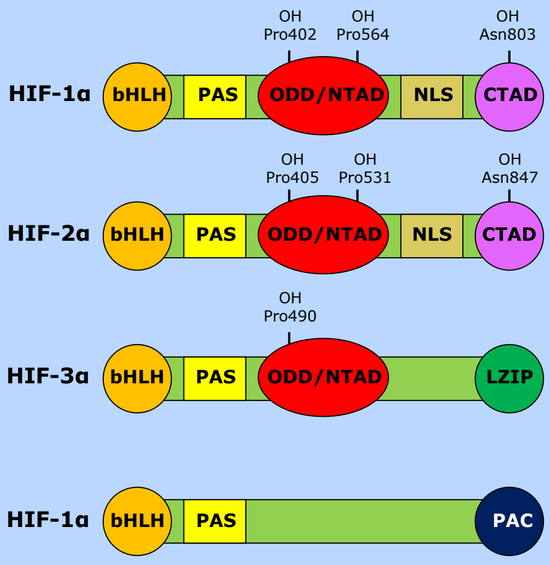


Figure 2. HIF isoforms. *Adapted from: Moniz S, Biddlestone J, Rocha S. Grow$_2$: the HIF System, energy homeostasis and the cell cycle (2014). Histol Histopathol 29(5):589-600*

Objectives: The aim of this review is to summarise the importance of the HIF system, both in physiologic but also in cancer conditions in order to suggest new therapeutic strategies.

Materials and methods

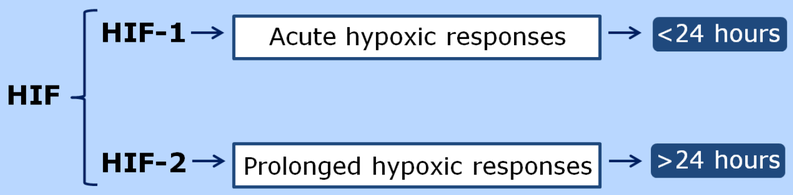
- Data comes from scientific articles and reviews found in PubMed.
- Papers were chosen according to some key words, but also considering the date of publication and the journal.
- Key words used for the research: hypoxia, HIF, HIF-1, HIF-2, VEGF, GLUT1, cancer.

Results

HIF Targets

The expression of over several hundred genes are known to be directly or indirectly influenced by HIFs and their multiple different functions, including angiogenesis and cell proliferation.

Gene	Function	HIF-1α	HIF-2α	Notes
GLUT1	Glucose transport	+	+	DR
VEGF	Angiogenesis	+	+	DR
EPO	Erythropoiesis	+	+	DR
BNIP3	Autophagy, apoptosis	+	-	DR
HKs	Glycolysis	+	-	DR
PFK	Glycolysis	+	-	DR
ALDA	Glycolysis	+	-	DR
PGK1	Glycolysis	+	-	DR
LDHA	Glycolysis	+	-	DR
P21	Cell cycle arrest	+	-	IR
Oct4	Stem cell phenotype	-	+	DR
c-Myc	Cell proliferation	-	+	IR
IL-8	Angiogenesis	-	+	IR
Cyclin D	Cell proliferation	-	+	IR



Figures 3-4. Target genes of HIF-1α and HIF-2α and their activity in response to hypoxia. *Nomenclature: expression (+); non-expression (-); direct regulation (DR); indirect regulation (IR)*

HIF-1 and HIF-2 have their own specific targets, but under some circumstances HIF-1 and HIF-2 can each one substitute the other's isoform-specific functions. Thus, it is said that the ability of these factors to activate specific targets genes is context dependent.

HIF in Cancer

Many cancers can take advantage of how HIF system works in order to increase tumor progression by different mechanisms.

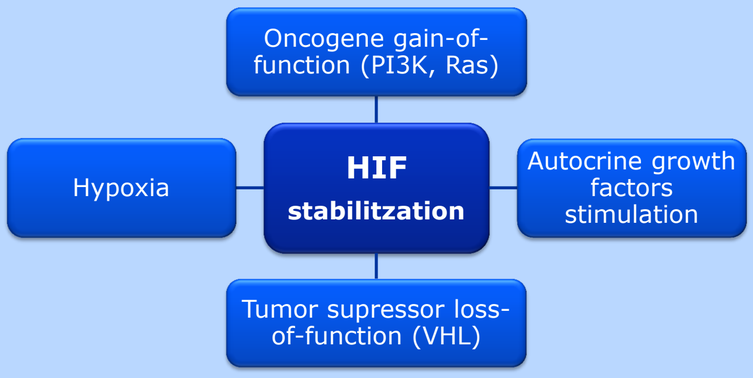


Figure 5. HIF stabilitzation through hypoxia and other different mechanisms

HIF targets can promote cancer progression, as they induce glycolytic metabolism, cell proliferation, tumor angiogenesis, metastasis and treatment resistance.

1) Energy homeostasis

Many of the HIF-1 target genes are important components in cellular energy homeostasis (figure 3), as they increase glycolytic rate even at a normal oxygen pressure, a phenomenon known as the Warburg effect.

This metabolic switch is a hallmark of cancer, as this effect is beneficial for cancer cells because they need some metabolic intermediaries to obtain some macromolecules required for the formation of new cells.

2) Cell proliferation

HIF-2 enhances c-Myc induction via stimulating the formation of complexes with Max. However, HIF-1 functions displacing c-Myc from the promoters of its target genes. Therefore, HIF-2 (but not HIF-1) exerts an important effect inducing cell proliferation via upregulation of cyclin D and downregulation of p21.

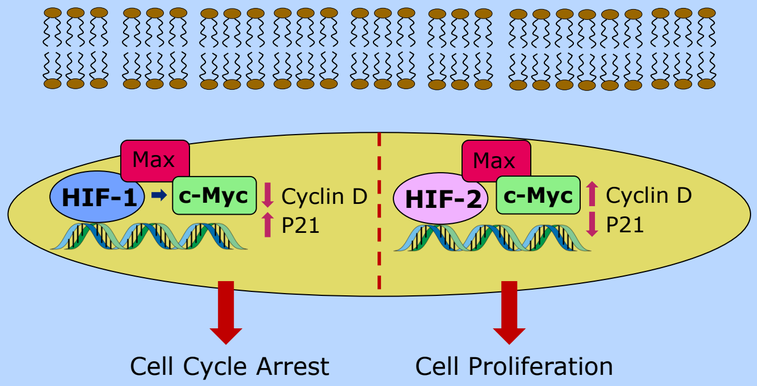


Figure 6. Cell proliferation. *Edited from: Ortmann B, Druker J, Rocha S. Cell cycle progression in response to oxygen levels. Cell Mol Life Sci. 2014; 71:3569-3582*

3) Tumor angiogenesis

HIF-1/HIF-2 can promote neovascularization when they induce the expression of VEGF or other pro-angiogenic factors through their own HRE promoter sequence.

4) Tumor invasion and metastasis

Warburg effect results in the increasing of the glycolytic metabolism but also in the increasing of protons, producing an acid environment.

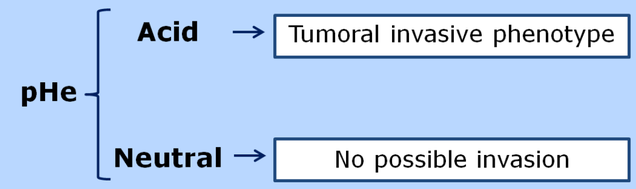


Figure 7. pHe effect in tumor invasion and metastasis

5) Therapy resistance

HIF also upregulates the expression of p-glycoprotein, an important protein that promotes the resistance to radiotherapy and chemotherapy. P-glycoprotein is a plasma membrane efflux pump that, when activated in cancer cells, can export the administrated drugs.

Increased expression of HIF-1α has been observed in a broad range of human cancers, often correlating with poor prognosis.

However, some controversial results have been reported, so this topic needs further investigation.

Conclusions

- HIF and its system play an important role in the adaptation response during hypoxia situations. However, in cancer, this pathway can be overexpressed even in normoxia.
- HIF and the proteins controlled by this factor are candidates for drug targeting, as they are responsible of different hallmarks of cancer.