

The Hypoxia-Inducible Factor-1 α Signaling Pathway and its Relation to Cancer and Immunology

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Abstract: Hypoxia-Inducible Factor 1 (HIF-1) is a transcription factor that is present in all metazoans from early embryonic development throughout adult life. It plays a major roles in the different stress responses that are triggered by low Oxygen (O₂) levels and its expression is associated with cell survival. HIF-1 is a heterodimer protein that comprises the subunits HIF-1 α and HIF-1 β . The HIF-1 α subunit is regulated by O₂-dependent hydroxylation of proline and asparagine residues, which results in ubiquitination and subsequent proteasome degradation. It may also be regulated independently of O₂. This review discusses the regulatory mechanisms and biological significance of HIF-1 α with regard to cancer development and immune regulation. HIF-1 α stabilization under hypoxic conditions is crucial to the survival of established tumors and cancer stem cells. HIF-1 α is included in the hallmarks of cancer that are related to energy metabolism, although there is clear evidence that this transcription factor might participate in other hallmarks, such as angiogenesis, invasion and metastasis, self-sufficiency in proliferation signals and even apoptosis evasion. With regard to immunology, HIF-1 α regulates Interleukin (IL)-1 β , IL-8 and Heme-Oxygenase-1 (HO-1) and despite some conflicting results, HIF-1 α is considered to be an important component of innate immune cell-mediated inflammation. With regard to the adaptive immune response, HIF-1 α expression is related to Th17 polarization and Treg inhibition. Thus, the HIF-1 α signaling pathway has been designated as a promising target for new drugs in several studies.

Keywords: Hypoxia-Inducible Factor 1, HIF-1 α , Hypoxia, Cancer, Immunology

Introduction

Oxygen (O₂) is essential to the physiology and homeostasis of animal cells. When cells are exposed to low O₂ levels (hypoxia), they express and stabilize the Hypoxia-Inducible Factor 1 (HIF-1) protein, blocking its degradation. HIF-1 plays a major role in different stress responses that are triggered by low O₂ levels and its expression is associated with cell survival (Wang *et al.*, 1995). *HIF-1* is present in all metazoans from early embryonic development throughout adult life. The HIF-1 protein belongs to the family of transcription factors with a basic Helix-Loop-Helix domain (bHLH) coupled to a PAS (PER-ARNT-SIM) domain, which

provides more stability to dimerizations that involve HIF-1 (Wang *et al.*, 1995).

The Hypoxia-Inducible Factor-1 Signaling Pathway and its Subunits

HIF-1 is a heterodimer protein that comprises the subunits HIF-1 α and HIF-1 β . It binds to DNA at a consensus sequence: 5'-[A/G]CGTG-3'; there may also be a second consensus sequence 5'-[A/C]ACAG-3' near the classical one (Semenza, 1998; 2007). Under normal oxygen conditions (normoxia), HIF-1 α is continuously synthesized and degraded and its regulation directly depends on O₂ levels (Fig. 1). Under hypoxic conditions,

the proteins that block interaction with HIF-1 α are degraded, favoring dimerization with HIF-1 β , which is constitutively expressed. Thus, HIF-1 α is stabilized, recruits coactivators and becomes structurally capable of regulating hundreds of genes in an extremely refined way (Fig. 1) (Semenza, 2007).

The HIF-1 α subunit is regulated by O₂-dependent hydroxylation of proline and asparagine residues, which results in ubiquitination and subsequent proteasome degradation. These hydroxylation reactions are responsible for the activation of a mechanism that responds to O₂ levels. This mechanism is then transduced to the cell nucleus and promotes the activation of specific genes through HIF-1 activity (Semenza, 1998; 2007).

The hydroxylation of proline residues occurs via the Prolyl Hydroxylase Domain protein 2 (PHD2) on Pro⁴⁰² or Pro⁵⁶⁴, or both. This hydroxylation promotes the binding of the Von Hippel-Lindau (VHL) protein, which interacts with Cullin-2, Elongin B and C proteins, blocking transcriptional elongation activity and recruiting the ubiquitin-protein ligase E3 complex and ultimately resulting in the ubiquitination and subsequent degradation of HIF-1 α via the 26S proteasome (Fig. 1). PHD2 also converts O₂ and α -ketoglutarate, generating succinate and CO₂ as products. The enzymatic activity of PHD2 is reduced in hypoxia due to a decrease in substrate availability. This occurs by direct inhibition of the catalytic center containing Fe (II) and/or by Reactive Oxygen Species (ROS) produced via the mitochondrial

respiratory chain. Although only PHD2 is described in this process, the three isoforms (PHD1, PHD2 and PHD3) also promote HIF-1 α degradation. The hydroxylation of asparagine is catalyzed by Factor Inhibiting HIF-1 (FIH-1) on Asn⁸⁰³, which blocks the binding of transcriptional co-activating proteins p300 (300-kilodalton coactivator protein) and CBP (CREB-binding protein), consequently reducing the transcription of the HIF-1 α target genes (Semenza, 2007).

The half-life of HIF-1 α may also be regulated independently of O₂, whereby the Receptor for Activated C Kinase 1 (RACK1) competes for the binding site of the chaperone Heat Shock Protein 90 (HSP90), which is involved in the protein stabilization of HIF-1 α and several growth factors (Sawai *et al.*, 2008). Thus, RACK1 protein interacts directly with Elongin C, routing HIF-1 α for ubiquitination and proteasomal degradation independently of PHD2 or VHL (Benezra *et al.*, 1990). It is important to emphasize that HIF-1 α is not completely degraded after it is ubiquitinated, due to the ubiquitin removal by VHL Deubiquitinating Enzyme 2 (VDU2), which stabilizes the HIF-1 α . Recently, Foxler *et al.* (2012) demonstrated the importance of the tumor suppressor LIM Domain-Containing Protein (LIMD1) in regulating the levels of HIF-1 α . LIMD1 acts as a scaffold for PHDs and VHL, thereby forming the PHD/LIMD1/VHL complex. The loss of function of LIMD1 triggers an increase in HIF-1 α levels under both hypoxia and normoxia conditions.

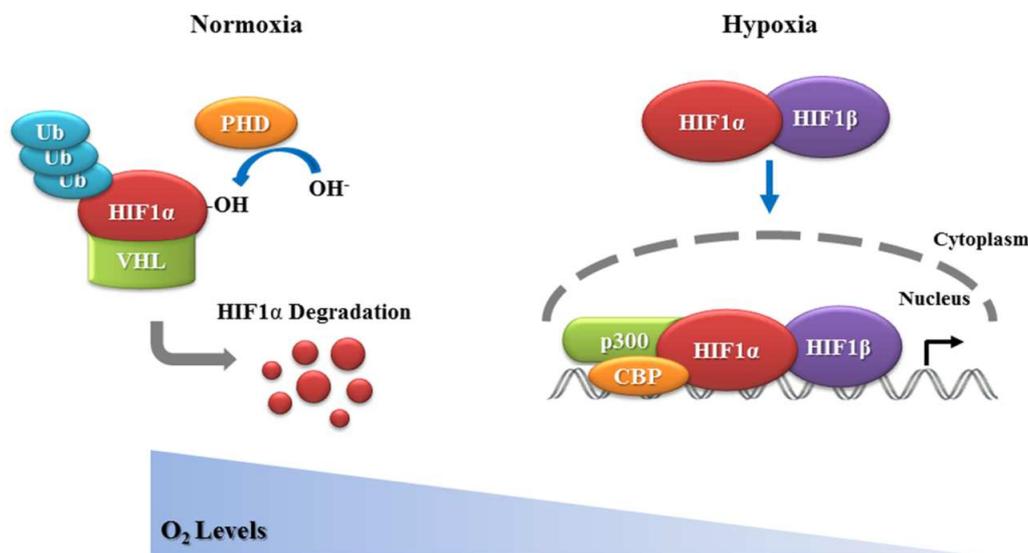


Fig. 1. Under normal oxygen conditions (normoxia), HIF-1 α is continuously synthesized and degraded. The HIF-1 α subunit is regulated by O₂-dependent hydroxylation reactions catalyzed by Prolyl Hydroxylase Domain Protein (PHD), that promotes the binding of the Von Hippel-Lindau (VHL) protein, resulting in the ubiquitination and subsequent degradation of HIF-1 α via proteasome. Under hypoxic conditions, the proteins that block interaction with HIF-1 α are degraded, favoring dimerization with HIF-1 β , which is constitutively expressed. Thus, HIF-1 α is stabilized, translocates into the nucleus, recruits the transcriptional co-activating proteins p300 (300-kilodalton coactivator protein) and CREB-Binding Protein (CBP) and becomes structurally capable of binding to DNA at a consensus sequence and activates the target genes

Hypoxia-Inducible Factor-1 α in Physiological Processes and Cancer

The HIF family genes are the major transcriptional factors involved in cell survival under low oxygen conditions. This ability allowed mankind to conquer physiologically challenging environments, such as the high altitudes of the Himalayas and the Andes where oxygen availability is diminished. Yi *et al.* (2010) sequenced the genome of 50 Tibetans who live in the Himalayas in order to find evidence of a genetic component in their ability to adapt to high altitudes. The results showed that the *EPAS1* gene in the high-altitude population had 78% more Single-Nucleotide Polymorphisms (SNPs) than the gene in the low-altitude population. This gene encodes the protein HIF-2 α and its polymorphism is strongly associated with protein stabilization and increased activity in different processes such as erythropoiesis. The HIF-2 α protein shares a 48% similarity with HIF-1 α and is also regulated by PHD2. HIF-2 α is also able to dimerize with HIF-1 β and bind to the same target sequence as the HIF-1 α /HIF-1 β heterodimer. Although there are many similarities, HIF-1 α and HIF-2 α must be considered as two separate entities because they perform different functions depending on where they are expressed in the tissue (Semenza, 2007). Because HIF-1 α has a greater association with cancer than HIF-2 α , this particular review focuses on HIF-1 α .

During embryonic development, HIF-1 α is responsible for stimulating the expression of many genes: Octamer-Binding Transcription Factor 4 (OCT4), which is essential for the maintenance of a pluripotent phenotype in embryonic stem cells (Nichols *et al.*, 1998); the inducer Vascular Endothelial Growth Factor (VEGF) (Ferrara *et al.*, 2003); the cytokine Erythropoietin (EPO) (Krantz, 1991); the embryonic growth factor Insulin-like Growth Factor 2 (IGF2) (Baker *et al.*, 1993); Inhibitor of DNA binding 2 (ID2), an inhibitor of the HLH binding domain of DNA (Benezra *et al.*, 1990) and *NOTCH1*, which plays a role in development by controlling cell fate (Artavanis-Tsakonas *et al.*, 1999). Mazumdar *et al.* (2010) proposed a close association between HIF-1 α and WNT/ β -catenin signaling, which results in embryonic, neural and hematopoietic stem cell maintenance, including self-renewal and proliferation. Interestingly, the deletion of HIF-1 α in mouse embryonic stem cells leads to the absence of *LEF1* and *TCF* expression, the effectors of WNT signaling. In addition, experiments confirmed the direct binding of HIF-1 α onto the *LEF1* and *TCF* promoter regions under hypoxic conditions. It is not completely clear how stem cell niche is regulated by hypoxia, but because research has shown that stem cells under lower oxygen conditions are less exposed

to ROS and consequently have a lower risk of mutagenesis (Kaufman, 2010; Adikwu and Bramaifa, 2012; Hazra *et al.*, 2012), a protective effect on the genome may be considered. The WNT/ β -catenin signaling pathway has been extensively studied in cancer research and is related to metastatic processes and resistance to therapies. Likewise, HIF-1 α plays an important function via WNT/ β -catenin activation, affecting tumor development and stem cell maintenance during cancer and death resistance (Kaufman, 2010).

In cancer, the loss of tumor suppressor VHL function is often observed. This loss triggers greater stability and accumulation of HIF-1 α and HIF-2 α , consequently enabling their role in carcinogenesis (Kaelin, 2008). Moreover, previous research has shown that stabilization of HIF-1 α under hypoxic conditions is crucial to the survival of both established tumors and cancer stem cells (Semenza, 2010).

HIF-1 α also orchestrates the Warburg Effect, an alternative metabolic process of cancer cells, in which more oxygenated cells transfer glucose to hypoxic cells that overexpress Glucose Transporter (GLUT1). Under hypoxia, glucose is anaerobically converted into lactate to generate ATP. The lactate is exported to the aerobic cells by overexpression of Monocarboxylate Transporter (MCT1). This lactate is converted into pyruvate by *LDH* (Lactate Dehydrogenase enzyme), which is expressed at a higher level in normoxia cells (Cairns *et al.*, 2011). Thus, a feedback system is created whereby energy sources are shuttled between metabolic cells that are located in different microenvironments. Interestingly, this entire process occurs in response to environmental conditions and is carried out by a gene expression pattern that is transcriptionally regulated by HIF-1 α . The effect that this transcription factor has on energy metabolism was described by Gregg Semenza, who showed that HIF-1 α acts as a regulator of glycolytic enzymes under low oxygen conditions and is overexpressed in the hypoxic regions of tumors (Denko, 2008).

The constitutive expression of the HIF-1 complex is frequently associated with tumor progression, poor survival and even resistance to therapies. In this context, the mechanism that implicates HIF-1 in radioresistance has been recently revised by Meijer *et al.* (2012). After radiotherapy, the hypoxic tumor cells that survive radiation are forced to re-oxygenate because the surrounding cancerous population has been killed. Therefore, a wide array of HIF-1-related events is triggered by this re-oxygenation process inside the tumor. A primary acute consequence of tumor irradiation is the downregulation of HIF-1 activity; however, the long-term accumulation of ROS re-stabilizes the HIF-1 molecule and results in increasing levels of HIF-1 in the hours soon after radiotherapy, which may last over a week. This

upregulation of HIF-1 triggers other pro-angiogenic cascades, such as VEGF, which protects the microvasculature of the tumoral mass against radiation-induced apoptosis. A secondary mechanism induced by HIF-1 involves enhancing the antioxidant capacity of cells by starting their glycolytic metabolism, which makes the tumor resistant to virtually any type of oxidative stress-driven chemotherapy (Meijer *et al.*, 2012). Regardless of the specific mechanism, augmented HIF-1 expression is strongly correlated with poor disease prognosis and death.

Hypoxia-Inducible Factor-1 α as a Hallmark of Cancer

Hanahan and Weinberg (2011) highlighted HIF-1 α in the group of cancer hallmarks that are related to energy metabolism, although there is clear evidence that HIF-1 α may participate in other hallmarks, such as angiogenesis, invasion and metastasis, self-sufficiency in proliferation signals and even apoptosis evasion. In response to hypoxia, HIF-1 α regulates the *VEGF* gene family during angiogenesis. This regulation occurs in a physiological manner that is independent of oxygen levels. Regarding invasion and metastasis, HIF-1 α has been positively correlated with other transcription factors, such as *TWIST1*, which is

one of the master regulators of epithelial-mesenchymal transition and is responsible for the phenotypic alteration of cancer cells during metastasis (Yang *et al.*, 2008). Self-sufficiency in proliferation signals was demonstrated in a recent study by Wang *et al.* (2012). The study showed that HIF signaling involves *CAV1* (Caveolin 1), the main component of caveolae in the plasma membrane (Okamoto *et al.*, 1998), culminating in the activation of Epidermal Growth Factor Receptor (EGFR), the cell surface receptor of the epidermal growth factor family and Extracellular-Signal-Regulated Kinases (ERK), which is also known as Mitogen-Activated Protein (MAP) Kinase that triggers several signaling pathways (Boulton and Cobb, 1991) leading to exacerbated cell proliferation. Zhang *et al.* (2008) investigated apoptosis evasion and found that mitochondrial autophagy is dependent on HIF-1 α , which aids cell survival in the absence of nutrients and decreases the generation of mitochondrial ROS. In addition, mitochondrial autophagy is consistently found in cancer, especially in environments of intratumoral hypoxia, inducing a “silent” death of the mitochondria without releasing cytochrome c, which triggers intrinsic apoptosis (Zhang *et al.*, 2008). A schematic picture about the biological processes and signalings regulated by HIF-1 α is shown in Fig. 2.

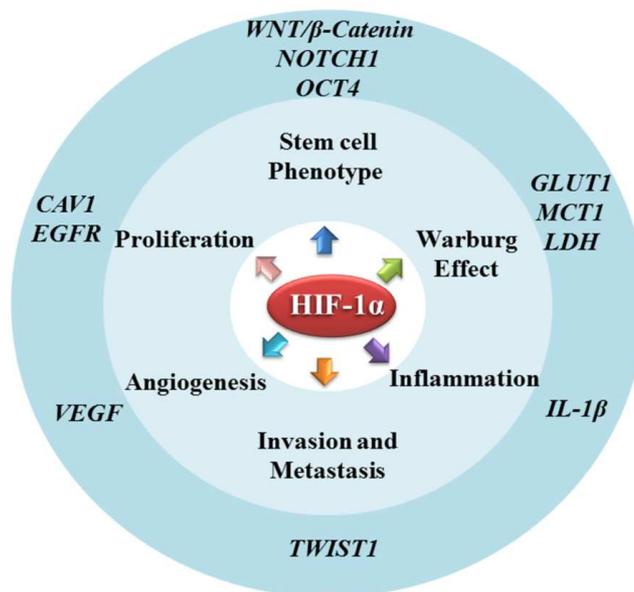


Fig. 2. HIF-1 α is responsible for stimulating many biological processes. In cancer, HIF-1 α activates the stem cell phenotype through the upregulation of OCT4, NOTCH1 and WNT/ β -catenin signalings. The activation of the metabolic enzymes Glucose Transporter (GLUT1), Monocarboxylate Transporter (MCT1) and LDH (Lactate Dehydrogenase enzyme) by HIF-1 α regulates the Warburg Effect. HIF-1 α supports inflammation and metastasis via upregulation of Interleukin (IL)-1 β and TWIST1, respectively. HIF-1 α also regulates the VEGF gene family, inducing angiogenesis in cancer. Regarding cell proliferation pathways, HIF signaling activates Caveolin 1 (CAV1), culminating in the activation of Epidermal Growth Factor Receptor (EGFR) and Extracellular-Signal-Regulated Kinases (ERK)

Hypoxia-Inducible Factor-1 and Immune Regulation

Recently, a comprehensive study performed by Tannahill *et al.* (2013) directly addressed the role of HIF-1 in Interleukin (IL)-1 β (a proinflammatory) cytokine secretion from macrophages stimulated with Lipopolysaccharide (LPS), which was derived from the external membrane of gram-negative bacteria (Yanti, 2011). HIF-1 binds to the promoter region of IL-1 β , allowing optimal transcription of pro-IL-1 β , the inactive form that generates IL-1 β through Caspase 1 activity. Research has shown that the accumulation of succinate is essential for HIF-1 α stability because high levels of succinate may directly inhibit PHD. Examining this mechanism, Tannahill *et al.* (2013) explained how cytoplasmic succinate increases after LPS stimulation (and the Warburg effect of the activated macrophage) and this may regulate HIF-1 α stability and subsequent IL-1 β secretion. IL-1 β is a cytokine that has been linked to cancer progression in murine models, as observed in cell lines of squamous cell carcinoma and melanoma (Chen *et al.*, 2012; Voronov *et al.*, 2003; Cheng *et al.*, 2009). Regarding other proinflammatory cytokines, research has shown that IL-1 β promotes cancer cell proliferation and is associated with cancer development during the initial stages, but it can also invoke antitumor immunity in later phases, where immune deviation is important for tumor establishment. These antagonistic effects of IL-1 β explain why opposing therapies were efficacious in murine models versus clinical trials. Administration of IL-1 β resulted in antitumor activity in melanoma patients, whereas administration of IL-1 β inhibitors showed promising results in cancer murine models (reviewed by Lewis *et al.*, 2006).

In another study (Loboda *et al.*, 2009), the authors described the inhibitory effects of HIF-1 on IL-8 expression in human endothelial cells. This result is interesting because IL-8 is known for its pro-angiogenic activity, which seems inconsistent because HIF-1 α is a hypoxia stress-responsive factor. Similar to its role in angiogenesis, IL-8 can improve cell survival, proliferation and metastasis (Waugh and Wilson, 2008). Therefore, this cytokine is considered a promising target for cancer immunotherapies. Loboda *et al.* (2009) also discussed the inhibitory effect of HIF-1 on Heme-Oxygenase-1 (HO-1) expression, which is an enzyme that catalyzes the degradation of heme in biliverdin, CO and Fe⁺². HO-1 is associated with cell protection against a number of oxidative agents (including heme itself); thus, the inhibitory effect of HIF-1 α on HO-1 seems

counterintuitive as well. Additionally, two other studies (Li and Dai, 2004; Dawn and Bolli, 2005) have shown opposite results, in which HIF-1 α promotes HO-1 expression. Because of these opposing results, it is difficult to conclude if HIF-1 α expression is detrimental or beneficial to the cancer microenvironment and tumor establishment in relation to IL-8 and HO-1. HIF-1 α expression may be beneficial to the host by inhibiting IL-8 and HO-1, but it could be detrimental if it promotes HO-1 activity. In the latter case, it would increase cancer cell survival and potentially change the immune response indirectly. HO-1 expression by innate immune cells is linked to Treg generation, which is a lymphocyte T CD4+ helper subtype that is associated with cancer progression by inhibiting antitumor immunity (reviewed by Mougiakakos *et al.*, 2010).

In addition to these controversial results, HIF-1 α is considered an important component of innate immune cell-mediated inflammation. In the mouse global trauma hemorrhagic shock model, partial deletion of HIF-1 was associated with reduced Tumor Necrosis Factor α (TNF α), IL-1 β , inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenase 2 (COX2) (the inflammatory biomarkers; Yanti *et al.* 2011) levels in the ileal mucosa, which was correlated with reduced lung and intestinal injury (Feinman *et al.*, 2010). Van Uden *et al.* (2008) found evidence of Nuclear Factor (NF)- κ B binding on the promoter region (mediating the expression) of HIF-1 α . This study correlated two crucial transcription factors and directly linked HIF-1 α expression to inflammatory stimuli (Pires *et al.* 2013). It also provided a possible positive feedback mechanism within the inflammatory *milieu* because HIF-1 appears to be important for proinflammatory cytokine expression (Fig. 3).

HIF-1 can also influence the expression of NOS in macrophages that are polarized for M1 (proinflammatory), thereby supporting this phenotype (Takeda *et al.*, 2010). Interestingly, HIF-2 α is expressed in macrophages polarized for the M2 phenotype and drives the expression of arginase (Takeda *et al.*, 2010). In the tumor microenvironment, the presence of these two phenotypes is linked to opposite prognostic values, where M1 macrophages are usually associated with a good prognosis and M2 with a poor one (reviewed by Biswas *et al.*, 2008). Recently, an interesting study from Casazza *et al.* (2013) showed that HIF-2, unlike HIF-1, was associated with NF- κ B induction and subsequent inhibition of Neuropilin-1 (Nrp-1)-mediated migration of macrophages. Through this mechanism, the

macrophages were restricted to hypoxic areas and differentiated to a tumor-supportive phenotype. Both studies linked HIF-2 with tumor-supportive immune responses through directly regulating the innate response and, consequently, affecting the adaptive response as well. As such, it is tempting to speculate about therapies that inhibit the effects of HIF-2 or even induce HIF-1 α in Tumor-Associated Macrophages (TAMs) as a way to inhibit the M2 phenotype in these cells, at least in the tumor microenvironment. Complex studies addressing the direct role of HIF-1 in innate immune cells could add important perspectives related to this transcription factor. In this sense, HIF-1 could have antagonistic effects during different periods of cancer development. Its proinflammatory effects could be detrimental in the early phase, inducing cell proliferation by cytokine secretion; however, it could

also support the M1 phenotype of TAMs, thereby inducing a protective anti-tumor immune response.

Furthermore, HIF-1 might influence on Natural Killer (NK) cells activity, another important immune cell in antitumor response (Fernandez *et al.*, 1999). HIF-1 stabilization are associated to a lower expression of surface receptors like NKp46, NKp30, NKp44 and NKG2D in response to IL-2 and other activating cytokines (Balsamo *et al.*, 2013). HIF-1 expression on cancer cells have been linked to MICA shedding (a component of the major histocompatibility complex family and ligand of NKG2D, an activating receptor found in NK and T CD8 cells), reducing the ability of NK cells to recognize malignancy. Besides that, soluble MICA reduces NKG2D surface expression on NK cells, further reducing the NK activity on tumor sites (Barsoum and Faleskog, 2011; Siemens *et al.*, 2009).

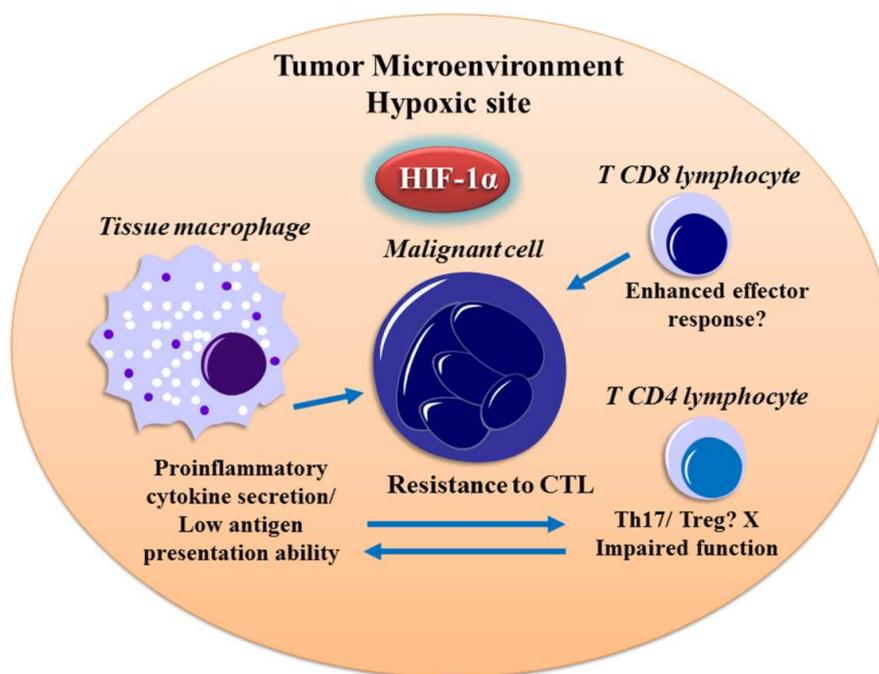


Fig. 3. HIF-1 α influence on immune response against cancer cells. Under hypoxic environment, both cancer and immune effector cells express HIF-1 α as a crucial adaptive transcription factor. This implies different kinds of interaction among cells within this microenvironment. Cancer cells seems to be more resistant to several insults, including TCD8 mediated Cytotoxic Lytic (CTL) and secrete several chemokines, like CCL28 and other soluble factors. Macrophages secrete proinflammatory cytokines, reduce antigen presentation ability and depending on HIF-1 or HIF-2 expression can drive into M1 or M2 phenotype. The lower ability of antigen presentation in this environment is another factor that might contribute to an insufficient Tcell response. Besides that, HIF-1 α is associated to Treg development or inhibition, depending on the circumstances, as well as impaired T CD4 proliferation. Contradictory results about the HIF-1 α influence on TCD8 activity are also present. It seems that HIF-1 α expression supports the cancer cell development, however, as shown by different studies, HIF-1 α stabilization, under different circumstances, can drive macrophage M1 development, enhanced T CD8 activity and Th17 polarization, features that can drive antitumor response. Although HIF-1 α is associated to a lower NK mediated response, the final role of each immune effector and the type of response mediated by HIF-1 α expression can define the tumor fate

In the adaptive immune response, HIF-1 role is under debate. Initially, HIF-1 was associated to T cell functional inhibition (Reyren *et al.*, 2007; Lukashev *et al.*, 2006; Kurobe *et al.*, 2010). In agreement with this, Ben-Shoshan *et al.* (2008) demonstrated a role of HIF-1 on Treg development. However, it is important to note that HIF-1 stabilization is induced by several stimuli on T cells in different levels. T Cell Receptor (TCR) activation induces high HIF-1 activity, higher than hypoxia itself, as well as IL-6, a proinflammatory cytokine (Nakamura *et al.*, 2005). Thus, HIF-1 activity can be modulated and its levels vary a lot on different circumstances, what may generate distinct phenotypes. HIF-1 stabilization is also related to a lower ability of T cells to proliferate and lower T CD8 activity (Lukashev *et al.*, 2006), although Caldwell *et al.* (2001) had demonstrated different results. Furthermore, HIF-1 seems to regulate the secretion of CCL28 by cancer cells, promoting Treg migration (Facciabene *et al.*, 2011). Although tumor associated macrophages have lower antigen presentation ability, recently HIF-1 stabilization on myeloid cells was associated to increased MHC and costimulatory molecules expression promoting T cell activation (Bhandari *et al.*, 2013). In addition, HIF-1 was also associated to Th17 polarization and Treg inhibition (Dang *et al.*, 2011) as well. It is possible that the higher expression of HIF-1 on TH17 is directly linked to IL-6 induced differentiation of these subtype. Both Th17 and Treg sub-types have been linked to a poor prognosis in different types of cancers (Martin *et al.*, 2012; Mougiakakos *et al.*, 2010) and more research investigating Th17 induction and Treg inhibition is needed to better define the role of HIF-1 in adaptive antitumor immunity, although TH17 antitumor response have already been described in some models (Muranski *et al.*, 2008).

Thus, HIF-1 seems to play different roles on tumor microenvironment and its level of stabilization and expression may trigger antitumor immunity or a permissive ambient for tumor progression. The majority of studies described HIF-1 as host detrimental and its expression on cancer cells are related to increased resistance to Cytotoxic Lytic (CTL) response and tumor progression. However, a better understanding on HIF-1 induced phenotypes on immune cells and the exact influence of its expression levels and molecular interactions with other players can imply new perspectives to antitumor immunity. As such, the induction of M1 macrophage phenotype, the inhibition of Treg cell and the enhancement on TCD8 function can all support a protective antitumor immunity (Fig. 3).

Anti-Hif-1 α Therapies

HIF-1 α and its signaling pathway are indicated as molecular targets for the new generation of drugs that are

part of personalized cancer therapies. Current examples of HIF-1 α inhibitors include EZN-2968, an oligonucleotide antisense to the HIF-1 α mRNA and Tanespimicina (17-AAG), which interferes with the chaperone HSP90 and destabilizes the structure of HIF-1 α . Chetomin and its analogues influence the interaction between HIF and p300, impairing its role in transcriptional regulation. Drugs have also been developed for the major regulatory targets of HIF-1 α in the Warburg effect: Glufosfamide and α -cyano-4-hydroxycinnamate, which interfere with the functions of *GLUT1* and *MCT1*, respectively (reviewed by Wilson and Hay, 2011).

Conclusion

The hypoxia survival mechanism is essential to cell survival during the crucial stages of life development or in an anoxic microenvironment, such as that found in some tissue compartments. The effects of the hypoxia-signaling pathway are widespread when considering the complexity of the biological alterations and crosstalk with other signaling pathways. However, deregulation of this pathway could promote cellular alterations that encourage disease development, such as cancer progression and an increase in tumor cell resistance to conventional treatments. Inflammation and cancer have been intricately correlated (Miller and Shukla, 2012), due to the activation of hypoxia-related proteins that are in the inflammatory cascade. HIF-1 α has been included this pathway as one of the hallmarks of cancer. The understanding of the regulatory role of HIF-1 α in pathological conditions has advanced, however, further studies are necessary to elucidate its value as a target for therapies.

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Author's Contributions

All authors equally contributed in this work.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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