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Minireview

Oxygen tension level and human viral infections ☆

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ABSTRACT

The role of oxygen tension level is a well-known phenomenon that has been studied in oncology and radiotherapy since about 60 years. Oxygen tension may inhibit or stimulate propagation of viruses *in vitro* as well as *in vivo*. In turn modulating oxygen metabolism may constitute a novel approach to treat viral infections as an adjuvant therapy. The major transcription factor which regulates oxygen tension level is hypoxia-inducible factor-1 alpha (HIF-1α). Down-regulating the expression of HIF-1α is a possible method in the treatment of chronic viral infection such as human immunodeficiency virus infection, chronic hepatitis B and C viral infections and Kaposi sarcoma in addition to classic chemotherapy. The aim of this review is to supply an updating concerning the influence of oxygen tension level in human viral infections and to evoke possible new therapeutic strategies regarding this environmental condition.

Introduction

As soon as 1936 Magill and Francis (1936) found that in conditions of reduced oxygenation influenza virus does not propagate *in vitro*. In 1952 Kalter and Tepperman (1952) reported that hypoxia down-regulates influenza replication in mice. But on the other hand, Polonis et al. (1991) published an article in 1991 reporting that anaerobic conditions induce HIV expression in infected T cell lines. Likewise Ebbesen et al. (1991) suggested that the replication of Sendai virus, a murine parainfluenza virus responsible for respiratory disease, was enhanced when infected rhabdomyosarcoma cells were incubated at low oxygen pressure (3% O_2). In tissues, *in vivo* oxygen tension is low in regard to ambient air (21%), ranging between 1% in the bone marrow and 14% in the lung (Ebbesen and Zachar, 1998), implicating that this relative physiological chronic hypoxia may influence the tropism and expression of human viruses. Modulating the expression of the major transcription factor implicated in the regulation of oxygen tension level, i.e. hypoxia-inducible factor-1α (HIF-1α) (Semenza and Wang, 1992), seems an interesting approach as a complement to traditional viral chemotherapy, notably to fight the inescapable emergence of mutant resistant viral strains, a frequent cause of treatment failure.

Overview of oxygen sensors

Hypoxia-inducible factor (HIF) is the main transcription factor that governs the alterations in gene expression that allow organisms to adapt to hypoxia. HIF is expressed by all metazoan species analyzed to date (Kaelin and Ratcliffe, 2008; Loenarz et al., 2011; Semenza, 2012). HIF is a heterodimeric DNA-binding protein composed of an O_2-regulated α-subunit (HIF-1α) and a constitutively expressed β-subunit (HIF-1β). Three HIF-α isoforms have been found (HIF-1α, -2α and -3α). HIF-1α is thought to be the primary mediator of hypoxia-induced gene expression. In normoxic conditions, HIF-1α has a <5 min half-life because of ubiquitination by an ubiquitin-ligase complex containing the von Hippel–Lindau (pVHL) protein, and subsequent rapid degradation by the proteasome. pVHL binding requires hydroxylation of proline residues on HIF-1α by prolyl-hydroxylase domain proteins

☆Search strategy and selection criteria.
We searched articles in Pubmed database with the terms "Hypoxia", "Hypoxia Inducible Factor 1 alpha", "HIF-1 alpha inhibitor" "Hypoxia and Viruses" and "Oxygen Tension Level and viruses" and only considered papers published in English. We mainly selected publications from the past 20 years, but we did not exclude older, highly regarded publications.

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(PHDs), members of the Fe(II) and of the 2-oxoglutarate-requiring dioxygenase family (Ivan et al., 2001; Jaakkola et al., 2001; Hirota and Semenza, 2005). In hypoxic conditions, pVHL is no longer able to bind HIF-1α, resulting in HIF stabilization, increase in its concentration, nuclear translocation and thus induction of transcription of the HIF-1α target genes (Berra et al., 2006; Maxwell et al., 1999).

HIF-1α activity is also regulated by O_2-dependent transactivation: HIF-1α contains two transactivation domains (TAD) that bind coactivators like CBP p300; transactivation by the coactivator protein CBP p300 is prevented by hydroxylation of an asparagine residue in TAD-C by the asparaginyl hydroxylase FIH-1 (factor inhibiting HIF-1) (Hewitson et al., 2002; Lando et al., 2002). Both stabilization and transactivation of HIF-1 induce the transcription of over 200 genes, including those involved in angiogenesis, erythropoiesis and anaerobic glycolysis The canonical DNA sequence (HRE: Hypoxia responsible element) recognized by the heterodimer HIF-1α/HIF-1β transcription factor is 5′RCGTG3′ where *R* is a purine (Semenza and Wang, 1992).

Recently, substantial evidence has indicated that others additional O_2-sensitive signalling pathways are involved in the response to hypoxia: signalling through the mammalian targets of mTOR and through activation of the unfolded protein response (UPR) (Wouters and Koritzinsky, 2008; Calfon et al., 2002). Low oxygen tension enhances Hepatitis C virus (HCV) replication in an HIF-1 alpha independent manner (Vassilaki et al, 2013). It was also suggested that the STAT5 pathway is involved during hypoxia to induce the enhancement of parvovirus B19 viral expression in erythroid cells (Pillet et al., 2004; Chen et al., 2011). So, it is probable that, in addition to the canonical pathway involved in response to hypoxia, i.e. HIF-1α/VHL/PHD, other pathways exist and they may play a role in activating or down-regulating cellular and viral genes in hypoxic conditions (Majmundar et al., 2010).

In addition to this hypoxia – dependent stabilization system, a range of other post – translational modifications and signalling pathways, such as the PI3K/Akt and p42/p44 MAPkinases pathways, also affect HIF-1α synthesis, stability and activity (Bardos and Ashcroft, 2005; Richard et al., 1999).

Viruses as modulators of oxygen sensing

If classical interaction of HIF with the target site is observed in hypoxia, it is now admitted that even in normoxia some factors are able to stabilize HIF-1α (Quintero et al., 2006). Viral proteins may induce PHD degradation. In addition, nitric oxide (NO) and reactive oxygen species (ROS) can lead to HIF-1α stabilization (Fig. 1A).

Induction of PHD degradation

While PHDs are down-regulated, HIF-1α is stabilized in normoxic conditions. This mechanism has been observed *in vitro* in nasopharyngeal cells infected by the Epstein–Barr virus (EBV). More precisely, the Latent Membrane viral Protein-1 (LMP-1) up-regulates the level of E3 ubiquitin ligase which subsequently induces the degradation of PHD-1 and -3 by the proteasome (Kondo et al., 2006). It is necessary to be cautious since Benders and colleagues, by examining 18 EBV positive nasopharyngeal carcinoma tissue specimens, did not observe any correlation between LMP-1 and HIF-1α expressions (Benders et al., 2009). Nevertheless, it has more recently been reported that Epstein–Barr nuclear antigens (EBNA), EBNA-5 and EBNA-3, bind to PHD 1 and 2, respectively, thus inhibiting HIF-1α hydroxylation and degradation (Darekar et al., 2012).

Role of NO and ROS produced during viral infection

Respiratory syncytial virus (RSV) is the major cause of serious lower respiratory disease in infancy and early childhood. RSV is characterized by a particularly prominent inflammation of the pulmonary mucosa in both natural and experimental infections. In a mouse model of RSV infection, HIF-1α was stabilized *in vivo* during murine RSV pneumonia, and *in vitro* in RSV-infected cell cultures. The addition of an NO inhibitor blocked RSV-mediated HIF-1α expression (Haeberle et al., 2008; Kilani et al., 2004).

ROS are produced during many viral infections and are the stigma of chronic viral infections such as Human Immunodeficiency Virus (HIV) infection. Two articles described an up-regulation of HIV gene expression by HIF-1α in normoxic conditions. In the first work, the viral protein vpr induces ROS which contribute to HIF-1α expression that, in turn, stimulates HIV-1 gene transcription by forming an heterodimer with vpr (Deshmane et al., 2009, 2011). Interestingly, this heterodimer binds a GC-rich region of the Long Terminal Repeat (LTR) and not the canonic consensus site 5′RCGTG3′ recognized by the complex HIF-1α/HIF-1β. In an HIV transgenic rat model, the production of ROS by HIV gp120 and tat induces the synthesis of platelet derived growth factor (PDGF) via HIF-1α stabilization and leads to pulmonary vascular remodelling (Mermis et al., 2011). Nevertheless, only a fraction of HIV-infected individuals (0.5%) develops a pulmonary hypertension suggesting that the aetiology of this clinical situation is more complicated than suggested.

Both microarray and proteomic studies have demonstrated increased expression of oxidative stress response genes in HCV-associated fibrosis and cirrhosis. Oxidative stress, which stabilizes HIF-α, has been recognized as a major procarcinogenic cofactor in chronic HCV and hepatitis B virus (HBV) infections, especially by inducing angiogenesis during hepatocarcinogenesis (Fung et al., 2009; Moon et al., 2004).

Activation of intracellular kinases

The activation of HIF-1α by cellular kinases can be done by inducing either RNA transcription or protein translation, or via post-translational phenomena. Several viral proteins could interfere with these kinases leading to an increase of HIF-1α activity.

At transcriptional level the human cytomegalovirus infection resulted in an increase of HIF-1α-specific RNA; this phenomenon was observed with irradiated viruses indicating that components of the initial infecting virion are responsible, but it was not clear whether Akt phosphorylation was vital for this induction (McFarlane et al., 2011). It has also been shown in dermal human endothelial cells that latent HHV-8 infection activates the transcription of HIF-1α via Src kinase in normoxia (Carroll et al., 2006).

At translational level, the LMP1 protein of EBV increases HIF-1α activity through induction of its protein expression, which is controlled by the p42/p44 MAPK activity (Wakisaka et al., 2004).

At post translational level the protein encoded by the ORF3 of Hepatitis E virus (HEV)stabilizes HIF-1α and also binds to MAPK phosphatase that activates CBPp300 phosphorylation and consequently the transcriptional activity of HIF-1α (Moin et al., 2009; Kar-Roy et al., 2004). The HBx protein stabilizes HIF-1α *via* the p42/p44MAPK pathway; it also induces the deacetylation of the oxygen-dependent degradation domain of HIF-1α, leading to the dissociation of PHD and pVHL from HIF-1α (Yoo et al., 2008, 2003). For HCV, MEK and PI3-kinase inhibitors abolished HIF-1 α stabilization induced by the viral non-structural proteins from NS3 to NS5B (Nasimuzzaman et al., 2007). Several human papillomavirus (HPV) types cause an enhancement of HIF-1α expression in hypoxia, an effect that is mediated by increasing the stability of the HIF-1α protein; this effect does not involve the PI3K/mTOR pathway as suggested by the

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