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Virus–host interactions under hypoxia

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Abstract

Oxygen tension can exert a significant effect on viral propagation *in vitro* and possibly *in vivo*. In general, hypoxia restricts the replication of viruses that naturally infect tissues exposed to ambient oxygen and induces the growth of viruses that naturally target tissues exposed to low oxygen. Some viruses can reprogram cell bioenergetics towards lowering cellular respiration and therefore oxygen consumption in order to support their replication. Aim of this review is to summarize findings on the interplay between viral infection and oxygen levels, highlighting the implicated oxygen tension-sensitive elements and metabolic determinants and concluding with possible therapeutic approaches targeting these mediators.

Keywords: Viruses; Hypoxia; Hypoxia inducible factor; Metabolism; Bioenergetics

1. Introduction

Since the beginning of the 20th century, accumulating evidence has demonstrated a bidirectional relationship between viruses and levels of tissue oxygen. When the oxygen tension (or partial pressure) in tissue culture infection models is maintained at an *in vivo* physiological level, several viruses show different levels of replication as compared to conventional culturing under atmospheric oxygen (20% (v/v) O_2), which is an artificial context [1]. Moreover, a number of viruses, in order to assist their replication induce a hypoxic response, by reprogramming the energy metabolism of their host cells towards a lower mitochondrial respiratory rate (oxidative phosphorylation). This results to a lower oxygen consumption and triggers a rapid Warburg-like shift to anaerobic glycolysis (to lactate production). Interestingly, in some cases, there is a feedback interaction between oxygen sensors and virus proliferation.

In vivo, rapid blood circulation supplies adequate oxygen to organs and tissues for their metabolic requirements. Thus, in a physiological condition, as a result of the balance between oxygen delivery and its consumption, organs and tissues are characterized by their own unique 'normoxia' status, with median values for the majority of them ranging between 3% and 10% (23–70 mmHg) O_2. In the liver, for example, normoxia range from 12% O_2 around the portal vein to 1% O_2 near the central vein [2], with a median value of 3% O_2 [3]. As compared to other tissues [4,5], it is more characterized in the case of the liver that this oxygen gradient is important for generating zones of metabolic activity supported by an asymmetric distribution of key enzymes [6]. Evidence is abundant that the capacity for oxidative energy metabolism, gluconeogenesis and fatty acid oxidation is higher in the periportal area of the liver, whereas for glucose uptake, glycolysis, glutamine formation and fatty acid synthesis is higher in the pericentral area [7]. These data prompted us to study the impact of oxygen tension on the life cycle of the hepatotropic virus HCV under culture conditions that mimic hepatic normoxia (3% O_2). Specifically, transferring of infected hepatocytes from ambient to low oxygen was found to reprogram cellular energetic metabolism towards anaerobic glycolysis, an adaptation that mimics the *in vivo* situation and enhances viral replication [8].

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Aim of this review is to provide an update on the interplay between viruses and tissue oxygen by summarizing existing information on the oxygen tension-sensitive elements and metabolic determinants known to be involved in this interaction. It concludes with a discussion on the importance of applying this knowledge to the development of new therapeutic strategies.

2. O_2-sensitive factors and signaling pathways involved in the interplay between virus replication and hypoxia

Hypoxia-inducible factors (HIFs) are important transcription factors of the cellular metabolic state under low oxygen [9] and key mediators of the interplay between virus replication and cellular response to hypoxia. They are stabilized and activated below 5% O_2 [10]. They are heterodimeric proteins that are composed of a constitutively expressed HIF-1β subunit and an O_2-regulated HIF-α subunit that is known to exist in three isoforms. The two subunits interact as a complex with gene promoters containing the hypoxia response element (HRE) 5′-RCGTG-3′ (R: purine). Under atmospheric conditions (Fig. 1), HIF-α is unstable as a result of hydroxylation on proline residue 402 and/or 564 by prolyl hydroxylase domain (PHD) proteins, principally PHD2, members of the Fe(II) and of the 2-oxoglutarate-requiring dioxygenase family. Prolyl hydroxylation is required for the binding of the von Hippel-Lindau protein (VHL), which thereby recruits a ubiquitin ligase complex. Ubiquitination targets HIF-α for proteasomal degradation. Moreover, the factor inhibiting HIF-1 (FIH-1) binds to HIF-1α and negatively regulates its function by hydroxylating asparagine residue 803, which blocks the interaction of the HIF-1α transactivation domain with the co-activator p300 or CBP. In hypoxic conditions (Fig. 1), the hydroxylation reactions are inhibited as a result of substrate (O_2) deprivation and/or increased mitochondrial production of reactive oxygen species (ROS), increasing HIF-α stability, nuclear translocation and induction of transcription of the HIF target genes. HIF-1 can also be activated under atmospheric oxygen levels during infection with human pathogens, including viruses [11]. HIF-1 and HIF-2 induce transcriptional response to hypoxia, controlling anaerobic glycolysis (predominantly HIF-1), angiogenesis and erythropoiesis (HIF-2). On the other hand, HIF-3, which is less well studied acts as a dominant negative regulator of HIF-1 preventing its DNA binding. In addition to this hypoxia-dependent HIF-1α stabilization mechanism, there are various signaling pathways, such as the PI3K/AKT/mTOR, p42/44 (ERKs) and p38 MAPkinase, p53-Mdm2 (mouse double minute 2 homolog) and HSP90 pathways that affect HIF synthesis, stability and activity [11]. PI3K/AKT/mTOR activation increases HIF-1α

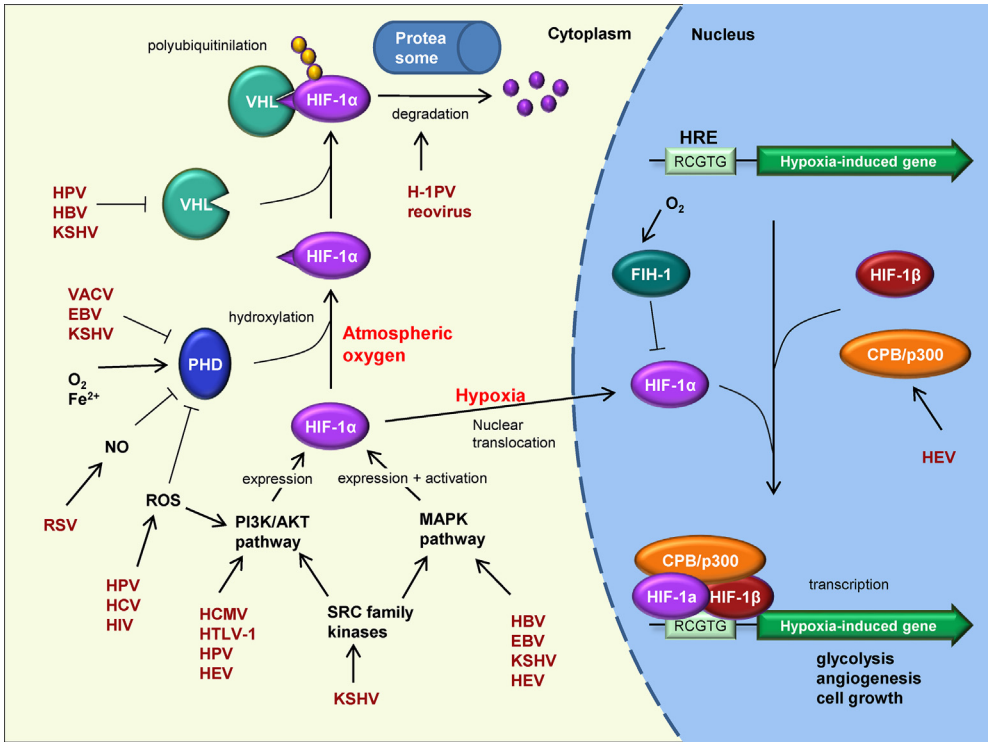

Fig. 1. HIF-1α signaling pathway modulation from oxygen levels or virus infection. Under atmospheric oxygen, HIF-1α is mostly degraded by the proteasome after prolyl-hydroxylation by PHDs (in the presence of O_2) and interaction with VHL protein. Few amounts of HIF-1α reach the nucleus, where FIH-1 asparagyl-hydroxylates HIF-1α under normal oxygen levels, inhibiting its interaction with CBP/p300. In hypoxia, HIF-1α is stabilized and enters the nucleus, where it forms a complex with HIF-1β and CBP/p300 and interacts with a Hypoxia Response Element (HRE) on the target gene promoters. Some viruses are able to stabilize HIF-1α under atmospheric oxygen via NO and ROS production or PHD degradation and VHL inhibition. Other viruses target PI3K/AKT pathway, which induces HIF-1α expression, or MAPK pathway, which has been shown to increase HIF-1α expression, stability and activity. Consequently, HIF-1 induces the transcription of genes controlling anaerobic glycolysis, angiogenesis and cell growth.