Virology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Review

Hypoxia-inducible factor 1 and its role in viral carcinogenesis

Sean Cuninghame [a,b], Robert Jackson [a,b], Ingeborg Zehbe [a,b,*]

[a] Probe Development & Biomarker Exploration, Thunder Bay Regional Research Institute, 980 Oliver Rd, Thunder Bay, Ont., Canada P7B 6V4
[b] Department of Biology, Lakehead University, Thunder Bay, Ont., Canada

ARTICLE INFO

Article history:
Received 10 December 2013
Returned to author for revisions
17 January 2014
Accepted 26 February 2014

Keywords:
HIF-1
Oncoviruses
Metabolism
Angiogenesis
Invasion
Metastasis
Tumor microenvironment

ABSTRACT

The advent of modern molecular biology has allowed for the discovery of several mechanisms by which oncoviruses promote carcinogenesis. Remarkably, nearly all human oncogenic viruses increase levels of the transcription factor hypoxia-inducible factor 1 (HIF-1). In this review, we highlight HIF-1's significance in viral oncogenesis, while providing an in-depth analysis of its activation mechanisms by the following oncoviruses: human papillomaviruses (HPVs), hepatitis B/C viruses (HBV/HCVs), Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV), and human T-cell lymphotropic virus (HTLV-1). We discuss virus-induced HIF-1's role in transcriptional upregulation of metabolic, angiogenic, and microenvironmental factors that are integral for oncogenesis. Admittedly, conclusive evidence is lacking as to whether activation of HIF-1 target genes is necessary for malignant transformation or merely a result thereof. In addition, a complete understanding of host–virus interactions, the effect of viral genomic variation, and the clinical (and potential therapeutic) relevance of HIF-1 in viral oncogenesis warrant further investigation.

Contents

Abbreviations: 4E-BP, 4E binding protein; AP-1, activator protein-1; Ad-AH, EBV-negative adenocarcinoma cell line; Akt, serine/threonine kinase; ARNT, aryl hydrocarbon receptor nuclear translocator; ATP/ADP, adenosine tri- or diphosphate; CAIX and CAXII, carbonic anhydrase IX and XII; E-cadherin, epithelial adhesion molecule; E6-AP, E6-associated Protein (E3 ubiquitin ligase); EBNA, EBV nuclear antigens; EBV, Epstein–Barr virus or HHV-4; eIF-4E, elongation initiation factor 4E; EMT, epithelial–mesenchymal transition; ERBB2, growth factor receptor; ERK, extracellular signal-regulated kinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLUT-1, GLUT-3, glucose transporters; HBV/HCV, hepatitis B or C virus; HCC, hepatocellular carcinoma; HDAC, histone deacetylases; HHV, human herpes virus; HIF, hypoxia-inducible factor; HK1/2, hexokinase 1 & 2; HPV, human papillomavirus; HRE, hypoxia response element; Huh-7, cell type permissive to infection by HCV; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; KSHV, Kaposi's sarcoma-associated herpes virus or HHV-8; LANA, latent nuclear antigen, LANA-2 is the viral homolog of cellular interferon regulatory factor 3; LCL, lymphoblastoid cell lines, created by EBV-transformed B cells; LDHA, lactate dehydrogenase; LMP, EBV latent membrane proteins; MAPK, mitogen-activated protein kinase; MEK, activator of ERK (kinase); MMP, matrix metalloprotease; MNK, MAPK-interacting kinase; mTOR, mammalian target of rapamycin, a PI3K; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ODD, oxygen-dependent domain of HIF-1; ORF, open reading frame; PA-1, cell type permissive to infection by HPV; PDK1, pyruvate dehydrogenase kinase 1; PFK, phosphofructokinase; PGK1, phosphoglycerate kinase 1; PHD, prolyl hydroxylase; PI3K, phosphatidylinositol-3-kinase; PTEN, tumor suppressor; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; SUMO, small ubiquitin-like modifier; SP-1, specificity protein-1; STAT-3, signal transducer and activator of transcription 3; TCA, mitochondrial tricarboxylic acid; URR, upstream regulatory region; VEGF, vascular endothelial growth factor; vGPCR, viral G-protein coupled receptor; VHL, von Hippel Lindau E3 ligase protein

* Corresponding author at: Probe Development & Biomarker Exploration, Thunder Bay Regional Research Institute, 980 Oliver Road, Thunder Bay, Ont., Canada P7B 6V4. Tel.: +1 807 684 7246.
E-mail address: zehbei@tbh.net (I. Zehbe).

http://dx.doi.org/10.1016/j.virol.2014.02.027
0042-6822

Introduction

Approximately 16% of yearly cancer diagnoses worldwide are attributable to an infectious agent (de Martel et al., 2012). The fraction of cancers linked to infection varies greatly by geographical location and socioeconomic factors: while only 7.4% of cancer diagnoses are the result of infection in developed countries, up to 22.9% of cancers in developing parts of the world arise due to infection. In Sub-Saharan Africa, a striking one-third of cancer diagnoses are the result of infection (de Martel et al., 2012); the majority of these cancers are the result of infection with an oncovirus. Thus, oncovirus-induced cancers are an important global concern.

Oncoviruses contribute to carcinogenesis by altering the function of cellular targets that play pivotal roles in the development of cancer. Over the past few decades, many of the cellular mechanisms by which oncoviruses induce malignant transformation have been elucidated. One of the best-documented cases of oncogenic viruses disrupting normal cellular functions involves the tumor suppressor protein, p53. Several oncogenic viral proteins—such as the E6 oncoprotein of high-risk human papillomavirus (HPV) types and the HBx oncoprotein of hepatitis B virus (HBV)—have inhibitory effects on the pro-apoptotic ability of p53. The high-risk HPVs have additional cellular targets: the E6 oncoprotein increases telomerase activity and the E7 oncoprotein degrades the retinoblastoma tumor suppressor protein (Scheffner et al., 1993; Boyer et al., 1996; Klingelhutz et al., 1996).

There is strong evidence that activation of the hypoxia-inducible factor 1 (HIF-1) transcription factor is a common pathway affected by human oncogenic viruses. HIF proteins are major components of the innate hypoxic stress response in non-cancerous cells, acting as transcription factors for a multitude of genes required for adaptation under low oxygen conditions (Wang et al., 1995a). Three HIF isoforms have been identified (*i.e.*, HIF-1, HIF-2 and HIF-3), however research to date has focused primarily on HIF-1. As such, this review will focus on HIF-1, but HIF-2 and HIF-3 could be assessed in future studies of viral carcinogenesis.

Transcriptionally active HIF-1 is a heterodimer made up of α- and β-subunits (the β subunit is also known as aryl hydrocarbon receptor nuclear translocator (ARNT), which also dimerizes with several other transcription factor subunits). The dimer is a member of the basic helix loop helix-PER-ARNT-SIM (bHLH-PAS) family of transcription factors that play a role in cancer development (Bersten et al., 2013). In normal, non-hypoxic cells, HIF-1α is continually synthesized and degraded, while HIF-1β is constitutively expressed to levels that remain relatively constant within the nucleus (Fig. 1A). HIF-1 activity is largely dependent on the regulation of its α subunit at several levels including transcription, translation, ubiquitin-mediated protein breakdown, nuclear translocation, and association with transcriptional co-activators. HIF-1α mRNA is ubiquitously expressed and its levels are similar for most cell types studied between hypoxic and normoxic conditions (Wenger et al., 1997). However, some cell types, such as hepatocellular carcinoma (HCC) Hep3B cells, exhibit an increase in *HIF-1α* transcription under hypoxic conditions (Wang et al., 1995a). *In vivo* investigations initially uncovered the potential for environmental hypoxia inducing *HIF-1α* transcription (Wiener et al., 1996), but

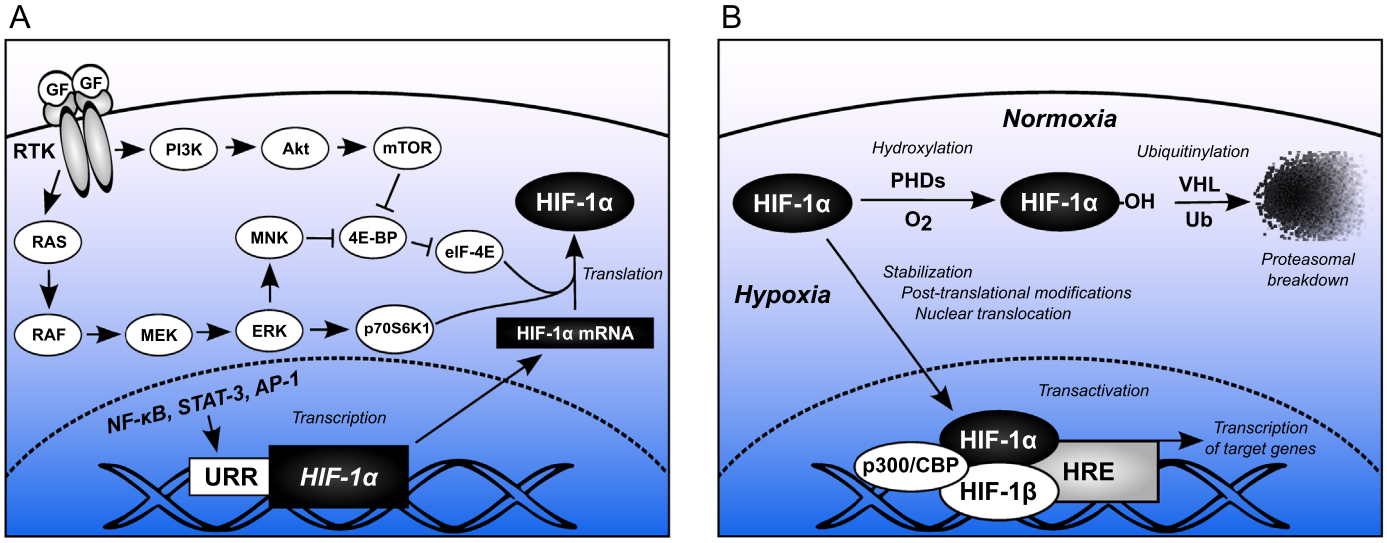

Fig. 1. Regulation of HIF-1 protein levels. The level of HIF-1 in a given cell is subject to its oxygen-independent synthesis (A) and oxygen-dependent degradation (B). (A) The synthesis of HIF-1α is augmented in an oxygen-independent manner by transcription factors acting on its upstream regulatory region (URR) and the PI3K/Akt and ERK/MAPK pathways acting on its translation. When a growth factor binds to its respective tyrosine kinase receptor, PI3K (in the PI3K pathway) or RAS (in the ERK/MAPK pathway) is activated. In the PI3K pathway, PI3K then activates Akt and subsequently mTOR. In the ERK/MAPK pathway, RAS activates RAF, which activates MEK and subsequently ERK. ERK activates MNK that, together with mTOR, deactivates the 4E-BP, which allows for the formation of the eIF-4E complex. Along with p70S6K1, that is also activated by ERK, eIF-4E enhances the translation of HIF-1α mRNA. (B) When oxygen is present, PHDs are active and hydroxylate HIF-1α at Pro-402 and/or Pro-564. HIF-1α-OH becomes ubiquitinylated by VHL and subsequently broken down by the 26S proteasome. Conversely, under hypoxic conditions, PHDs cannot hydroxylate HIF-1α and it will accumulate in the cytoplasm before translocating to the nucleus to complex with HIF-1β and p300/CBP to enhance target gene expression. A rectangular border represents nucleic acids and circles are proteins. Black and white backgrounds represent specific HIF-1 and effector cellular components, respectively. The dotted line represents the nuclear membrane. Refer to abbreviation list for full names.

Please cite this article as: Cuninghame, S., et al., Hypoxia-inducible factor 1 and its role in viral carcinogenesis. Virology (2014), http://dx.doi.org/10.1016/j.virol.2014.02.027