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Invited review

Recent advances in hypoxia-inducible factor (HIF)-1 inhibitors

Yan Xia, Hyun-Kyung Choi, Kyeong Lee*

College of Pharmacy, Dongguk University-Seoul, 26 Pildong-3-ga, Jung-gu, Seoul 100-715, Republic of Korea

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ABSTRACT

Tumor hypoxia has been recognized as a common feature of solid tumors and a negative prognostic factor for response to treatment and survival of cancer patients. The discovery of hypoxia-inducible factor-1 (HIF-1), a molecular determinant of responses to hypoxia in mammalian cells, has renewed enthusiasm for discovery and development of targeted therapies exploiting the hypoxic tumor microenvironment. HIF-1 activity in tumors depends on availability of the HIF-1α subunit, the levels of which increase under hypoxic conditions and through activation of oncogenes and/or inactivation of tumor suppressor genes. Increased HIF-1 has been correlated with increased angiogenesis, aggressive tumor growth, and poor patient prognosis, leading to current interest in HIF-1 as promising anticancer drug target. In spite of an ever increasing number of putative small molecule inhibitors of HIF-1, only a few are progressing through preclinical and early clinical development. In this review, we will discuss recent advances in discovery and development of small molecule inhibitors that target the HIF-1 pathway as potential anticancer agents.

1. Introduction

Hypoxia-inducible factor-1 (HIF-1) is a transcription factor that is activated in response to intratumoural hypoxia and as a result of genetic alterations that activate oncogenes and inactivate tumor suppressor genes. It plays a pivotal role in adaptation of tumor cells to hypoxia by activating transcription of target genes that regulate several biological processes including angiogenesis, cell proliferation and survival, glucose metabolism, pH regulation and migration. HIF-1 activity in tumors depends on availability of the HIF-1α subunit, the levels of which increase under hypoxic conditions and through activation of oncogenes and/or inactivation of tumor suppressor genes. Increased tumor HIF-1 has been correlated with increased angiogenesis, aggressive tumor growth, and poor patient prognosis, leading to current interest in HIF-1 as an anticancer drug target. A growing number of anticancer agents have been shown to inhibit HIF-1 activity, but none of these drugs have been shown to directly and specifically target HIF-1. For many of them, the mechanism of action has been fully established and involves signaling pathways related to HIF-1, HIF-1α mRNA expression, HIF-1α protein translation, HIF-1α protein degradation, HIF-1α DNA binding activity, or HIF-1α-mediated transcription of target genes. So far, many reviews on HIF-1 as a target for drug development have been reported [1–8]. This review includes more updated information on small molecule HIF-1 inhibitors as potential anticancer agents.

2. The structure of HIF

Hypoxia-inducible factor (HIF) is a transcription factor that is found in mammalian cells cultured under reduced oxygen tension and that plays a key role in the cellular response to hypoxia. HIF is a heterodimer consisting of two subunits, an oxygen-sensitive HIF-α and a constitutively expressed HIF-β (also known as an aryl hydrocarbon receptor nuclear translocator (ARNT)), the heterodimeric partner of the aryl hydrocarbon receptor (AHR) [9]. Both subunits are members of the basic helix–loop–helix (bHLH) proteins of the PER-ARNT-single-minded protein (SIM) (PAS) family of transcription factors [10]. Three HIF-α homologs have been identified: HIF-1α, HIF-2α and HIF-3α [11–13]. HIF-1α and HIF-2α share a high degree of sequence identity, which is highlighted by their common ability to heterodimerise to HIF-β [11,12]. Heterodimers that contain HIF-1α or HIF-2α appear to have overlapping but distinct tissue-specific expression patterns and target genes. Less is known about HIF-3α compared with the other HIF-α homologs. It has been shown that the inhibitory PAS domain protein (IPAS) is an alternatively spliced variant of HIF-3α and functions as a dominant-negative regulator of HIF-α, adding to the complexity in the regulation of hypoxia-inducible genes by the HIF

* Corresponding author. Tel.: +82 2 2260 8906; fax: +82 2 2260 8769.
E-mail address: kaylee@dongguk.edu (K. Lee).

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family of transcription factors [14]. HIF-1α has two transactivation domains located in its COOH-terminal half: the NH_2-terminal transactivation domain or (N-TAD) (amino acids 531–575) and the COOH-terminal transactivation domain or C-TAD (amino acids 786–826) [15]. The C-TAD of HIF-1α is involved in modulating the transcriptional activation of HIF-1α under hypoxic conditions, in contrast to the N-TAD, which is involved in the stabilization of HIF-1α. Under hypoxia, the C-TAD is able to interact with transcriptional co-activators, such as p300/CBP. This interaction is unable to occur under normoxia due to the oxygen-dependent hydroxylation of N803, located within the C-TAD. Hydroxylation of N803 is mediated by an asparaginyl hydroxylase, known as factor inhibiting HIF-1 (FIH-1), which prevents HIF-1α from interacting with the transcriptional co-activators p300/CBP [16]. Thiol-redox regulation of C-TAD activity by Trx-1 via the Ref-1 system also has been reported to promote interaction of the C-TAD with p300/CBP resulting in increased HIF-1 transactivation [17].

3. Regulation of HIF-1α protein levels

Cells transduce decreased O_2 concentration into increased HIF-1 activity via a O_2-dependent post-translational modification (Fig. 1A). In normoxic conditions, O_2-dependent hydroxylation of proline (P) residues 402 and 564 in HIF-1α by the enzymes PHD (prolyl hydroxylase-domain protein) 1–3 is required for the binding of the von Hippel–Lindau (VHL) tumor-suppressor protein, which is the recognition component of an E3 ubiquitin-protein ligase. VHL binding is also promoted by acetylation of K532 residue by the ARD1 acetyltransferase. Ubiquitylation of HIF-1α targets the protein for degradation by the 26S proteasome. O_2 also regulates the interaction of HIF-1α with transcriptional co-activators. O_2-dependent hydroxylation of N803 residue in HIF-1α by the enzyme FIH-1 blocks the binding of p300/CBP to HIF-1α and therefore inhibits HIF-1-mediated gene transcription [6]. Under hypoxic conditions, the rate of N803 and K532 hydroxylation decreases. VHL cannot bind to HIF-1α that is

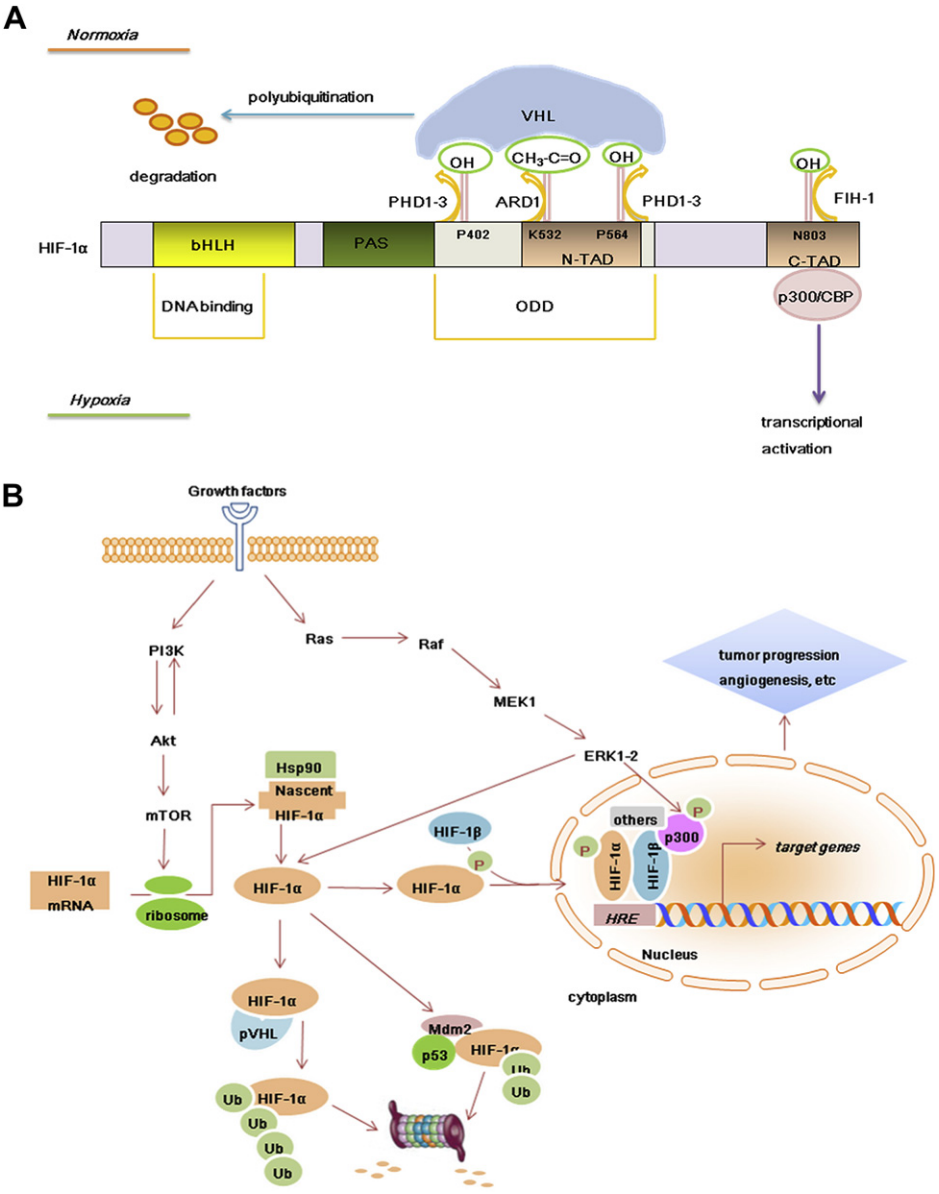

Fig. 1. (A). Oxygen-dependent regulation of HIF-1α activity. The figure has been adapted, with some modifications, from Ref. [6]. (B) Hypoxia signaling through HIF-1. The figure has been adapted, with some modifications, from Ref. [18].