Hypoxia inducible factor (HIF)

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Abstract: Under the condition of low oxygen tension (hypoxia) for cells and tissues it leads to the transcriptional induction of genes that participate in angiogenesis, iron metabolism, glucose metabolism, and cell proliferation/survival. The primary factor mediating this response is the hypoxia-inducible factor (HIF). HIF consists of an oxygen-regulated subunit HIF-1α, HIF-1β, HIF-2α and HIF-3α. The stability and activity of HIF-α are regulated by the post-translational modifications such as hydroxylation, ubiquitination, acetylation, and phosphorylation, etc. Overexpression of HIF-1 has been found in disease condition.
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Keywords: hypoxia; hypoxia inducible factor (HIF); HIF-1α; HIF-1β; HIF-2α; HIF-3α; oxygen

Abbreviations:
HIF, hypoxia inducible factor;
HIF-α, hypoxia-inducible transcription factor-α
pVHL, von Hippel-Lindau protein
PHD, HIF prolyl hydroxylase
RA, rheumatoid arthritis
IPAS, inhibitory PAS
TNF-α, tumor necrosis factor
VEGF, vascular endothelial growth factor
IGF, insulin-like growth factor
EPO, erythropoietin

Introduction

Oxygen is one of the key factors for the living things in the earth, and it is basic for the biochemical metabolic reactions of animals and plants. Oxygen availability is a critical signal for the proper development of many tissues. Hypoxia has been recognized as an important tumoral feature related to resistance to radiotherapy since 1933 (Giatromanolaki and Harris 2001). The transcription factor hypoxia-inducible factor (HIF) plays an important role in maintenance of oxygen homeostasis in all metazoans. Numerous growth and transcription factors have been implicated in the development of the skeletal system (Sun and Wei 2009). Adaptation of cancer cells to their microenvironment is an important driving force in the clonal selection that leads to invasive and metastatic disease. O_2 concentrations are markedly reduced in many human cancers compared with normal tissue, and a major mechanism mediating adaptive responses to reduced O_2 availability (hypoxia) is the regulation of transcription by HIF) (Semenza) (Cunshuan Xu 2006).

HIF is a transcription factor that responds to decreases of oxygen in cell. The α subunit of HIF-1 is a target for prolyl hydroxylation by HIF prolyl-hydroxylase (Cockman et al. 2009). This occurs only in normoxic conditions. In hypoxic conditions, HIF prolyl-hydroxylase is inhibited since it utilizes oxygen as a cosubstrate. Hypoxia results in a build up of succinate, due to inhibition of the electron transport chain in the mitochondria. The build up of succinate further inhibits HIF prolyl-hydroxylase action since it is an end product of HIF hydroxylation (Tanaka and Nangaku 2009). The oxygen-dependent hydroxylation of proline residues in α subunit of hypoxia-inducible transcription factor (HIF-α) is the central to the hypoxic response in animals. Prolyl hydroxylation of HIF-α increases its binding to the von Hippel-Lindau protein (pVHL), so signaling for degradation via the ubiquitin-proteasome system. The HIF prolyl hydroxylases (PHDs) are related to the collagen prolyl hydroxylases, but form unusually stable complexes with their Fe(II) cofactor and 2-oxoglutarate cosubstrate (Chowdhury et al. 2009).

HIF-1 is a dimeric protein complex and serves as a transcription factor regulator for many target genes, and it is one of the major factors responsible for the activation of compensation processes during cell hypoxia (Rekwirowicz and Marszalek 2009). As a heterodimeric transcription factor composed of an oxygen-dependent α-subunit and constitutively expressed beta subunit, it plays a central role in cellular adaptation to hypoxia by transcriptionally upregulating its target genes involved in angiogenesis, erythropoiesis, glycolysis, and so on. Recent studies demonstrated that hypoxia in the tubulointerstitium is involved in the pathology of progressive renal diseases and that HIF, which is activated in experimental kidney diseases, may serve to protect tubulointerstitium from the ischemic insult. The expression of HIF α-chains is post-translationally regulated and hydroxylation at one or two of the conserved proline residues by PHDs is a critical step

for the oxygen-dependent recruitment of the pVHL. Modalities to inhibit the enzymatic activities of PHDs have been shown to activate HIF irrespective of oxygenation status and are regarded as candidate targets of pharmacological approaches against chronic kidney diseases characterized by hypoxia (Tanaka and Nangaku 2009).

Angiogenesis plays an important role in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA). The site and extent of inflammation and subsequent joint destruction in the rheumatoid synovium is dependent on the development of new vasculature. Inhibition of angiogenesis, extensively studied in cancer, might therefore be of interest as treatment option for RA (Westra et al. 2009). HIF-1 has been reported to play a critical role in the regulation of hypoxia driven angiogenesis that is constitutively expressed in many cells. It gains transcriptional activity in hypoxic cells leading to the expression of genes involved in angiogenesis. The synovium is hypoxic, but also in an inflammatory environment such as seen in RA, inflammatory cytokines may be important inducers of HIF-1 expression and activation (Brouwer et al. 2009). Blocking of tumor necrosis factor-α (TNF-α), for instance, reduces TNF-α induced vascular endothelial growth factor (VEGF) production (Ma Hongbao 2007). Inhibition of HIF-1 expression or activation, either by blocking signal transduction pathways leading to HIF-1 induction or by inhibiting accumulation of HIF-1 protein, represents a new strategy, which is of interest for the treatment of RA (Westra et al. 2009).

HIF-1α

HIF-1 is discovered by the identification of a hypoxia response element (HRE; 5′-RCGTG-3′) in the 3′ enhancer of the gene for erythropoietin (EPO), a hormone that stimulates erythrocyte proliferation and undergoes hypoxia-induced transcription (Lim et al. 2009). Inhibition of HIF-1 is an attractive therapeutic strategy to target the tumor microenvironment. HIF-1**α** inhibitors may have limited activity as single agents and combination therapies may be required (Rapisarda et al. 2009). The protein that binds to the HRE under hypoxic conditions as HIF-1, a heterodimeric complex consisting of a hypoxically inducible subunit HIF-1α and a constitutively expressed subunit HIF-1β (Clottes 2005). HIF-1**α** plays important roles in modulating the developmental plasticity of stem cells by integrating physiological, transcriptional and epigenetic inputs (Maltepe et al. 2005).

Human HIF-1 protein sequence and mRNA are given In Figure 1 and Figure 2.

HIF-2α

HIF-1**α** and HIF-2**α** have been identified as key proteins that directly respond to hypoxic stress. HIF-2α shares 48% amino acid sequence identity with HIF-1α and accordingly shares a number of structural and biochemical similarities with HIF-1α. In contrast to ubiquitously expressed HIF-1α, HIF-2α is predominantly expressed in the lung, endothelium, and carotid body. Following hypoxia, stabilisation and nuclear binding of HIF-2**α** triggers the expression of a variety of genes related to erythropoiesis, glycolysis and angiogenesis (Marti et al. 2000).

HIF-3α

HIF-3**α** is the third member of the HIF transcription factor family. HIF-3α protein could be detected under normoxia in the cytoplasm and nuclei, but increased under hypoxic conditions. Promoter analyses and chromatin immunoprecipitation experiments localized a functional hypoxia-responsive element 5' to the transcriptional start of HIF-3α. Immunohistochemistry revealed an overlap of HIF-1α-positive and HIF-3α-positive areas in human renal cell carcinomas (Tanaka et al. 2009). HIF-3α is expressed in a variety of tissues. Tissue hypoxia is a pathologic feature of many human diseases including cancer, myocardial infarction, stroke, and kidney disease. A splice variant of HIF-3α, inhibitory PAS (IPAS), which is predominantly expressed in the Purkinje cells of the cerebellum and corneal epithelium. IPAS can be induced by hypoxia in the heart and lung, contributing to a negative feedback loop for HIF-1 activity in these tissues (Hatanaka et al. 2009). An evolutionarily conserved oxygen-sensing mechanism enables cells to adapt and maintain homeostasis under hypoxic conditions by transcriptional activation of a host of genes that mediate metabolic adaptation, angiogenesis, energy conservation, erythropoiesis, and cell survival. Inappropriate activation of the HIF system is linked to the development and progression of many human malignancies including clear cell renal cancer (Gunaratnam and Bonventre 2009).

Regulation of HIF-1

Basophils play a pivotal role in regulating chronic allergic inflammation as well as angiogenesis. HIF-1 facilitates cellular adaptation to hypoxic conditions such as inflammation and tumour growth by controlling glycolysis, angiogenesis and cell adhesion. Abrogating HIF-1α expression in basophils using siRNA demonstrated that this protein is essential for VEGF mRNA expression and, consequently, release of VEGF protein (Sumbayev et al. 2009).

In normoxia, the HIF-1α proteins are rapidly degraded, resulting in essentially no detectable HIF-1α protein. During hypoxia, HIF-1α becomes stabilized and translocates from the cytoplasm to the nucleus, where it dimerizes with HIF-1β, and the HIF complex formed becomes transcriptionally active (Adams et al. 2009). In normoxia, hydroxylation of two proline residues and acetylation of a lysine residue (Hagele et al. 2009).

The proliferation-specific Forkhead box M1 transcription factor is overexpressed in cancer cells and acts as an important regulator of cancer cell growth and survival (Xia et al. 2009).

Target Gene of HIF-1

HIF-1α, HIF-2α and HIF-3α play critical roles in the cellular and systemic adaptation to hypoxia. There are more than 100 HIF-1 downstream genes identified. HIF-3α2 and HIF-3α4 transcripts, HIF-3α splice variants expressed in Caki-1 renal carcinoma cells, rapidly increased after exposure to hypoxia or chemical hypoxia mimetics. Promoter analyses and chromatin immunoprecipitation experiments localized a functional hypoxia-responsive element 5' to the transcriptional start of HIF-3α2. siRNA-mediated knockdown of HIF-3α increased transactivation of a HIF-driven reporter construct and mRNA expression of lysyl oxidase. Immunohistochemistry revealed an overlap of HIF-1α-positive and HIF-3α-positive areas in human renal cell carcinomas (Tanaka et al. 2009).

Angiogenesis

Angiogenesis is a complex process that involves multiple gene products expressed by different cell types. A large number of genes involved in different steps of angiogenesis have been shown to increase by hypoxia challenge. Among them, VEGF is the most potent endothelial-specific mitogen, and it directly participates in angiogenesis by recruiting endothelial cells into hypoxic and avascular area and stimulates their proliferation. HIF-1 regulates genes that are involved in governing the vascular tone such as nitric oxide synthase, heme oxygenease 1, endothelin 1, adrenomedulin, and the α1B-adrenergic receptor (Westra et al. 2009). Tumor hypoxia is a common feature of many cancers. A master regulator of hypoxic response is the transcription factor HIF-1. It functions as a master regulator of oxygen and undergoes conformational changes in response to varying oxygen concentrations (Otrock et al. 2009).

Angiogenesis plays an important role in the pathogenesis of inflammatory diseases, including RA. The site and extent of inflammation and subsequent joint destruction in the rheumatoid synovium is dependent on the development of new vasculature. Inhibition of angiogenesis, extensively studied in cancer, might therefore be of interest as treatment option for RA. HIF-1 has been reported to play a critical role in the regulation of hypoxia driven angiogenesis. HIF-1 is a transcription factor that is constitutively expressed in many cells. It gains transcriptional activity in hypoxic cells leading to the expression of genes involved in angiogenesis. The synovium is hypoxic, but also in an inflammatory environment such as seen in RA, inflammatory cytokines may be important inducers of HIF-1 expression and activation. Many drugs currently used in the treatment of RA have anti-angiogenic effects, which are exerted at different levels. Blocking of TNF-α, for instance, reduces TNF-α induced VEGF production. Studies aiming at direct inhibition of pro-angiogenic factors, such as inhibiting VEGF-receptor or FGF-receptor signalling or blocking VEGF by monoclonal anti-VEGF antibody therapeutics, are potential treatments in clinical applications. Inhibition of HIF-1 expression or activation, either by blocking signal transduction pathways leading to HIF-1 induction or by inhibiting accumulation of HIF-1 protein, represents a new strategy (Hongbao Ma 2005b; Westra et al. 2009).

Glucose Metabolism

In the tumor cells exposed to hypoxia, HIF-1-mediated adaptation responses such as angiogenesis and anaerobic metabolism are induced for their survival (Chen et al. 2003). Under low oxygen supply, cells switch their glucose metabolism pathway away from the oxygen-dependent tricarboxylic acid (TCA) cycle to the oxygen-independent glycolysis. With only 2 ATP molecules from each glucose molecule produced by glycolysis, instead of 38 ATP provided by TCA cycle, hypoxic cells elevate their ability to generate ATP by increasing the glucose uptake. This is achieved by up-regulating the expression of glycolytic enzymes and glucose transporters. Hypoxia and HIF-1 increase virtually all the enzymes in the glycolytic pathway, as well as the glucose transporters 1 and 3 (GLU1, GLU3). Furthermore, the glycolysis metabolic products, such as lactate and pyruvate, have been reported to cause HIF-1α accumulation under normoxia and regulate hypoxia-inducible gene expression, hence establishing a potential positive feedback loop (Staab et al. 2007).

Apoptosis

There are two ways for cell dying: (1) By injury or disease. (2) Suicide. Programmed cell death is also called apoptosis - cell suicide. Apoptosis is that the cells undergo death to control cell

proliferation. There are 3 different mechanisms by which a cell commits suicide by apoptosis: (1) Generated by signals arising within the cell; (2) Triggered by death activators binding to receptors at the cell surface; (3) Triggered by disadvantaged environment. Besides animal, plant also performs the apoptosis (Hongbao Ma 2005a). Cell adaptation to hypoxia leads not only to cell survival but also to cell death. Hypoxia has been shown to induce apoptosis, where HIF-1 plays a complex role. Genetic studies using embryonic stem cells harboring a deletion of HIF-1α showed decreased apoptosis compared with wild type when challenged with low oxygen. Activation of caspase-3 and Apaf-1-mediated caspase-9, and the release of cytochrome c, have been reported in several cell types under hypoxic conditions. HIF-1 also regulated many other target genes implicated in diverse processes such as adipogenesis, carotide body formation, B lymphocyte development, and immune reactions. High expression of HIF-1α may be responsible for the high apoptosis (Chunjing Fu 2005; Xinsheng liu 2008; Yunwei Li 2008).

Role of HIF-1 in Development and Diseases

The site and extent of inflammation and subsequent joint destruction in the rheumatoid synovium is dependent on the development of new vasculature. HIF-1 plays a critical role in the regulation of hypoxia driven angiogenesis. It gains transcriptional activity in hypoxic cells leading to the expression of genes involved in angiogenesis (Adams et al. 2009). Hypoxia and HIF pathway have been linked to the embryonic development and pathophysiology of numerous human diseases (Higgins et al. 2008). Inhibition of HIF-1 expression or activation, either by blocking signal transduction pathways leading to HIF-1 induction or by inhibiting accumulation of HIF-1 protein, is potentially useful for the treatment of RA (Ma 2007; Westra et al. 2009).

Implication of HIF-1 in Therapy

The importance of HIF-1 as a transcription factor and the broad spectrum of processes influenced by HIF suggest that it could have important clinical implications (Ding et al. 2006). HIF-1 regulation provides a variety of possibilities for therapeutic intervention. In contrast to the inhibition of HIF-1 activation in cancer therapy, promoting its activation could be advantageous in ischemic diseases. Ischemic diseases such as stroke and heart attack are caused by localized hypoxia manifested as cerebral and myocardial ischemia, respectively. Increase of the VEGF expression by HIF-1α or HIF-2α could induce the formation of new blood vessels of the target area in the brain and heart, thereby providing an increased blood flow and oxygen supply and reduce harmful response to ischemia. HIF-1α in epidermis showed increased expression of VEGF and marked induction of hypervascularity without induction of edema, inflammation, or vascular leakage. VEGF overexpression is correlated with HIF-1α and MMP-2 expression, underlining the role of VEGF in psoriasis as a key factor in the link between inflammation and angiogenesis (Simonetti et al. 2006). HIF-1α has a potential ability to treat common clinical hypoxic-ischemic injuries (Tang et al. 2009) (Kwon et al. 2004).

The distinct role of enzymes modifying HIF-1α post-translationally, the interplay among the HIF-1α post-translational modifications, the identity of additional target genes of HIF-1, the function of the paralogs of HIF-1α (such as HIF-2α and HIF-3α), the link between HIF-1 activation and other oncogenic or tumor suppressor pathways, the mechanism by which the HIF-1 pathway contribute to tumor growth and other pathological responses (Nikiforov et al. 2007).

HIF-1 protein sequence:

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   1 megaggandk kkisserrke ksrdaarsrr skesevfyel ahqlplphnv sshldkasvm
  61 rltisylrvr klldagdldi eddmkaqmnc fylkaldgfv mvltddgdmi yisdnvnkym
 121 gltqfeltgh svfdfthpcd heemremlth rnglvkkgke qntqrsfflr mkctltsrgr
 181 tmniksatwk vlhctghihv ydtnsnqpqc gykkppmtcl vlicepiphp snieipldsk
 241 tflsrhsldm kfsycderit elmgyepeel lgrsiyeyyh aldsdhltkt hhdmftkgqv
 301 ttgqyrmlak rggyvwvetq atviyntkns qpqcivcvny vvsgiiqhdl ifslqqtecv
 361 lkpvessdmk mtqlftkves edtsslfdkl kkepdaltll apaagdtiis ldfgsndtet
 421 ddqqleevpl yndvmlpspn eklqninlam splptaetpk plrssadpal nqevalklep
 481 npeslelsft mpqiqdqtps psdgstrqss pepnspseyc fyvdsdmvne fklelveklf
 541 aedteaknpf stqdtdldle mlapyipmdd dlqlrsfdql splesssasp esaspqstvt
 601 vfqqtqiqep tanattttat tdelktvtkd rmedikilia spspthihke ttsatsspyr
 661 dtqsrtaspn ragkgvieqt ekshprspnv lsvalsqrtt vpeeelnpki lalqnaqrkr
 721 kmehdgslfq avgigtllqq pddhaattsl swkrvkgcks seqngmeqkt iilipsdlac
 781 rllgqsmdes glpqltsydc evnapiqgsr nllqgeellr aldqvn
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(Iyer, et al, 1998)

HIF-1 mRNA sequence:

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   1 ccgattcacc atggagggcg ccggcggcgc gaacgacaag aaaaagataa gttctgaacg
  61 tcgaaaagaa aagtctcgag atgcagccag atctcggcga agtaaagaat ctgaagtttt
 121 ttatgagctt gctcatcagt tgccacttcc acataatgtg agttcgcatc ttgataaggc
 181 ctctgtgatg aggcttacca tcagctattt gcgtgtgagg aaacttctgg atgctggtga
 241 tttggatatt gaagatgaca tgaaagcaca gatgaattgc ttttatttga aagccttgga
 301 tggttttgtt atggttctca cagatgatgg tgacatgatt tacatttctg ataatgtgaa
 361 caaatacatg ggattaactc agtttgaact aactggacac agtgtgtttg attttactca
 421 tccatgtgac catgaggaaa tgagagaaat gcttacacac agaaatggcc ttgtgaaaaa
 481 gggtaaagaa caaaacacac agcgaagctt ttttctcaga atgaagtgta ccctaactag
 541 ccgaggaaga actatgaaca taaagtctgc aacatggaag gtattgcact gcacaggcca
 601 cattcacgta tatgatacca acagtaacca acctcagtgt gggtataaga aaccacctat
 661 gacctgcttg gtgctgattt gtgaacccat tcctcaccca tcaaatattg aaattccttt
 721 agatagcaag actttcctca gtcgacacag cctggatatg aaattttctt attgtgatga
 781 aagaattacc gaattgatgg gatatgagcc agaagaactt ttaggccgct caatttatga
 841 atattatcat gctttggact ctgatcatct gaccaaaact catcatgata tgtttactaa
 901 aggacaagtc accacaggac agtacaggat gcttgccaaa agaggtggat atgtctgggt
 961 tgaaactcaa gcaactgtca tatataacac caagaattct caaccacagt gcattgtatg
1021 tgtgaattac gttgtgagtg gtattattca gcacgacttg attttctccc ttcaacaaac
1081 agaatgtgtc cttaaaccgg ttgaatcttc agatatgaaa atgactcagc tattcaccaa
1141 agttgaatca gaagatacaa gtagcctctt tgacaaactt aagaaggaac ctgatgcttt
1201 aactttgctg gccccagccg ctggagacac aatcatatct ttagattttg gcagcaacga
1261 cacagaaact gatgaccagc aacttgagga agtaccatta tataatgatg taatgctccc
1321 ctcacccaac gaaaaattac agaatataaa tttggcaatg tctccattac ccaccgctga
1381 aacgccaaag ccacttcgaa gtagtgctga ccctgcactc aatcaagaag ttgcattaaa
1441 attagaacca aatccagagt cactggaact ttcttttacc atgccccaga ttcaggatca
1501 gacacctagt ccttccgatg gaagcactag acaaagttca cctgagccta atagtcccag
1561 tgaatattgt ttttatgtgg atagtgatat ggtcaatgaa ttcaagttgg aattggtaga
1621 aaaacttttt gctgaagaca cagaagcaaa gaacccattt tctactcagg acacagattt
1681 agacttggag atgttagctc cctatatccc aatggatgat gacttccagt tacgttcctt
1741 cgatcagttg tcaccattag aaagcagttc cgcaagccct gaaagcgcaa gtcctcaaag
1801 cacagttaca gtattccagc agactcaaat acaagaacct actgctaatg ccaccactac
1861 cactgccacc actgatgaat taaaaacagt gacaaaagac cgtatggaag acattaaaat
1921 attgattgca tctccatctc ctacccacat acataaagaa actactagtg ccacatcatc
1981 accatataga gatactcaaa gtcggacagc ctcaccaaac agagcaggaa aaggagtcat
2041 agaacagaca gaaaaatctc atccaagaag ccctaacgtg ttatctgtcg ctttgagtca
2101 aagaactaca gttcctgagg aagaactaaa tccaaagata ctagctttgc agaatgctca
2161 gagaaagcga aaaatggaac atgatggttc acttttcaa gcagtaggaa ttggaacatt
2221 attacagcag ccagacgatc atgcagctac tacatcactt tcttggaaac gtgtaaaagg
2281 atgcaaatct agtgaacaga atggaatgga gcaaaagaca attattttaa taccctctga
2341 tttagcatgt agactgctgg ggcaatcaat ggatgaaagt ggattaccac agctgaccag
2401 ttatgattgt gaagttaatg ctcctataca aggcagcaga aacctactgc agggtgaaga
2461 attactcaga gctttggatc aagttaactg agcttttct taatttcatt ccttttttgg
2521 ac
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(Rupert, et al, 1999)

Conclusion

HIF is a transcription factor found in mammalian cells cultured under reduced oxygen tension that plays an essential role in cellular and systemic homeostatic responses to hypoxia. HIF-1 is a heterodimer composed of an alpha subunit and a beta subunit. The beta subunit has been identified as the aryl hydrocarbon receptor nuclear translocator. HIF plays a critical role in the regulation of hypoxia (Adams et al. 2009). Hypoxia and HIF pathway have been linked to the life development and pathophysiology of numerous diseases. HIF has a potential ability to treat clinical hypoxic-ischemic diseases.

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