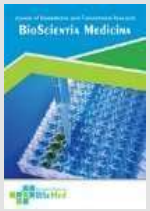
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Role of Hypoxia Inducible Factor (HIF) 1α in the Pathogenesis of Liver Cirrhosis: A Narrative Literature Review

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ARTICLE INFO

Keywords:
Hypoxia-inducible factor
Liver cirrhosis
Pathogenesis
Role

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i4.974

A B S T R A C T

The small changes in oxygen tension that occur during viral hepatitis, metabolic disorders, steatohepatitis, inflammation, and carcinogenesis are sufficient to increase hypoxic response, namely an increase in HIF. HIF is a protein that belongs to the PAS (period circadian protein-aryl hydrocarbon receptor nuclear translocator-single-minded protein) family. HIF regulates the adaptation of cells to oxygen. HIF is a transcription factor containing α and β subunits. The expression of the α subunit is oxygen-dependent, while the β subunit is expressed continuously and independently of oxygen. HIFs regulate various signaling events by binding to specific DNA sequences known as hypoxia response elements (HREs) in target genes, leading to an increase or decrease in their transcription. HIF-1α is a key regulator of hypoxia signaling.

1. Introduction

Liver cirrhosis is the final stage of the process of diffuse progressive liver fibrosis characterized by distortion of liver architecture and the formation of regenerative nodules. Cirrhosis of the liver is the third largest cause of death in patients aged 45-46 years after cardiovascular disease and cancer. Throughout the world, liver cirrhosis is the seventh leading cause of death. In advanced stages, liver cirrhosis can develop into hepatocellular carcinoma. In Southeast Asia, the main causes of liver cirrhosis are hepatitis B and C. The incidence of liver cirrhosis in Indonesia due to hepatitis B ranges from 21.2-46.9%, and hepatitis C ranges from 38.7-73.9%.[1,2]

Currently, there are no pharmacological drugs that are effective in preventing liver fibrosis or can even stop the fibrotic process. Meanwhile, treatment strategies for liver fibrosis are mostly aimed at reducing the causes of fibrosis, including the development of antivirals to inhibit the hepatitis virus. In the final stages, liver transplantation is the only alternative, which is still difficult and expensive. So, it is necessary to identify potential new treatment targets in the management of liver fibrosis. Several studies have been developed using various laboratory markers to become targets for treating liver fibrosis so that liver cirrhosis can be prevented. One of the markers that is currently receiving attention because it is considered the most promising regarding pathogenesis is hypoxia-inducible factor 1α.[3,4]

Hypoxia-inducible factor

The liver has a unique anatomical and functional role that influences its physiology and oxygen homeostasis, where the liver receives highly oxygenated blood through the hepatic artery and less oxygenated blood through the hepatic portal vein. This directional blood flow towards the central vein of the lobule creates a physiologic oxygen gradient, resulting in an oxygen pressure (PO_2) of approximately 60-65 mmHg (8%) in the periportal area to 30-35 mmHg (4%) in the perivenous area of the parenchyma. This oxygen gradient is related to hepatic zonation, a phenomenon in which hepatocytes exhibit distinct functional and structural heterogeneity throughout the parenchyma. The definition of relative terms such as normoxia and hypoxia depends on the normal oxygen tension to which an organ is subjected. The small changes in oxygen tension that occur during viral hepatitis, metabolic disorders, steatohepatitis, inflammation, and carcinogenesis are sufficient to increase hypoxic response, namely an increase in HIF. HIF is a protein that belongs to the PAS (period circadian protein-aryl hydrocarbon receptor nuclear translocator-single-minded protein) family. HIF regulates the adaptation of cells to oxygen. HIF is a transcription factor containing α and β subunits. The expression of the α subunit is oxygen-dependent, while the β subunit is expressed continuously and independently of oxygen. HIFs regulate various signaling events by binding to specific DNA sequences known as hypoxia response elements (HREs) in target genes, leading to an increase or decrease in their transcription. HIF-1α is a key regulator of hypoxia signaling.[5]

There are three α subunits, namely HIF-1α, HIF-2α, and HIF-3α, which accumulate in the cytoplasm and translocate into the nucleus to form heterodimers with the β subunit. After translocation to the nucleus, HIF heterodimers associate with co-activators and bind to hypoxia response elements (HREs) in gene promoters to initiate gene transcription. Hypoxia induces stabilization and translocation of the HIF α subunit and its transcriptional activity by inhibiting the activity of prolyl hydroxylase and the inhibitory factor HIF1. Hypoxia increases the half-life of HIF-1α from 5 minutes to approximately 60 minutes. HIF-1α has 3 hydroxylation sites. 2 parts are found in the prolyl residue in the oxygen-dependent degradation domain (ODDD) and the asparaginyl residue in the C-terminal transactivation domain (C-TAD). The α subunit is destroyed rapidly under normal conditions but stabilizes when hypoxia occurs. The initial stage of destruction of the α subunit is hydroxylation of the proline residue by proline hydroxylase domain enzymes (PHD1, PHD2, or PHD3). Then, von Hippel Lindau protein (pVHL), a component of the tumor suppressor E3 ubiquitin ligase, mediates HIF1α ubiquitination through specific binding to two hydroxylated proline residues, leading to faster degradation of the α subunit via the ubiquitin-proteasome pathway. HIF-1 inhibitory factor (FIH1) and reactive oxygen species (ROS) may also influence HIF-1α stability. FIH1 hydroxylates the asparagine residue (Asn803) of HIF-1α in the C-terminal transactivation domain by blocking HIF binding to the transcriptional coactivator cAMP response element-binding protein (CBP)/p300 and inhibiting HIF-1α transcriptional activation. FIH1 also interacts with pVHL to function as a coinhibitor in suppressing transactivation by recruiting histone deacetylases (HDACs). ROS prevents HIF-1α degradation by blocking PHD activation to inhibit HIF-1α acetylation. HDAC4 and HDAC5 enhance HIF1 transactivation function by increasing HIF-1 release from FIH-1 and association with p300. FIH-1 hydroxylates hARD1/NAA10, a component of N-terminal acetyltransferase (NatA), under normoxia conditions, thereby increasing the binding of pVHL to HIF-1α through acetylation. HIF1α is stabilized by p300 via Lys-709 acetylation, and SIRT2-mediated deacetylation of HIF-1α is critical for HIF-1α destabilization. PHD activity is limited by oxygen availability. In the absence of oxygen, hydroxylation of HIF-1α is also inhibited, causing HIF-1α subunits to stabilize and accumulate in the cytoplasm. The accumulated HIF1α then moves to the nucleus, forms its dimer with HIF-1β (ARNT), and interacts with the

transcriptional coactivator CBP/p300 to form transcription initiation complexes known as hypoxia response elements (HREs) on the promoters of target genes to induce transcription.[6,7]

Genes targeted by HIF-1α

Strong evidence suggests that HIF-1α plays a key role in vascular remodeling under hypoxic conditions. The extensive and cumulative vascular remodeling of arterioles that accompanies chronic hypoxia results in some internal organ fibrosis. HIF1α is involved in producing excessive ECM, which is the cause of fibrosis. Fibrosis is usually characterized by prolonged and/or excessive activation of fibroblasts. Strong and stable expression of HIF-1α was found in fibrotic dermal fibroblasts cultured under hypoxic conditions, 1% oxygen, equivalent to PO_2 values 7 mmHg, which is close to the 10th percentile measured in the involved dermal areas of fibrotic disease patients. Furthermore, increased HIF-1α expression occurred in subcutaneous fibroblasts from healthy skin and fibrotic skin exposed to hypoxic conditions in vitro. Fibroblasts isolated from human arteries also showed remarkable upregulation of HIF-1α under hypoxic conditions. In a more detailed study, HIF-1α was completely translocated from the cytosol to the nucleus in dermal fibroblasts from fibrotic disease patients after exposure to hypoxia. HIF-1α expression is increased in a number of fibrotic diseases, and the overt upregulation of HIF-1α in the skin of naïve SSc patients observed compared with normal skin, further suggests that HIF1α is involved in the pathogenesis of fibrotic diseases, especially in SSc. Moreover, HIF-1α was mainly associated with a subgroup of SSc patients with prominent vascular manifestations. Therefore, HIF-1α inhibition represents a rational strategy for the development of new therapies because effective therapies are not yet available for fibrotic diseases.[8]

HIF-1α and ECM (extracelullar matrix)

Fibrosis is characterized by excessive deposition of ECM in organs or tissues, including various types of collagen, hyaluronic acid, fibronectin, and proteoglycans. HIF-1α contributes to increasing the expression of genes regulating ECM and non-ECM in fibroblasts. HIF-1α induces collagen hydroxylation and normal collagen secretion in hypoxic environments by directly activating the transcription of the collagen enzymes prolyl 4-hydroxylase (P4H) and pyruvate dehydrogenase kinase 1 (Pdk1). HIF-1α deficiency results in impaired collagen secretion in the presence of hypoxia. Similarly, HIF-1α mediates ECM accumulation via NADPH oxidase (NOX). The gene expression underlying fibrosis is in the transforming growth factor β (TGF-β) pathway, and TGF-β is closely involved in ECM induction. HIF-1α is upstream of TGF-β production, and hypoxia-induced TGF-β production requires HIF-1α. This suggests that HIF-1α inhibition reduces TGF-β expression in vivo as well. Epithelial-to-mesenchymal transition (EMT) results in the production of more ECM, including α-smooth muscle actin (α-SMA) and vimentin, and requires HIF-1α expression. Increased HIF-1α expression may enhance fibrogenesis by facilitating EMT. Plasminogen activator inhibitor-1 (PAI-1), found in the ECM and a key inhibitor of fibrinolysis, inhibits proteolytic processes associated with fibrosis. In vivo, hypoxia-induced heterodimers of HIF-1α with HIF-1β bind to the HRE on the PAI-1 promoter and induce PAI-1 expression. Lysyl oxidase (LOX) is important for the normal synthesis of collagen and elastin. LOX is a transcriptional target for the HIF-1α-HIF-1β heterodimer that translocates to the nuclear compartment of fibrogenic cells and is regulated during fibrogenesis. HIF-1α can regulate LOX expression in the accumulation of collagen and other components involved in building and remodeling the ECM. LOX plays a role in HIF-1α-mediated ECM deposition. In addition, connective tissue growth factor (CTGF) increases cell proliferation and ECM production in fibroblasts. Under hypoxic conditions, CTGF induction is directly mediated by HIF-1α-HIF-1β heterodimers that bind HRE-associated CTGF. HIF-1α contributes to persistent pathofibrogenesis in many organs by stimulating excessive ECM production.[9,10]

HIF-1α and vascular remodeling

Vascular remodeling primarily consists of the irregular proliferation of endothelial cells and an increase in the number (hyperplasia) and volume (hypertrophy) of arterial smooth muscle cells (ASMC), resulting in progressive vascular occlusion and chronic hypoxia. High expression of HIF-1α in plexiform endothelial lesions and ASMCs suggests a strong correlation between HIF1α and proliferative vasculopathy. Hyperproliferation of arterial smooth muscle cells is important in vascular remodeling. Transient receptor potential channel (TRPC) 1 is a non-selective cation channel that is permeable to Ca^{2+} ions where the increase in TRPC1 levels mediated by bone morphogenetic protein4 (BMP4) depends on HIF-1α in ASMC. Reduction of voltage-gated K^+ results in membrane depolarization and activation of voltage-dependent Ca^{2+} channels and subsequently increases Ca^{2+} influx. It is also regulated by HIF-1α. Both voltage-gated K^+ (Kv) channels and TRPC1, mediated by HIF-1α, contribute to the increase in cytosolic free Ca^{2+} that is a major trigger of ASMC proliferation. ASMC proliferation may be a consequence of aquaporin 1 being up-regulated as a result of increased cytosolic-free Ca^{2+}. Furthermore, both silencing of TRPC1 with small interfering RNA (siRNA) and TRPC1 knockout impaired hypoxia-induced ASMC proliferation. In addition, hypoxia induces the expression of Na^+/H^+ exchanger isoform 1 (NHE1) and alkalinization of intracellular pH regulated by HIF-1α. Both activation of the Na^+/H^+ exchanger and alkalinization of intracellular pH are required for ASMC proliferation. Additionally, HIF-1α regulates mir-322 expression, leading to ASMC proliferative response via BMPR1a and smad5. Similarly, Platelet-derived growth factor bb (PDGFbb) can induce ASMC proliferation through excessive deposition of hyaluronic acid (HA) in smooth muscle cells). The possible mechanism is through tyrosine 31 (Y31) and 118 (Y118) phosphorylation of paxillin, which is attenuated by HIF-1α knockdown.[11]

HIF-1α is also involved in endothelial cell proliferation. Abnormally proliferating endothelial cells are characterized by a low number of mitochondria. The reduced number of mitochondria in abnormally proliferating endothelial cells is caused by increased expression of HIF-1α. HIF-1α-inducible factors include hepatocyte growth factor (HGF) and stromal-derived factor-1a (SDF-1a). Hematopoietic endothelial stem cells, $CD34^+$ $CD133^+$ hemangioblasts, can promote vascular remodeling. Local production of chemoattractants, such as SDF-1α and HGF, by the injured endothelium can recruit large numbers of $CD34^+$ $CD133^+$ hemangioblasts to the endothelial site. Both signal transducer and activator of transcription (STAT) 3 and chloride intracellular channel 4 (CLIC4) contribute to EC hyperproliferative pathology having an important role in increasing HIF-1α in vascular fibrosis.[12]

HIF-1α in alcoholic liver disease

Alcohol-induced liver damage activates HIF-1α mRNA expression, and interleukin (IL)-8 worsens alcoholic fatty liver in mice via the Akt/HIF-1α pathway. HIF-1α mRNA levels in liver tissue of ALD patients and mice were increased compared with the control group. Lipid accumulation in liver cells due to alcohol consumption involves activation of HIF-1α. There are studies that found that oroxylin A reduces the accumulation of lipid droplets associated with lipid metabolism regulatory genes and significantly inhibits nuclear translocation of HIF-1α in cells exposed to ethanol. Where oroxylin A prevents and treats hepatic steatosis caused by alcohol by inhibiting HIF-1α. In addition, vitamin C reduced HIF-1α protein expression levels and lipid accumulation.[13]

HIF-1α in NAFLD (non-alcoholic fatty liver disease)

HIF-1α-induced expression of lipin1 prevents abnormal lipid accumulation by inhibiting peroxisomal fatty acid oxidation. HIF-1 regulates lipid metabolism, specifically in the liver, by detecting the cellular microenvironment under various conditions. Insertion of HIF-1α exacerbates NAFLD in vitro by inhibiting PPAR-α/ANGPTL4 signaling. Another study using HepG2 cells also reported a protective effect of

HIF-1α expression against fatty acid-induced toxicity. Regardless, many studies have shown that HIF-1 in hepatocytes promotes liver fibrosis in NAFLD, mainly by activating the PTEN/p65 signaling pathway. By inhibiting Nrf2-mediated oxidative stress and inhibiting the expression of various fibrosis factors through the miR-122/HIF1α signaling pathway, isochlorogenic acid B (ICAB) has a significant protective effect against fibrosis in non-alcoholic steatohepatitis (NASH). In addition, HIF-2α is also an important regulator of hepatic lipid metabolism. HIF-2α promotes the development of NAFLD by triggering the release of serum-rich glycoproteins from liver cells. During obesity, activation of intestinal HIF-2α can lead to liver cirrhosis.[14]

HIF-1α in hepatitis virus

Several studies have elucidated the role of HIF-1α in the pathogenesis of viral hepatitis, especially hepatitis B and C. Hepatitis B virus (HBV) encodes a viral tumor transactivator protein called protein X (HBx), which promotes extracellular matrix modification through the HIF/LOX pathway in cancer liver, and HBx mutations affect HIF-1α activation in HCC to varying degrees. Direct interaction of HBx with the bHLH/PAS domain of HIF-1α reduces pVHL binding to HIF-1α and prevents ubiquitin-dependent degradation of HIF-1α. HBx can also induce angiogenesis by stabilizing HIF-1α. Previous studies showed that hepatitis C virus (HCV) infection increases autotaxin protein expression through hypoxia-inducible transcription factors and provides an environment in the liver that promotes fibrosis and liver injury. Additionally, HCV-associated mitochondrial dysfunction facilitates HIF-1α-mediated glycolytic adaptation. HCV glycoproteins disrupt tight junctions and adhesion connexins and promote HCC migration and epithelial-to-mesenchymal transition (EMT) by stabilizing HIF-1α.[15]

Potential therapeutic value related to HIF-1α

Systemic inactivation of 4-hydroxylase 2, a product of HIF, may prevent alcohol-induced fatty liver disease. PHD inhibitors act as stabilizers of HIFs in vivo. JTZ-951 inhibits PHD, which can reduce liver disease in mice fed a high-fat diet. In HCC, VEGF intervention inhibits hypoxia-induced HIF-1α, preventing resistance to the drug. Several drugs targeted at HIF are progressing through clinical trials. EZN-2968, an antisense oligonucleotide inhibitor of HIF-1α, is used primarily in the treatment of HCC, and clinical trials have been completed (NCT01120288). Additionally, the PHD inhibitor ethyl 3,4-dihydroxybenzoate has been shown to activate HIF-1α and its target HMOX1, thereby inhibiting mitochondrial permeability transition and reducing IR-induced liver damage. Severe liver fibrosis is associated with sustained HIF-1α accumulation caused by chronic or prolonged hypoxia in the disease, suggesting that HIF-1α may be a promising target for novel treatments in fibrosis-related diseases, in this case, liver cirrhosis. As a potential therapeutic target, HIF-1α provides a new perspective for the treatment of various liver diseases, especially in the process of fibrogenesis before liver cirrhosis occurs.[16-18]

2. Conclusion

Liver cirrhosis is the final stage of the process of diffuse progressive liver fibrosis characterized by distortion of liver architecture and the formation of regenerative nodules. In Southeast Asia, the main causes of liver cirrhosis are hepatitis B and C. The incidence of liver cirrhosis in Indonesia due to hepatitis B ranges from 21.2-46.9%, and hepatitis C ranges from 38.7-73.9%. Meanwhile, treatment strategies for liver fibrosis are mostly aimed at reducing the causes of fibrosis, including the development of antivirals to inhibit the hepatitis virus. In the final stages, liver transplantation is the only alternative, which is still difficult and expensive. Severe liver fibrosis is associated with sustained accumulation of HIF-1α, caused by chronic or prolonged hypoxia in the disease, suggesting that HIF-1α may be a promising target for new treatments in liver cirrhosis.

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