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Hypoxia and fatty liver

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Abstract

The liver is a central organ that metabolizes excessive nutrients for storage in the form of glycogen and lipids and supplies energy-producing substrates to the peripheral tissues to maintain their function, even under starved conditions. These processes require a considerable amount of oxygen, which causes a steep oxygen gradient throughout the hepatic lobules. Alcohol consumption and/or excessive food intake can alter the hepatic metabolic balance drastically, which can precipitate fatty liver disease, a major cause of chronic liver diseases worldwide, ranging from simple steatosis, through steatohepatitis and hepatic fibrosis, to liver cirrhosis. Altered hepatic metabolism and tissue remodeling in fatty liver disease further disrupt hepatic oxygen homeostasis, resulting in severe liver hypoxia. As master regulators of adaptive responses to hypoxic stress, hypoxia-inducible factors (HIFs) modulate various cellular and organ functions, including erythropoiesis, angiogenesis, metabolic demand, and cell survival, by acti-

vating their target genes during fetal development and also in many disease conditions such as cancer, heart failure, and diabetes. In the past decade, it has become clear that HIFs serve as key factors in the regulation of lipid metabolism and fatty liver formation. This review discusses the molecular mechanisms by which hypoxia and HIFs regulate lipid metabolism in the development and progression of fatty liver disease.

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Key words: Hypoxia; Fatty liver disease; Hypoxia-inducible factor; Lipid metabolism; Obstructive sleep apnea

Core tip: Hypoxia occurs in the development and progression of fatty liver disease. Recent reports have shed light on the pathological significance of hypoxia inducible factors (HIFs), master regulators of the hypoxic response, with regard to their regulation of lipid metabolism in context- and isoform-dependent manners. In this review, we summarize recent findings on the various roles of HIF-dependent regulation in fatty liver disease.

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INTRODUCTION

Fatty liver disease (FLD), whether it is alcoholic (AFLD) or non-alcoholic (NAFLD), is a major cause of chronic liver disease worldwide^[1,2]. FLD initially begins with simple hepatic steatosis but can irreversibly progress to steatohepatitis, fibrosis, cirrhosis, or hepatocellular carcinoma. Hepatic steatosis was initially thought to be a benign state of FLD, but recent studies have revealed that

fat accumulation in the liver clearly predisposes the organ to injury. NAFLD is also highly associated with obesity and diabetes, and insulin resistance is evident in livers that accumulate fat, leading to impaired glucose tolerance^[3,4]. Thus, hepatic steatosis is a key step in the development and progression of subsequent pathology. However, pharmacological approaches have not successfully treated hepatic steatosis; therefore, a greater understanding of the mechanisms underlying the disease is required for the development of therapeutics.

In hepatic steatosis, five major pathways determine liver fat volume: (1) the uptake of free fatty acids (FAs) and triglycerides (TG) from the diet; (2) *de novo* lipogenesis; (3) FA oxidation; (4) the export of TG as very low-density lipoprotein (VLDL) into the bloodstream; and (5) the flux of FAs released from adipose tissue through lipolysis. In the case of AFLD, increased *de novo* lipogenesis and impaired FA oxidation in the liver are major contributors to lipid accumulation^[5]. In contrast, in patients with NAFLD, adipose tissue lipolysis and hepatic *de novo* lipogenesis accounts for 59% and 26% of fat accumulation in the liver, respectively, with lower amounts derived from the diet (15%), emphasizing the importance of the former two pathways^[6]. However, lipid disposal *via* β -oxidation and VLDL formation is only slightly affected^[7]. Thus, various pathways related to hepatic lipid metabolism are implicated in the development of hepatic steatosis.

To date, studies in humans and rodents have revealed several major regulators of lipid metabolism. The sterol response element binding protein (SREBP) is a transcription factor that controls *de novo* lipogenesis^[8,9]. SREBP has three isoforms: SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1a and SREBP-1c are splice variants, and the liver predominantly expresses the SREBP-1c isoform together with SREBP-2. SREBP-1 is mainly involved in *de novo* FA and TG synthesis, whereas SREBP-2 controls cholesterol homeostasis. SREBP-1c promotes FA synthesis by inducing the expression of lipogenic genes such as fatty acid synthase (FAS), acyl-CoA carboxylase (ACC), and stearoyl-CoA desaturase (SCD)-1. These lipogenic genes have been reported to be associated with the development of FLD^[5,7,10,11], whereas the importance of SCD-1 in FLD is still controversial^[12-15]. Peroxisome proliferator-activated receptors (PPARs) also act as crucial regulators of FA metabolism^[16]. The PPAR subfamily consists of PPAR α , PPAR β/δ , and PPAR γ . PPARs heterodimerize with retinoid X receptor (RXR) α , and bind to peroxisome proliferator hormone response elements (PPREs) of target genes. The PPAR α /RXR α complex promotes the expression of genes involved in FA oxidation, such as long-chain acyl CoA dehydrogenase (LCAD), medium-chain acyl CoA dehydrogenase (MCAD), and carnitine palmitoyl-CoA transferase-1 (CPT-1). In AFLD, the expression of these genes is well known to be reduced, which leads to impaired FA oxidation^[1,5,10,11]. PPAR γ is reportedly upregulated in patients with NAFLD and promotes lipogenesis in the liver^[11,17].

However, recent reports found that PPAR γ agonists have beneficial effects on NAFLD by improving peripheral insulin sensitivity and may reduce hepatic fat content and fibrotic scarring^[18-21]. Furthermore, the carbohydrate response element binding protein (ChREBP) and X-box binding protein (XBP)-1 are also involved in the regulation of hepatic lipid metabolism^[4,7,22,23].

Although *in vitro* and *in vivo* studies have elucidated the various signaling pathways that regulate lipid metabolism in FLD, little is known regarding upstream stimuli. Historically, in AFLD, hypoxia has been reported in the pericentral zone of hepatic lobules^[24-26], and it has also been suggested that an aberrant oxygen gradient can induce hepatic steatosis and subsequent disorders^[27]. Recent studies have demonstrated that hypoxia is also observed in NAFLD^[28]. In this review, we discuss the role of hypoxia in FLD, focusing on hypoxia-inducible factors (HIFs), which regulate the cellular and tissue adaptive responses to hypoxia, and the association between hypoxia and lipid metabolism.

HYPOXIA INDUCIBLE FACTORS

Aerobic organisms have evolved by using an innovative energy-producing system, mitochondrial oxidative phosphorylation, which requires oxygen as a final electron acceptor. Oxidative phosphorylation generates energy far more efficiently than anaerobic glycolysis, which was a major factor in the evolutionary progression to larger, multicellular organisms with multifunctional cells and organs. Oxygen, in turn, is required for homeostasis and survival of these organisms. However, oxygen deprivation occurs during development and in the cornea and bone marrow where oxygen supply is quite limited. Thus, cells need to activate specific molecular programs to overcome hypoxic challenges in these conditions.

Hypoxia inducible factors (HIFs) play central roles in the cellular and tissue adaptation to hypoxia. HIF was first discovered as a transcriptional regulator of erythropoietin, which is a hematopoietic regulator protein expressed predominantly in the kidney and, to a lesser extent, in the liver^[29]. HIFs consist of an oxygen-sensitive α subunit (HIF α) and a constitutively expressed β -subunit [aryl hydrocarbon receptor nuclear translocator (ARNT), HIF-1 β]^[30]. Three isoforms of HIF α subunits (HIF-1 α , HIF-2 α , and HIF-3 α) have been identified. Both HIF-1 and HIF-2 exert overlapping roles in the regulation of erythropoiesis, angiogenesis, cell proliferation, and apoptosis, and each HIF regulates a unique subset of target genes (Table 1)^[31-34]. HIF-1 upregulates almost all glycolytic enzymes, including hexokinase (HK) 1/2, phosphofructokinase, and pyruvate kinase (PK), especially in solid tumors and stem cells^[33]. HIF-2 is an important inducer of anti-oxidant genes, including superoxide dismutase (SOD)-2^[35]. HIF-3 α lacks a transactivation domain and therefore is considered to be transcriptionally inactive. However, a splice variant of HIF-3 α , named inhibitory of PAS domain protein, interacts directly with HIF-1 α

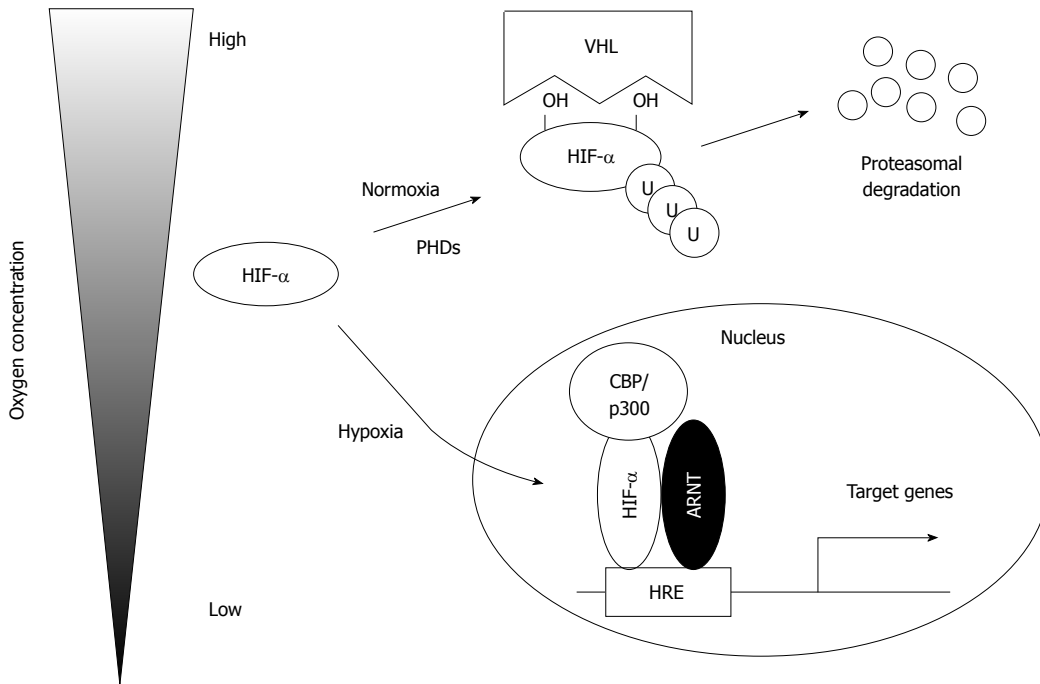


Figure 1 Regulation of hypoxia-inducible factors under normal and low oxygen concentrations. Under normoxia conditions, hypoxia-inducible factor α (HIF- α) is hydroxylated at specific proline residues in an oxygen-dependent manner, ubiquitinated by von Hippel-Lindau (VHL) protein (pVHL), and, subsequently, degraded by the proteasome. Under hypoxia conditions, stabilized HIF- α translocates to the nucleus and binds aryl hydrocarbon receptor nuclear translocator (ARNT) to activate its target genes. PHD: Prolyl hydroxylase domain; HRE: Hypoxia-response element.

Table 1 Downstream target genes of hypoxia-inducible factor isoforms

Hypoxia inducible gene	Function	HIF-1 target gene	HIF-2 target gene
Oxygen supply			
<i>Erythropoietin</i>	Erythropoiesis	+	+
<i>VEGF</i>	Angiogenesis	+	+
<i>iNOS</i>	Vasodilation	+	-
<i>PAI-1</i>	Blood flow	+	+
<i>ANGPTL2</i>	Vascular remodeling	-	+
Cellular metabolism			
<i>HK1/2</i>	Glycolysis	+	-
<i>PGK1</i>	Glycolysis	+	-
<i>LDHA</i>	Glycolysis	+	-
<i>GLUT-1</i>	Glucose transporter	+	+
<i>ADRP/ADFP</i>	Lipid metabolism	+	+
<i>DEC1/2</i>	Lipid metabolism	+	-
<i>ANGPTL3</i>	Lipid metabolism	+	+
Cell cycle			
<i>TGFα</i>	Growth factor	-	+
<i>Cyclin D1</i>	Cell cycle progression	-	+
<i>BNIP3</i>	Apoptosis	+	-
Oxidative stress			
<i>HO-1</i>	Anti-oxidant	+	-
<i>SOD1/2</i>	Anti-oxidant		+
<i>Catalase</i>	Anti-oxidant		+
<i>GPX1</i>	Anti-oxidant		+

HIF: Hypoxia-inducible factor.

and prevents its binding to DNA, which inactivates its ability to induce downstream targets^[36].

The stability of HIF α subunits is strictly regulated by oxygen concentration (Figure 1)^[31]. In the presence

of oxygen, HIF α subunits are hydroxylated at specific proline residues by prolyl hydroxylase domain proteins (PHD1, PHD2, and PHD3) in an oxygen-dependent manner^[37,38]. HIF α subunits are subsequently recognized and targeted for degradation by the von Hippel-Lindau protein, which has E3 ubiquitin ligase activity^[37,39]. However, under hypoxic conditions, HIF α subunits escape from proteasomal degradation and translocate to the nucleus to heterodimerize with ARNT to exert their transcriptional activity with its cofactor CREB-binding protein (CBP)/p300. In addition, factor-inhibiting HIF (FIH) also hydroxylates the asparagine residue of HIF α , which prevents the interaction between HIF α and CBP/p300, leading to suppressed transcriptional activity^[40].

Hypoxia is associated with the progression of various diseases, such as cardiovascular disease, cancer, and inflammatory diseases^[41-43], and is also present in rodent models of liver disease^[44]. In fatty liver disease, the “hypermetabolic state” may be a driving force for lobular hypoxia. Chronic ethanol consumption promotes the expression of cytochrome P450 2E1 (CYP2E1) in the pericentral zone of hepatic lobules, which metabolizes ethanol and acetaldehyde using oxygen as a co-substrate^[45,46]. In addition, hepatocytes reoxidize excessive reducing equivalents of NADH produced by oxidation of ethanol *via* alcohol dehydrogenase and aldehyde dehydrogenase in mitochondria^[47-49]. Indeed, oxygen consumption has been reported to increase in the liver of alcohol-fed rats, leading to a reduction in the oxygen content of hepatic venous blood^[50]. In NAFLD, the excessive intake of foods containing lipids may promote β -oxidation of FA,

which requires a considerable amount of oxygen^[51,52]. Constriction of hepatic sinusoids and/or prevention of substrate exchange due to swelling of hepatocytes and accumulation of a fibrotic scar may trigger the development of hypoxia in NAFLD^[53]. In addition, reactive oxygen species (ROS) are produced in the pathogenesis of liver disease, which leads to the stabilization of HIF α subunits by inhibition of PHDs. Indeed, HIF expression is increased in liver diseases, including AFLD and NAFLD^[54-60]. These observations imply that HIFs are involved in the development of fatty liver and the pathological sequelae.

ROLE OF HIFS IN FATTY LIVER

Hypoxia is tightly associated with lipid homeostasis, as both *in vitro* and *in vivo* studies reveal that ischemic and hypoxic stress increases cellular lipid deposition^[61-64]. Hypoxia also upregulates genes involved in lipogenesis, lipid uptake, and lipid droplet formation^[65-67]. In addition, several studies have implicated the role of HIFs in lipid homeostasis. In von hippel-lindau (VHL)-deficient renal cell carcinomas that highly express both HIF-1 α and HIF-2 α , neutral lipids accumulate, which makes the cells appear clear^[68]. Moreover, heterozygous deletion of VHL or liver-specific inactivation of VHL results in hepatocellular steatosis^[69,70].

These observations have encouraged researchers to investigate whether HIFs play a role in lipid metabolism in the liver. Rankin *et al.*^[71] demonstrated that HIF-2 functions as an important regulator of hepatic lipid metabolism, as it impairs FA β -oxidation and increases lipid storage capacity. In VHL-deficient mice, deletion of HIF-2 α results in reduced lipid accumulation, whereas this effect is not observed in HIF-1 α -deleted mice. In VHL-null animals, HIF-2 reduces the expression of genes involved in β -oxidation (Acs11, Cpt1, Crot) and promotes lipid droplet formation by inducing the expression of a lipid droplet associated protein (Adfp). A subsequent investigation using Adeno-Cre mediated liver-specific disruption of VHL suggested that downregulation of β -oxidation in VHL-deficient mice may be attributable to impaired mitochondrial respiration, which is due in part to a decrease in the Fe-S cluster assembly protein levels, IscU1/2^[72]. In addition, tamoxifen-induced temporal disruption of VHL in the liver results in increased hepatic lipid accumulation, which is reversed by the simultaneous disruption of HIF-2 α but not HIF-1 α ^[73]. Interestingly, the mechanisms involved in lipid accumulation appear to differ depending on the time after tamoxifen treatment. The expression of genes involved in FA synthesis (Srebp-1c and Fasn) increases 3 d post-treatment, but it is significantly suppressed by 14 d. Genes involved in β -oxidation (Cpt1a, Cpt2, Acox1, and Ppara) are also reduced 14 d post-treatment. Moreover, angiopoietin-like 3 (Angptl3), an endogenous lipoprotein lipase inhibitor, is induced after disruption of VHL and is strongly upregulated by HIF-2. The importance of HIF-2 in lipid metabolism is further confirmed in Phd2/3-double knockout mice^[74]. Although

the majority of studies indicate that HIF-2 promotes fat accumulation, some reports indicate the contrary. Germ-line deletion of HIF-2 α paradoxically results in severe steatosis due to impaired β -oxidation through ROS-mediated mitochondrial dysfunction^[35]. In addition, activation of HIF-2 in hepatocytes only has a minimal effect on hepatic lipid accumulation^[75]. Simultaneous activation of HIF-1 and HIF-2 results in severe steatosis, suggesting that the regulation of lipid metabolism *via* HIFs may be more complex than originally thought.

On the other hand, recent studies have also demonstrated the physiological and pathological effect of HIF-1 levels in the fatty liver. Using a liver-specific HIF-1 α -deleted mouse model, we found that HIF-1 α prevents excessive lipid accumulation by suppressing the SREBP-1c-dependent lipogenic pathway in the alcoholic fatty liver^[59]. Chronic ethanol administration results in hypoxia in the pericentral zone of hepatic lobules and HIF-1 α is correspondingly expressed in this region. HIF-1 enhances the expression of a circadian helix-loop-helix (HLH) transcription factor, differentiated embryochondrocyte 1 (DEC1), which reduces the expression of SREBP-1c and its downstream lipogenic genes. These findings are in a good agreement with previous reports that HIF-1 induces transcriptional activation of DEC1, which in turn represses SREBP-1c-mediated gene expression by competing with other HLH transcription factors to bind the E-box of the SREBP promoter and/or by directly interacting with the SREBP-1c protein^[76,77]. In addition, the administration of DMOG, a pharmacological inhibitor of PHDs, reduces ethanol-induced lipid accumulation in the liver in a HIF-1-dependent manner. It has been consistently shown that the ablation of ARNT promotes lipogenic gene expression (SCD-1, FAS) in the liver, which suggests that HIF-1 prevents lipid synthesis^[78]. Protective effects of HIF-1 activation against fatty liver disease are further supported by a recent report suggesting that HIF-1 promotes mitochondrial β -oxidation and prevents lipid peroxidation by regulating mitochondrial biogenesis in the liver of high-fat diet (HFD)-fed animals^[58]. Collectively, these results indicate that HIF-1 serves as a protective factor against the development of fatty liver and that pharmacological prolyl hydroxylase inhibitors may lead to the development of therapies for the disease. In contrast, Nath *et al.*^[60] found that HIF-1 is critical for the development of hepatic steatosis. The authors demonstrated that a combined treatment of ethanol and an inflammatory stimulus (LPS) aggravates hepatic steatosis through induction of HIF-1 *via* monocyte chemoattractant protein1 (MCP1). It is not clear why opposing results are obtained from these two studies. One possible explanation is that the presence of inflammation may rewire the HIF-1 pathway, which leads to a different gene expression profile compared to that observed in simple steatosis. In support of this hypothesis, a combination of hypoxia and proinflammatory stimuli strongly enhances the expression of HIF-1 due to a positive feedback loop mechanism between HIF-1 and nuclear factor κ B (NF κ B), which may mimic the overex-

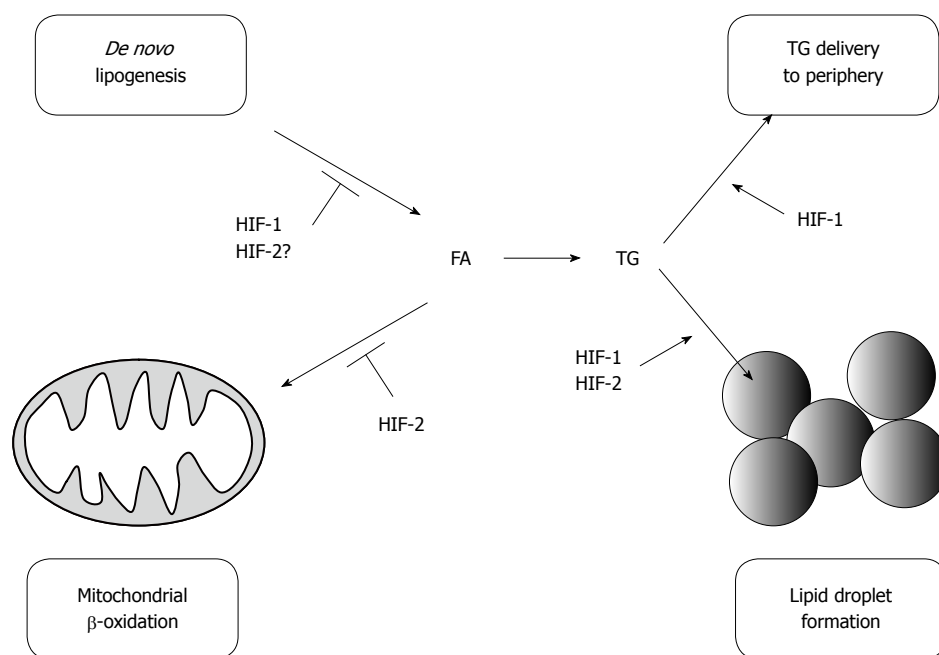


Figure 2 Hypoxia-inducible factors regulate hepatic lipid metabolism. HIF-2 promotes lipid accumulation mainly by preventing mitochondrial β -oxidation and promoting lipid droplet formation. In contrast, HIF-1 suppresses lipid accumulation by inhibiting *de novo* lipogenesis. HIF-1 also promotes lipid storage and lipid export. HIF: Hypoxia-inducible factor; FA: Fatty acids; TG: Triglycerides.

pression studies of HIF-1 α ^[79-82]. In addition, it is implicated that inflammation promotes lipid accumulation by the tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) pathways^[83-86].

In addition to the development of fatty liver, HIFs also play a critical role in the pathological sequelae, especially in hepatic fibrosis. Consistent observations suggest that angiogenesis is tightly associated with fibrogenesis in experimental models and human diseases. In fact, vascular endothelial growth factor (VEGF) is now a potential target for the treatment of fibrosis^[87-89]. Hypoxic areas are present in the fibrotic liver and co-localize with VEGF expression in endothelial cells, hepatocytes, and hepatic stellate cells (HSCs)^[90-92]. In addition, a clinical study revealed that in the human cirrhotic liver, heme oxygenase-1, a well-known target of HIF-1, and HIF-2 α are detected in the hepatocytes of regenerative nodules and cells of fibrotic septa^[92]. In agreement with these reports, Moon *et al.*^[93] demonstrated that bile duct ligation in mice induces hypoxia and HIF-1 α activation. Deletion of HIF-1 α attenuates fibrogenesis due to the reduced expression of profibrogenic genes, such as platelet-derived growth factor (PDGF)-A, PDGF-B, and plasminogen activator inhibitor-1. Considering the lack of transcriptional activation of PDGFs in the hepatocytes of the fibrotic liver, non-parenchymal cells, presumably macrophages and/or stellate cells, are major contributors to hepatic fibrosis^[94-96]. Consistent with this hypothesis, ARNT in myeloid cells contributes to the development of hepatic fibrogenesis *via* induction of PDGF-B expression^[97]. In addition, another report found that overexpression of HIF-2 but not HIF-1 in hepatocytes promotes inflammation and fibrosis in the liver^[73]. Although, these *in vivo*

studies have provided evidence that HIFs are important regulators of hepatic fibrosis, the role of each HIF isoform in each cell type is not fully understood, particularly in the context of NAFLD. It is worth noting that macrophages have opposing roles during the progression of and recovery from hepatic fibrosis^[98]. It is hypothesized that alternatively activated macrophages (AAMs) promote fibrosis by inducing profibrogenic factors, while classically activated macrophages (CAMs) mediate recovery responses by secreting matrix metalloproteinases and/or removing fibrillar collagen^[99]. In addition, CAMs and AAMs predominantly express HIF-1 α and HIF-2 α , respectively^[100]. These observations suggest that HIF-1 and HIF-2 in macrophages may have different roles during fibrosis development.

Overall, the regulation of lipid metabolism by HIFs is complex (Figure 2), and genetic and environmental factors may affect its role in the pathogenesis of fatty liver. The involvement of DEC and ChREBP in the HIF-1 pathway suggests that lifestyle and diet may affect HIF-1-mediated lipid metabolism *via* lipogenic transcription factors, such as SREBP-1c and PPAR γ ^[76,77,101]. In addition, the role of different HIF isoforms in various cell types during the progression of NAFLD needs to be elucidated. Further studies are required to identify the functional interactions between HIFs and other factors that produce mixed phenotypes observed in FLD.

OBSTRUCTIVE SLEEP APNEA AND FATTY LIVER

Obstructive sleep apnea (OSA) is another risk factor for

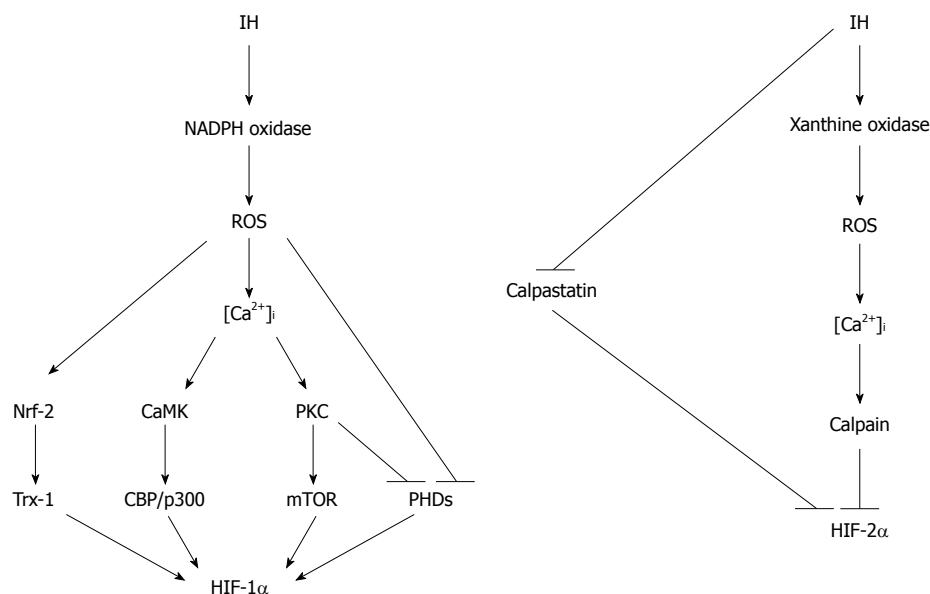


Figure 3 Distinct regulations of hypoxia-inducible factor-1 α and hypoxia-inducible factor-2 α under intermittent hypoxia conditions. ROS and Ca^{2+} play crucial roles in the regulation of HIF activity in response to intermittent hypoxia, which results in the activation of HIF-1 and suppression of HIF-2. IH: Intermittent hypoxia; OSA: Obstructive sleep apnea; NADPH: Nicotinamide adenine dinucleotide phosphate; PKC: Protein kinase C; mTOR: Mammalian target of rapamycin; CBP: CREB-binding protein; PHD: Prolyl hydroxylase domain; HIF: Hypoxia-inducible factor.

the development of NAFLD. OSA is an obstruction of the upper airway and is associated with intermittent hypoxia (IH), temporal deprivation of oxygen from the blood^[102]. Studies of human OSA have revealed an association between OSA and NAFLD. Independent of the presence of obesity, IH induces insulin resistance, liver injury, and fibrosis, and the effects are more severe in obese patients^[103-107]. While the presence of hepatic steatosis and inflammation in lean patients with OSA was not conclusively determined in these studies, other clinical studies have demonstrated that a combination of OSA and obesity promotes excessive fat accumulation and progression of NAFLD to non-alcoholic steatohepatitis (NASH)^[108,109]. Recently, an important meta-analysis of 11 clinical studies with 404 controls and 668 OSA patients was conducted, clarifying that OSA is associated with liver injury, fatty liver and fibrosis but not inflammation^[110]. To investigate the role of OSA in the development of disease, Fletcher *et al*^[111] first established a rodent model of IH, in which N_2 or air is repeatedly infused into a chamber, mimicking the abnormal fluctuation of oxyhemoglobin saturation observed in OSA patients. This model has been used to elucidate the mechanism(s) by which IH affects lipid metabolism in the fatty liver. Short-term exposure to IH in lean mice induces hepatic steatosis and dyslipidemia through SREBP-1c and its downstream target SCD-1^[112], whereas long-term exposure abolishes this effect^[113]. In contrast, long-term IH exposure increases lipid accumulation in the liver of leptin-deficient mice (*ob/ob*), which upregulates lipogenic genes such as SREBP-1, SCD-1, and glycerol 3-phosphate acyltransferase^[114]. Furthermore, a combination of high fat diet-induced obesity and long-term IH exacerbates hepatic steatosis and inflammation^[115]. Overall, these ob-

servations suggest that long-term IH better mimics human OSA in NAFLD.

IH and chronic hypoxia control the stability of HIF proteins *via* different mechanisms (Figure 3). In the case of HIF-1 α , IH induces ROS production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which then increases Ca^{2+} concentration in the cytoplasm^[116]. This increase in Ca^{2+} activates protein kinase C, which in turn inactivates PHDs and stimulates translation of HIF-1 α by activating mammalian target of rapamycin. Ca^{2+} also activates calmodulin kinase, which enhances transcriptional activity of HIF-1 by phosphorylating CBP/p300^[117]. In addition, ROS inhibit the activity of PHDs, independent of Ca^{2+} concentration, which leads to reduced prolyl hydroxylation of HIF-1 α ^[116]. Moreover, ROS also induce the expression of thioredoxin 1 *via* nuclear factor erythroid 2-related factor 2, which further augments HIF-1 signaling^[118]. In contrast, Ca^{2+} signaling activates calpain protease, which in turn degrades HIF-2 α ^[119]. IH also reduces the expression of calpastatin, which serves as an inhibitor of calpain. Moreover, a recent study found that xanthine oxidase, but not NADPH oxidase, is required for ROS-mediated HIF-2 α degradation^[120]. These results clearly suggest that IH promotes the expression of HIF-1 α , while destabilizing HIF-2 α .

HIFs also serve as central regulators in the development of NAFLD in OSA. Li *et al*^[121] demonstrated that the heterozygous deletion of HIF-1 α in mice reduces serum and hepatic TG contents. HIF-1 induces the expression of SREBP cleavage activation protein in hepatocytes, which escorts SREBP from the ER to the Golgi apparatus and triggers SREBP cleavage. The subsequent accumulation of active SREBP fragments in the nucleus

results in SCD-1 up-regulation. Thus, IH causes hepatic steatosis and hyperlipidemia presumably through the induction of HIF-1 α in the liver. However, neuronal or inter-organ effects must be considered to interpret the mechanisms involved in NAFLD development of OSA. In fact, HIF-1 in the carotid body regulates systemic responses to IH by activating the sympathetic nerve system (SNS), which in turn stimulates adipose tissue lipolysis^[122], suggesting that SNS affects hepatic lipid content. In addition, HIF-1 prevents the secretion of adiponectin from adipose tissue, which suppresses *de novo* lipogenesis in the liver^[123-125]. Therefore, the extent to which HIF-1 in the liver contributes to serum and hepatic lipid contents during IH remains to be determined.

CONCLUSION

Hypoxia is associated with the development of fatty liver, and it is now clear that hypoxia-inducible transcription factors regulate lipid metabolism in hepatocytes. OSA is an independent risk factor for developing NAFLD. Obesity and OSA synergistically accelerate tissue hypoxia, which further leads to the development of severe hepatic steatosis and inflammation. In addition to the imbalance between oxygen supply and demand, other factors such as inflammation and nutrients as well as inter-organ metabolic and signaling crosstalk must be considered to interpret the hypoxic response during fatty liver development. In addition, each HIF target gene has a unique optimal dose of HIFs for their transcription, and the context-dependent regulation of this process is a major contributor to disease outcome. Therefore, the manipulation of HIF activity may be a desirable therapeutic target for the treatment of fatty liver.

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