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Chapter 1

The Multifaceted Role of Hypoxia-Inducible Factor 1 (HIF1) in Lipid Metabolism

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Abstract

Hypoxia-inducible factor 1 (HIF1) is a master transcription factor and regulates expression of a large number of genes involving many aspects of biology. In addition to HIF1's roles in glucose metabolism and angiogenesis, numerous studies have revealed an emerging role of HIF1 in controlling lipid homeostasis. In this chapter, we discuss that lipid accumulation is related to HIF1's activity in several diseases and the growing evidence demonstrating the functional importance of HIF1 in controlling lipid metabolism. The functions include lipid uptake and trafficking, fatty acid metabolism, sterol metabolism, triacylglycerol synthesis, phospholipid metabolism, lipid droplet biogenesis, and lipid signaling. Defining the role of HIF1 in lipid metabolism is crucial to understand the pathophysiology of lipid in disease and may help us to identify additional target sites for drug development. This review would shed light on our understanding of the critical role of HIF1 in lipid metabolism.

Keywords: hypoxia-inducible factor 1, lipid accumulation, lipid metabolism

1. Introduction

Hypoxia has been identified as a common symptom in many diseases, such as cancer [1, 2], obesity [3], atherosclerosis [4], and ischemic heart disease (IHD) [5]. Adaptation to hypoxia involves hypoxia-inducible factor 1 (HIF1) and requires reprogramming of essential elements of cellular metabolism [6]. HIF1 was described about 20 years ago [7]. It is a heterodimeric transcription factor that is composed of an oxygen-regulated HIF1α subunit and a constitutively expressed HIF1β subunit [7, 8]. HIF1α is mainly regulated by protein degradation. Under normoxic conditions, HIF1α is subjected to oxygen-dependent hydroxylation by three

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prolyl hydroxylase domain proteins (PHD1–3) on two proline residues in the oxygen-dependent degradation (ODD) domain [9]. The prolyl-hydroxylated HIF1*α* is targeted for degradation by the tumor suppressor protein von Hippel-Lindau (VHL), an E3 ubiquitin-protein ligase [10, 11]. HIF1*α* is also regulated in an oxygen-dependent manner by factor inhibiting HIF1 (FIH1) [12, 13]. In this case, FIH1 mediates the hydroxylation of an asparagine residue in the C-terminal trans-activation domain, which prevents the binding of HIF1*α* with coactivators p300 and CBP [13–15]. Hydroxylation of proline and asparagine is inhibited under hypoxic conditions causing HIF1*α* to rapidly accumulate [12, 13]. HIF1*α* subsequently heterodimerizes with HIF1β, and the complex binds to hypoxic responsive elements (HREs) within the promoter regions of target genes, and allows for recruitment of coactivators and activation of transcription [16]. In addition to hypoxia, HIF1 accumulation can also be induced by growth-factor stimulation, gene mutations, and intermediate metabolites [17] (**Figure 1**).

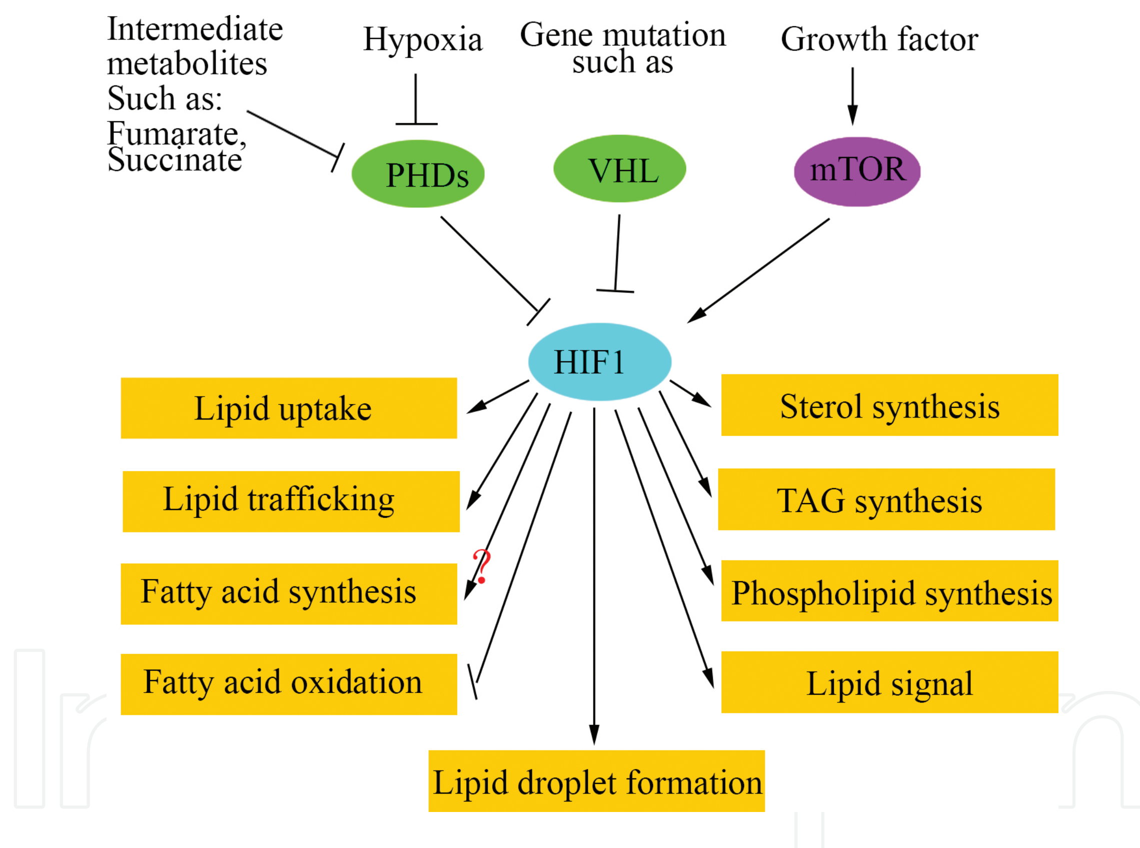

Figure 1. Regulation of HIF1 and its downstream roles related to lipid metabolism. HIF1 accumulation can be induced by hypoxia, gene mutations, intermediate metabolites, and growth factors. HIF1 plays a pivotal role in lipid metabolism. It can increase lipid uptake and trafficking, fatty acid synthesis, sterol synthesis, TAG synthesis, lipid droplet biogenesis, and lipid signal production, and suppress fatty acid β-oxidation. Lipid droplet accumulation may be the final result of HIF1 in lipid metabolism. It is unclear about its role in phospholipids metabolism.

It has been reported that HIF1 regulates the transcription of hundreds of genes involving many aspect of biology, especially energy metabolism and vascularization [16]. The role of HIF1 in glucose metabolism had been well established [17]. Most of genes involving glucose uptake and glycolysis are directly regulated by HIF1 [17]. Recent studies demonstrated that HIF1 also

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plays an important role in lipid metabolism [1, 2, 18–21]. Currently, our understanding of HIF1 in regulating lipid metabolism has lagged behind that of glucose metabolism. Lipids, structurally and functionally important in all organisms, are not only one of the major components of cellular membrane systems, but also the source of energy storage. Moreover, signal molecules, such as prostaglandin E2 (PGE2), hydroxyeicosatetraenoic acid (HETE), and steroid hormones, are derived from lipids. This review would focus on the HIF1's activity related to dysregulation of lipid metabolism in several diseases, including atherosclerosis [4], fatty liver disease (FLD) [19], heart failure diseases [5], obesity [3], and cancer [1, 2] as well as the involvement of HIF1 in lipid metabolism, including lipid uptake and trafficking, fatty acid metabolism, sterol metabolism, triacylglycerol (TAG) synthesis, phospholipid metabolism, lipid droplet (LD) biogenesis, and lipid signaling.

2. Lipid accumulation is associated with HIF1's activity in diseases

Most of the studies have demonstrated that HIF1's activity is associated with lipid accumulation positively [3, 18, 20–27], while few researches have indicated the opposite effect [28–31]. PHD2 inhibition or deletion, increasing HIF1's activity (**Figure 1**), decreased lipid accumulation in different animal models [28, 30, 31]. It indicated that the role of HIF1 in lipid metabolism may be different in different animal models. Details were described and discussed in the following sections.

2.1. Atherosclerosis

Hypoxia has been demonstrated in atherosclerotic plaques [4]. Arterial wall hypoxia exists in a rabbit atherosclerosis injury model [32–34], confirmed in rabbit atherosclerotic plaques [35, 36] as well as in several mouse models [23, 37, 38]. Recently, in vivo studies have demonstrated hypoxia in human atherosclerotic plaques [39]. Macrophages are the major cell types in human plaques that display signs of hypoxia. TAG-loaded foam cells derived from macrophages are characteristic of both early and late atherosclerotic plaques [40, 41]. Exposure of human macrophages to hypoxia causes an accumulation of TAG-containing lipid droplets [42]. HIF1α is expressed in various cell types of atherosclerotic lesions and is associated with lesional inflammation [43]. Knockdown of HIF1α with small interfering RNAs inhibits TAG-loaded foam cell formation in the human monoblastic cell line U937 [22]. Dyslipidemia are regarded as the key risk factors for the development of atherosclerosis, and HIF1 has been suggested to have both detrimental and beneficial roles in atherosclerosis [28, 44, 45]. In murine atherosclerosis, the hypoxia-induced accumulation of cholesterol was substantially reversed in vitro by reducing the expression of the HIF1α [23]. While in another model, PHD2 inhibition stabilized HIF1α and reduced serum cholesterol levels in low-density lipoprotein receptor-deficient mice that were fed a high-fat diet (HFD) [28]. So the role of HIF1 should be further studied in atherosclerosis lipid metabolism.

2.2. Heart failure diseases

Ischemic heart disease, systemic hypertension, and pathological cardiac hypertrophy eventually result in heart failure. Myocardial hypoxia has been associated with these clinical conditions [25, 46]. Several studies showed a correlation between TAG accumulation and heart failure [26, 47–49]. Hypoxia promotes TAG accumulation in cardiomyocytes [48, 50]. Overexpression of the constitutive active form of HIF1α in cardiomyocytes promotes intracellular lipid accumulation under normoxia [24]. The specific deletion of VHL in mice cardiac myocytes results in lipid accumulation [25, 26]. In a pathological cardiac hypertrophy mouse model, cardiac TAG accumulation in ventricles was abolished in HIF1α knockout mice [26].

2.3. Fatty liver disease (FLD)

Lipid accumulation is a common feature of fatty liver disease, whether it is alcoholic (AFLD) or nonalcoholic (NAFLD) [19]. FLD initially begins with simple hepatic steatosis, but can irreversibly progress to steatohepatitis, fibrosis, cirrhosis, or hepatocellular carcinoma [19]. Hypoxia in liver has been documented in vivo in rats on a continuous ethanol diet at a constant rate for prolonged periods [51–54]. Recent studies have demonstrated that hypoxia is also observed in NAFLD [55]. Indeed, HIF1 expression is increased in fatty liver diseases [19]. Nath and his colleagues found that ethanol feeding resulted in liver steatosis in wild-type mice compared with isocaloric diet-fed controls [27]. Constitutive activation of HIF1α in hepatocytes accelerates lipid accumulation with chronic ethanol feeding compared with wild-type mice [27]. In contrast, hepatocyte-specific deletion of HIF1α protected mice from alcohol-induced liver lipid accumulation [27]. However, another group reported that hepatocyte-specific HIF1α-null mice developed severe hyper-triglyceridemia with enhanced lipid accumulation in the liver of mice after 4 weeks of exposure to a 6% ethanol-containing liquid diet [29]. Different genetic techniques used to create specific gene expression or knockout mice in each of these studies may offer some explanation of the different results each described. The other 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 [19].

2.4. Obesity

Hypoxia has been directly demonstrated in adipose tissue of several obese mouse models, such as ob/ob mice [56, 57], KKAy obese mice [58], and high-fat diet-induced obese mice [56–58]. In HFD-induced obese mice, HIF1 activation in visceral white adipocytes is critical to maintain dietary obesity [3] and adipocyte-specific HIF1β or HIF1α knockout mice exhibit reduced fat formation compared with wild-type controls [59]. Conversely, another group, using transgenic mice with adipose tissue selective expression of a dominant negative version of HIF1, found that mice with inhibition of HIF1's activity developed a more severe obesity in HFD-induced obese mice [60]. Inactivation of PHD2 resulted in the activation of HIF1. Transgenic mice with PHD2-specific deletion in adipocyte were resistant to HFD-induced obesity and decreased lipid accumulation [30]. In another PHD2-deficient mice model, they also had improved glucose tolerance and insulin sensitivity. Whether fed normal chow or HFD, PHD2 inhibition had less adipose tissue, smaller adipocytes, and less adipose tissue inflammation than their

littermates. In addition, serum cholesterol level and de novo lipid synthesis were decreased, and the mice were protected against hepatic steatosis in PHD2-deficient mice [31]. It seems that HIF1 in adipocyte of obesity had different effect on lipid metabolism compared with other models. Thus, the effect of HIF1 in lipid metabolism of obesity has yet to be defined.

2.5. Cancer

Hypoxia in the tumor microenvironment leads to the metabolic changes in cancer cells. Over 50% cellular energy is produced by glycolysis and HIF1 plays a central role in the changes [16, 61]. Recently disorders of lipid metabolism had been demonstrated in solid tumors [62, 63], such as pancreatic cancer [64], liver cancer [1], breast cancer [65], colon cancer [66], and ovarian cancer [67]. Lipid accumulation is observed in human tumor tissue [66, 68]. Accumulation of cholesterol also has been reported in prostate cancer [69]. Indeed, recent researches had demonstrated that HIF1's activity is really involved abnormal lipid metabolism of cancer cells. Hypoxia-induced lipid accumulation depends on HIF1's activity in cancer cells [18, 20, 21]. Under hypoxic condition, the flux from glutamine into fatty acid is mediated by reductive carboxylation, and HIF1α plays an important role in this metabolic shift in tumor cells [70]. HIF1α also inhibits fatty acid β-oxidation to promote lipid accumulation in human hepato-cellular carcinoma [1]. Valli and his colleagues revealed that hypoxia induced many changes in lipid metabolites. Enzymatic steps in fatty acid synthesis and the Kennedy pathway were modified in an HIF1α-dependent fashion in HCT116 cell line [2]. However, the role of HIF1 in cancer lipid metabolism has not been well addressed, so more researches should be further studied.

3. The role of HIF1 in lipid metabolism

Lipid metabolism is more complicated than glucose metabolism. Besides as major components of membrane, lipids are also a source of energy storage and signal molecules. HIF1-induced genes involving lipid metabolism are listed in **Table 1**. We would discuss the role of HIF1 in lipid metabolism from the following linked aspects: lipid uptake and trafficking, fatty acid metabolism, sterol metabolism, TAG synthesis, phospholipids metabolism, lipid droplets biogenesis, and lipid signaling (**Figure 1**).

3.1. Lipid uptake and trafficking

3.1.1. Free fatty acid (FFA) uptake

At the plasma membrane, uptake of fatty acid is mainly regulated by the fatty acid transport protein family, such as CD36 [89–91], and plasma membrane-associated fatty-acid-binding proteins (FABPs). Fatty acid transporter CD36 transports long chain fatty acid (LCFA) across plasma membrane. In cardiac myocytes, acute hypoxia (15 min) induced the redistribution of CD36 from an intracellular pool to the plasma membrane [92]. Similarly, in intact Langendorff-perfused heart, a similar effect was demonstrated [92]. Thus, indicating the increased intra-

cellular lipid accumulation in hypoxic hearts is attributable to accumulation of fatty acid in the heart [92]. CD36 also can be regulated at the transcriptional level. In neonatal mouse cardiac myocytes, phenyl-epinephrine (PE) induced free fatty acid uptake in an HIF1α -dependent fashion while inhibition of CD36 led to decreased TAG accumulation upon PE stimulation [26]. In this model, CD36 was induced through HIF1-PPARγ axis [26]. In human retinal pigment epithelial cells, CD36 is mediated by HIF1 binding on its promoter region [71]. Hypoxia also markedly induced CD36 mRNA in corneal and retinal tissue in in vivo [71].

Products of HIF1's target genes	Functions in lipid metabolism	References
CD36, PPARγ, FABP3, FABP7	Fatty acid uptake	[21, 26, 71]
VLDLR, LRP1	LDL and VLDL uptake	[18, 48, 72, 73]
CAV1, RAB20	Endocytosis and lipid trafficking	[74, 75]
PPARα*, TWIST1, Sirt2*	Fatty acid β-oxidation	[3, 76, 77]
DEC1	Fatty acid synthesis	[30, 78]
ABCA1*	Cholesterol efflux	[79]
PPARγ, Lipin1	TAG synthesis	[20, 26]
CHKA	Phospholipids synthesis	[80, 81]
ADRP, HIG2, CAV1	Lipid droplet biogenesis	[42, 74, 82–85]
COX2, PTGES1	Lipid signaling	[86–88]

PPARγ, peroxisome proliferator-activated receptor gamma; VLDLR, very-low-density lipoprotein receptor; LRP1, low-density lipoprotein receptor-related protein 1; CAV1, caveolin 1; PPARα, peroxisome proliferator-activated receptor alpha; TWIST1, twist family bHLH transcription factor 1; SIRT2, sirtuin 2; DEC1, deleted in esophageal cancer 1; ABCA1, ATP-binding cassette subfamily A member 1; LPIN1, lipin 1; HIG2, hypoxia inducible gene 2; CHKA, choline kinase alpha; COX2, cyclooxygenase 2; PTGES, prostaglandin E synthase 1.

"*" genes suppressed by HIF1.

Table 1. HIF1 targets genes that regulate lipid metabolism.

FABPs are part of a larger family of cytoplasmic proteins comprising nine members (FABP1–FABP9) [93], and are involved in reversibly binding intracellular hydrophobic ligands and trafficking them throughout cellular compartments [89]. Some evidence suggested that FABPs could interact directly with CD36 [94]. In *in vitro*, FABP3 and FABP7 were induced by hypoxia in a HIF1-dependent manner, and both are involved in fatty acid uptake [21]. Knockdown of endogenous expression of FABP3 or FABP7 significantly impaired lipids droplets formation under hypoxia [21]. More specifically, the role of FABP3 is evident from the phenotype of FABP3 knockout mice, which show a rate of palmitate uptake reduced by 50% in cardiac myocytes [95, 96]. FABP7 binds long-chain polyunsaturated FA (PUFA), allowing uptake and intracellular trafficking [97], and is involved in proliferation and invasion of melanoma cells [98] and glioblastoma cells [21]. High expression of FABP7 in glioblastomas is associated with poor prognosis and more invasive tumors [99].

3.1.2. LDL and VLDL uptake

LDL and VLDL are major source of extracellular lipid, and HIF1 has been implicated in the transport of LDL and VLDL into cells. LDL receptor (LDLR) and VLDL receptor (VLDLR) are major receptors that are responsible for LDL and VLDL uptake. It had been reported that hypoxia significantly increased LDL uptake and enhances lipid accumulation in arterial smooth muscle cells (SMCs), exclusive LDLR activity [100]. In addition, hypoxia increased VLDL uptake in cardiac myocytes, which might be partially dependent on up-regulating VLDLR expression [101]. Some studies had also reported that VLDLR could be induced under hypoxia [102]. In human cancer cell lines, we had demonstrated that HIF1-mediated VLDLR induction influenced intracellular lipid accumulation through regulating LDL and VLDL uptake under hypoxia [18]. In hepatocellular carcinoma, expression of VLDR was associated positively with HIF1 [18]. In mice, hypoxia-induced VLDLR expression in HL-1 cells was dependent on HIF1α through its interaction with an HRE in the *VLDLR* promoter. VLDLR promoted the endocytosis of lipoproteins, and causes lipid accumulation in cardiomyocytes [48].

Low-density lipoprotein receptor related protein 1 (LRP1) belongs to LDL receptor superfamily, and is a key receptor for selective cholesterol uptake in human vascular smooth muscle cells (VSMCs). Hypoxia increased LRP1 expression through HIF1α, and overexpression of LRP1 mediated hypoxia-induced aggregated LDL (agLDL) uptake in human VSMCs [72] as well as VLDL-cholesteryl ester (VLDL-CE) uptake in neonatal rat ventricular myocytes (NRVMs) [73]. In contrast to the strong impact of LRP1 inhibition on VLDL-CE uptake in hypoxic cardiomyocytes, LRP1 deficiency did not exert any significant effect on VLDL-TG uptake or VLDL-TG accumulation [73]. This indicated that VLDLR might be a key receptor for VLDL-TG uptake. Therefore, more experiments should be done to value the precise contribution of VLDLR and LRP1 in myocardial VLDL-CE and VLDL-TG uptake in pathophysiological situation in the heart.

LDL and VLDL uptake are through vesicular transport pathways [103]. The LDL receptor superfamily has NPXY motif in cytoplasmic domain that interacts with the endocytotic machinery to mediate rapid clathrin-dependent endocytosis of the receptor-ligand complex [104, 105]. Caveolaes are formed in the process of receptor-mediated endocytosis. Numerous proteins are involved in caveolae formation, including caveolins, Rabs, VAT-1, SNAP, and VAMP [106]. Caveolin-1 (CAV1) is an essential structural constituent of caveolae that is involved in constitutive endocytic vesicular trafficking. Loss of VHL function, an E3 ligase involving HIF1α degradation, was associated with increased caveolae formation [74]. CAV1, as a direct target of HIF1, accentuated the formation of caveolae [74]. Knockdown expression of CAV1 inhibited uptake of oxidized LDL (oxLDL) without changing its binding to the plasma membrane [107]. These results indicated that CAV1 was part of the pathway that allowed cells to take up oxLDL [107]. Rab20, a member of the Rab family of small GTP-binding proteins, regulating intracellular trafficking and vesicle formation, had also been characterized as an HIF-1 target [75]. Although there was no direct evidence of the involvement of CAV1 and Rab20 in hypoxia-induced LDL and VLDL uptake, we hypothesized that they might play role in hypoxia-induced LDL and VLDL uptake and/or intracellular lipid trafficking.

Taken together, HIF1 promoting lipid accumulation may increase lipid uptake and intracellular lipid trafficking by inducing related genes directly. It should be further studied if there are more genes targeted by HIF1 in the process.

3.2. Fatty acid metabolism

3.2.1. Fatty acid β-oxidation

Hypoxia increased intracellular lipid accumulation through suppression of fatty acid β-oxidation (FAO) in several models, and the molecular mechanism involvement of HIF1 in the process had been demonstrated (**Figure 2**). Under hypoxic condition, human macrophages showed in an increased TAG accumulation that was associated with a decreasing rate of FAO. The decreasing rate of FAO was shown to be partly dependent on the reduced expression of enzymes involved in FAO [42]. Peroxisome proliferator-activated receptors (PPARs), including α, γ, and β/δ, belong to the nuclear receptor family of ligand-activated transcription factors that were originally described as gene regulators of various metabolic pathways. PPARα and PPARβ/δ control expression of genes implicated in FAO. PPARγ, in contrast, is a key regulator of glucose homeostasis and adipogenesis [108].

Muscle carnitine palmitoyltransferase 1 (M-CPT1), a known PPARα target gene, catalyzes the rate-limiting step in the mitochondrial import of fatty acids for the FAO cycle [109]. In cardiomyocytes, hypoxia and adenovirus-mediated expression of a constitutively active form of HIF1α reduced the mRNA and protein levels of PPARα and M-CPT1 [24, 50, 110] as well as the DNA binding activity of PPARα [24, 50]. $CoCl_2$ treatment also decreased PPARα and M-CPT1 mRNA levels [110]. In intestinal epithelial cells, hypoxia rapidly down-regulated PPARα mRNA and protein in an HIF1-dependent manner in vitro and in vivo [76]. HIF1 could down-regulate PPARα directly through binding a functional HRE in the promoter region [76]. These results suggested that the mechanism of HIF-1 suppression of FAO involved the partial reduction of the expression of PPARα and M-CPT1.

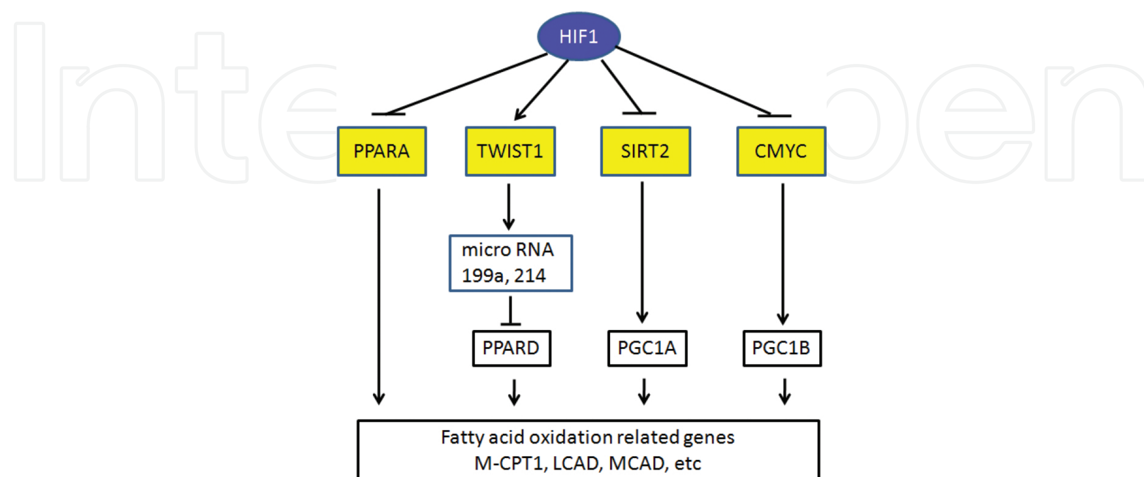

Figure 2. The molecular mechanism involving HIF1 repression of fatty acid β-oxidation. HIF1 targets PPARα, PPARδ, and Sirt2 directly and thereby suppresses the genetic expression of fatty acid β-oxidation.

HIF1 also suppressed FAO by inhibition of PPARδ's activity. In a pathological cardiac hypertrophy mouse model, myocardial hypoxia provoked Dnm3os activation and concomitantly mir-199a and mir-214 expression through the HIF1-TWIST1 axis [49]. TWIST1 is a direct target gene of HIF1 [77]. DNM3os is a noncoding RNA transcript that harbors the mi-RNA cluster mir-199a~214, for which PPARδ is a target. Increased expression of mir-199a and mir-214 decreased cardiac PPARδ expression and mitochondrial fatty acid oxidative capacity. Reduced expression of enzymes involved in FAO, for example long-chain acyl-CoA dehydrogenase (LCAD) and medium-chain acyl-CoA dehydrogenase (MCAD), was also observed. Conversely, antagomir-based silencing of miR-199a~214 in mice subjected to pressure overload derepressed cardiac PPARδ, LCAD and MCAD levels, and restored mitochondrial FAO [49].

PPARγ coactivator 1α (PGC-1α) has been prominently associated with the expression of the genes involving FAO and energy expenditure [111]. In obese mouse model, HIF1α suppressed FAO in visceral white adipocytes, in part, through transcriptional repression of sirtuin 2 (Sirt2), an NAD^+-dependent deacetylase [3]. Reduced Sirt2 function directly translated into diminished deacetylation of PGC1α and the expression of FAO genes. HIF1α negated adipocyte-intrinsic pathway of fatty acid catabolism by negatively regulating the Sirt2-PGC1α regulatory axis [3].

PPARγ coactivator 1β (PGC-1β) is a transcription factor that also plays critical roles in regulating mitochondrial function and lipid metabolism [112, 113]. PGC-1β could regulate FAO through activating medium-chain acyl-CoA dehydrogenase (MCAD) and long-chain acyl-CoA dehydrogenase (LCAD), which catalyzes the first step of FAO in mitochondria [1, 112]. It had been documented previously that hypoxia inhibited PGC-1β activity through HIF1-dependent c-Myc suppression in VHL-null RCC4 renal carcinoma cells [114]. Under hypoxic condition in Hep3B and HepG2 cells, and also in PC3 prostate cancer cells, Huang and his colleagues revealed a role of the HIF1/C-MYC/PGC-1β regulatory axis in hypoxia-mediated regulation of MCAD and LCAD by which HIF1 suppressed FAO [1]. This study confirmed that hypoxia inhibited FAO in an HIF1-dependent mechanism in cancer cells [1].

In summary, it had been confirmed by different models that hypoxia inhibits FAO depending on HIF1's activity (**Figure 2**). However, HIF1 did not target FAO-related genes directly, and it was always cross-talk with other pathway to suppress FAO indirectly. It should be further studied if HIF1 could involve cross-talk with more pathways to suppress FAO.

3.2.2. Fatty acid synthesis

De novo fatty acid synthesis begins with acetyl coenzyme A (Ac-CoA). Ac-CoA is primarily generated from glucose through tri-carboxylic acid (TCA) cycle in the mitochondrion, the citrate shuttle and ATP citrate lyase in the cytosol. Under hypoxic condition, cells converted glucose to lactate and the TCA cycle is largely disconnected from glycolysis [70, 115–117], thereby directing glucose carbon away from fatty acid synthesis. Recently, several groups had found that hypoxic tumor cells maintain proliferation by running the TCA cycle in reverse [70, 115–117]. In these cells, the source of carbon for Ac-CoA and fatty acid switched from glucose to glutamine. This hypoxic flux from glutamine to fatty acid was mediated by the reductive carboxylation of glutamine-derived α-ketoglutarate.

The reductive carboxylation of glutamine was part of the metabolic reprogramming associated with HIF1. Glutamine-derived α-ketoglutarate is reductively carboxylated by the cytosolic isocitrate dehydrogenase 1 (IDH1) [70, 115] and the mitochondrial isocitrate dehydrogenase 2 (IDH2) to form isocitrate [70, 115, 116], which could then be isomerized to citrate. The combined action of IDH1 and IDH2 was necessary and sufficient to affect the reverse TCA flux [115]. Citrate was converted into Ac-CoA by ATP citrate lyase in the cytosol. Renal cell lines deficient in the VHL preferentially used reductive glutamine metabolism for lipid biosynthesis even at normal oxygen levels [70]. Constitutive activation of HIF1 recapitulated the preferential reductive metabolism of glutamine-derived α-ketoglutarate even in normoxic condition [116]. This regulation by HIF1 of the reverse TCA cycle occurred partly through HIF1-inducing PDK1. Knocking down PDK1 suppressed reductive carboxylation [70, 118]. However, more details should be studied about the role of HIF1 in TCA cycle reverse.

The first step of fatty acid synthesis is catalyzed by AcCoA carboxylase (ACC) which converts Ac-CoA to malonyl-CoA. Then fatty-acid synthase (FASN) catalyzes acetyl-CoA and malonyl-CoA to palmitate. Further elongation and de-saturation of newly synthesized fatty acid takes place at the cytoplasmic face of the endoplasmic reticulum membrane. It had been reported that hypoxia regulated FASN expression [78, 119, 120]. However, different conclusions on hypoxia regulation of FASN had been reported. One group using human breast cancer cell lines found that FASN was significantly up-regulated by hypoxia via activation of the Akt and HIF1 followed by the induction of the SREBP1 gene [119]. Another group, using several cell lines other than breast cancer cell lines, found that hypoxia suppressed FASN expression through HIF1-DEC1 and/or DEC2-SREBP1 axis. They found that HIF1 repressed the SREBP1 gene by inducing DEC1 and DEC2, and further repressing FASN expression [78]. These results might indicate that HIF1 regulated FASN in a cell-type specific manner. In addition, it had been reported that hypoxia could induce the expression of SCD1 which introduces a double bond in the $\Delta 9$ position of palmitic acid and stearic acid to produce mono-unsaturated fatty acid [42, 121]. It is unknown if HIF1 is involved in hypoxic-induced SCD1.

Taken together, the role of HIF1 in de novo fatty acid synthesis may depend on different models and conditions, and more researches should be done in the direction.

3.3. Cholesterol metabolism

Cholesterol is an essential structural component of membrane. It modulates membrane permeability and fluidity and also forms microdomains named lipid rafts that integrate the activation of some signal transduction pathways [14]. Intermediates generated by the cholesterol biosynthesis pathway were required for the posttranslational modification of small GTPases, such as the farnesylation of Ras and the geranyl-geranylation of Rho [15]. Finally, cholesterol also serves as a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D.

Cellular cholesterol level can be modulated by three processes: cholesterol uptake, synthesis, and efflux [122]. In the preceding paragraph, we had discussed the role of HIF1 in LDL and VLDL uptake that are main source of extracellular cholesterol. Here, we discuss the cholesterol synthesis and efflux. Cholesterol biosynthesis begins with the condensation of AcCoA with

acetoacetyl-CoA to form 3-hydroxy-3-methylglutaryl (HMG)-CoA. Then HMG-CoA reductase (HMGCR) reduces of HMG-CoA to mevalonate. Early research found that Hypoxia also suppressed cholesterol synthesis in cultured rabbit skin fibroblasts [123]. However, recently research indicated that hypoxia increased sterol synthesis depending on HIF1's activity [23, 124]. In hypoxic macrophages, the increase of intracellular cholesterol content was correlated with elevated HMGCR's activity and mRNA levels [23]. In HepG2 cells, HIF1α accumulation was able to increase the level and activity of HMGCR by stimulating its transcription [124]. But it was unclear if HIF1 regulated HMGCR directly.

Hypoxia suppressed the efflux of cholesterol, and this efflux was substantially reversed in vitro by reducing the expression of HIF1 [23, 123]. ATP-binding cassette transporter A1 (ABCA1) plays a major role in cholesterol efflux. Hypoxia severely reduced ABCA1-mediated cholesterol efflux, which could be explained by subcellular redistribution of ABCA1 protein under acute hypoxia and decreased protein level under prolonged hypoxia [23]. One group reported that HIF1 could repress the transcription of ABCA1 directly [79]. Hypoxia, partly mediated by HIF1α, increased intracellular cholesterol content due to the induction of cholesterol synthesis and the suppression of cholesterol efflux [23]. In addition, accumulation of cholesterol in hypoxic cells was in esterified form [23, 100]. At 2% O_2 tension, twice the total cholesteryl ester was observed compared with that at 21% O_2. At the same time, no significant difference was found in the concentration of cellular-free cholesterol [100]. Accumulation of cholesteryl ester in hypoxic cells might depend on the increased activity of AcCoA:cholesterol acyltransferases (ACATs) [123], which are important enzymes for the esterification of cholesterol. Therefore, more studies should be done to define the role of HIF1 involving the cholesterol metabolism in detail.

3.4. TAG synthesis and phospholipids metabolism

3.4.1. TAG synthesis

TAG is formed by the addition of three molecules of fatty acid to glycerol. There are two major pathways for TAG biosynthesis in mammalian cell: the glycerol phosphate pathway and the mono-acylglycerol (MG) pathway. In the glycerol phosphate pathway, two molecules of fatty acyl-CoA are esterified to glycerol-3-phosphate to yield 1,2-diacylglycerol (DAG) phosphate (commonly identified as phosphatidic acid). The phosphate is then removed to yield 1,2-diacylglycerol, which is followed by addition of the third fatty acid to form TAG. TAG accumulation under hypoxia could be mediated by HIF1-inducing Lipin1 [20], a phosphatidate phosphatase isoform that catalyzes the penultimate step in TAG biosynthesis, the removal of phosphate from diacylglycerol phosphate to yield DAG. It also had been reported that hypoxia produced a marked intracellular accumulation of diacylglycerol in different cell types [125]. DAG may also serve a feedback role regulating HIF1's activity [125]. In a mouse model of pathological hypertrophy, HIF1α promoted TAG accumulation in cardiomyocytes via the regulation of PPARγ expression. PPARγ was the principal mediator of TAG anabolism through its transcriptional regulation glycerol-3-phosphate generation (via GPD1), and downstream esterification processes (via GPAT) [26].

3.4.2. Phospholipids metabolism

Phospholipids are indispensable for cell growth. Phospholipids synthesis and TAG synthesis share similar steps. DAG is a precursor for phosphatidylcholine and phosphatidylethanolamine. Phosphatidic acid utilizes cytidine triphosphate (CTP) as an energy source to produce a CDP-DAG intermediate followed by conversion to phosphatidylcholine. It had been reported that the intracellular level of phosphatidic acid (PA) and DAG rose in response to hypoxia [125, 126]. However, PA accumulation in response to hypoxia was both HIF1 and VHL-independent [127]. Choline kinase α (ChKα) catalyzes the phosphorylation of choline, the first step of phosphatidylcholine synthesis. In cancer cells, one group had shown that hypoxia increased ChKα expression and this was driven by HIF1 [80]. Conversely, another group had shown that choline kinase activity and choline phosphorylation were decreased, that might be mediated via HIF1α binding to the promoter of ChKα gene [81]. Thus, further studies should be done to address the role of HIF1 in phospholipids metabolism.

3.5. Lipid droplet (LD) biogenesis and lipid signaling

Lipid droplet, also named lipid body, has been largely associated with neutral lipid storage and transport in cells [106]. The internal core of the LD is rich in neutral lipids, predominantly TAGs or cholesteryl esters, that are surrounded by an outer monolayer of phospholipids and associated proteins [128]. LD was considered to be highly regulated, dynamic and functionally active organelle [106]. Proteins on the surface of lipid droplets are crucial to the droplet structure and dynamics. Currently, the complete protein composition of LD has not been defined. The best characterized LD' proteins are the perilipin/ADRP/TIP47 (PAT) domain family. Apart from the PAT domain proteins, there are other lipid droplets associated proteins which involve the catabolism of lipids, vesicular transport, eicosanoid-forming enzymes, protein kinases, etc. [106]. Hypoxia increased LD number and size [42, 129]. Several LD-associated proteins were induced by HIF1 and might also involve HIF1-induced LD biogenesis and lipid signaling (**Figure 3**).

3.5.1. Lipid droplet biogenesis

Adipose differentiation-related protein (ADRP), a PAT domain protein, is a structural component of LD and had been reported by several groups to be inducible by HIF1 [42, 82–84]. Lipid accumulation was associated with high expression level of ADRP in solid tumors [68, 130], especially in clear cell lesions [131]. During the process of carcinogenesis, the ADRP expression was increased during early tumorigenesis and was associated with the proliferation rate [68]. The expression of ADRP was also correlated with atherosclerosis [132]. In mouse macrophages in vitro, ADRP expression facilitated foam cell formation induced by modified lipoproteins [132]. In apolipoprotein E-deficient mice, ADRP inactivation reduced the number of LD in foam cells in atherosclerotic lesions [132]. Under hypoxia, knockdown of ADRP in U87 and T98G or in MCF-7 and MDA-MB-231 cells significantly decreased the formation of LD, and resulted in decreased fatty acid uptake [21]. It indicated that ADRP promoted LD formation mainly through increasing FA uptake under hypoxic condition. It had been reported

that ADRP can also stimulate LCFA uptake [133]. While another research reported that ADRP did not involve LDL- and VLDL-induced LD formation under hypoxia [84].

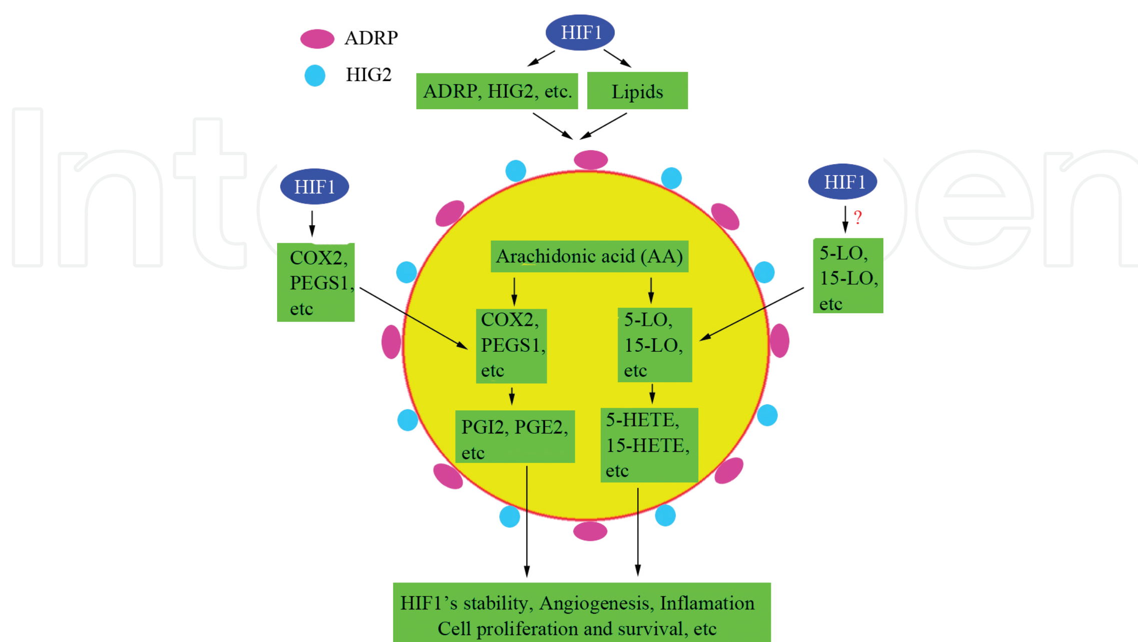

Figure 3. A hypothetical representation of molecular mechanism involving hypoxia-induced lipid droplet biogenesis and function. HIF1-induced structural proteins of the LD, such as ADRP, HIG2, combine with HIF1-increased lipids to form the LD. Enzymes involving eicosanoid production are also induced by HIF1, and are recruited to the LD. These proteins can increase lipid signaling that can involve many aspects of biology, such as HIF1α's stability, angiogenesis, inflammation, cell proliferation and survival.

Hypoxia-inducible protein 2 (HIG2), a newly identified protein associated with LD, was up-regulated by hypoxia and was a direct and specific target gene of HIF1 [85]. Overexpression of HIG2 under normoxic condition was sufficient to increase LD in HeLa cells. HIG2-driven LD might contribute to an inflammatory response. Overexpression of HIG2 stimulated cytokine expression of vascular endothelial growth factor-A (VEGFA), macrophage migration inhibitory factor (MIF), and interleukin-6 (IL-6). Increasing expression of HIG2 was also detected under several conditions of pathological lipid accumulation, such as atherosclerotic arteries and fatty liver disease [85]. We had mentioned that CAV1 was a target of HIF1. CAV1 could distribute to LD under several conditions [134–137] and the association with LD was reversible [134]. However, It is unknown if hypoxia can redistribute CAV1 to LD and CAV1 involves LD biogenesis under hypoxia.

3.5.2. Lipid signaling

Eicosanoids are signaling molecules made by oxidation of 20-carbon fatty acids, mainly from arachidonic acid. Cyclooxygenases and Lipoxygenases are two families of enzymes catalyzing fatty acid oxygenation to produce the eicosanoids. There are multiple subfamilies of eicosanoids, including prostaglandins, prostacyclins, thromboxanes, lipoxins, and leukotrienes. Prostaglandins, such as PGI_2 and PGE_2, are synthesized via cyclooxygenase (COX) by oxidation

of arachidonic acid. PGE_2 is synthesized in three steps catalyzed by phospholipase (PL) A2, COX, and terminal prostaglandin E synthase (PTGES), where each catalytic activity is represented by multiple enzymes and/or isoenzymes. It had been reported that hypoxia could increase prostaglandins (PGI_2 and PGE_2) synthesis [138]. Hypoxia-induced synthesis of PGE_2 was accompanied by up-regulation of COX2, which is a direct target gene of HIF1 [86]. Several studies had indicated that LD was reservoirs of COX2 and sites of PGE_2 synthesis [66, 139, 140]. PTGES1 could also be regulated by HIF1 directly [87, 88]; however, it is unknown if PTGES1 localizes to hypoxia-induced LD.

Lipoxygenases are a family of nonheme iron-containing enzymes which dioxygenate polyunsaturated fatty acid to hydroperoxyl metabolite, and mainly include 5-lipoxygenase (5-LO), 12-lipoxygenase (12-LO), and 15-lipoxygenase (15-LO). 5-LO and 15-LO were shown by immuno-cytochemistry, immuno-fluorescence, ultrastructural postembedding immuno-gold EM and/or western blotting from subcellular fractions to localize within lipid droplets stimulated in vitro [141–144]. Increasing level of 5-LO was detected in lung tissue of rodent model of hypoxia-induced pulmonary hypertension [145]. Hypoxia increased 12-LO in rat lung and in in vitro cultured rat pulmonary artery smooth muscle cell (PASMC) and may contribute to the production of 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) [146]. Increasing 12(S)-HETE had also been demonstrated in hypoxic macrophage cells [147]. Under hypoxia, increased levels of 15-LO had been demonstrated by different groups [147, 148] and its product, 15-hydroperoxyeicosatetraenoic acid (15-HETE), was up-regulated [147]. Up-regulation of 15-LO/15-HETE in response to hypoxia might be partially mediated by HIF1α [149]. In addition, HIF1α was shown to be regulated by 15-HETE in a positive feedback manner [149]. However, it is unknown if lipoxygenases are regulated by HIF1 directly.

4. Conclusions and perspectives

HIF1 plays an important role in lipid metabolism and a number of studies support the findings that HIF1 promotes lipid accumulation. Nevertheless, many questions remain. HIF1, as a master transcriptional factor, may target many genes directly or indirectly involved in lipid metabolism. HIF1 plays a pivotal role in glucose metabolism. Inhibition of GULT3, an HIF1 target gene, could significantly reduce both glucose uptake and hypoxia-induced de novo lipid synthesis in human monocyte-derived macrophages [150]. PGAM1, induced by hypoxia [151], catalyzes the reversible reaction of 3-phosphoglycerate (3-PGA) to 2-phosphoglycerate (2-PGA) in the glycolytic pathway. Inhibition of PGAM1 led to significantly decreased glycolysis and de novo lipid synthesis in cancer cells [152]. Thus, it is possible that glucose metabolism might couple with lipid metabolism under hypoxia. The source of carbon for fatty acid switched from glucose to glutamine under hypoxia [70]. The question thus arises. Does HIF1 induce lipid accumulation through targeting genes involving glucose metabolism, and how does glucose metabolism affect lipid metabolism under hypoxia?

HIF1 could interact with other pathways to regulate lipid metabolism besides PPARα, PPARγ, PPARδ, PGC1α, and SREBP1. There might be a pivotal role for mTOR in controlling

lipid homeostasis in many settings, both physiological and pathological [153]. AMPK is a cellular energy sensor that normalizes lipid, glucose, and energy imbalances [154]. Inhibition of cMYC was accompanied by accumulation of intracellular LD in tumor cells as a direct consequence of mitochondrial dysfunction [155]. Recently, p53 had also been shown to regulate lipid metabolism [156]. The role of HIF1 in these pathways and the molecular mechanism will require further investigation.

Lipid accumulation in diseases, including obesity, atherosclerosis, ALD, heart failure disease and cancer, had been associated with HIF1's activity. There may be additional pathologies with lipid metabolism disorder associated with HIF1. HIF1 is an attractive target candidate for therapeutic intervention in diseases with disorder of lipid metabolism including cancer. Its involvement in the etiology of a number of diseases and its interaction with a number of regulatory genes make it an important area for further study.

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