Hypoxia-Inducible Factors and the Regulation of Lipid Metabolism

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Oxygen deprivation or hypoxia characterizes a number of serious pathological conditions and elicits a number of adaptive changes that are mainly mediated at the transcriptional level by the family of hypoxia-inducible factors (HIFs). The HIF target gene repertoire includes genes responsible for the regulation of metabolism, oxygen delivery and cell survival. Although the involvement of HIFs in the regulation of carbohydrate metabolism and the switch to anaerobic glycolysis under hypoxia is well established, their role in the control of lipid anabolism and catabolism remains still relatively obscure. Recent evidence indicates that many aspects of lipid metabolism are modified during hypoxia or in tumor cells in a HIF-dependent manner, contributing significantly to the pathogenesis and/or progression of cancer and metabolic disorders.

HIF cancer hypoxia lipids

1. The Involvement of Hypoxia-Inducible Factors in the Regulation of Lipid Metabolism

When oxygen is sparse, cells adapt to hypoxia by reprogramming the expression of a number of genes involved in energy metabolism. The role of HIF-1 in the activation of genes encoding for proteins involved in carbohydrate metabolism has long been established (reviewed in [1][2]). HIF-1 not only promotes glucose uptake by activating the transcription of transporters GLUT1 and GLUT3, but also enhances anaerobic energy production, as it upregulates most of the glycolytic enzymes (including HK1/2, ENO1, PGK1 and PKM2) and proteins that facilitate the synthesis and excretion of lactate (LDH and MCT4). Moreover, in order to reduce mitochondrial function for decreasing consumption of oxygen and ROS production, HIF-1 stimulates the expression of pyruvate dehydrogenase kinase (PDK1) and BNIP3 [3][4][5]. PDK inhibits the pyruvate dehydrogenase complex and blocks the conversion of pyruvate, the glycolytic end product, to acetyl-CoA, which normally feeds into TCA cycle by producing citrate. Therefore, the flow of pyruvate into the mitochondria is decreased, fueling the production of lactate by LDH in the cytoplasm. On the other hand, BNIP3 triggers mitochondrial autophagy, further reducing mitochondrial metabolic processes.

Despite the extensive literature on HIF-dependent regulation of carbohydrate metabolism, the effects of hypoxia and HIFs on lipid metabolism have only recently become the focus of closer examination (**Figure 1**). Fatty acids (FAs), provided either by exogenous FA uptake or de novo synthesis, are used as substrates for oxidation and energy production, membrane synthesis, energy storage in form of triacylglycerols (TAGs) and production of signaling molecules and, therefore, are essential for cell survival and proliferation both under normoxia and

hypoxia. However, as FA oxidation takes place inside mitochondria and requires oxygen, FA metabolism has to be modified under hypoxia in order to serve mainly processes other than energy production. Furthermore, as conversion of glucose into citrate—the major source of cytoplasmic acetyl-CoA and FA precursor—is prohibited under hypoxia due to the inhibition of the TCA cycle, alternative sources of FA precursors have to be exploited. In tumor cells, which usually have to grow in a hypoxic microenvironment, these hypoxia-mediated changes in lipid metabolism are especially important in order to maintain the high proliferation rate that characterizes cancer cells.

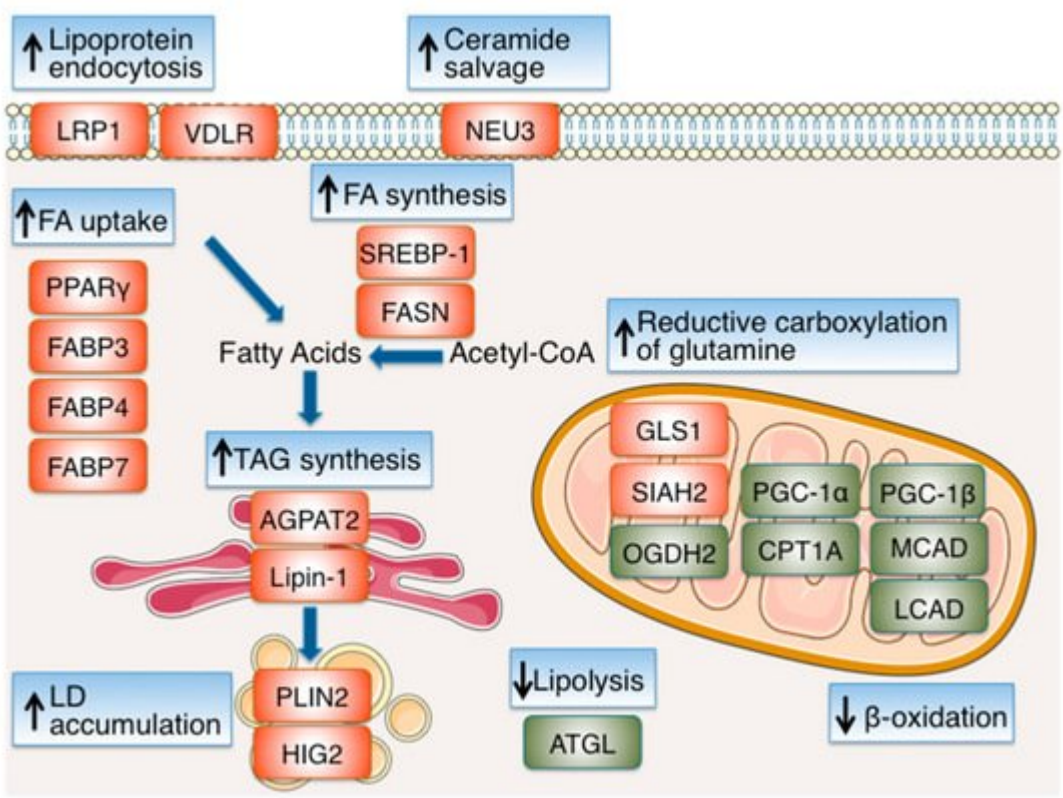

Figure 1. Reprogramming of lipid metabolism under hypoxia. Hypoxia enhances lipogenesis by HIF-dependent modulation of proteins involved in fatty acid (FA) uptake, synthesis, storage and usage. Uptake of extracellular FA is promoted under hypoxia by activation of the transcription factor PPARγ and the increased expression of FABPs 3, 4 and 7. Endocytosis of lipoproteins is enhanced by the upregulation of LRP1 and VLDLR, while ceramide levels are increased by upregulation of NEU3. To maintain de novo FA synthesis under hypoxia, preservation of citrate levels and synthesis of acetyl-CoA is achieved by stimulation of reductive glutamine metabolism, mediated, at least in part, by induction of GLS1 and proteolysis of the OGDH2 subunit of the α-ketoglutarate dehydrogenase complex (αKGDH) by SIAH2. Adequate FA supply is further supported by activation of SREBP-1, which in turn upregulates the expression of FASN. To avoid lipotoxicity and/or replete lipid stores, FAs are converted to neutral triacylglycerols (TAGs), which are stored in lipid droplets (LDs). Formation of LDs under hypoxia is favored by the upregulation of the TAG biosynthesis pathway enzymes AGPAT2 and lipin-1, and the LD membrane proteins PLIN2 and HIG2. Finally, lipid accumulation under hypoxia is additionally supported by the inhibition of β-oxidation through downregulation of PGC-1α, CPT1A, PGC-1β, MCAD and LCAD. The proteins upregulated or activated under

hypoxia are shown in red and the proteins downregulated or inhibited under hypoxia are shown in green. See text for details and references.

Uptake of extracellular FA and TAG synthesis are promoted under hypoxia by transcription factor PPARγ, the gene of which is a directly activated by HIF-1 [6]. Extracellular FA influx and lipogenesis under hypoxia are also enhanced via HIF-1-mediated induction of the expression of FABP (fatty acid binding protein) 3 and 7 in cancer cells [7] and FABP4 in primary mouse hepatocytes [8]. In addition, HIF-1 can promote the endocytosis of lipoproteins, by upregulating the expression of low-density lipoprotein receptor–related protein (LRP1), the receptor that internalizes LDL in vascular smooth muscle cells [9], as well as the expression of VLDL receptor (VLDLR) in cardiomyocytes [10].

To also maintain de novo FA synthesis under hypoxia, production of FA precursors is supported in human renal cell carcinoma (RCC) as well as other cancer cells through HIF-dependent stimulation of reductive glutamine metabolism [11][12]. This proceeds via conversion of glutamine to α-ketoglutarate and its subsequent reductive carboxylation that produces citrate, in a reversion of the TCA cycle reaction catalyzed by IDH (isocitrate dehydrogenase). This may be an indirect result of the HIF-mediated decrease of intracellular citrate levels (due to upregulation of PDK1) but IDH1 or 2 may also actively contribute to the preservation of citrate levels under hypoxia [13][14][15]. Moreover, HIF-1 increases the amount of α-ketoglutarate, which can be used as substrate for citrate synthesis and FA/lipid production, by inducing the expression of GLS1 (glutaminase 1) [16], as well as, by inducing the E3 ubiquitin ligase SIAH2, which in turn mediates the proteolysis of the E1 subunit (OGDH2) of the α-ketoglutarate dehydrogenase complex (αKGDH) [15]. Adequate FA supply is further supported by Akt- and HIF-1-dependent activation of SREBP-1, which in turn upregulates the expression of FASN (fatty acid synthase), an essential lipogenic enzyme, the activity of which is correlated with cancer progression and hypoxia induced chemoresistance [17].

As FA catabolism is impaired under hypoxia, an excess of intracellularly accumulated free FAs could cause lipotoxicity. To avoid this, cells can convert FAs to neutral TAGs, that are stored in lipid droplets (LDs) and can serve as the main form of energy depots [18][19]. Two enzymes of the TAG biosynthesis pathway, AGPAT2 (acylglycerol-3-phosphate acyltransferase 2) [20] and lipin-1 [21], have been shown to mediate hypoxia-induced LD accumulation. AGPAT2, or else LPAATβ (lysophosphatidic acid acyltransferase β), catalyzes the conversion of lysophosphatidic acid (LPA) to phosphatidic acid (PA). Interestingly *AGPAT2*, which is a direct target of HIF-1 [20], is one of the genes mutated in patients with congenital generalized lipodystrophy, and is upregulated in biopsies from cancer patients. Likewise, HIF-1 also directly upregulates the expression of lipin-1, a phosphatidic acid (PA) phosphatase that catalyzes the conversion of PA to diacylglycerol (DAG) in TAG synthesis [21]. AGPAT2 and lipin-1 upregulation is necessary for LD accumulation and increased viability and chemoresistance under hypoxia [20][21][22]. The importance of the hypoxic upregulation of AGPAT2 and lipin-1 may extend beyond the formation of lipid droplets. The products of their catalytic activity LPA and PA can either be used as precursors of TAGs or as precursors for the synthesis of phospholipids, which are important blocks for new membrane formation [19]. Formation of lipid droplets under hypoxia is further favored by the hypoxic induction of essential constituents of LD membranes. Stimulation of the LD coat protein adipophilin/perilipin 2 (PLIN2) expression by HIF-2 promotes RCC

lipid storage, ER homeostasis and viability [23], and the induction of HIG2/HILPDA (Hypoxia-inducible protein 2/hypoxia-inducible lipid droplet associated) by HIF-1 increases lipid accumulation in both cancer and normal cells [24][25]. Furthermore, HIG2 upregulation under hypoxia inhibits the adipose triglyceride lipase (ATGL) and impairs intracellular lipolysis in various cancer cells [26].

Finally, lipid accumulation under hypoxia is additionally supported by the inhibition of enzymes involved in fatty acid degradation. Under low oxygen concentration, fatty acid β-oxidation is actively reduced by HIF-1- and HIF-2-dependent downregulation of the transcriptional coactivator of β-oxidation enzyme PGC-1α (proliferator-activated receptor-γ coactivator-1α) [27] and carnitine palmitoyltransferase 1A (*CPT1A*), the limiting component of mitochondrial fatty acid transport, in both hepatoma and RCC cells [27][28] as well as by the HIF-1-mediated decreased expression of MCAD and LCAD (medium- and long-chain acyl-CoA dehydrogenases) in hepatoma cells, which depends on the hypoxic inhibition of PGC-1β, a transcription factor involved in mitochondrial regulation [29]. As HIFs have not been shown to possess intrinsic transcription repressor activity, downregulation of these enzymes may be mediated by the action of HIF-1 target genes that remain, in most cases, to be identified. In summary, hypoxia overall causes enhanced lipogenesis by HIF-dependent induction of genes involved in FA uptake, synthesis and storage (**Table 1**). Importantly, as discussed below, induction of these genes and subsequent lipid accumulation are indispensable for cancer cell proliferation under hypoxia.

Table 1. Representative HIF direct or indirect target genes that mediate reprogramming of lipid metabolism under hypoxia.

Functional Category /Protein Name	HIF Isoform & Effect	Outcome & Experimental Evidence	Ref.
FA & Lipoprotein Uptake			
PPARγ	HIF-1 Positive	Increased expression HIF-1 binds to the promoter of *PPARγ* and activates its transcription	[6]
FABP3	HIF-1 Positive	Increased expression HIF-1α depletion inhibits the induction of *FABP3* under hypoxia	[7]
FABP4	HIF-1 Positive	Increased expression HIF-1 binds to the promoter of *FABP4* and activates its transcription	[8]
FABP7	HIF-1 Positive	Increased expression HIF-1α depletion inhibits the induction of *FABP7* under hypoxia	[7]
LRP1	HIF-1 Positive	Increased expression HIF-1α binds to the *LRP1* promoter and activates its transcription	[9]

Functional Category /Protein Name	HIF Isoform & Effect	Outcome & Experimental Evidence	Ref.
VDLR	HIF-1 Positive	Increased expression HIF-1α depletion inhibits activation of VDLR promoter under hypoxia	[10]
Reductive Carboxylation of Glutamine			
GLS1	HIF-1 Positive	Increased expression HIF-1α depletion inhibits the induction of *GLS1* under hypoxia	[16]
OGDH2	HIF-1 Negative	Increased proteolysis SIAH2 (a HIF-1 target) mediates proteolysis of OGDH2	[15]
Ceramide Salvage			
NEU3	HIF-2 Positive	Increased expression HIF-2α binds to the *NEU3* promoter and activates its transcription	[30]
FA Synthesis			
SREBP-1	HIF-1 Positive	Up-regulation Inhibition of HIF-1 impairs phospho-SREBP-1 increase under hypoxia	[17] [27]
FASN	HIF-1 Positive	Increased expression Inhibition of HIF-1 impairs the induction of FASN under hypoxia Increased binding of SREBP-1 to the FASN promoter under hypoxia	[17]
TG Synthesis			
AGPAT2	HIF-1 Positive	Increased expression HIF-1 binds to the promoter of *AGPAT2* and activates its transcription	[20]
Lipin-1	HIF-1 Positive	Increased expression HIF-1 binds to the promoter of *LPIN1* and activates its transcription	[21]
LD Accumulation			
PLIN2	HIF-2 Positive	Increased expression HIF-2α depletion inhibits the induction of *PLIN2* under hypoxia	[23]
HIG2	HIF-1 Positive	Increased expression HIF-1 binds to the promoter of *HIG2* and activates its	[24]

Functional Category /Protein Name	HIF Isoform & Effect	Outcome & Experimental Evidence	Ref.
		transcription	
β-Oxidation			
PGC-1α	HIF-1 & HIF-2 Negative	Reduced expression HIF-1α or HIF-2α depletion inhibits reduction of PGC-1α expression under hypoxia	[27]
CPT1A	HIF-1 & HIF-2 Negative	Reduced expression HIF-1α or HIF-2α depletion inhibit reduction of CPT1A expression under hypoxia	[27] [28]
MCAD	HIF-1 Negative	Reduced expression HIF-1α depletion inhibits reduction of MCAD expression under hypoxia	[29]
LCAD	HIF-1 Negative	Reduced expression HIF-1α depletion inhibits reduction of LCAD expression under hypoxia	[29]
PGC-1β	HIF-1 Negative	Reduced expression HIF-1α depletion inhibits reduction of PGC-1β expression under hypoxia	[29]

2. Hypoxia-Inducible Factors-Dependent Regulation of Lipid Metabolism in Cardiovascular Disease

Deregulation of the adipose tissue function and ectopic lipid accumulation is a main factor for the development of cardiovascular disease. A number of studies indicate that many of the HIF-target genes involved in lipid metabolism can contribute to cardiovascular pathogenesis. Upregulation of LRP1 by HIF-1 contributes to the deposition of lipids in atherosclerotic plaques in human vascular smooth muscle cells, while vascular cell LRP1 and HIF-1α co-localize in immunohistochemical samples of human advanced atherosclerotic plaques [9]. Another HIF-1 target gene, HIG2/Hilpda, stimulates lesion formation and development of atherosclerosis, as the expression of various atherosclerotic pathogenic markers was decreased by conditional Hilpda KO in macrophages of ApoE-/- mice [25]. This is in line with older in vitro studies showing hypoxia-dependent formation of cytosolic lipid LDs in macrophages [31]. Concerning the direct effects of hypoxia on cardiac function, experiments with ventricular HIF-1α KO mice have shown that HIF-1-induced PPARγ activation contributes to metabolic reprogramming and development of contractile dysfunction under pathological stress [6]. Similarly, VHL null hearts, in which HIFs were activated, developed a number of features associated with human heart failure, including lipid accumulation, myofibril rarefaction, altered nuclear morphology, myocyte loss, and fibrosis, resulting in premature death [32]. These pathogenic features were prevented by the simultaneous cardiac ablation of both VHL and HIF-1α, strongly suggesting the involvement of HIF-1. Interestingly, deletion of VHL specifically in mice adipocytes also caused the development of lethal cardiac hypertrophy, which was, however rescued by genetic deletion of HIF-2α but not HIF-

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