

REVIEW ARTICLE

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The crosstalk between HIFs and mitochondrial dysfunctions in cancer development

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Abstract

Mitochondria are essential cellular organelles that are involved in regulating cellular energy, metabolism, survival, and proliferation. To some extent, cancer is a genetic and metabolic disease that is closely associated with mitochondrial dysfunction. Hypoxia-inducible factors (HIFs), which are major molecules that respond to hypoxia, play important roles in cancer development by participating in multiple processes, such as metabolism, proliferation, and angiogenesis. The Warburg phenomenon reflects a pseudo-hypoxic state that activates HIF-1 α . In addition, a product of the Warburg effect, lactate, also induces HIF-1 α . However, Warburg proposed that aerobic glycolysis occurs due to a defect in mitochondria. Moreover, both HIFs and mitochondrial dysfunction can lead to complex reprogramming of energy metabolism, including reduced mitochondrial oxidative metabolism, increased glucose uptake, and enhanced anaerobic glycolysis. Thus, there may be a connection between HIFs and mitochondrial dysfunction. In this review, we systematically discuss the crosstalk between HIFs and mitochondrial dysfunctions in cancer development. Above all, the stability and activity of HIFs are closely influenced by mitochondrial dysfunction related to tricarboxylic acid cycle, electron transport chain components, mitochondrial respiration, and mitochondrial-related proteins. Furthermore, activation of HIFs can lead to mitochondrial dysfunction by affecting multiple mitochondrial functions, including mitochondrial oxidative capacity, biogenesis, apoptosis, fission, and autophagy. In general, the regulation of tumorigenesis and development by HIFs and mitochondrial dysfunction are part of an extensive and cooperative network.

Facts

- Mitochondrial dysfunction is closely related to different types of disease, including cancer.
- HIFs as major molecules that respond to hypoxia and regulate multiple processes such as metabolism, proliferation, and angiogenesis.

- The Warburg effect (aerobic glycolysis), a core hallmark of cancer cells, results in the activation of HIF-1 α , and is related to mitochondrial dysfunction.
- Both HIFs and mitochondrial dysfunction can cause complex reprogramming of energy metabolism.

Open questions

- Is there a relationship between HIFs and mitochondrial dysfunction in cancer development?

Introduction

Mitochondria are essential cellular organelles that play important roles in regulating cellular energy, metabolism, survival, and proliferation^{1,2}. Furthermore, dysfunction of mitochondria is closely associated with different types of

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diseases, including cancer³. Mitochondrial dysfunction of cancer cells includes enhancing glycolysis, reducing oxidative phosphorylation (OXPHOS), decreasing apoptosis, and increasing resistance to radiotherapy^{4–6}. Mitochondrial dysfunction is also characterized by an inadequate number of mitochondria, aberrant mitochondrial morphology, dysfunction in electron transport, accumulation of mitochondrial reactive oxygen species (ROS), increased production of mitochondrial DNA (mtDNA) mutations, and oxidative damage to nucleic acids, proteins, and lipids^{7–9}. Reprogramming of mitochondrial metabolism is a common sign of cancer. Abnormal energetic metabolism of cancer cells is known as the Warburg effect, which includes increased glucose uptake and high rates of glycolysis in combination with increased production of lactic acid, even under normoxic conditions^{10–12}.

Hypoxia-inducible factors (HIFs) are major molecules that respond to hypoxia and regulate multiple processes such as metabolism, proliferation, and angiogenesis. All members are composed of two different subunits, including the α -subunit (HIF-1 α , HIF-2 α , or HIF-3 α) and β -subunit (HIF-1 β)^{13,14}. Under hypoxic conditions, HIF- α combines with HIF-1 β subunit to form a dimer, binds to hypoxia response elements (HREs), and causes expression of target genes^{15,16}.

Many studies have established the role of HIFs in managing different signaling pathways in cancer, including cellular metabolism, cell proliferation and survival, angiogenesis, apoptosis, autophagy, extracellular matrix remodeling, and others^{17,18}. The Warburg phenomenon reflects a pseudo-hypoxic state that activates HIF-1 α ^{19,20}. The product of the Warburg effect, lactate, also induces HIF-1 α and HIF-2 α production^{11,21,22}. However, Warburg proposed that aerobic glycolysis occurs due to a defect in the mitochondria²³. More importantly, both HIFs and mitochondrial dysfunction can cause complex reprogramming of energy metabolism, including reduced mitochondrial oxidative metabolism, increased glucose uptake, and enhanced anaerobic glycolysis^{4–6,18,24}. Thus, there is likely a connection between HIFs and mitochondrial dysfunction.

In fact, multiple studies have reported various relationships between HIFs and mitochondria. First, the stability and activity of HIFs are closely influenced by mitochondrial dysfunction related to the tricarboxylic acid (TCA) cycle, components of the electron transport chain (ETC), mitochondrial respiration, and mitochondria-related proteins. Furthermore, activation of HIFs can cause mitochondrial dysfunction by affecting numerous mitochondrial functions (i.e., mitochondrial oxidative capacity, biogenesis, apoptosis, fission, and autophagy). In this review, we systematically discuss the role of the crosstalk between HIFs and mitochondrial dysfunctions in cancer development.

Role of mitochondrial dysfunction in cancer development

Mitochondria are essential organelles within the cell that regulate cellular energy, metabolism, survival, and proliferation. The mitochondria supply energy in the form of adenosine triphosphate (ATP), the synthesis of which is driven by a proton gradient^{1,2,25}. Mitochondria are also recognized as a metabolic hub as the TCA cycle, which takes place within the mitochondria, coordinates the metabolism of carbohydrates, proteins, and fats into ATP²⁶. Thus, with such a significant cellular role, dysfunction of the mitochondria has been shown to be related to various diseases, including cancer³. Mitochondrial dysfunction alters cellular energy metabolism, which contributes to carcinogenesis and tumor development^{4,27,28}.

Mitochondrial dysfunction of cancer cells can include increasing glycolysis, reducing OXPHOS, decreasing apoptosis, and increasing resistance to radiotherapy^{4–6}. In addition, mitochondrial dysfunction is often characterized by an inadequate number of mitochondria, aberrant mitochondrial morphology, dysfunction in electron transport, accumulation of mitochondrial ROS, increased production of mtDNA mutations, and oxidative damage to nucleic acids, proteins, and lipids^{7,8}.

The reprogramming of mitochondrial metabolism is a common hallmark of cancer¹⁰. Cancer cells often switch metabolism from OXPHOS to aerobic glycolysis in order to produce energy, which can allow them to better adapt to the hypoxic tumor microenvironment and aid rapid proliferation^{29,30}. The Warburg effect is associated with increased levels of glucose uptake and high rates of glycolysis, combined with the production of lactic acid, even in the presence of oxygen¹¹. However, Warburg proposed that aerobic glycolysis occurs due to defects in mitochondria²³. In addition, glycolysis is further enhanced by variation of mitochondrial function as well as aberrant accumulation of metabolites by affecting the nuclear genome through HIF-dependent pathways and histone modification²¹. The production of the Warburg effect and lactate also induces HIF-1 α and HIF-2 α ^{11,21,22}. HIF-1 α , in turn, drives the expression of several glycolytic enzymes, including phosphofructokinase, glucose transporter-1, -3, hexokinase II (GLUT-1, -3), lactate dehydrogenase A (LDHA), and aldolase, which is involved in reprogramming aerobic glycolysis^{31,32}. Moreover, the Warburg effect can be inhibited by targeting HIF-1 α ³³.

Role of HIFs in tumor progression

Production of HIFs is the major cellular response to hypoxia. All members of the HIF family are comprised of two different subunits, including an oxygen-labile α -subunit (HIF-1 α , HIF-2 α , or HIF-3 α) and a constitutively expressed β -subunit (HIF-1 β). HIF-1 α is ubiquitously expressed across all tissues, while HIF-2 α and HIF-3 α are expressed in

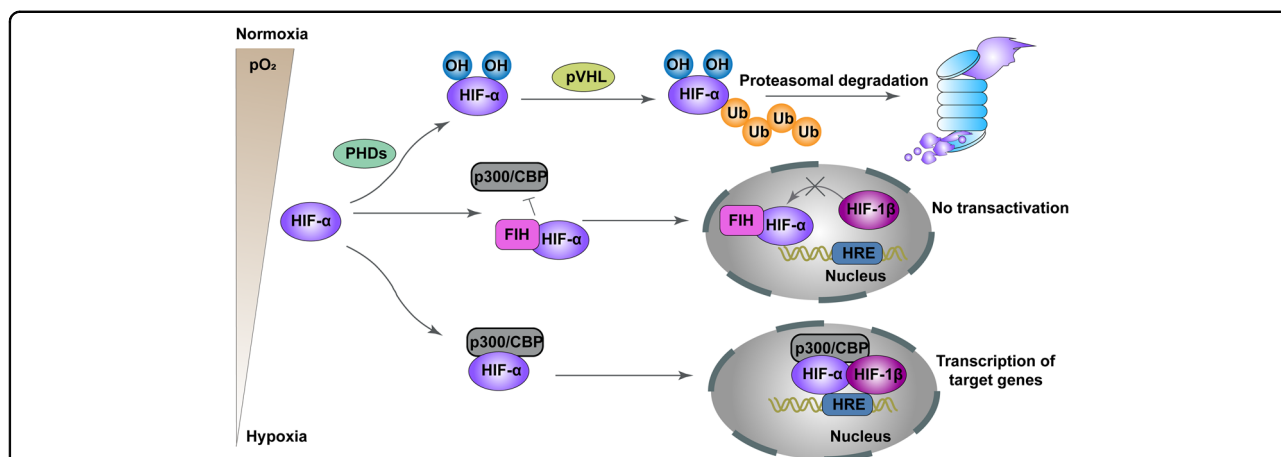


Fig. 1 Schema of regulation of HIF-α degradation and transcriptional activity. Under conditions of normoxia, HIF-1α and HIF-2α are continuously degraded through the key oxygen sensor PHD1–3, especially PHD2 which enables HIF-α to bind to the pVHL. FIH also inhibits HIF-1α by binding to HIF-α and impeding the combination of HIF-α to the transcriptional coactivators CBP and p300. Under hypoxic conditions, the hydroxylation of HIFα is restrained, leading to stabilization of HIF-α. Next, HIF-α dimerizes with HIF-1β to comprise a transcriptional activation complex, which binds to HRE and stimulates the transactivation of target genes.

specific tissues^{13,14}. While oxygen is available, HIF-1α and HIF-2α are constantly degraded by the key oxygen sensor prolyl hydroxylase (PHD)1–3, particularly PHD2 which enables HIF-α to bind to pVHL. Factor inhibiting HIF-1 (FIH-1) can also inhibit HIF-1α by binding to HIF-1α and inhibiting its transactivation^{34,35}. However, under hypoxic conditions, PHD is inhibited, which allows HIF-α to accumulate and further dimerize with the HIF-1β subunit, bind to HRE, and lead to the activation of numerous genes (Fig. 1)^{36–38}. However, HIF-3α plays a negative role in hypoxia-related gene expression, and overexpression of HIF-3α is associated with attenuation of angiogenesis and proliferation³⁹.

Cancer cells frequently encounter hypoxia, and HIFs play a major role in the cellular mechanisms that are triggered in response to hypoxia⁴⁰. Moreover, HIFs have a wide range of target genes that function to manage different types of signaling pathways in cancer (Fig. 2). As an example, HIFs modulate cellular metabolism, cell proliferation and survival, angiogenesis, apoptosis, autophagy, extracellular matrix remodeling, and additional tumor properties^{17,18}.

Reprogramming of energy metabolism

Cancer is both a genetic and metabolic disease due to mitochondrial dysfunction. Therefore, energy metabolism pathways are reprogrammed to meet the requirements of tumor cell proliferation and survival⁴¹. It has been shown that cancer cells prefer glycolysis as their energy source instead of OXPHOS, even in the presence of oxygen. Certain molecules like HIFs are essential to the survival of cancer cells in a hypoxic environment as transcriptional regulators of aerobic glycolysis^{42,43}. The activation of HIFs in cancer can cause complex reprogramming of energy

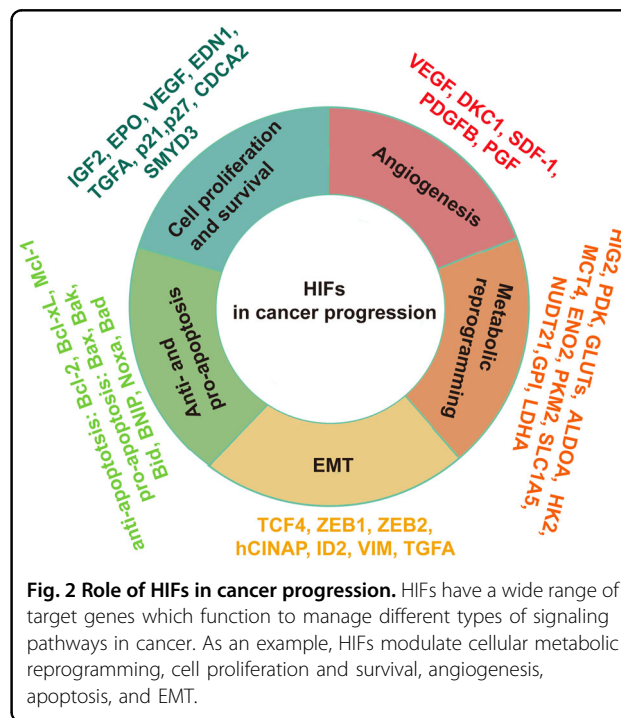


Fig. 2 Role of HIFs in cancer progression. HIFs have a wide range of target genes which function to manage different types of signaling pathways in cancer. As an example, HIFs modulate cellular metabolic reprogramming, cell proliferation and survival, angiogenesis, apoptosis, and EMT.

metabolism, including mitochondrial oxidative metabolism, glucose catabolism, glucose uptake, and energy production¹⁸. Activation of HIF-1 suppresses mitochondrial oxidative capacity by decreasing oxygen consumption, and preserves oxygen homeostasis in hypoxia. HIF-1 activation inhibits adipose triglyceride lipase-mediated lipolysis by hypoxia-inducible gene 2 (HIG2), leading to lipid droplet (LD) storage and declining mitochondrial fatty acid oxidation under hypoxia⁴⁴. Furthermore, HIF-1α

inhibits pyruvate conversion to acetyl-CoA by regulating pyruvate dehydrogenase kinase (PDK). Pyruvate plays a significant role in OXPHOS and mitochondrial electron transport⁴⁵.

HIF-1 α also regulates tumor growth by adjusting anaerobic and aerobic oxidation of glucose⁴⁶. Glycolytic reprogramming is a key feature of metabolic reprogramming in tumors; thus, HIF-1 α regulates glycolytic reprogramming by directly stimulating the transcription of all 12 enzymes that are necessary for glycolysis^{47,48}. As an example, neuronal PAS domain protein 2 (NPAS2) upregulates glycolytic genes *GLUT1*, *HK2*, *ALDOA*, *GPI*, *MCT4*, *ENO2*, and *PKM2* by transcriptional upregulation of HIF-1 α in hepatocellular carcinoma (HCC)⁴⁹.

Moreover, HIF is related to glutamine metabolism in cancer development⁵⁰. As an example, HIF-2 α is involved in glutamine-induced ATP production by regulating the expression of *SLCIA5* variant in pancreatic cancer cells⁵¹. HIF-1 α is also involved in glutamine metabolism by regulating *NUDT21* in small cell lung cancer⁵².

Cell proliferation and survival

The alterations in mitochondrial OXPHOS, energy production, glucose uptake and oxidation, and angiogenesis regulated by HIF-1 leads to enhanced cancer cell proliferation and survival¹⁸. The HIF pathway is involved in cancer cell proliferation through several molecular mechanisms. Vascular endothelial growth factor (*VEGF*), erythropoietin, insulin-like growth factor-2 (*IGF2*), transforming growth factor- α (*TGFA*), and endothelin 1 (*EDNI*) are particularly noteworthy target genes of the HIF pathway that are associated with aiding cell proliferation and survival. HIFs can alter cell cycle progression by directly targeting cyclin D1 and indirectly modulating p21 and p27^{53–55}. In addition, the cell division cycle-associated protein (CDCA) family has vital functions in cell division and proliferation. CDCA2 promotes cell proliferation in prostate cancer and is known to be directly regulated by the HIF-1 α pathway⁵⁶. Pleomorphic adenoma gene like-2 (*PLAGL2*) has been shown to play an important role in tumorigenesis. In particular, the *PLAGL2*-*EGFR*-HIF-1/2 α signaling loop has been reported to promote cellular proliferation in HCC⁵⁷. SET and MYND domain-containing protein 3 (*SMYD3*) is a histone methyltransferase that is associated with gene transcription and oncogenesis. Depletion of *SMYD3* leads to an inhibition of renal cell carcinoma (RCC) cell proliferation, and HIF-2 α can directly bind to the *SMYD3* promoter in order to stimulate *SMYD3* transcription and expression⁵⁸. In Jak2V617F-positive myeloproliferative neoplasms, HIF-1 is required for cell growth and survival. Furthermore, suppression of HIF-1 binding to HREs by echinomycin causes damage to survival and growth of cancer cells by stimulating apoptosis and cell cycle arrest⁵⁹.

Angiogenesis

Inhibiting tumor angiogenesis by preventing the HIF-1 α /VEGF/VEGFR-2 signaling pathway is believed to be a potential solid tumor-targeted therapy⁶⁰. The HIF-1 α /VEGF pathway is activated by multiple pathways⁶¹. Dyskeratosis congenita 1 is dysregulated across several cancers. In colorectal cancer (CRC), *DKC1* stimulates angiogenesis and metastasis by stimulating HIF-1 α and VEGF expression⁶². In addition to VEGF, HIFs also modulate angiogenic growth factor levels, including platelet-derived growth factor B, stromal-derived factor-1, and placenta growth factor⁵⁵. However, HIF-3 α hampers angiogenesis and proliferation by forming a complex with HIF-1 α and preventing HIF transcription⁶³.

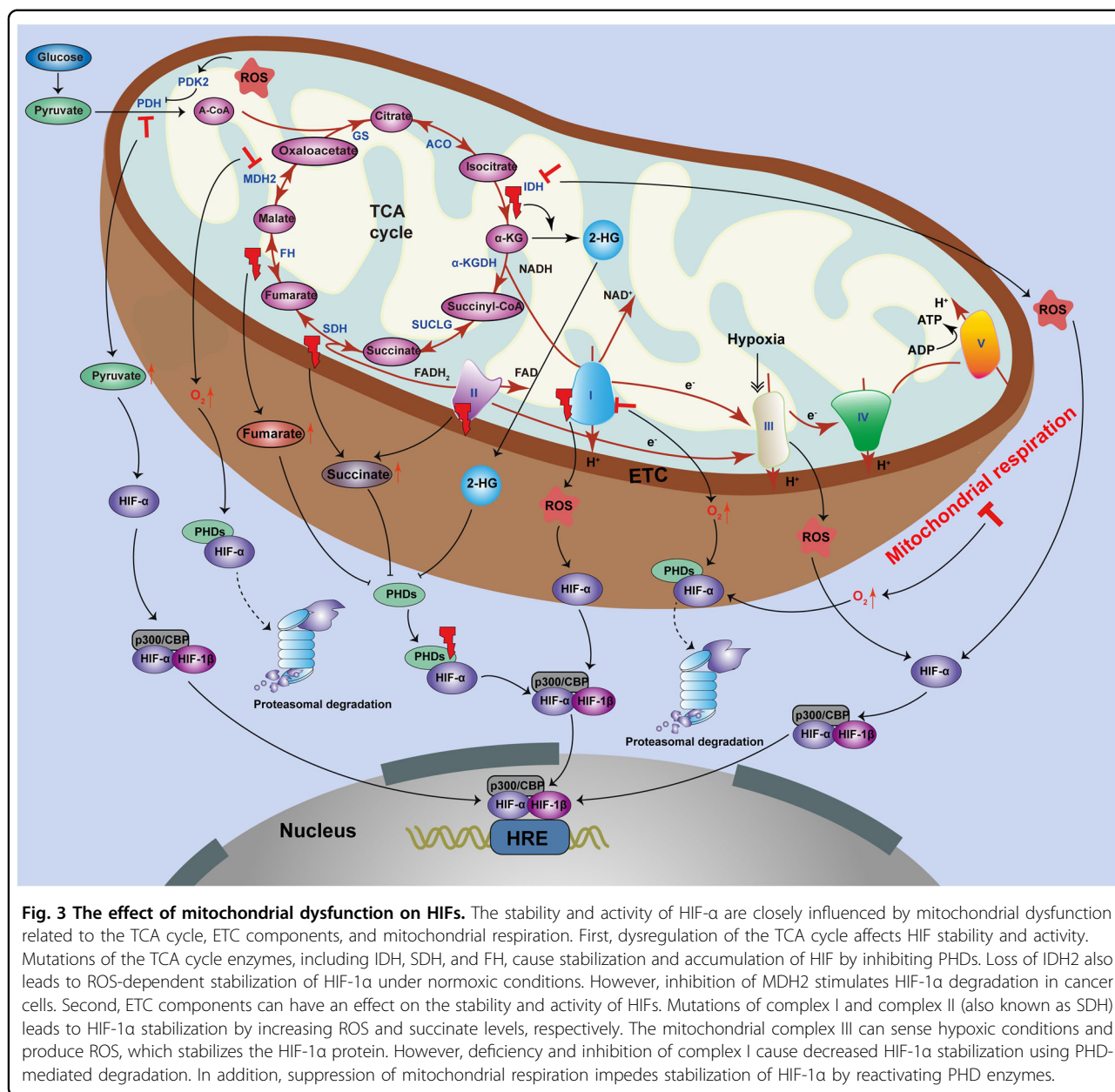
Apoptosis and autophagy

Studies conducted on the effect of HIF-1 α on apoptosis have conflicting results. Many reports propose that HIF-1 α can induce as well as antagonize apoptosis. HIF-1 α is known to regulate both proapoptotic proteins (BNIP, Noxa, Bid, Bax, Bak, and Bad) and antiapoptotic proteins (Bcl-2, Bcl-xL, and Mcl-1)⁶⁴. The Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) is a proapoptotic member of the Bcl-2 family that can be activated by HIF⁶⁵. Although it has been strongly recommended that HIF-1 α is an effective inducer of cellular apoptosis, recent studies indicate that apoptosis among colon cancer cells is enhanced by downregulating expression of HIF-1 α and Slug with dictamnine⁶⁶. Lung cancer apoptosis is also induced by inhibition of HIF-1 α /VEGF signaling in A549 cells with tetrandrine⁶⁷. The impact of HIF-2 on cellular apoptosis has been studied to a lesser extent, but points specifically to an antiapoptotic function⁶⁴. For instance, HIF-2 α knockdown promotes apoptosis and autophagy under hypoxic conditions in cervical cancer⁶⁸.

Increasing evidence demonstrates that HIF-1 is directly involved in regulating mitochondrial autophagy by inducing expression of BH3-only proteins (BNIP3 and BNIP3L), which enables the release of Beclin-1, a significant regulator of autophagy⁶⁹. The HIF-1 α /BNIP3 signaling pathway has a significant function in activating hypoxia-induced autophagy in adenoid cystic carcinoma⁷⁰. Furthermore, HIF-1 α regulates hypoxia-stimulated autophagy by translocating ANKRD37, whose higher expression is correlated with decreased survival rates in colon cancer⁷¹. A novel HIF-1 α /VMP1-autophagy pathway has also been reported in colon cancer cells⁷².

Epithelial-mesenchymal transition (EMT)

EMT is a crucial regulator of cancer progression and metastasis⁷³. HIFs are involved in EMT by the regulation of multiple pathways. HIF-1 α inhibits E-cadherin expression by activating Snail, which facilitates EMT. In CRC cells, HIF-1 α binds to β -catenin by competing with



the transcription factor 4, which leads to induction of EMT. Moreover, HIF-1 α enhances EMT and cancer metastasis by initiating the expression of zinc-finger E-box-binding homeobox 1 (ZEB1)⁷⁴. In cervical cancer cells, HIF-1 induces EMT by binding to the human coilin-interacting nuclear ATPase protein (*hCINAP*) promoter and initiating expression of the gene under hypoxic conditions⁷⁵. In HCC, thioredoxin-promoting EMT is HIF-2 α -dependent⁷⁶. In addition, ZEB2, inhibitor of differentiation 2, vimentin, and TGFA are all involved in EMT and are regulated by HIF expression⁵⁵.

Interplay between mitochondrial dysfunctions and HIFs

Effects of mitochondrial dysfunction on HIFs

The stability and activity of HIFs are closely related to mitochondrial dysfunction (Fig. 3). First, dysregulation of the TCA cycle can have an effect on the stability and activity of HIFs. The mitochondrial TCA cycle forms a center in cellular metabolism due to the participation of multiple substrates, and disruption or deregulation of the TCA cycle enzymes can cause metabolic-mediated stabilization of HIF-1 α by inhibiting PHDs^{77,78}.

As an example, isocitrate dehydrogenase 2 (IDH2) is a TCA cycle enzyme that has been shown to be mutated in subsets of acute leukemias and gliomas. Loss of IDH2 in prostate cancer cells leads to ROS-dependent stabilization of HIF-1 α under normoxic conditions, which is essential for increased mitochondrial trafficking and tumor cell movements¹⁰. IDH1 and IDH2 mutations fail to catalyze the conversion of isocitrate to α -ketoglutarate (α -KG), which leads to gaining de novo enzymatic activity. Eventually, this results in the reduction of α -KG to the metabolite 2-hydroxyglutarate (2-HG), which, in turn, inhibits PHDs, causing stabilization and accumulation of HIFs^{79,80}.

Succinate dehydrogenase (SDH; also known as mitochondrial complex II), fumarate hydratase (FH), and malate dehydrogenase 2 (MDH2) are key TCA cycle enzymes, alterations of which have been shown to stimulate the activation of HIF signaling pathway. In pheochromocytomas (PHEOs) and paragangliomas (PGLs), SDH mutations cause high succinate accumulation. As a competitive inhibitor of PHDs, succinate leads to the activation of HIF-1 α signaling pathway and the consequent expression of HIFs target genes. In the Hep3B hepatoma cell line, silencing of SDHB also stabilizes HIF-1 α /2 α and causes enrichment of functionally diverse genes, including hypoxia-related genes. Germline mutations of multiple subunits (SDHB/C/D) in RCC are associated with SDH-RCC hereditary cancer syndrome, a new type of aggressive kidney cancer. SDH mutations result in increased succinate levels, leading to the accumulation of HIFs in RCC. Inactivation or mutations of FH cause fumarate accumulation, and similar to succinate, fumarate causes HIF-1 α activation by inhibition of PHD^{81–85}. Mutations in SDH and FH have also been shown in patients with uterine and skin leiomyoma and papillary renal carcinoma. The consecutive accumulation of succinate and fumarate result in HIFs stabilization. In the SK-N-BE² neuroblastoma cells, fumarate, but not succinate, has been shown to stabilize HIF-1 α under normoxic conditions, while both fumarate and succinate induce HIF-2 α ⁸⁶. Correspondingly, a reduction of transketolase in breast cancer cells leads to decreased HIF-1 α by increasing levels of SDH, FH, and MDM2, causing inhibition of tumor metastasis⁸⁷. MDH2 is a TCA cycle enzyme that is essential for energy production through respiration. Inhibition of MDH2 restrains mitochondrial respiration and causes a reduction in oxygen consumption, thus stimulating HIF-1 α degradation in cancer cells^{88,89}. As mentioned before, acid-enhanced production of L-2-HG leads to stabilization of HIF-1 α under normoxic conditions. Furthermore, acid-enhanced conversion of α -KG to L-2-HG also can be stimulated by LDHA and MDH2. Thus, combined targeting of both LDHA and MDH2 abolishes L-2-HG production and reverses the

ability of cells to stabilize HIF-1 α ⁹⁰. Mitochondrial aconitase, the second enzyme of the TCA cycle, is involved in tumor development, which originates from the discovery that hypoxic conditions upregulate the HIF-1 α target miR-210^{83,91}.

Second, the stability and activity of HIFs can be influenced by components of the ETC. For instance, genetic ablation or pharmacologic inhibition of ETC components hinders stabilization of HIF- α in hypoxia⁸⁴. In the CRC cell line, HCT116, and the osteosarcoma cell line, 143B, having a nuclear-encoded NDUFS3 knockout, where respiratory complex I deficiency leads to the PHD-mediated degradation of HIF-1 α ⁹². This was confirmed in another study⁹³. A small inhibitor of complex I, AG311, has been shown to reduce HIF-1 α stabilization by increasing oxygen tension in two breast cancer mouse models (MDA-MB-231 and MDA-MB-435). Furthermore, mutations of *MT-ND1*, *MT-ND2*, and *MT-ND5* genes, which encode components of complex I and play a role in OXPHOS, have been widely detected in various cancers. Both the *MT-ND1* (missense m.3460G > A, A52T) and *MT-ND2* (m.4776G > A, A103T) mutations are able to form tumors and represent a potential tumorigenic link to cytoplasmic ROS accumulation and HIF-1 α stabilization. However, the osteosarcoma cybrids did not form tumors in vivo when the *MT-ND1*m.3571insC frameshift mutation induces accumulation of NADH, which, in turn, inhibits α -KG dehydrogenase, leading to increased α -KG and HIF-1 α destabilization^{2,94}.

SDH, an enzyme of the TCA, is also known as complex II and is comprised of four subunits: SDHA, SDHB, SDHC, and SDHD. SDH is responsible for producing mitochondrial energy and suppressing tumor activity. Mutations in SDH can cause succinate accumulation, which promotes glycolysis by stabilizing HIF-1 α , as described earlier^{95,96}. The R22X nonsense SDHD mutation of complex II has been shown to be present in hereditary PGL and PHEO, leading to a loss of complex II activities and succinate accumulation. Succinate has been shown to inhibit the activity of PHD, and it subsequently induces HIF-1 α stabilization^{2,5}. Mitochondrial complex III can sense hypoxic conditions and produce ROS, which stabilizes the HIF-1 α protein. It has been reported that binding of terpestacin to the ubiquinol-cytochrome *c* reductase binding protein (UQCRB) subunit of complex III restrains HIF-1 α stabilization by inhibiting ROS production, causing suppression of angiogenesis, which coincides with decreased VEGF levels⁹⁷. Thus, the ETC components including complex I, complex II (SDH), and complex III play an important role in HIF stabilization^{2,98}.

In addition, suppression of mitochondrial respiration causes oxygen redistribution from mitochondria to the cytoplasm, and obstructs stabilization of HIF-1 α by

reactivating the PHD enzymes⁹⁹. Moreover, mutations in proteins that are involved in OXPHOS can also assist in increasing cellular ROS levels, which are regulated by catalase, glutathione peroxidase, and superoxide dismutase. The increased ROS production is known to upregulate HIF-1 α expression by activating the PI3K/AKT signaling pathway. ROS production also activates PDK2, which suppresses pyruvate dehydrogenase (PDH) and leads to the accumulation of pyruvate, which can activate HIF-1 α ^{2,100}. In triple-negative breast cancer (TNBC), MYC and MCL1 cooperate in order to maintain chemotherapeutic resistance of CSCs by increasing mitochondrial OXPHOS, leading to increased levels of ROS and accumulation of HIF-1 α ¹⁰¹. Furthermore, in CRC, inhibition of the c-Myc/ROS signaling pathway increases HIF-1 α degradation, causing cell death under hypoxic conditions¹⁰².

Last, in addition to enzymes related to the TCA cycle, ETC components, and mitochondrial respiration, additional mitochondrial-related proteins can also have an effect on the stability and activity of HIFs. SIRT3, a member of Sirtuin (SIRT) family, is a major mitochondrial deacetylase. Reduced expression of SIRT3 in cancer cells stimulates ROS production, leading to HIF-1 α stability and increased aerobic glycolysis. SIRT4, which plays a significant role in mitochondrial behaviors, is associated with increased ROS production, leading to stabilization of HIF-1 α protein by hindering the catalytic activity of PHD¹⁰³. Signal transducer and activator of transcription (STAT) proteins are known to be essential regulators of metabolism. To date, evidence exists that STAT3 and STAT5 can be found in mitochondria, and they influence the regulation of metabolic enzymes by mediating upregulation of HIF-1 α expression. The constitutive activation of STAT3 induces HIF-1 α expression, stimulates glycolysis, and decreases mitochondrial activity. Furthermore, STAT5 can induce HIF-2 α expression¹⁰⁴. In addition, the stability and activity of HIFs are associated with pVHL, casein kinase 2, and monoamine oxidase A, which are mitochondrial-related proteins^{105–107}.

Function of HIFs on mitochondrial dysfunction

The activation of HIFs can cause mitochondrial dysfunction by affecting multiple mitochondrial activities, including mitochondrial oxidative capacity, biogenesis, apoptosis, fission, and autophagy, through various mechanisms (Fig. 4).

HIF-1 activation downregulates mitochondrial oxidative capacity by decreasing oxygen consumption and preserving oxygen homeostasis under hypoxic conditions. Earlier studies did not fully elucidate the mechanism by which HIF-1 functions to accelerate these two metabolic alterations. Recent studies have shown that HIF-1 activation inhibits adipose triglyceride lipase-mediated lipolysis by HIG2,

leading to LD storage and declining mitochondrial fatty acid oxidation under hypoxic conditions⁴⁴. Moreover, mitochondrial function and oxygen consumption are negatively regulated by HIF-1 by stimulating PDK, which inhibits PDH, and, consequently, blocks the flow of pyruvate into the TCA cycle⁷⁴. If the inhibition of pyruvate flow is complete, the TCA cycle and OXPHOS would have to stop¹⁰⁸. It has also been suggested that overexpression of HIF-1 α contributes to inhibition of mitochondrial and oxidative damage induced by exposing antitumor drugs¹⁰⁹. HIF-1 α also stimulates catabolism of mitochondrial serine and NADPH production, which regulates mitochondrial redox by transactivation of serine hydroxymethyltransferase 2 and phosphoglycerate dehydrogenase (PHGDH), respectively. Reduced NADPH is used to maintain glutathione, the primary cellular antioxidant in a reduced situation. Furthermore, PHGDH-deficient breast cancer stem cells exhibit heightened oxidant levels and apoptosis in response to treatment with carboplatin or doxorubicin^{110–112}.

Aberrant expression of miR-210 has been primarily correlated to the accumulation of HIF-1 α . Meanwhile, it has been shown to be upregulated across various malignancies, including head and neck cancers, breast cancers, and pancreatic cancer. Furthermore, increased expression of miR-210 restrains the expression of the Fe-S cluster assembly proteins ISCU-1 and ISCU-2, which further restricts mitochondrial ROS generation^{110,113}. It has been shown that miR-210 expression in proximal tubule cells may induce a shift of energetic metabolism from OXPHOS to glycolysis through the loss of mitochondrial inner membrane. Furthermore, a marked reduction of mitochondrial inner membrane and the metabolic shift towards glycolysis can imitate early events of clear cell renal cell carcinoma (ccRCC) development¹¹³. While promoting glycolytic activity, HIF-1 reduces mitochondrial activity by inducing activation of the less active ETC components, including NDUFA4L2, COX4-2, complex I, and complex IV, in order to delay electron transfer through the ETC. Hence, the process blocks the accumulation of ROS and reduces ROS-mediated apoptosis. In addition, HIF-1 α prompts the expression of mitochondrial LON peptidase, which leads to degradation of the mitochondrial protein COX4-1 in order to decrease mitochondrial flux under hypoxic conditions¹¹⁴. It has also been demonstrated that HIF-1 α is able to prevent the metabolism of coenzyme A (CoA) in mitochondria, as well as mitochondrial biogenesis¹¹⁵.

NPAS2, a critical oncogene in hepatocellular carcinogenesis, plays an important role in HCC tumor progression. It has been demonstrated that NPAS2 inhibits mitochondrial biogenesis and OXPHOS by downregulating peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α) by transcriptionally

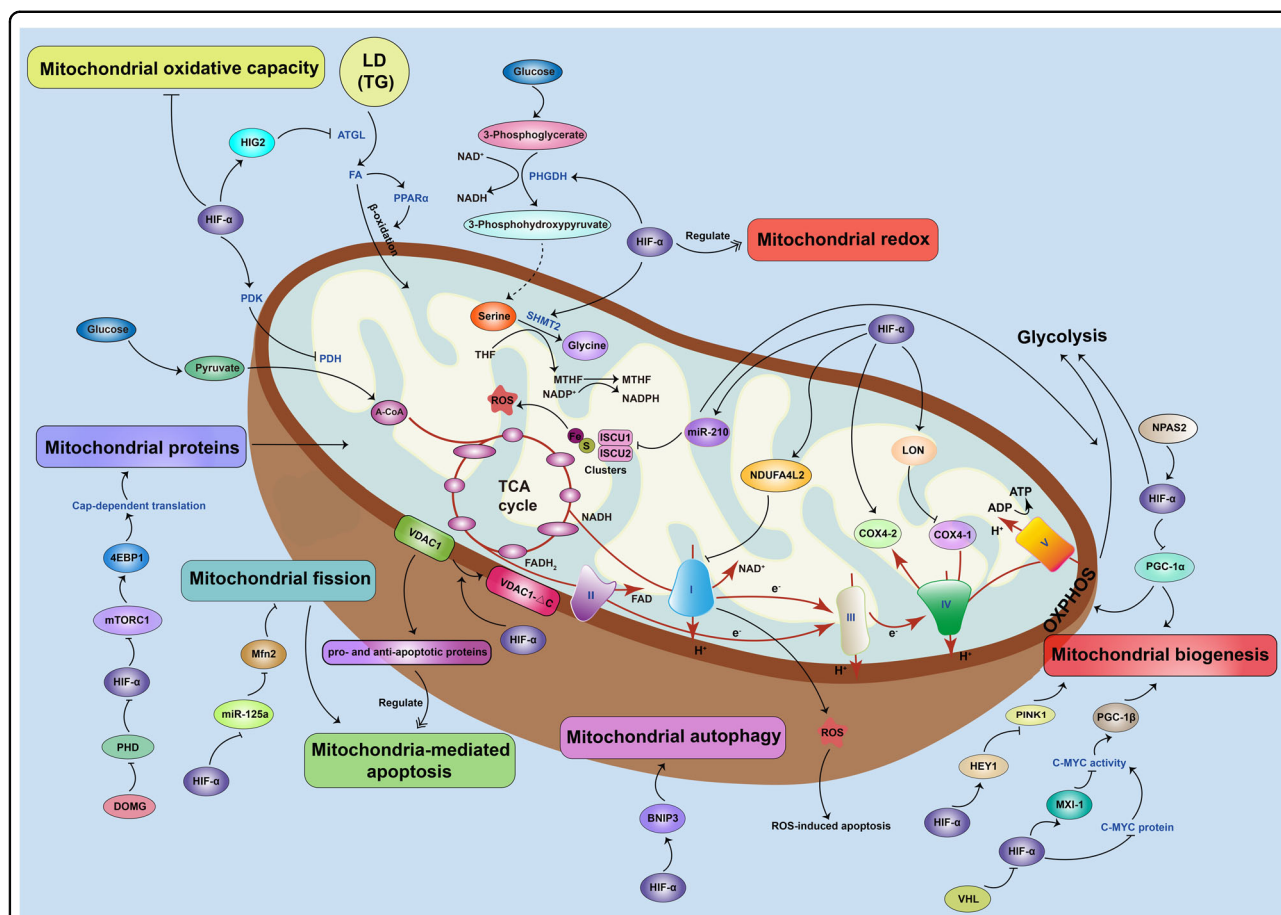


Fig. 4 Function of HIFs on mitochondrial dysfunction. HIFs have an effect on multiple mitochondrial functions, including mitochondrial oxidative capacity, OXPHOS, biogenesis, apoptosis, fission, and autophagy. HIF-1 activation downregulates mitochondrial oxidation by inhibiting ATGL-mediated lipolysis via HIG2, which leads to LD storage and subsequently declines mitochondrial FA oxidation under hypoxic conditions, and by inducing PDK, which inhibits PDH, thereby inhibiting the flow of pyruvate into the TCA cycle. HIF-1 also regulates mitochondrial redox by inducing mitochondrial serine catabolism and the production of NADPH. Furthermore, miR-210, which is upregulated by HIF-1, restrains expression of the Fe-S cluster assembly proteins ISCU-1 and ISCU-2, which further restricts mitochondrial ROS generation and induces a shift of energy metabolism from OXPHOS to glycolysis. HIF-1 stimulates the less active ETC components, including NDUFA4L2, COX4-1, COX4-2, complex I, and complex IV, to delay the electron transfer through the ETC, therefore blocking the accumulation of ROS and reducing ROS-mediated apoptosis. HIF-1 α reduces mitochondrial biogenesis by targeting PGC-1 α , MXI, and HEY1. Meanwhile, NPAS2 increases the expression of glycolytic genes by transcriptionally upregulating HIF-1 α . HIF-1 also regulates apoptosis by promoting the formation of VDAC1- Δ C from VDAC1. Mitochondrial fission, which results in the activation of mitochondria-associated apoptosis, is negatively regulated by the HIF/miR-125a/Mfn2 pathways during carcinogenesis. Mitochondrial proteins can also be inhibited by suppression of the mTORC1/p70S6/S6 signaling pathway via action of HIF-1 α . HIF-1 α also induces BNIP3 to promote mitochondrial autophagy.

upregulating HIF-1 α in HCC cells. Furthermore, PGC-1 α also upregulates glycolytic genes through the transcriptional activation of HIF-1 α ⁴⁹. In addition, HIF-1 reduces mitochondrial biogenesis by targeting MAX interactor 1, which restrains C-MYC-mediated transcription of the peroxisome PGC-1 β . Apart from these, it has been shown that HIF decreases mitochondrial biogenesis by increasing HEY1 and transcriptionally repressing PTEN-induced putative kinase 1¹¹⁶.

The voltage-dependent anion channel 1 (VDAC1) is a protein present in the outer mitochondria membrane (OMM) that mediates the transport of nucleotides, Ca²⁺,

and additional metabolites via the OMM. VDAC1 also modulates mitochondria-mediated apoptosis by inducing the release of pro- and antiapoptotic proteins. Under hypoxic conditions, VDAC1 is truncated at the C terminus (VDAC1- Δ C). Studies have demonstrated that VDAC1- Δ C is highly expressed at the advanced stage of lung cancer. Furthermore, under hypoxic conditions, HIF-1 α expression activates a cascade of events that lead to VDAC1- Δ C formation in HeLa cells¹¹⁷. In pancreatic cancer cell line PANC-1, studies have shown that mitochondrial fission (involved in apoptosis, migration, and energy metabolism) is regulated by the HIF/miR-125a/

Mfn2 pathways during pancreatic carcinogenesis. Furthermore, miR-125a, which is negatively regulated by HIF-1, promotes cancer cell-mediated mitochondrial death by inducing mitochondrial fission, which leads to the activation of mitochondria-associated apoptotic pathways¹¹⁸.

Moreover, the expression of mitochondrial proteins can be inhibited by dimethylxaloylglycine, a PHD inhibitor, that results from the suppression of the mTORC1/p70SK/S6 signaling pathway through HIF-1 α ¹¹⁹. During hypoxia, HIF-1 induces BNIP3 to promote mitochondrial autophagy in order to contribute to chemoresistance and facilitate cell survival by cooperating with BECLIN-1 and ATG544^{110,120}.

Targeting HIF or mitochondria in cancer

Small-molecule inhibitors of HIFs have been identified as inhibiting numerous activities, including inhibition of HIF messenger RNA (mRNA) expression, HIF protein synthesis, transcriptional activities of HIF, a combination of HIF with its coactivators, heterodimerization of HIF- α and HIF- β , and the HREs-DNA binding. Some of the small-molecule inhibitors have been studied in a phase II or III clinical trial, including 2-methoxyestradiol (2ME2), tanespimycin, vorinostat, PT2385, PT2977, and CRLX101^{13,121}. Inhibition of HIFs can have a profound effect on mitochondrial function and can affect numerous processes such as mitochondrial OXPHOS, ROS accumulation, lipid peroxidation, and ATP generation. 2ME2, an inhibitor of HIFs, has been identified as a novel anticancer agent. In acute myeloid leukemia, 2ME2 increases ROS generation, and stimulates the mitochondrial apoptotic pathway by inhibiting HIF-1 α expression¹⁴. Vosaroxin, a quinolone-derivative anticancer agent, inhibits HIF-1 α protein synthesis and impedes the dimerization of HIF-1 α and HIF-1 β . Vosaroxin significantly increases levels of mitochondrial ROS and lipid peroxidation, and induces mitochondrial swelling and ATP generation by acting through the AMPK/Sirt3/HIF-1 pathway in the cervical cancer cell line HeLa¹²². Cardamonin, a chalcone isolated from *Alpinia katsumadai*, suppresses HIF-1 α expression at both the mRNA and protein levels by impeding the mTOR/p70S6K pathway. Cardamonin inhibits the growth of the TNBC MDA-MB-231 cells by suppressing HIF-1 α . Subsequently, it enhances mitochondrial OXPHOS and induces ROS accumulation¹²³. NDUFA4L2, a less active complex I subunit within the ETC, is significantly overexpressed in HCC and other human cancers. Furthermore, NDUFA4L2 is HIF-1-regulated in HCC cells. Mitochondrial activity and oxygen consumption are also increased by inhibition of the HIF-1/NDUFA4L2 pathway, which results in ROS accumulation and apoptosis¹¹⁴.

In addition, HIF-1 α is known to be a contributor to resistance to chemotherapy and radiation. In fact, many mechanisms involved in the activation of the HIF-1 α -mediated DNA repair pathway, metabolic reprogramming,

apoptotic inhibition, and autophagy activation have roles in HIF-1 α -mediated chemo-/radioresistance¹²⁴. Thus, HIF-1 α can be targeted to overcome chemo-/radioresistance. HIF-1 α has a central role in resistance of pancreatic ductal adenocarcinoma towards chemotherapy and radiotherapy. Inhibition of HSP90, a key chaperone protein of HIF-1 α , overcomes resistance to chemotherapy and radiotherapy in pancreatic cancer¹²⁵. Bortezomib, a reversible proteasome inhibitor, sensitizes esophageal squamous cancer cells to radiotherapy by decreasing HIF-1 α and VEGF expression¹²⁶.

Mitochondria-targeting drugs are also a promising and effective strategy for cancer treatment^{127,128}. Likewise, targeting mitochondrial function can also help alter HIF expression. AG311, a small anticancer molecule, has been shown to competitively inhibit complex I activity. HIF-1 α stabilization is decreased by inhibition of mitochondrial oxygen consumption with AG311 by increasing oxygen tension under hypoxic conditions⁹³. The ccRCC demonstrates inhibition of mitochondrial function and preferential use of glycolysis, even under normoxic conditions. Dichloroacetate, the PDK inhibitor, reactivates mitochondrial function, which includes enhancing respiration and levels of TCA metabolites (i.e., α -KG), and subsequently reduces HIF transcriptional activity in an FIH-dependent manner. FIH is associated with mitochondrial function as it requires α -KG as a cofactor¹²⁹. The UQCRB of mitochondrial complex III is a novel therapeutic target for cancer treatment. UQCRB inhibitors regulate mitochondrial function in glioblastoma stem-like cells by decreasing mitochondrial ROS generation, as well as the mitochondrial membrane potential. The inhibition of mitochondrial ROS generation through the use of UQCRB inhibitors block HIF activation¹³⁰.

Conclusions

An ever-increasing number of studies show that tumors are likely a complex disease associated with impairment of energetic metabolism. Cancer cells depend on metabolic adaptations in order to preserve energy production, support cell growth, and produce signaling molecules for various tumor-promoting activities. Therefore, it is essential to do an in-depth study of the process of metabolic adaptation in order to ascertain weaknesses of tumor metabolic pathways and establish an effective treatment strategy. Both HIFs and mitochondrial dysfunction are important regulatory factors that play a role in metabolic adaptations of cancer cells. Both of these mechanisms cause complex reprogramming of energy metabolism, including reduced mitochondrial oxidative metabolism, increased glucose uptake, and enhanced anaerobic glycolysis. Furthermore, dynamic changes to the response and use of oxygen by tumor cells are the source of abnormal energy metabolism in tumors. HIF and mitochondria are also two central weapons for tumor

cells to cope with changes in oxygen dynamics. Despite the fact that more evidence is needed to prove our hypothesis, this review reveals that a relationship between HIFs and mitochondria can actively promote a new understanding of tumor occurrence and development, and provide a novel entry point for the formulation of tumor prevention and treatment programs.

Numerous scientific studies have illustrated that the stability and activity of HIFs are closely influenced by mitochondrial dysfunction related to the TCA cycle, ETC components, mitochondrial respiration, and mitochondrial-related proteins. In addition, activation of HIFs can cause mitochondrial dysfunction by influencing multiple mitochondrial functions, including mitochondrial oxidative capacity, biogenesis, apoptosis, fission, and autophagy. In addition, targeting HIFs can not only affect mitochondria function but mitochondria-targeting drug can also affect the stability and activity of HIFs. In general, the regulation of tumorigenesis and development by HIFs and mitochondrial dysfunction are part of an extensive and cooperative network. However, the current studies have only investigated the regulation of HIFs or mitochondrial dysfunction from a single aspect, and have ignored their collaboration in regulating carcinogenesis and progression. Future research is needed to expose the full spectrum of interplay between HIFs and mitochondrial dysfunction in specific tumor settings, and to reveal how they synergistically influence the oxygen dynamics in cancer development. Novel insight into this process will likely open up additional diagnostic and therapeutic approaches that can help improve outcomes for patients with tumors.

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Author contributions

H.Z. and C.S., as co-corresponding authors, designed the framework for this review; C.X. and Z.D. were responsible for the retrieval and collation of relevant literature; J.Y. mainly provided suggestions and new ideas in the study of HIFs and mitochondrial dysfunctions; X.B. mainly wrote the paper; J.Z. and G.H. modified the paper; all authors approved the final version.

Ethical statement

This study did not require ethical approval.

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