v. 5, n. 2, 2025

International Journal of Human Sciences Research

Acceptance date: 23/01/2025

THE IMPACT OF HYPOXIA ON CARCINOGENESIS: MECHANISMS AND METABOLIC ALTERATIONS IN CANCER MICROENVIRONMENT

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Abstract: Hypoxia, or low oxygen availability, plays a major role in carcinogenesis by influencing the growth and metastasis of cancers. The lowered oxygen levels in rapidly growing tumors compel cancer cells to alter their molecular composition and metabolism in order to live and proliferate. Hypoxia-inducible factors (HIFs) mainly control these alterations; HIF-1α and HIF-2α, in particular, stimulate the expression of genes related to invasion, angiogenesis, metabolic reprogramming, and metastasis. These changes facilitate the development of tumors in hypoxic environments and increase resistance to traditional treatments. Hypoxia has an effect on a variety of cancer progression, increasing the risk of malignancy and decreasing the prognosis. This study investigates the fundamental processes by which hypoxia affects the biology of tumors. These processes include the encouragement of the epithelial-to-mesenchymal transition (EMT), increased angiogenesis through vascular endothelial growth factor (VEGF), and the switch from oxidative phosphorylation to glycolysis. Here in this review we try to explain the overall intricate interplay of metabolic and molecular mechanisms within the cancer microenvironment related to hypoxic condition which not only enhances tumour growth but also contributes to therapeutic resistance, making hypoxia as a crucial scenario for cancer treatment strategies.

Keywords: Chronic Intermittent Hypoxia, Cancer Adaptation to Hypoxia, Hypoxia-Induced Pathways, Hypoxia-Responsive Genes, Molecular mechanisms in Hypoxia, Hypoxia and cancers

INTRODUCTION

Cancer progression and Hypoxia, or low oxygen availability, is a hallmark sign of many solid tumours and plays a significant role in tumour microenvironment (TME). To promote growth, survival, proliferation, metastasis of a cells majority of the tumour cells adapt to the hypoxic environment by activating various molecular pathways related to hypoxia [1][2]. An imbalance between the supply and demand of oxygen causes hypoxia, a crucial aspect of the tumour microenvironment (TME). The aberrant blood vessel creation in solid tumours is caused by a disruption in the control of pro- and anti-angiogenic signals, which limits the supply of oxygen. The TME's hypoxic circumstances are further exacerbated by the fast proliferating tumour cells' high oxygen consumption rates and the infiltration of immune cells. The molecular stabilization of HIF-1 and HIF-2, which activates gene expression programs involved in angiogenesis, glycolysis, cell invasion, migration, and erythropoiesis, allows for cellular adaptability [3]. To further treatment approaches, it is imperative to get understanding of these hypoxia-induced mechanisms.

Hypoxia inside tumours arises from a variety of causes, including anaemic hypoxia, diffusion-limited hypoxia, and perfusion--limited hypoxia. The tumour's oxygenation levels are significantly heterogeneous as a result of these processes. Tumour blood vessels are disordered and lack the basic structure of healthy vasculature, in contrast to normal tissues. Oxygen supply is reduced by perfusion due to the notable anatomical and functional anomalies of the blood arteries in tumours [4] [5]. Blood flow is disrupted by geometric resistance created by irregular vessel geometries. In addition, the lack of smooth muscle cells and the irregularities in the linings of endothelial cells and basement membranes make the vessel walls of tumours more permeable.

Ischemic hypoxia is caused by these anatomical abnormalities of the tumour vasculature. "Acute" hypoxia refers to the immediate onset of hypoxia where blood vessels in neoplastic tissues may form farther from the cells, cutting off their oxygen supply. In tumours fed by a main artery, cells at the periphery often experience oxygen deprivation due to their distance from the vascular supply, a condition also known as "chronic" or diffusion-limited hypoxia [6]. Anaemia, which can be caused by the tumour itself or its treatment, can exacerbate this issue. Tumours with low perfusion rates are especially prone to anaemic hypoxia. While normal tissues can adapt by increasing local blood flow and extracting more oxygen from the blood, tumours lack this ability to compensate for reduced oxygen availability.

Hypoxia sets in when tumours can no longer control falling oxygen levels. A tumour's innate capacity to multiply through damaging local development and spread is what distinguishes malignancy [7][8][9]. The hypoxic environment in solid tumours strongly impacts both malignant and non-cancerous stromal cells, such as fibroblasts and macrophages. This effect is crucial when considering the proteome changes that cells experience in vitro under hypoxic changes. These proteome alterations result from post-transcriptional and post-translational modifications brought on by hypoxia or anoxia, as well as from the activation or inhibition of gene expression and leading towards uncontrolled cell progression.

It has been well known that HIF-1 and HIF-2 are linked clinically to metastasis and reduced patient survival across various solid tumour types [10]. Additionally, HIF signalling is both essential and sufficient for enhancing the metastatic capabilities of tumour cells, indicating that HIF and its downstream targets play a crucial role in driving metastasis. Hypoxia inducible factors (HIFs) are activated by tumours to undergo acclimatization and are crucial in the transition to anaerobic energy generation. In turn, HIFs enhance the expression of many genes linked to angiogenesis, metabolic control, pH homeostasis, and cell death, all of which support the survival of tumours. Solid tumours are challenging to treat because of the critical role HIFs play in vascular protection, tumour blood recovery, and food delivery. This can result in resistance to immunotherapy, chemotherapy (CT), and radiation.

The function of hypoxia in carcinogenesis is enhanced by the interaction of metabolic alterations, environmental variables, and genetic abnormalities. These elements stimulate angiogenesis, activate HIFs, and induce metabolic changes that allow cancer cells to proliferate in low-oxygen conditions. Comprehending these pathways is essential for creating tailored treatments meant to interfere with the hypoxia pathway in cancer. Understanding the mechanisms by which HIF promotes metastasis could lead to the development of targeted therapies aimed at disrupting this pathway and potentially improving patient outcomes [11]. Further research is needed to fully elucidate the complex interplay between HIF signalling and metastatic progression in order to identify novel therapeutic strategies.

This review's primary objective is to gather up-to-date findings from clinical and experimental research that demonstrate the relationship between hypoxia and the occurrences of malignant development. Therefore, the second objective of this analysis is to highlight some of the danger's molecules associated with the molecular mechanisms within the tumour microenvironment. So, precisely clinicians can target a molecule to overcome the hypoxic environment as a result to diminish the spread of metastatic burden across different cancers.

HYPOXIA-INDUCIBLE FACTOR (HIF) PATHWAY

The transcription factors belonging to the HIF (hypoxia-inducible factor) family, particularly HIF-1α, are essential for the cellular response to hypoxia [12]. HIF-1α stabilizes in low oxygen environments and moves to the nucleus, where it attaches itself to target genes' hypoxia-responsive elements (HREs). HIFs are heterodimeric proteins made up of a constitutively expressed HIF-1β component, often referred to as ARNT, and an oxygen-sensitive subunit (HIF-1α, HIF-2α, or HIF-3α) [13].

The mechanism by which variations in oxygen availability are translated into HIF-mediated changes in gene expression is relatively straightforward: under normoxic conditions, one of the three HIF prolyl hydroxylases (PHD1, PHD2, or PHD3) inserts an oxygen atom into a specific proline residue on HIF-1α, HIF-2α, or HIF-3α (Camagni et al., 2023[14]). This modification allows the von Hippel-Lindau (VHL) protein to bind to the hydroxylated HIF-α subunits, targeting them for ubiquitination and subsequent proteasomal degradation. In hypoxic conditions, hydroxylation is inhibited, leading to the accumulation of non-hydroxylated HIF-α subunits. These subunits then dimerize with HIF--1β and bind to hypoxia-responsive elements (HREs) on target genes, initiating transcription [15] [16]. Additionally, Factor Inhibiting HIF-1 (FIH-1) hydroxylates an asparagine residue in the transactivation domain of HIF-α subunits, preventing the interaction with coactivator proteins p300 and CBP, thus providing further regulation of HIF transcriptional activity. In an oxygen-dependent manner, the prolyl and asparaginyl hydroxylation of HIF-α subunits negatively regulates their stability and transcriptional activity, respectively. This regulation governs the expression of genes involved in increased invasion, metabolic reprogramming, angiogenesis (via VEGF), and the epithelial-to-mesenchymal transition (EMT). A clear example of the HIF pathway's critical role in maintaining oxygen homeostasis is the hereditary disorder familial erythrocytosis, where affected individuals produce an abnormally high number of red blood cells. Conversely, as discussed in more detail below, elevated HIF activity contributes to the pathophysiology of cancer, a major cause of mortality [17] [18].

HIF-1 AND TUMOUR PROGRESSION

A Dual Role: In mild and acute hypoxic condition, adaptation in the environmental stress is necessary for survival of cells, in contrast severe and prolonged exposure in the hypoxia results in apoptosis. Thus, hypoxia maintains a fine tune balance in the regulation of both cell survival and cell death. Several studies reported that hypoxia has dual role in both pro-apoptosis as well as anti-apoptosis. Deprivation of oxygen in hypoxic environment suppress transfer of protons that reduces mitochondrial membrane potential. This lower rate of ATP production signals cells to activate Bak or Bax mediated initiation of cell apoptosis via releasing Cytochrome-c in the cytosol. In neuroblastoma cells, generation of ROS also involves in hypoxia mediated apoptotic cell death [19] [20]. During hypoxia, Nip3 protein which is a member of pro-apoptotic Bcl-2 family, its enhanced expression was reported. This induced expression was not found in cells that lack HIF-1α [21] [22]. Also, researchers reported that in the Nip3 promoter site, HRE region was present that express HIF-1α in response to hypoxia. In osteocyte like MLO-Y4 cells, researchers reported that HIF-1α induces JNK/Caspase-3 pathway that enhances Caspase-3 gene expression which is very much crucial for apoptotic pathway [23]. Hypoxia also involves in stabilization of tumour suppressor p53 protein that promote

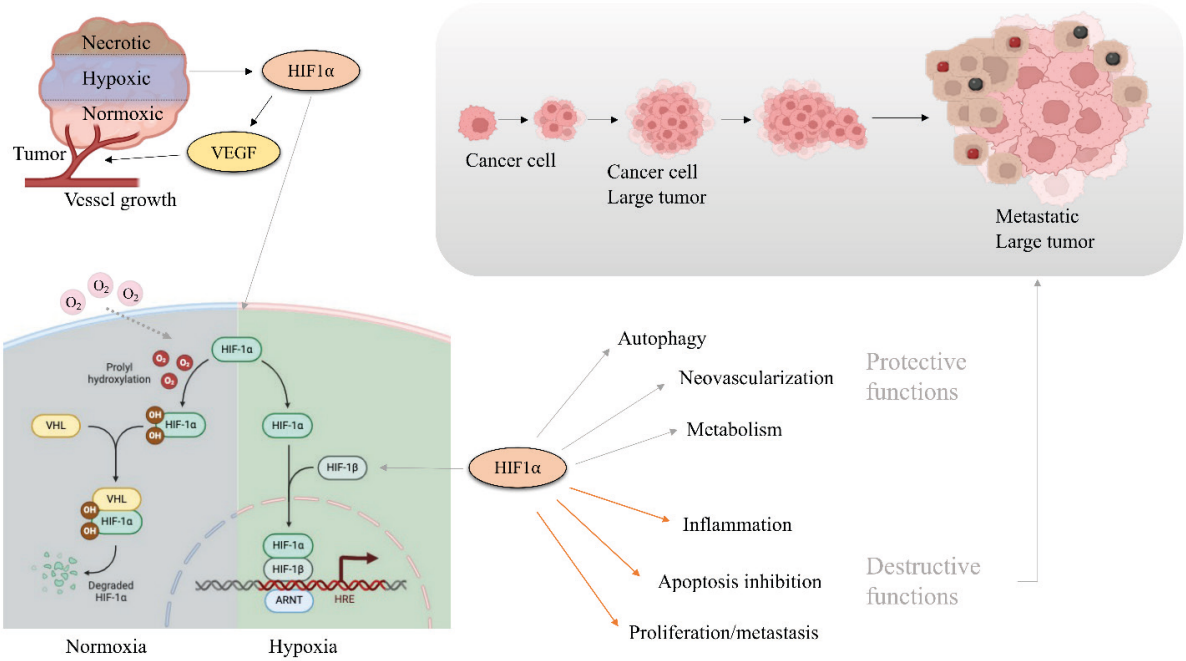

Figure 1. Dual role of hypoxia in tumour microenvironment

cell death or arrest cell growth. During hypoxia, accumulation of HIF-1α was reported to be parallel of the stabilization of p53 [24]. In addition, in co-immunoprecipitation study, association of HIF-1α and p53 were detected. However, stable p53 also downregulates transcription of HIF-1α target genes. P53 stabilization leads to p21 gene expression induction that reduce cell apoptosis. However, hypoxia also has role in inhibition of apoptosis. In Fig.1 hypoxia induced dual roles have been depicted in cancer microenvironment.

In HIF-1α -/- ES cells, Carmeliet and colleagues found more rapid development of tumour cells due to decrease in apoptosis while tumour cells that lack p53 induces HIF-1α that enhance VEGF expression in response to hypoxia which ultimately contributed in angiogenesis dependent oncogenesis. During hypoxia, increased expression of anti-apoptotic protein Mcl-1 was reported. HIF-1 mediated enhanced expression of VEGF is played a crucial role in protecting cells from apoptosis. HIF-1 induces enolase and erythropoietin genes expression that helps in suppression of oxidative stress induced cell death [25] [26] [27]. Hypoxia can also make cells resistant to apoptosis. In a study, Dong and colleagues reported that use of staurosporine that induces apoptosis, showed much lesser sensitivity in hypoxic condition rather than normoxic condition. They found that this may be due to hypoxia can induces the expression of anti-apoptotic IAP-2 protein that in turn also helps in the expression of another anti-apoptotic protein XIAP that eventually protect cells from apoptosis mediated cell death. In case of pancreatic cancer Akt mediated overexpression of HIF 1α was reported in normoxia. As hypoxia takes part in activation of several cell survival pathways along with induction of various apoptotic protein expression better understanding of hypoxia and its target genes are very much important for better therapeutic efficacy against cancer.

HYPOXIA AND THE TUMOUR MICROENVIRONMENT

An enough amount of O2 must be chemically synthesised and actively transported in order to sustain a sustainable energy supply. The hypoxic environment that causes intracellular acidosis in tumour cells often hinders the collapse of Na+ and K+ gradients, depolarization of membranes, mitochondrial O2 consumption, and cytosolic pH equilibrium [28]. This environment aids tumour cells in secreting chemo attractive substances such as ET-1, ET-2, Semaphorin 3A (Sema3A), and Endothelial monocyte-activating polypeptide II (EMAPII) to promote M2 polarization as a recall of classically activated M1 macrophages that incite angiogenesis and tumour progression, ultimately leading to metastasis [29] [30] [31] [32]. There are reports showing tumour-associated neutrophils (TANs), major component of tumour microenvironment is deeply influenced by HIF1-α and HIF2-α. Through the HIF-dependent synthesis of cytokines like IL-8 and chemokines like CXCL1, CXCL2, and CXCL5, hypoxia can draw TANs [33]. Furthermore, HIF-1α-dependent pathways increase neutrophils' surface adhesion molecule β2 integrin expression, which improves neutrophil activity. Additionally, HIF--2α is essential because it increases colon carcinogenesis by recruiting neutrophils to colon malignancies by upregulating the powerful neutrophil chemokine CXCL1. Moreover, it has been demonstrated that hypoxia promotes the development of neutrophil extracellular traps (NETs), which are made of several proteins, including neutrophil elastase (NE), and DNA. FoxP3 is induced by hypoxia, and the T-cell intrinsic HIF-1α pathway facilitates the development of Tregs (iTregs) from naïve T cells. Hypoxia is in fact thought to be a sign of an inflammatory milieu, and a rise in the percentage of Tregs is an anti-inflammatory mechanism that limits the harmful consequences of inflammatory hypoxia. Immune checkpoint regulation is another way that hypoxia suppresses the anti-tumour response. The immune suppressive protein programmed cell death ligand-1 (PD-L1) is upregulated in hypoxic tumour cells by HIF1-α and, on occasion, HIF2-α. HIF-1α also increases the expression of inhibitory receptors on CD8+ T lymphocytes, such as CTLA-4, lymphocyte activating gene 3 (CD223), and programmed cell death 1 (PD-1) [34] [35]. Therefore, T cell fatigue and tumour resistance to CTL-mediated lysis are encouraged by hypoxia. All things considered, hypoxia is a major force behind the malignant features of tumours and profoundly modifies the tumour microenvironment, which makes it an essential target for therapeutic interventions meant to sabotage the cancer cells' adaptive responses.

HYPOXIA AND CANCERS

Even while hypoxia and tumour heterogeneity are associated, it is still unknown what molecular processes lead from normoxic cancer cells to hypoxic ones. Cancer cells that are hypoxic have a greater ability to spread [36]. When hypoxic CRC cells are cocultured with normoxic CRC cells in colorectal cancer research, the treated hypoxic cells have a higher capability for metastatic spread due to their enrichment in interleukin 8 (IL-8). Based on experimental findings, recombinant human IL-8 can increase normoxic cells' ability to metastatically spread via phosphorylate the p65 subunit and subsequently induce epithelial-mesenchymal transition (EMT). The prometastatic potential of normoxic CRC cells was reduced by IL-8 suppression in hypoxic CRC cells or by using an anti-IL-8 antibody, as p65 inhibition or knockdown reversed the prometastatic effects of IL-8 [37]. The most aggressive type of adult brain tumour is called glioblastoma (GBM). In GBM, the immunosuppressive enzyme tryptophan-2,3-dioxyge-

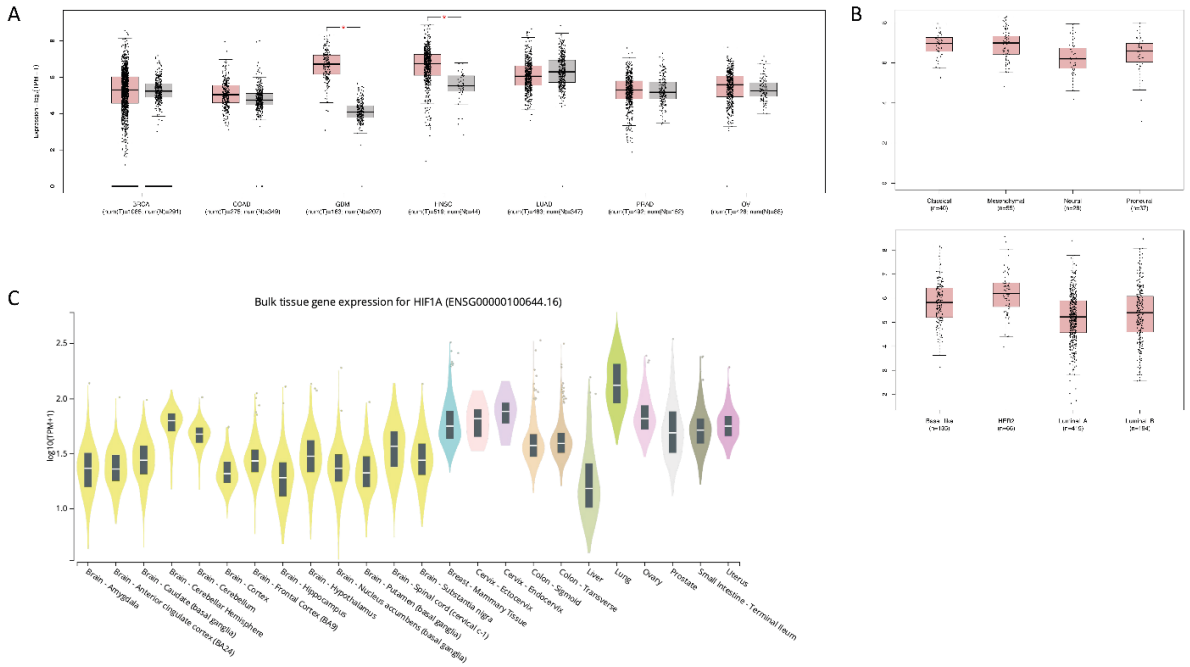

Figure 2. Bulk tissue gene expression for HIF1A across different cancers.

nase (TDO2), which is involved in tryptophan catabolism, was found to be downregulated in a way that was reliant on HIF-1α [38]. T-cell proliferation was boosted as a result. Likewise, Tyrakis and colleagues showed that hypoxia induction of 2-hydroxyglutarate via HIF-1α improved CD8+ T-cell proliferation, survival, and antitumor activity [39] [40] [41]. The majority of glioblastomas are glycolytic brain tumours, and variables generated by hypoxia are essential for the metabolic reprogramming of these tumours. Pseudo palisading necrosis areas are produced by abnormal vascular development, which shields cancer stem cells from healing agents and promotes tumour growth. However, treatments like bevacizumab that target hypoxia-induced factors have not improved overall survival; instead, they have just stabilized the illness. Given its superior efficaciousness in treating glioblastoma patients, hypoxia-activated TH-302, a nitroimidazole prodrug of cytotoxin bromo-isophosphoramide mustard, seems more appealing. In Fig.2 HIF-1A tissue expression profile across different cancers have been shown.

Renal cell carcinomas and other human malignancies have high expression levels of HIF-α and HIF-induced proteins, which impact the prognosis and aggressiveness of the tumour [42] [43]. RCC serves as a model to comprehend the function of HIF in the advancement of cancer. Also, survival rates are correlated with high BNIP3 expression in non-small lung cancer and breast cancer. By grouping genes related to hypoxia-regulated genes including VEGF, GLUT1, and CAIX, Winter et al. produced an in vivo hypoxia signature in head and neck squamous cell carcinomas (HNSCCs). In addition to novel genes like Metaxin 1, BCAR1, PSMA7, and SLCO1B3, the metagene included 99 genes, including Aldolase A, GAPDH, PGF, and BNIP3 [44] [45]. The hypoxia response in vivo may be significantly influenced by these genes. In order to produce a more reliable and universal signature, Buffa et al. employed a meta-analysis approach to identify a hypoxic signature that was shared by HNSCC and breast cancer. In separate datasets of lung, HNSCC, and breast cancer, they discovered that the predictive

value of a reduced metagene with as little as three genes (VEGFA, Phosphoglycerate mutase 1, and Solute carrier family 2 member 1) was equivalent to that of a huge signature [46] [47] [48].

So, we underscore the critical role that HIF-1, the principal factor triggered by hypoxia, plays in propelling tumour growth within the tumour microenvironment. Tumour aggressiveness has been associated with the oxygen-dependent transcription factor HIF-1. Angiogenesis, immunosuppression, and metabolic reprogramming are all triggered by HIF-1, which facilitates tumour growth by promoting cell invasion and survival. Furthermore, HIF-1 in glioblastoma (GBM) is controlled by hypoxia circumstances as well as oncogenic signalling pathways such as p53-MDM2 axis, MAPK/ERK axis, and PI3K/PTEN-Akt axis.

METABOLIC SHIFT IN CANCER CELLS DURING HYPOXIA

In multicellular organism oxygen mediated generation of ATP is indispensable to almost all biological processes. Even in the presence of oxygen, hypoxia is essential for the metabolic reprogramming of cancer cells, especially the transition from oxidative phosphorylation to glycolysis (a process called the Warburg effect). Hexokinase, phosphofructokinase, and lactate dehydrogenase are among the important glycolytic enzymes that are upregulated when hypoxia-inducible factor 1-alpha (HIF--1α) is stabilized [44]. Although glycolysis is less effective than oxidative phosphorylation, this metabolic change enables cancer cells to produce ATP more quickly [49]. This change in glycolysis is essential for promoting tumour growth. It guarantees a steady flow of metabolic intermediates for biosynthetic processes, including lipid and nucleotide synthesis, which are necessary for cell division.

Tumour cells are rapidly growing cells that sustain their chronic proliferation. When tumour expands, it generally grows distant from the local blood circulation, resulting hypoxic tumour microenvironment. For this reason, tumour cells are adapted to alternative metabolic pathways that support their high rate of energy demands which is independent of oxygen. Cancer cells upregulate expression of HIF and switching towards glycolysis to overcome lower oxygen demand in highly proliferating cells. Tumour cells mediated reprogramming of metabolic pathways are one of the well-recognized hallmarks of cancer. Cancer cells mediated metabolic reprogramming also affects liver, adipose tissue and skeletal muscles which promotes overall dysregulation of energy metabolism. This severe state is termed as cancer cachexia, which causes weakening and anorexia due to loss of muscle mass and adipose tissue, resulting reduced anti-cancer therapeutic efficacy. Moreover, in this section we have discussed the detailed altered metabolism in hypoxic tumour microenvironment which induces cancer cell survival, proliferation, epithelial-mesenchymal transition, invasion and metastasis.

GLUCOSE METABOLISM

During aerobic metabolism, breakdown of glucose produces pyruvate that enters into tricarboxylic acid (TCA) cycle and oxygen is function as terminal electron acceptor in oxidative phosphorylation (OXPHOS) to generate ATP which is the energy currency of cells [50]. Although aerobic metabolism produces 32 molecules of ATP per glucose, interestingly cancer cells favour aerobic glycolysis (also called Warburg effect) even in the presence of oxygen [51]. This is because higher amounts of ATP produced through increase rate of glycolysis flux in a very short span of time that ultimately fuels high rate of tumour cells growth and proliferation [49]. GLUTs are responsible

for import of extracellular glucose. HIF-1α induces overexpression of GLUT1 and GLUT3 genes through activating SLC2A1 and SLC2A3 genes transcription, resulting increase glucose import inside tumour cells. HIF-1α also promotes hexokinase 2 (HK2) enzyme that converts glucose into glucose 6 phosphate and phosphofructokinase 1 (PFK1) which is crucial for phosphorylating fructose 6 phosphate to fructose 1,6 bisphosphate. HIF-1α directly binds to the promoter region of PFK1 as well as HIF-1 also induces PFKFB2 gene that encode PFK1. In addition, HIF-1α also binds in the lactate dehydrogenase-A (LDHA) gene promoter and induces its expression to convert pyruvate into lactate and generate NAD+ from NADH [52] [53]. As HIF-1α promotes lactate synthesis, it also regulates intracellular acidification. It promotes transport of lactate through transmembrane monocarboxylate transporter 4 (MCT4) protein and induces overexpression of carbonic anhydrase IX (CA-IX) and XII (CA-XII). These are coupled with extracellular lactate and creates an acidic tumour microenvironment. Moreover, HIF-1 also induces other glycolytic enzymes such as aldolases (ALDOA and ALDOC), enolases (ENO1 and ENO2), phosphoglycerate kinase 1 (PGK1) and pyruvate kinase M (PKM) [54]. Activated PKM2 induces β-catenin, HIF-1α and HIF-2α and helps cancer cell progression. Under hypoxic condition, HIF-1 also stimulates conversion of glucose into glycogen and used by cancer cells. Hypoxia induces GYS1 gene in glioblastoma that encodes the enzyme glycogen synthase to accumulate glycogen from glucose [55]. In clear cell renal cell carcinoma, HIF was reported to regulate glycogen synthesis. Hypoxia also induces other glycogen pathway enzymes such as UDP- glucose pyro-phosphorylase (UGP2), phosphoglucomutase1 (PGM1), glycogen branching enzyme (GBE1) as well as glycogen phosphorylase that degrades glycogen, indicating dynamic glycogen synthesis and degradation is regulated by hypoxia that depends on the metabolic demand of individual tumour cells [55] [56]. Inhibition of glycogen phosphorylase by C-320626 induce apoptosis and reduced proliferation in pancreatic cancer cells. Moreover, knockdown of glycogen phosphorylase encoding PYGL also stimulates senescence and ROS levels in U87 glioma cells.

LIPID METABOLISM

During hypoxia, HIF-1α induces fatty acid binding proteins FABP3 and FABP7 and ADRP enzyme that promotes accumulation and uptake of lipid droplets [57]. HIF-1 also promotes ex novo fatty acid biosynthesis that ultimately protects cancer cells from ROS. In mitochondria, HIF-1α also inhibits fatty acid oxidation via suppression of long chain Acyl--CoA dehydrogenase (LCAD) and medium chain Acyl-CoA dehydrogenase (MCAD) that leads to inhibition of PTEN pathway and ROS reduction [58] [59]. HIF-1α mediated repression of c-Myc and carnitine palmitoyl-transferase 1A which forces lipid droplet formation and reduce mitochondrial transport. In rapidly proliferating tumour cells biosynthesis of lipid molecules has very important role in production of organelle membrane, modification of membrane fluidity, triglyceride mediated energy storage and production of various signalling molecules for example lysophosphatidic acid and sphingosine 1-phosphate that promotes tumour cell survival, inflammation and migration. In cancer cells, fatty acid biosynthesis precursor molecule acetyl Co-A comes from other than glucose pathway such as glutamine or some other amino acids or acetate. Besides fatty acid biosynthesis this acetyl Co-A mediated acetylation of HIF 2 also promotes tumour cell invasion.

AMINO ACID METABOLISM

In hypoxic cancer cells metabolism of glutamine and serine have crucial role to maintain rapid growth of cancer cells. Due to reduced amount of pyruvate enters into TCA cycle, cancer cells utilize glutamine as one of the major carbon and nitrogen source that supports their biosynthesis and energetics. This glutamine then converted to glutamate and then into α-ketoglutarate (α-KG) and ultimately succinate to enter into TCA cycle or generate isocitrate and citrate via isocitrate dehydrogenase (IDH) mediated reductive carboxylation [60] [61]. In hypoxic condition, HIF-1α also has role in reductive carboxylation. In case of hypoxic glioblastoma, it has found that reductive carboxylation is responsible for citrate production from glutamine and they could not proliferate in IDH 2 silencing condition or citrate starvation. In a model of Burkitt lymphoma, P493 cells, when HIF-1 was induced, increased utilization of glutamine was reported. Cancer cells also utilize glutamate to generate aspartate mediated de novo synthesis of pyrimidines and for other process such as trans amination reaction, glutathione synthesis and biosynthesis of precursor molecules to produce other amino acids. Besides glutamine, serine also has important role in cancer cells as its depletion suppress cancer cells growth in vitro and in vivo. Serine is utilized for the production of phospholipids, other amino acids (such as glycine and cysteine), and one carbon unit donor in folate cycle. Overexpression of phosphoglycerate dehydrogenase (PHGDH) enzyme that produce serine from glucose was reported in cervical, non-small cell lung, breast and colorectal cancer. Interestingly, studies by Lu and colleagues found that HIF is responsible for induction of PHGDH amplification in breast cancer cells. Moreover, HIF-1 induces SLC7A11 mediated cysteine transporter and GCLM to increase synthesis of glutathione [62] [63]. During one carbon cycle, metabolism of serine produces NADPH that generates reduced glutathione which protects from ROS. In hypoxic breast cancer, NADPH was reported to maintain reduced glutathione that protect cancer cells. HIF-1 also induces folate pathway enzymes such as serine hydroxy-methyltransferase 2 (SHMT2), methylene tetra-hydro folate dehydrogenase-1 like (MTHFD1L) and methylene tetra-hydro folate dehydrogenase 2 (MTHFD2) are also produces NADPH and protects cancer cells from ROS [64]. HIF also induces ubiquitin ligase SIAH2 mediated degradation of α keto-glutarate dehydrogenase (α-KGDH) and hamper α-KG oxidation [9]. In vitro, in tumour cells it was found that 50% non-essential amino acids are derived from glutamine during protein synthesis. In breast cancer and neuroblastoma glutamine dependent suppression of integrated stress response or (ISR) was also reported that ultimately helps survival of cancer cells. Glutamine also protects cancer cells from autophagy via inducing mTOR pathway and suppressing amino acid sensing serine/threonine kinase GCN2. Glutamine dependent HIF-1α stabilization was also reported in prostate cancer, pancreatic cancer and lung cancer.

TCA CYCLE

The Krebs cycle (TCA cycle) is dramatically changed by hypoxia, which interferes with mitochondrial metabolism and promotes carcinogenesis. HIF-1α also plays an important role in repressing oxidative phosphorylation [65] [66]. HIF-1α promotes pyruvate dehydrogenase kinase-1 (PDK1) expression that encodes a kinase which results in phosphorylation mediated inhibition of the key mitochondrial enzyme pyruvate dehydrogenase (PDH) that facilitates pyruvate to acetyl co-A conversion which enters into TCA cycle. Furthermore, hypoxia modifies the regular activity of important Krebs cycle enzy-

mes as fumarate hydratase (FH) and succinate dehydrogenase (SDH). Further stabilizing HIF-1α and sustaining the hypoxic response, the build-up of metabolites like as fumarate and succinate inhibits prolyl hydroxylases (PHDs), which are in charge of HIF-1α breakdown [67]. A hypoxic microenvironment that is favourable to tumour growth is produced by these disturbances. While the build-up of Krebs cycle intermediates encourages oncogenic signalling pathways, the mitochondria's reduced oxygen consumption protects oxygen for vital cellular functions and aids in angiogenesis. When combined, these changes create an environment that is both proliferative and adaptable, allowing cancer cells to flourish in the face of metabolic stress.

Mutations in the key TCA cycle enzymes such as succinate dehydrogenase (SDH1), iso-citrate dehydrogenase (IDH1 & IDH2) and fumarate hydratase results in succinate, L-2-hydroxy-glutamate (L-2HG) and fumarate accumulation that decreases PHDs activities and ultimately leads to HIF-1α stabilization and promotes metastasis [68]. On the other hand, although α-KG functions as PHD co-substrate, accumulation of α-KG produce L-2HG via LDHA and malate dehydrogenase MDH1 and MDH2 [69]. In addition, enantiomeric form of L-2HG inhibits PHD. Thus, dysregulation of key TCA cycle enzymes promotes HIF-1 stability and decreased rate of oxidative metabolism in hypoxic tumour cells.

ETC

In prolonged hypoxic condition, HIF-1 also disrupts normal ETC function. It upregulates mitochondrial LON protease that degrades complex IV subunit COX411 and nuclear encoded COX412 that replace COX411 and efficiently perform electron transfer in hypoxic condition along with reduced ROS production and ATP generation [70] [71]. Moreover, HIF-1 also induces NDUFA4L2 mediated suppression of complex I activity and ROS production. Besides that, HIF-1 also promotes miRNA-210 that target complex I, II and IV in hypoxic tumour cells [72] [73]. HIF-1α also activates MXI1 gene that has role in inhibition of mitochondrial DNA replication, transcription and mitochondrial DNA packaging into nucleoids.

ALTERED IMMUNE METABOLISM

Recently, researchers found that besides supporting tumour cell survival, therapy resistant and metastasis, hypoxia also has crucial role in suppression of immune response. Acidic microenvironment severely disrupted antitumor immune function. Glycolysis is also very important for T-lymphocytes. However, in hypoxic tumour microenvironment, tumour cells rapidly uptake maximum glucose leading to deprivation of glucose for T cells and resulting T cell anergy or death [74]. Besides T cells, glycolysis is also the primary energy source for M1 macrophages, neutrophils and iNOS expressing dendritic cells (DCs). Activated B cells also depend on glycolysis [75]. Thus, intake of more amount of glucose by tumour cells restrict anti-tumour immune cells function. Altered lipid metabolism also affect DCs activation. Lactate driven extracellular acidification also inhibits proliferation and activation of CD8+, CD4+, NK cells and dendritic cells [76]. In hypoxia, arginase 1 (ARG1) expression was induced and promotes absorption of lactate by macrophages that differentiate them into M2 macrophages with immune-suppressive property. Glutamine was necessary for T effector cells differentiation. Similar to glucose, deficiency of glutamine also impairs differentiation of T effector cells. In addition, differentiation of Th1 cell also disrupted due to low α-KG in hypoxic condition. A-KG is crucial for transcription factor T-bet expression for proper differentiation of Th1 cell. Like glutamine,

Serine also plays important role in optimal proliferation and expansion of T cells [77]. This is because, like cancer cells, serine is also utilized in T cell for de novo biosynthesis of nucleotides and source of glycine and helps in maintaining proper proliferation capacity of T cells. Thus, due to competition with tumour cells lack of serine also affect T cells proliferation ability. Hypoxia promotes expression of cytoplasmic acetyl Co-A synthetase (ACSS2) to produce acetate from acetyl Co-A and utilizes it for generation of lipid biomass in cancer cells [78]. It also interacts with CBP and induces HIF-2 acetylation that promotes invasion ability of cancer cells. HIF-1 mediated lipid storage through LPIN1 and synthesis of fatty acids via FASN were also reported [57] [58]. In ccRCCs, upregulation of adipogenesis genes were found where HIF was constitutively active. Increasing concentration of lactate and H+ reduces T cell mediated interferon γ (IFN--γ), interleukin-2 (IL-2), perforin and granzyme production. NK cell function was also decreasing in acidic condition [79]. In addition, concentration dependent decrease of tumour necrosis factor (TNF) secretion was also found. Although, as regulatory T cells (Treg) are depending on FAO for energy metabolism, acidic condition does not hamper their immune suppressive function. Purine adenosine nucleotide levels are increased in case of many solid tumours, where hypoxia induces extracellular adenosine accumulation. HIF induces adenosine production via upregulating CD39 that convert extracellular ATP into AMP and CD73 that use AMP for adenosine production. It also suppresses adenosine deaminase and adenosine kinase function that ultimately increase adenosine level. Increased AMP to ATP ratio in glucose limiting condition also stimulates CD4+ differentiation into Treg cells rather than CD4+ effector T cells and produces more anti-inflammatory type of M2 macrophages [80] [81] [82]. A2 adenosine receptor (A2AR) mediated signalling on CD8+ T effector cells hamper its cytotoxic function and also reduces secretion of IFN-γ [83] [84]. Moreover, ovarian cancer cells utilize adenosine to suppress cytotoxic activity of NK cells via activation of A2AR. Adenosine accumulation in hypoxic tumour microenvironment also increases pro-angiogenic and immune suppressive Treg cells and myeloid derived suppressor cells that promote immune cell evasion. Deletion or blocking of A2AR activates tumour infiltrating T cells and reduces tumour growth. Also, in myeloid cells, selective A2AR deletion leads to activation of NK cells and CD8 + T cells and decreases myeloid cell mediated IL-10 generation [85]. Thus, hypoxia acts many ways to create immune suppressive microenvironment that promote cancer cell growth.

CONCLUSION AND FUTURE PERSPECTIVES

Tumour survival, metastasis, and invasiveness have all been shown to be significantly aided by hypoxia. This study emphasizes how hypoxia-inducible factors (HIFs) play a critical role in tumour growth, the advancement of malignancy, and the development of resistance to immunotherapy, chemotherapy, and radiation. The expression of target genes that promote tumour adaptability and aggressiveness is triggered by HIF stabilization in hypoxic tumour cells. These genes encode proteins that are involved in the process of neo-angiogenesis. These proteins include VEGF (vascular endothelial growth factor), metastasis, epithelial-to-mesenchymal transition (EMT), glucose transporters, glycolytic enzymes, and cancer stemness. Furthermore, HIFs promote tumour invasion and metastasis by modulating important molecules including E-cadherin and chemokine receptors like CXCR4. A key factor in the development of chemoresistance is the acidic microenvironment cre-

ated by hypoxia, which is fuelled by VATPase, NHE, and MCT. Therapeutic approaches with a focus on the tumour microenvironment have encouraging prospects. Consequently, pinpointing possible targets for cancer treatment requires a knowledge of the regulation of these molecules. An important limitation of cancer immunotherapy appears to be the shift of N1 toward N2 TANs caused by hypoxia, which promotes tumour progression by suppressing anti-tumour responses from regulatory T-cells (Treg). Moreover, it is believed that tumour hypoxia stimulates the synthesis of chemokines and cytokines, which attract immune cells that support the tumour and reduce tumour immunity. Thus, a deeper comprehension of the hypoxia signalling cascade may provide new avenues for the development of HIF-targeting tactics and the control of the hypoxic tumour microenvironment. More research is needed to determine the significance of HIF-induced gene products as prognostic indicators for various malignancies. The first evidence that the hypoxic response of tumours may be addressed came from the discovery of anti-angiogenic drugs, which hold great promise as a cancer treatment. Thus, targeting hypoxia is one possible treatment to prevent the spread of various types of cancer and give patients a better chance of survival.

DECLARATIONS

Ethics approval and consent to participate
Not applicable

AUTHOR CONTRIBUTIONS

Carlos Mas Bermejo: Writing, Investigation, Administration project, methodology

Carlos Mas Gomez: Review and editing

Gema Marin Zafra: Conceptualization

Jesus Abrisqueta: Review

Jose Luis Alonso: Review and Methodology

Luis Alberto Bravo: Methodology and review

ACKNOWLEDGEMENT

Not Applicable

FUNDING ACQUISITION

Not Applicable

COMPETING INTEREST

No competing interests to declare.

DATA AVAILABILITY

Not applicable

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