REVIEW

Regulation of Hypoxia Dependent Reprogramming of Cancer Metabolism: Role of *HIF-1* and Its Potential Therapeutic Implications in Leukemia

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Abstract

   Metabolic reprogramming occurs to meet cancer cells' high energy demand. Its function is essential to the survival of malignancies. Comparing cancer cells to non-malignant cells has revealed that cancer cells have altered metabolism. Several pathways, particularly mTOR, *Akt, PI3K*, and *HIF-1* (hypoxia-inducible factor-1) modulate the metabolism of cancer. Among other aspects of cancer biology, gene expression in metabolism, survival, invasion, proliferation, and angiogenesis of cells are controlled by *HIF-1*, a vital controller of cellular responsiveness to hypoxia. This article examines various cancer cell metabolisms, metabolic alterations that can take place in cancer cells, metabolic pathways, and molecular aspects of metabolic alteration in cancer cells placing special attention on the consequences of hypoxia-inducible factor and summarising some of their novel targets in the treatment of cancer including leukemia. A brief description of *HIF-1α*'s role and target in a few common types of hematological malignancies (leukemia) is also elucidated in the present article.

Keywords: Metabolic Reprogramming- Cancer Cell Metabolism- Hypoxia-Inducible Factor-1 (*HIF-1*)

Introduction

   Cancer cells require a higher rate of energy for their active proliferation and growth, due to which tumors become hypoxic and they need to rely on non-oxidative energy sources. The first observation of abnormal metabolism in cancer cells was identified by Otto Warburg and is called as Warburg effect. Hypoxia is considered a normal finding in tumors. Cancer cells adapt to hypoxia by using pathways of physiological adaptation that encourage a shift from oxidative to glycolytic metabolism. In healthy cells, energy homeostasis is maintained by different metabolic pathways like Glycolysis, Tricarboxylic acid cycle, and lipogenesis and these cells have a relatively low rate of cell division. These cells primarily use glucose as an energy source, which is entirely oxidized by glycolysis, TCA/Kreb cycle, and oxidative phosphorylation. Most non-proliferating cells depend on ATP production for their metabolic needs which are produced through oxidative phosphorylation. In cancer cells, a series of mutations impact multiple signaling and metabolic pathways leading to metabolic reprogramming. Both genetic mutations and tumor microenvironment are responsible for altering the metabolic pathways in cancer cells which leads to enhancement in cell growth and accelerates the rate of cell division. Both internal and external influences can affect cancer cells. Genetic mutations are among the inside contributors. A number of tumor suppressor genes and oncogenes regulate the metabolic reprogramming of cancer cells. Genes like *HIFI, P13K-ATK/mTOR, MYC, KRAS*, and *P53* are responsible for altering signaling in metabolic pathways in cancer cells. MYC, Phosphatidylinositol 3-kinase, and HIFs have been observed in increasing glycolytic activity. Oncogenes like Ras and Src are thought to promote glycolysis by activating glucose transporter 1. P53 is one of the most important tumor suppressor proteins which is responsible for blocking the glycolytic pathway. Activation of the P13 kinase/ serine/threonine kinase AKT pathway is responsible for enhanced glucose uptake and glycolysis.

   Cancer cells are influenced by external stimuli like the tumor microenvironment. The hypoxia, PH, and nutrient content in the tumor microenvironment have an effect on the metabolism of cancer cells. Both these internal and external factors lead to abnormal metabolism in cancer cells. Metabolic adaptations include Increased ATP production, increased biosynthesis of essential macromolecules like carbohydrates, proteins, lipids, and nucleic acids, and maintaining redox status. Cancer cells control their redox status and maintain a number

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of reactive oxygen species (ROS) that promote tumor development. The electron transport chain in mitochondria and a number of oxidizing substances that damage DNA through processes like depurination, single and double DNA breaks, etc. are the main mechanisms for creating ROS in vivo. The persistent change of the genetic material brought on by oxidative damage is one of the crucial processes involved in mutagenesis leading to carcinogenesis. Also, it is believed that increased ROS levels alter the activity of protein kinases. It is thought that phosphatases are inhibited by elevated ROS levels due to which protein kinases remain activated which leads to uncontrolled cell growth and proliferation because signaling cascades cannot be turned off.

HIF-1-induced Metabolic Reprogramming in Hypoxia Glucose metabolism

A central process in tumorigenesis is the reprogramming of glucose metabolism. Pyruvate, the end product of glycolysis is either reduced to lactate by anaerobic glycolysis in the absence of oxygen or oxidized to produce acetyl-coenzyme A when there is oxygen present, depending on the availability of oxygen to the cells. The tricarboxylic acid cycle then completely oxidizes pyruvate to CO_2 and H_2O. Most cancer cells rely on high glycolysis concentrations for growth and survival, even though there is adequate oxygen [1]. It has become apparent that higher glycolysis rates enable metabolic fluxes to be diverted to more effective biomass production in continuously proliferating cells and establish the molecular foundation for cancer detection using PET scans [2]. HIF-1 mediates metabolic conversion, which increases the input of glucose into tumor cells by activating the glycolysis-associated enzymes and over-expressing glucose transporters (*GLUT1* and *GLUT3*) that increases the cytoplasm's ability to produce glucose for energy [3]. In particular, a significant feature separating tumor cells from normal cells is the rise in glucose uptake. This discrepancy has been widely exploited in the imaging modality of utilizing radiolabeled glucose analogs, such as 18F-fluorodeoxyglucose, as a tumor visualization tracer in positron emission tomography (PET) [4]. In poorly differentiated endometrial and breast tumors, studies have shown that *GLUT1* and *GLUT3* both have been found overexpressed at the mRNA and protein levels [5].

In several cancer forms, it has been determined how *GLUTs, HIF-1*, and glycolytic enzymes interact with one another. For instance, it has been demonstrated that the expression of *HIF-1* alpha correlates with tumor size, amount of invasion, distant metastasis, disease stage, and differentiation status in human gastric cancer. Additionally, both at the mRNA and protein levels, it has been documented that the expression of HIF-1 α interacts positively with that of *GLUT1* and *LDH-5* [6]. Studies have shown that the ribosomal protein S7 (RPS7) prevents glycolysis in colorectal cancer by blocking both HIF-1 alpha and GLUT4 and lactate dehydrogenase B expression [7]. *HIF-1* affects the SCL2A solute carrier family, which includes members that express various enzymes involved in the glycolysis pathway like Hexokinase II (HK II), Alpha-enolase (ENO1), fructose-bisphosphate aldolase

A (ALDOA), pyruvate kinase M2, lactate dehydrogenase A (LDH-A or LDH-5), phosphofructokinase 1, along with influencing and contributing to the development of cancer through affecting the genes for the pentose phosphate pathway enzymes and PDK [8]. Studies have shown a correlation between HK II and *HIF-1* alpha co-localization and overexpression in cancer cells close to necrosis sites. There are four isoforms of hexokinases and recently a fifth hexokinase has been identified out of these isoforms, cancer cells express more HK2 to boost glucose flux through several metabolic pathways [9]. The Voltage-dependent Anion Channel (VDAC), which controls the flow of metabolites into and out of the mitochondrial intermembrane gap, is intact in HK2, which has the capacity to bind to mitochondria. The connection of HK2 with VDAC prevents the pro-apoptotic protein Bax from binding to VDAC, which prevents the opening of a channel via which apoptosis can be triggered by cytochrome-c releasing in the mitochondria. Thus, HK2 over-expression in cancer cells causes a switch from HK1 to HK2, which benefits metabolism by protecting cancer cells from apoptosis [3].

Fructose-6-phosphate is converted to fructose-1, 6-bisphosphate by activating 6-phosphofructo-1-kinase and utilizing Mg and ATP as a phosphoryl donor. *HIF-1α* is also involved in the regulation of Fructose-2,6-bisphosphate as a strong allosteric regulator to monitor carbon flux through glycolysis [10]. By attaching to the hypoxia-response elements (HREs) located inside the first PKM2 gene intron, *HIF-1α* regulates the expression of pyruvate kinase M2 (PKM2). PKM2 catalyzes phosphoenolpyruvate conversion into pyruvate, the last step in the glycolytic pathways. Esophageal squamous cell carcinoma (ESCC) chemoresistance has been consistent with PKM2 expression. Additionally, the development of prostate cancer has also been linked to the up-regulation and specific modulation of PKM2 [11]. It has been demonstrated that PKM2 interacts with *HIF-1α* in the nucleus in a specific manner and functions as a transcriptional co-activator in the cervical carcinoma cell line (HeLa) and hepatoblastoma cell line (Hep3B) [12]. The analysis also reveals that histone demethylase, JMJD1A, facilitates the development of urinary bladder cancer by increasing glycolysis by co-activating HIF1 alpha [13](Figure 1).

Lactate Metabolism:

HIF-1 stimulates pyruvate dehydrogenase kinase 1 (PDK1) expression that phosphorylates the PDH complex and inhibits it. This reduces glycolytic carbon entry into the TCA cycle and enhances pyruvate-to-lactate conversion with the help of lactate dehydrogenase (LDH) [14]. Intratumorally lactate levels are believed to be 10 to 20 mM and have been indirectly correlated to tumor recurrence, progression, and growth [15]. In the vertebrates, four LDH genes have been identified, including LDHA, LDHB, LDHC, and LDHD. The first three use L-lactate, while the fourth, LDHD, uses D-Lactate [16]. LDHA helps to quickly transform pyruvate to lactate in cancer cells and high LDHA levels enable cancer cells to grow and proliferate by promoting the transition of mesenchymal
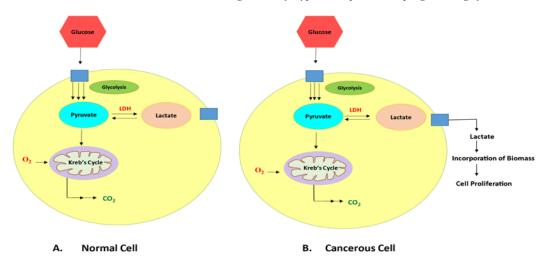
Figure 1. Glucose Metabolism is an Essential Process for Every Animal Cell. The end product of complete mitochondrial respiration in humans may be lactate or CO_2 under normal circumstances, but the "Warburg Effect" refers to a situation in which glucose uptake dramatically increases and lactate production begins despite the presence of oxygen and fully functional mitochondria.

cells from epithelial cells, angiogenesis, cytoskeletal remodeling, enhancing cell movement, invasion, and migration [16]. Studies also show that increased activity of LDHB contributes to tumor progression. For instance, research with sirtuin 5 (SIRT5) protein and LDH5 demonstrates that SIRT5 interacts directly with LDH5 and results in LDHB deacetylation at Lys-329 position which in turn enhances the LDHB activity and favors autophagy which increases the development of colorectal cancer cells [17]. Lactate also modulates the role of immune cells to inhibit host immunosurveillance and to facilitate tumor cell migration and metastasis [15]. The tumor lactate exchange mechanism takes place with the aid of monocarboxylate transporters (MCTs), which are part of the SLC16A family of genes and consist of 14 members. It has been shown that MCT1 and MCT4 are considerably raised and associated with poor prognosis in an abundance of malignant tumors, including prostate cancer, peritoneal carcinomatosis, oral cavity cancer, and lymphoma. They play a crucial role in the transportation of monocarboxylates (lactate and pyruvate) [18].

Both of these isoforms have different biochemical roles and tissue distributions. For example, MCT4 has a low affinity for lactate and is best suited for exporting lactate from glycolytic cancer cells, MCT1, on the other hand, stimulates lactate intake to encourage oxidative phosphorylation and is implicated in lactate efflux from malignant cells [18]. A local inflammatory reaction brought on by lactate efflux is considered to recruit immune cells like macrophages, which release cytokines and growth factors that promote the development and spread of tumor cells. [19]. Under normal circumstances, MCTs also encourage the transport of lactate across different cell types, such as between neurons that express MCT2 and astrocytes that produce lactate and express MCT1 and MCT4. Three lactate shuttling theories are being put out for cancer: the metabolic symbiosis, the "Reverse Warburg Effect," and the endothelial cell shuttling in the

blood vessels [19]. The reaction of up-regulation of lactate concentration is helpful because it helps regenerate NADH which is used in the sixth reaction of glycolysis and aids in speeding up glycolysis. Additionally, lactate lowers the levels of reactive oxygen species (ROS), which aids in the activation of metalloproteases for the destruction of the extracellular matrix and increases the survival of tumors. It also lowers the pH of the extracellular microenvironment [4].

Lipid metabolism

Living cells obtain fatty acids from two main outlets, one is from external food intake and another is the de novo synthesis, for their metabolic requirement. However, cancer cells tend to be strongly dependent on de novo lipogenesis for their proliferation and differentiation [20]. Research shows that in cancer cells, hypoxia causes induction of HIF-1 and protein kinase Akt, accompanied by elevated expression and activation of sterol regulatory-element binding protein-1 (SREBP-1) that in effect increases the expression of fatty acid synthase (FASN), the enzyme catalyzes fatty acid synthesis [21]. Studies also revealed that under hypoxia, lipogenesis and extracellular fatty acid influx are stimulated by HIF1mediated expression of the fatty acid-binding protein (FABP) 3 and 7 in cancer cells [22]. Since HIF1 inhibits the TCA cycle in cancer cells, which hinders the production of acetyl-CoA, the primary substrate in lipid biosynthetic pathways, cancer cells primarily synthesize fatty acids from glutamine or acetate [21]. According to the most recent research, acetate is a vital resource that can encourage the formation of cancer when there is metabolic stress. Histone deacetylases and acetyl-CoA hydrolysis can both be used to create acetate by removing acetyl groups from histones. Extra metabolome research focused on 1H-NMR spectra showed that cancer cells consume more than 80% acetate during hypoxic conditions [23]. Acetate primarily stimulates the Acetyl-CoA Carboxylase

Alpha (ACACA) and FASN lipogenic genes by increasing the levels of H3K9, H3K27, and H3K56 acetylation in their promoter regions, thereby improving de novo lipid synthesis and Acetyl-CoA synthetases (ACSS1, ACSS2) are used in this acetate-mediated epigenetic control [23].

Amino acid metabolism/ Glutaminolysis

Glutamine and serine are two major non-essential amino acids that are mainly affected in cancer cells during hypoxia conditions. A cell's ability to grow depends on the metabolism of amino acids since they are the simplest building block for protein production. Glutamate serves as the main substrate for cancerous cells. It serves as a nitrogen and carbon source for the tricarboxylic acid (TCA) cycle, which is essential for biosynthesis and bioenergetics and controls cellular homeostasis. By inducing the glutamine transporters SLC1A5 and SNAT2/SLC38A2 on the plasma membrane, the TCA cycle causes various anaplerotic reactions and increases glutamine absorption if the concentration of pyruvate in the mitochondria drops [24, 25]. In the cell, glutamine is converted into α-ketoglutarate (α-KG) via glutamate through various transaminases. α-KG can be converted into citrate or isocitrate by reductive carboxylation by using the enzymes isocitrate dehydrogenase (IDH) [26]. This metabolic shift to the reductive carboxylation process from oxidation is totally controlled by *HIF-1α*. The majority of the citrate produced by glioblastoma cells under hypoxic conditions is produced via the reductive carboxylation of glutamine. The targeted ubiquitination and proteolytic destruction of the E1 subunit's 48 KDa splice variant of the α-KGDH complex by SIAH-2 occurs when HIF-1 is active. A research study on the model of Burkitt lymphoma stated that HIF-1 increases the utilization of glutamine in the P-493 cell line [27]. Furthermore, in carcinoma of renal cells, tumor suppressor gene inactivation is responsible for HIF-1 stabilization. When HIF-1 is stable, there is an increase in the expression of platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). All these factors affect the tumor physiology so it is indirectly used as a prognostic marker of various carcinoma [28]. In this carcinoma, aspartate is converted from glutamine via a reductive carboxylation process and used in the synthesis of pyrimidine, transamination reaction of amino acids, and glutamine biosynthesis [29]. Serine is essential for the development of malignant cells. In both in vitro and in vivo settings, cancer cells' ability to proliferate is inhibited by serine depletion [30]. Serine performs a variety of dynamic tasks, including the production of phosphatidylserine, the synthesis of other amino acids like glycine and cysteine, and the contribution of single-carbon units to the folate pathway. When the oxygen level is low (hypoxic conditions), the amino acid serine is synthesized from the glucose molecule by the three enzymes phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase, and phosphoserine phosphatase. PHGDH has been observed to be overexpressed in several cancer types, including breast cancer, cervical cancer, non-small cell lung cancer (NSCLC), and colon cancer [31-33]. However, a study indicated that the researcher failed to overexpress PHGDH

in the breast cancer cell line, which can only be amplified in a HIF-dependent way under hypoxic circumstances [34]. In order to boost the synthesis of glutathione, the genes HIF-1, which codes for the cysteine transporter, and GCLM, which codes for the glutamate-cysteine ligase regulatory subunit, activate the transcription of the SLC7A11 gene. Serine metabolism is strictly related to the One-carbon cycle [35]. It directly regulates the production of NADPH + H+ in the process of redox regulation, and NADPH + H+ shields the mitochondria from ROS that is produced in the electron transport chain by converting oxidized glutathione (GSSG) to its reduced form (GSH), which scavenges ROS [36]. According to a study, breast cancer cells exposed to hypoxia release NADPH to keep glutathione in its reduced state and aid in cell survival. When PHGDH is knocked out, NADPH + H+ synthesis falls, glutathione is less reduced, and ROS production rises, leading to an excess of apoptosis [37]. In hypoxia conditions, HIF-1 increases the synthesis of 3 mitochondrial enzymes hydroxymethyltransferase-2 (SHMT2), methylenetetrahydrofolate dehydrogenase, and methylenetetrahydrofolate dehydrogenase-1. Serine is degraded to CO_2 and NH_4 by the mitochondrial enzyme SHMT2 which increases NADPH production and results in the mitigation of antioxidants in hypoxic conditions. In the MYC-dependent cells, the knockdown of the enzyme SHMT2 or the in vivo suppression of this enzyme triggers the hypoxia-induced cell death, impairs the growth of the tumor, and also increases the production of ROS but reduces the cellular NADPH level [38].

Major metabolic alterations in cancer cells and Responsible genetic factors

The modification of metabolism in cancer cells is triggered by a variety of genes. An increase in glycolysis, glutaminolytic flux, mitochondrial biogenesis, and various macromolecule biosynthesis, an increase in lipid and amino acid synthesis as well as pentose phosphate pathway activation, are some of the most notable changes in tumor cell bioenergetics [4]. Several signaling molecules and transcription factors like *HIF-1α*, mTOR, Akt, and c-Myc are considered the main regulator which received special attention. Cancer metabolism is also influenced by a number of oncogenes, including the tumor-suppressor gene p53, K-Ras, the adenosine monophosphate-activated protein kinase (AMPK), members of the sirtuin family, non-coding RNAs, and deacetylation [38]. Several glycolytic enzymes are also increased in tumors as a result of increased transcriptional activity of c-Myc and HIF-1 alpha but inadequate p53-mediated control [4].

Hypoxia-Inducible Factor-1 (HIF-1)

Hypoxia-inducible Factor-1 (HIF-1) is hypothesized to play a role in regulating the hypoxic state that all cancer cells experience at some time. A heterodimeric transcription factor HIF-1 has two subunits, one of which is ubiquitously expressed as HIF-1 α and is oxygen sensitive, while the other subunit is constitutively expressed as HIF-1β and is often referred to as the aryl hydrocarbon nuclear translocator (ARNT). Both domains contain a basic helix-loop-helix motif. HIF-2

α and HIF-3 α are known to be HIF-1 α analogs [39]. It is believed that HIF-3α can bind to *HIF-1α* and restrict its ability to perform transcriptional functions, acting as a negative regulator of the activation of *HIF-1α* [12]. HIF-1 positively controls the transcription of more than 100 genes involved in angiogenesis, cell migration, cell proliferation, and glucose metabolism. Two transactivation domains (TADs), the NH2-terminal (N-TAD) and the COOH-terminal (C-TAD) are present in the HIF-1 Alpha subunit. For *HIF-1α* to perform its transcriptional function, these two domains are necessary. In comparison, all *HIF-1α* subunits vary from HIF-1β in that they all have an N-TAD overlapping oxygen-dependent degradation domain (ODDD) in their structures [39]. On the other side, where *HIF-1α* is predominantly expressed, Although HIF-2α does not explicitly affect glucose metabolism, it promotes cell cycle progression by interacting with the oncoprotein c-Myc and is expressed in many organs, including the cells of the liver, lung, renal, and endothelial tissues. Analysis reveals that in many human tumors, both *HIF-1* alpha and HIF-2 alpha are heavily expressed, but *HIF-3* alpha is downregulated in renal cell carcinomas [3]. The prolyl hydroxylase domain proteins (PHDs) of proline residues 402 and 564 regulate the stability of the HIF1α protein through oxygen-dependent degradation. These modifications favor association with the von Hippel-Lindau tumor suppressor protein (VHL), an E3 ubiquitin ligase, and subsequent proteasomal degradation [40]. Together with RBX1, cullin-2, elongin-B, and elongin-C, the VHL protein forms a complex to create an E3 ubiquitin ligase that can then engage with E1 ubiquitin-activating enzymes and E2 ubiquitin-conjugating enzymes to mediate the ubiquitination of *HIF-1α* [41]. Complete enzymatic hydroxylation of HIF-1 by the PHDs requires the presence of iron, oxygen, and 2-oxoglutarate [42].

It has been demonstrated that pVHL tumor suppressor genetic deficit causes *HIF-1* to stabilize and become activated, even under normoxic settings, along with tumor cell growth and survival. [8]. High *HIF-1* alpha levels in VHL syndrome contribute to the over-expression of growth factors that activate downstream receptor tyrosine kinases, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor-β, and transforming growth factor [43]. It is assumed that growth factors such as epidermal growth factors and insulin-like growth factor-2 act as a stimulator and target genes for HIF-1 and induction of HIF-1 by these factors leads to autocrine solicitation of proliferation and survival [42]. It is believed that HIF1AN (FIH1), an inhibitor of HIF1A may also repress the transcriptional activity of HIA-1A even under normoxic conditions through hydroxylation of Asp site803 of HIA1A protein [40]. HIF1A is primarily regulated at the level of protein however, regulation of *HIA1A* at transcriptional and translational levels also takes place. *PI3K/AKT/mTOR* signaling cascade activation is well known to control both the transcription of *HIF1A* mRNA and HIF1A protein translation [40]. Analysis to date shows that *HIF-1* can also be regulated by hormones, inflammatory cytokines, cyclin-dependent kinase, microRNAs, and reactive oxygen species in an oxygen-independent manner [43].

Pathways involve in Cancer Metabolism

Cell signaling pathway fluctuations, such as K-Ras, PI3K-Akt-mTROC1, and Myc signaling, play an important role in cancer cell mitochondrial metabolism [44]. Akt referred to as protein kinase B is an important serine/threonine-protein kinase that is directly activated by PI3 K and is important for several cellular processes involving cell development, metabolism, and survival. The phosphatidylinositol-3-kinases (PI3Ks) are a family of signaling enzymes and these enzymes include three main classes of lipid kinases, I-III, and a closely related Class IV [45]. Akt regulates glucose transporters and hexokinase thereby increasing glycolysis, which in turn generates nucleotides and amino acids for cell survival. For circulating glucose homeostasis, control of the glucose transporter *GLUT4* by Akt2 is important [46]. In regulating both *GLUT1* and *GLUT4* trafficking, studies have implicated thioredoxin-interacting protein (TXNIP) as a direct AKT substrate. Akt inhibits the TXNIP by phosphorylation, resulting in rapid rises in *GLUT1* and 4 in the plasma membrane and improved glucose uptake in different cell types [47]. It is also believed that Akt also enhances phosphorylation PDK1 activity during hypoxia. Moreover, Akt also triggers few downstream effectors involves, mTORC1, glycogen synthase kinase 3, and Forehead box O (FOXO) [47]. mTORC1 signaling increases the activity of HIF-1 which stimulates glycolysis and inhibits the TCA cycle [48]. Except for glucose metabolism, Akt is also believed to enhance de novo lipid synthesis at post-translational and transcription levels. Akt and mitogen-activated protein kinase (MAPK) signaling facilitates de novo lipid synthesis by activating transcription factor sterol regulatory element-binding protein (SREBP) [20]. SREBP-focused genes include ATP citrate lyase (ACLY), acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FASN), and the fatty acid transporters stearoyl-CoA desaturase 1 (SCD) [27]. mTOR modulates SREBP as well as other lipid metabolism regulators and activators. MTORC1 can also control SREBP by negative regulation of lipin1, a phosphatidic acid that suppresses SREBP activity. S6K1 also controls the processing of SREBP [49].

mTORC1 also controls the uptake of amino acids from intracellular vesicles to the plasma membrane by inducing the translocation of amino acid transporters [46]. mTORC 1 also controls the pentose phosphate pathway (PPP), mRNA translation, and autophagy. mTOR signaling leads to an increase in the expression of PPP enzyme glucose 6 phosphate dehydrogenase, resulting in increased PPP and enhancing the production of ribose-5-phosphate [50]. mTORC1 enhances flux through the PPP in a hepatocellular carcinoma (HCC) model, both by inducing glycolysis that provides PPP substrates and by increasing G6PD and R5P isomerase A (RPIA) levels [51]. Analysis indicates that O-GlcNAcylation signaling is implicated in the reprogramming of metabolism in cancer cells [52]. HIF-1 mediated metabolic reaction occurs inside the mitochondria shown in Figure 2.

Role of Oncogenes & Tumor Suppressor genes
Oncogenes

In transformed cells, several popular oncogenes,

including *c-Myc, KRAS, BRAF,* Src promote anabolic metabolism. In general, c-Myc proto-oncogene is a potent regulator of several metabolic pathways important to cancer development. In aerobic glycolysis, Myc directly stimulates the transcription of almost every glycolytic gene by interacting with the traditional E-box pattern (CACGTG) [53]. In vitro, rat fibroblast studies suggested that Enolase (ENO1) and *GLUT-1* are direct MYC target genes. Moreover, hexokinase 2 has also been known as a direct Myc target gene using Myc knockout and conditional cell lines [54]. The chromatin immunoprecipitation assay revealed that MYC was bound by hexokinase II (HK2), enolase 1 (ENO1), and lactate dehydrogenase A (LDHA) to the canonical MYC-binding E-box involving different species [53]. Both HIF and c-Myc coordinate to facilitate the expression of the main glycolytic enzymes. Studies also show that MCT1 (lactate transporter) is a Myc target and inhibition of MCT1 has resulted in intracellular lactate deposition in tumor cells which leads to cell death [54]. MYC is known to activate glycolytic genes not only through transcription but also by alternative splicing. As a product of mutually exclusive alternative mRNA splicing, the *PKM1* and *PKM2* isoforms differ from each other. The splicing decision is regulated by three heterogeneous nuclear ribonucleoproteins, hnRNP1, hnRNP2, and hnRNP3, which bind to the intron areas surrounding exon 9 and negatively regulate its splicing. Interestingly, Myc is positively controls hnRNP1

and hnRNP2 [Goetzman & Prochownik, 2018]. Typically, Myc activity is determined by its concentration and it is enhanced downstream of P13K-Akt signaling via a variety of transcriptional, translational, and post-translational levels [47]. Myc also enhances the fatty acid synthesis and oxidation, nucleotide synthesis, polyamine synthesis, reprogram cholesterol metabolism and also plays a key role in glutamine catabolism [53, 54].

In addition, mutations in *KRAS* or *BRAF* tend to have essential roles to perform Regulation of metabolic reprogramming in multiple cancers. About 90% of pancreatic tumors, and 50% of colorectal and 30% of pulmonary tumors have *KRAS* mutations [55]. Both oncogenes trigger the pathways of mitogen-activated protein kinase (MAPC), and NRAS stimulates the pathway for phosphoinositide 3-kinase (PI3 K) [55]. The DLD-1 and RKO colorectal cancer cell lines, that had oncogenic mutations in KRAS and BRAF respectively, demonstrate higher primary glucose transporter *GLUT1* expression and display a Warburg phenotype impact which in turn increases glycolysis rate [56]. An overexpressed Kras Pancreatic ductal adenocarcinoma (PDAC) mouse model shows that developed PDAC is strictly dependent on the expression of Kras and this mutant KRAS promotes tumor development by elevating uptake of glucose and channeling glucose intermediates into the hexosamine biosynthesis pathway (HBP) and the non-oxidative pentose phosphate pathway (PPP). These studies have
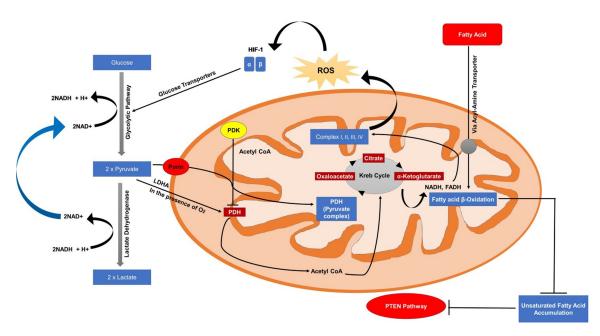

Figure 2. HIF-1 Targeted Regulation of Cancer Metabolism: By stimulating the expression of glucose transporters (GLUTs) and other enzymes involved in glycolysis, HIF-1 controls a wide range of metabolic changes brought on by hypoxia. This stimulates glycolysis and results in higher amounts of pyruvate. HIF-1 also encourages pyruvate conversion to lactate by triggering lactate dehydrogenase (LDH). Pyruvate conversion to lactate regenerates NAD+, enabling hypoxic cells to carry on with glycolysis and ATP synthesis. Moreover, Pyruvate dehydrogenase kinase (PDK) is activated by HIF-1, which prevents pyruvate from being converted to acetyl CoA, hence reducing Kreb cycle flux. The reduction of oxidative phosphorylation and the excessive production of mitochondrial reactive oxygen species are caused by decreased Kreb cycle activity (ROS). The induction of PDK1 reduces the persistence of potentially hazardous ROS levels because hypoxia cells already exhibit elevated ROS, which has been shown to enhance HIF-1 accumulation. By Controlling medium-chain acyl-CoA dehydrogenase and long-chain acyl-CoA dehydrogenase, HIF-1 prevents the breakdown of fatty acids in the regulation of lipid metabolism. This causes the accumulation of fatty acids and the decrease of ROS levels, which blunts the expression of PTEN and encourages the growth of cancerous cells.

also suggested that oncogenic Kras facilitates ribose biosynthesis [57]. Mutant KRAS improves glycolysis through the upregulation of hexokinase 1/2 encoding genes and reroutes glutamine flow to malate for pyruvate development and NADPH production [58]. Oncogenic KRAS has also been reported to support a de novo lipogenesis gene expression in non-small cell lung cancer (NSCLC). The rise in lipogenesis in cancer is due to increased ACC1, ACLY, and FASN expression in cancer [59]. Research shows that BRAFV600E upregulates a ketogenic enzyme named 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) expressions via an octamer transcription factor Oct-1 expressing human primary melanoma and hairy cell Leukemia cells. This raises intracellular levels of the product HMGCL, acetoacetate, which selectively raises the binding of BRAF V600 E but not of the wild form of BRAF to MEK1, for the activation of MEK-ERK signaling in cancer cells [41].

Tumor suppressor genes

Many Tumor suppressor genes such as *p53, PTEN, CDKN2A, RB, FBW7, BAP1,* and *LKB1* play a significant role in reprogramming metabolic pathways in cancer cells [60]. However, the role of p53 and PTEN is most important in metabolic reprogramming. *TP53* is the first and most notable tumor-suppressor gene to be described. *TP53* is regarded as the "guardian of the genome" because it plays a vital role in the maintenance of genomic stability and the prevention of tumorigenesis [60]. A P53 inducible gene TIGAR (*TP53*-induced glycolytic and apoptosis regulator) transforms the way glucose is used by cells. TIGAR shows sequence similarities to the bi-functional enzyme 6-phosphofructo2-kinase/fructose-2, 6-bisphosphatase (PFK-2 / FBPase-2). TIGAR lowers the level of FBPase-2 and inhibits glycolysis in cancer cells which in turn facilitates the flow of glucose to the pentose phosphate pathway [45]. Activation of the pathway to pentose phosphate raises NADPH levels, increasing reduced glutathione to scavenge ROS [Marbaniang & Kma, 2018]. Research shows that mutations in *TP53* alter metabolism by inhibiting mitochondrial respiration and simultaneous stimulation of glycolysis. Loss of P53 contributes to the impairment expression of cytochrome C oxidase and inefficient cytochrome oxidase complex (COX) assembly, thus decreasing oxidative phosphorylation, therefore, causing cells to rely on glycolysis for energy output [60]. P53 reduces the glucose uptake via transcription suppression of SLC2A1/4 which encodes GLUT 1/4 or by limiting the activity of NF-κB (nuclear factor kappa-B) which results in decreased *GLUT3* expression [61].

P53 can also control metabolic reprogramming by means of post-transcriptional pathways, for example, it can suppress glycolysis by microRNA-34a (miR-34a) modification, which targets multiple glycolytic enzymes, including hexokinase 1, hexokinase 2, glucose-6-phosphate isomerase and PDK1 [60]. Furthermore, p53 inhibits monocarboxylate transporter 1 transcription to prevent the movement of the glycolytic agent lactate into and out of cancer cells (MCT1). p53-deficient cancer cells with high levels of MCT1 adjust to their metabolic needs by boosting the export or import of lactate depending on the amount of glucose available [62]. PTEN and Parkin transcriptional activation is a mechanism by which p53 inhibits *PI3K/AKT* signaling, which in turn inhibits glycolysis [62]. In addition, p53 specifically inhibits cell growth by up-regulating AMPK, TsC2, and sestrin expression, members of the AMPK pathway [45]. In specific, p53 has been shown to facilitate glutaminolysis by driving glutaminase-2 (GLS2) expression, an enzyme that converts glutamine to glutamate. P53 has also been shown to upregulate glutamate/aspartate transporter (SLC1A3) expression in colorectal cancer cells under nutrient-restricted conditions, promoting the use of aspartate in the absence of glutamine [63]. In lipid metabolism, it was stated that p53 binds directly to the SREBP-1 promoter region and transcriptionally represses the expression of SREBP-1. It also controls the expression of proteins that leads to lipid breakdown and intestinal absorption, their transport via lipoproteins and intracellular flux [61]. Sirtuin-1 (SIRT1) targets proteins involved in the maturation and aggregation of fat, nutrient sensing, and cellular metabolism regulation. The expression of SIRT1 mRNA is triggered by a p53 complex and the forehead transcription factor Foxo3a. Acyl CoA dehydrogenase is also considered a p53 target and plays an important role in mitochondrial β-oxidation of fatty acids [64]. Additionally, the beta-oxidation enzymes LIPIN 1 and carnitine palmitoyl transferase CPT1C are activated by p53, leading to an increase in fatty acid oxidation. [62]. P53 also regulates the expressions of Malonyl-CoA Decarboxylase (MCD) and Dehydrogenase/Reductase 3 (DHRS3) [64]. *PTEN* (Phosphatase and TENsin homolog deleted on chromosome 10) is one of the most frequently mutated tumor suppressor genes in different tumors [65]. It is believed that *PTEN* negatively regulates the activity of PI3k/Akt and mTOR signaling cascades that regulate cell proliferation, development, survival, and metabolism [65]. Studies show that PTEN dephosphorylates and inhibits auto-phosphorylated phosphoglycerate kinase 1(PGK1), thus inhibiting glycolysis and proliferation of brain tumor cells [66]. Studies also suggested that PTEN loss will contribute to lipid metabolic reprogramming in prostate cancer, including an increase in beta-oxidation of fatty acid and their de novo synthesis and also enhances glutaminolysis [67] (Figure 2).

HIF Targeted Therapeutic Approach in Cancer

As key players in the metabolism of cancer, hypoxia, and the HIF systems found to be potential therapeutic targets in several cancer types. The fundamental strategy involves blocking various processes along the HIF activation pathway, including transcription, translation, HIF stability, transcriptional activity, binding to DNA, heterodimerization, and transport inside the nucleus.

A. Transcription can be inhibited by various metabolites-based drugs, including aminoflavone [68], GL331 [69], and anthracyclines [70], cardiac glycosides [71], steroids [72], topoisomerase inhibitors [73], and microtubule-binding agents [74]demonstrate the several strategies by which the translation rate of the HIF mRNA is inhibited.

B. Some molecules like Panobinostat, a known

inhibitor of histone deacetylase, [75], MPT0G157, another histone deacetylase inhibitor in case of colorectal cancer [76], Rapamycin in a wide range of malignancies, and N-acetyl cysteine (Antioxidant agent), [77] is known to degrade the HIF- subunit, which reduces the stability of HIF by causing it to degrade.

C. It has been discovered that the substances PT2399 and PT2385 exhibit anticancer properties and reduce HIF-2α activity in cellular and animal renal carcinoma. Clinical trials are being conducted on ccRCC patients who were treated with these medications since they showed extremely encouraging outcomes [78, 79]. Acriflavine prevents *HIF-1β* from binding to the PAS-B domain of *HIF-1α* and *HIF-2α* [80]. HIF exerts its activity into the nucleus as a transcription factor, Deterioration of HIF nuclear localization can therefore be a secondary tactic to be targeted. Both the phosphorylation of the *HIF-α* proteins and nuclear export of *HIF-α* dependent on CRM1 is affected by herbal products (like kaempferol) and synthetic compounds (U0126 and PD98059) that block the ERK1/2 pathway. There are some chemical agents like echinomycin and doxorubicin, that block the transcriptional activity by impairing the binding of HIF to chromatin [81, 80].

D. It is also possible to insert HIF-α isoforms with peptide-based amino acid sequences inside of the cell to block HIF activity or their interaction with inhibitory proteins. This is usually performed with the help of Transduction Technology. To perform this strategy, the structural knowledge of the HIF-α domain (DNA binding as well as transactivation or regulatory domain) is excellent for modeling peptides. Several peptides have been identified to prevent HIF activity.

E. Hypoxia-activated prodrugs (HAPs): These are bioreductive medications that, when used in hypoxic environments, may be selectively reduced by certain enzymes (reductases) to produce cytotoxic chemicals that precisely target hypoxic tumor cells but spare some healthy tissue [82]. Nitroaromatics, Quinones, aliphatic N-oxides, and hetero-aromatic N-oxides are a few of the HAPs classes that have currently been produced. Inhibiting the HIF pathway using HAPs has also been reported [83]. The most advanced HAP now available is nitroimidazole mustard evofosfamide (TH-302), which is undergoing phase III clinical studies for pancreatic cancer and soft tissue sarcoma [84, 85]. Another HAP that has been suggested for use in the surgical treatment of bladder cancer is praziqual (E09) [86]. The list of chemical agents that inhibit the HIF pathway is given in Table 1.

These findings suggested that the therapeutic potential of modulating the HIF-mediated pathway in treating numerous malignancies is quite interesting. Hence, in order to create novel and efficient therapeutic strategies for various tumors, we need to better understand each stage in the hypoxia pathway.

HIF-1α Vs. Hematological Malignancies/Leukemia

Research has shown that bone marrow (BM) has a very uncommon concentration of oxygen as low as 0.6% and that leukemic stem cells are protected and can self-renew in a hypoxic environment [93]. It is commonly recognized that the testis and the central nervous system (CNS) share a hypoxic environment with the bone marrow (BM), making them the most susceptible locations for extramedullary recurrence of acute lymphoblastic leukemia (ALL) [94]. Significantly, the prognosis of leukemia patients may be impacted by hypoxia-activated *HIF-1α*. The functional role of *HIF-1α*, their chemical target, and their mode of action have been depicted in Table 2.

Acute Lymphoblastic Leukemia (ALL)

T-cell acute lymphoblastic leukemia (T-ALL) is a highly aggressive hematological malignancy [95]. Drawing on relevant in vivo and in vitro T-ALL cell research, Fahy et al. concluded that hypoxia significantly inhibits CD45/CD7 T-ALL cell development, making them resistant to anti-leukemic medication while preserving their ability to proliferate beyond the end of therapy. Moreover, hypoxia T-ALL cells had reduced activation of mammalian rapamycin (mTOR) and enhanced drug resistance; in the meantime, hypoxic concentrations of mTOR activity were restored by *HIF-1α* knockdown, and the chemotherapeutic impact on leukemic cells had been reduced by mTOR suppression in *HIF-1α* knockdown T-ALL [96]. Consequently, leukemic cells may experience growth inhibition due to hypoxic activation of the *HIF-1α* /mTORC1 axis, which might lead to the emergence of treatment resistance. Likewise, in another T-ALL investigation, Notch1 has been shown to perform as an oncogenic agent during the disease's progression. The suppression of Notch1 signaling under hypoxic conditions was achieved by silencing *HIF-1α* through small interfering RNA (siRNA) transfection. This was demonstrated by decreased expression of its

Table 1. Inhibition of HIF Pathway and Examples of Chemical Agents Used

Sr No	Inhibition	Chemical Agents	References
I.	Transcription	Aminoflavone, GL331, and Anthracyclines	[Terzuoli et al., 2010], [Chang et al., 2003], [Pang et al., 2017]
II.	Translation	Cardioglycosides, Steroids, Topoisomerase inhibitors, and Microtubule Binding Agents	[Zhang et al., 2008], [Gkotinakou et al., 2020], [Rapisarda et al., 2004], [Thomas et al., 2008]
III.	HIF Stability (HDAC inhibitors)"	Panobinostat, MPT0G157, Romidepsin, Belinostat, Panobinostat, and Chidamide	[Kovacs et al., 2006], [Huang et al., 2015] [Prince et al., 2012], [Poole ,2014], [Cheng et al., 2015], [Ning et al., 2012]
IV.	DNA Binding and Transcriptional Activity	Echinomycin, Doxorubicin Chetomin	[Kong et al 2005], [Lee et al., 2009] [Kung et al., 2004]
V.	Hypoxia Activated Prodrugs (HAPs)	Nitroimidazole mustard evofosfamide (TH-302), and Praziqual (E09)	[Borad et al., 2015], [Chawla et al., 2014] [Shukla et al., 2017]

Table 2. The Functional Roles of *HIF-1α* in Diverse Types of Hematological Malignancies

Cancer type	Experiment Models	Functions/Mechanism	Signaling	Reference
ALL	Human T- ALL samples and Mice	Deferoxamine (DFO) reduced the development and multiplication of tumor cells and caused death in ALL cells.	ROS/HIF-1α /mTOR Signaling	[You et al., 2022] [Fahy et al., 2021]
CLL	Primary Cell Culture, Cell Line, and Mice	EZN-2208, which has been shown to suppress HIF-1α, may enhance the CLL cells' apoptotic response to fludarabine.	EZN-2208/HIF- 1α	[Valsecchi et al., 2020]
AML	AML Patients Cell Lines	PARP14 stimulated the proliferation of AML cells and glycolysis. Simvastatin modulated the miR-19a-3p/ HIF- 1α induce apoptosis and reduce the proliferation, migration, and invasion of AML cells.	PARP14/NF- kB/HIF-1α Simvastatin/miR-19a-3p/HIF-1α	[Zhu et al., 2022] [Tian et al., 2021]
CML	CML Cell Lines (K- 562)	2-methoxyestradiol (2-ME2) inhibited HIF- 1α expression and down-regulated C-Myc or Bcl-xl and Bcl-2 genes triggering apoptosis in CML cells.	2-ME2/HIF- 1α/C-Myc, Bcl- xl or Bcl-2	[Zhang et al., 2022]
Lymphoma	T-cell lymphoma cells	Sildenafil improved the capacity of cisplatin to kill tumor cells by suppressing the expression of HIF-1α and decreasing glucose metabolism in T-cell lymphoma cells.	HIF- 1α/glycolysis regulatory molecules/ ROS	[Rawat et al., 2022]

downstream target gene, Hes1, which hindered cell proliferation, invasion, and chemoresistance. Conversely, silencing Notch1 did not affect *HIF-1α* expression [97].

Chronic Lymphocytic Leukemia (CLL)

Hypoxic microenvironment (HME) in leukemia promotes CLL cell survival and proliferation by upregulating *HIF-1α*. Griggio et al. discovered in a prior study that leukemia cells originating from CLL patients with *TP53* (tumor suppressor gene) loss have increased HIF-1α transcriptional activity and expression, which aids in the growth of the tumor and puts this patient population at worse risk [98]. Furthermore, they consistently noted that CLL cell lines that are grown in hypoxic environments or in conjunction with stromal cells might enhance *HIF-1α* expression even more. An efficient way to lower HIF-1α protein levels in tumor cells is by using the specific HIF-1α inhibitor BAY87-2243 [99]. Both in vitro and in vivo investigations provide evidence that BAY87-2243, irrespective of functioning *TP53*, has anti-tumor activities and improves the effectiveness of fludarabine and ibrutinib in CLL [100]. Based on this, Seiffert hypothesized that fludarabine treatment is effective against CLL cells whose *TP53* was damaged due to HIF-1α suppression. The interactions between CLL cells and TME are also uniquely modulated by *HIF-1α*. Chemokine receptor and cell adhesion molecule expression in CLL cells is regulated by *HIF-1α*, which in turn controls how cancer cells interact with the BM and spleen microenvironment. In addition, the researchers showed that deactivating *HIF-1α* diminishes leukemic cells' chemotaxis and adherence to the stroma, lessens their colonization of the BM and spleen, and may even increase the life expectancy of animals with CLL in a mouse model [101].

Acute Myeloid Leukemia (AML)

Leukemic stem cells (LSCs) in AML can promote tumor cell proliferation, which can cause chemoresistance and a high recurrence rate in treated patients. This results in a dismal prognosis for most patients [102, 103]. By making AML cells more susceptible to

ADR in the presence of hypoxia, the *HIF-1α* inhibitor CdCl2 dramatically reduced the growth of AML cells. AML-derived macrophage migration inhibitory factor (MIF) expression can be up-regulated in the BM microenvironment by *HIF-1α*, which promotes AML cell survival and proliferation [104]. PML-RARα, an oncogenic fusion protein produced by the t (15;17) chromosomal translocation, is a characteristic shared by acute promyelocytic leukemia (APML) and other AML classes. To function as a transcriptional co-activator in APL, *HIF-1α* can cooperate with PML-RARα [105]. PML-RARα has been shown to enhance *HIF-1α* -driven pro-leukemic processes in vitro and in vivo, such as tumor cell self-renewal, BM neo-angiogenesis, and cell migration. Therefore, based on the particular conditions, our findings suggest that the involvement of *HIF-1α* needs to be carefully taken into account in practical applications.

Chronic Myeloid Leukemia (CML)

One of the key molecular biological characteristics that explain the pathophysiology and treatment resistance of CML patients is the oncogenic fusion gene BCR-ABL, which activates a variety of signaling pathways critical to the growth and survival of tumor cells, including the JAK/ STAT pathway [106]. Presently, it has been demonstrated that tyrosine kinase inhibitors (TKIs)—such as imatinib (IM)—are efficacious in treating chronic myeloid leukemia [106, 107]. Zhao and colleagues in 2010 noted that *HIF-1α* might induce increased BCR-ABL expression in CML cell lines when BCR-ABL drug resistance mutations were absent, resulting in leukemic cells with increased immunity to IM. Through its ability to speed up glycolysis, *HIF-1α* mechanistically upregulates the expression level of BCR-ABL, serving as a crucial anti-drug factor. Importantly, oxythiamine can prevent *HIF-1α* -induced glycolysis, which makes tumor cells more sensitive to medication [99]. Comparably, in the CML cell line K562, *HIF-1α* may increase the invasiveness of cancer cells by increasing glycolysis in response to fumarate hydratase (FH) expression downregulation, but this may also result in a decreased capacity for DNA repair

following damage [108]. Because of this dual impact, FH's function is compromised, which advances the CML illness. *HIF-1α* mRNA expression was significantly greater in BM specimens from CML patients than in healthy controls. In vitro findings consistently showed that *HIF-1α* deficiency down-regulated p21 and p53 mRNA and protein expression in K-562 cells, which ultimately resulted in the reduction of CML cell growth [109]. Our previous research [110] indicates that *HIF-1α* functions as a master regulator in the pathophysiology of CML and may be a potential target for its treatment.

Lymphoma

About 30% of all non-Hodgkin's lymphomas (NHLs) are diffuse large B-cell lymphoma (DLBCL), which is the most often aggressive kind of NHL [48]. The majority of DLBCL patients have stable expression of *HIF-1α*, according to earlier research. Individuals with low *HIF-1α* expression in the R-CHOP group had significantly better progression-free survival (PFS) and overall survival (OS) compared to those with high *HIF-1α* expression; however, individuals treated with CHOP showed no survival difference [111]. This data emphasizes the importance of *HIF-1α* as a prognostic factor when assessing the chance of survival for DLBCL patients receiving R-CHOP treatment [112]. *HIF-1α* is mostly expressed in the hypoxic side population (SP) of Hodgkin's lymphoma (HL) cells. Under normoxia, the *HIF-1α* stabilizer CoCl2 prevents the effects of hydrogen peroxide. In contrast, the HL cell lines' generation of hydrogen peroxide causes cell differentiation into the major population (MP), which includes enormous Hodgkin and Reed-Sternberg-like cells. According to additional research, patients have a bad prognosis because heme oxygenase-1 (HO-1), which is activated by *HIF-1α*, scavenges intracellular ROS from SP and prevents tumor cell development [113].

In conclusions, the majority of cancers are characterized by hypoxia, which has been linked to unfavorable patient outcomes and aggressive metastatic characteristics. In the current review, we have highlighted the numerous forms of metabolism that occur in cancer circumstances considering the role of the HIF-1 network in assisting the adaptation of cancer cells' metabolism to hypoxia, as a result, increasing cancer cell survival, cell proliferation, and metastasis. During the previous two decades, numerous research studies have examined the function of HIF-1 in the reprogramming of many metabolic pathways, including glycolysis, TCA cycles, the electron transport chain, glycogen synthesis, glutamine and serine synthesis, lipid metabolism, generation of ROS, as well as mitochondrial biogenesis and autophagy. Because HIF-1 lowers mitochondrial oxidative metabolism by lowering oxygen consumption, this interaction between HIF-1 and mitochondria is essential for dealing with the hypoxic state of tumor cells. As a result, tremendous progress has been achieved in understanding how HIF-1 controls cancer cell expansion and is a potential cancer therapeutic target. Still, there are a few details concerning HIF members that need to be clarified. Examples include the distinct roles played by each member of the family and the interactions of the *HIF-1α* family along with the other participants of

HIF i.e., HIF-2α and HIF-3α throughout the adaptation in hypoxia. Identification of specific therapeutic targets requires a thorough understanding of the regulatory system. Targeting hypoxia, which is closely related to HIF, is an alternative therapy that may be used to stop the spread of different malignancies and provide patients with a longer chance of life. Hypoxia Activated Prodrugs (HAPs) have a better safety profile and antitumor activity and along with some reliable biomarkers can be used in clinical trials and might be predictive of the hypoxia status in many cancers including leukemia. Summation of hypoxia-based biomarkers and personalized medicine might be a better translational approach from bench to bedside.

Author Contribution Statement

SP: Acquisition, assembly, analysis, interpretation of data, drafting of the manuscript, constructing tables and diagrams, and critical revision of the final manuscript. RS: Conceptualization, & revision in the final draft. NH, RMT, and RK: drafting and assembly of the initial manuscript. AAM: Overall guidance throughout the manuscript preparation. All authors listed have approved the final version of the manuscript.

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Ethical Approval

Since the study did not include human or animal material, the ethics committee does not need to approve this publication.

Informed Consent

This study does not require informed consent.

Data Availability Statement

The article does not fall under the category of data sharing because no datasets were created or examined in this particular study.

Conflicts of Interest

Each author declares that their interests do not conflict.

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