Therapeutic Targeting Hypoxia-Inducible Factor (HIF-1) in Cancer: Cutting Gordian Knot of Cancer Cell Metabolism

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Metabolic alterations are one of the hallmarks of cancer, which has recently gained great attention. Increased glucose absorption and lactate secretion in cancer cells are characterized by the Warburg effect, which is caused by the metabolic changes in the tumor tissue. Cancer cells switch from oxidative phosphorylation (OXPHOS) to aerobic glycolysis due to changes in glucose degradation mechanisms, a process known as "metabolic reprogramming". As a result, proteins involved in mediating the altered metabolic pathways identified in cancer cells pose novel therapeutic targets. Hypoxic tumor microenvironment (HTM) is anticipated to trigger and promote metabolic alterations, oncogene activation, epithelial-mesenchymal transition, and drug resistance, all of which are hallmarks of aggressive cancer behaviour. Angiogenesis, erythropoiesis, glycolysis regulation, glucose transport, acidosis regulators have all been orchestrated through the activation and stability of a transcription factor termed hypoxia-inducible factor-1 (HIF-1), hence altering crucial Warburg effect activities. Therefore, targeting HIF-1 as a cancer therapy seems like an extremely rational approach as it is directly involved in the shift of cancer tissue. In this mini-review, we present a brief overview of the function of HIF-1 in hypoxic glycolysis with a particular focus on novel therapeutic strategies currently available.

Keywords: genomic alterations, cancer, metabolism, warburg effect, hypoxia-induced tumor microenvironment, metabolic reprogramming, cancer therapies, clinical outcomes

INTRODUCTION

Increased incidence of cancer patients around the globe clearly alarms for more comprehensive research of this life-threatening problem. The initiation of cancer is a multi-step process that includes genomic alterations. Hannah and Weinberg have extensively described the "hallmarks of cancer", one of which is "metabolic reprogramming" that has recently emerged as a core trait of tumors (Hanahan and Weinberg, 2011; Hanahan, 2022). Specifically, the altered glycolytic metabolism pathway results in switching from oxidative phosphorylation (OXPHOS) in the mitochondria to aerobic glycolysis even in the abundance of oxygen in various cancer types. The "Warburg effect", proposed by Otto Warburg over a century ago, was the first to reveal basic metabolic distinctions between differentiated cells and rapidly proliferating tumor cells (Otto, 2016). Warburg effect is the result of the interplay between (normoxic/hypoxic) HIF-1 upregulation, activation of an oncogene (cMyc, Ras), loss of function of tumor suppressors (mutant-p53, mutant-PTEN, micro RNAs and sirtuins with suppressor functions), activation of (PI3K/Akt/mTOR; Ras/Raf/Mek/Erk/cMyc; Jak/

Stat3) or deactivation of (LKb1/AMPk) signalling pathways (Arora et al., 2015; Vaupel and Multhoff, 2021). Although Warburg's and others' findings have had a significant impact on our understanding of tumor biology, they constitute only one aspect of tumor metabolism.

In fact, cancer metabolism alterations span a wide range of metabolic pathways that serve a multitude of functions such as apoptosis, angiogenesis, anti-anoikis, and anchorage-independent expansion in cancer cells and in the tumor microenvironment (TME), in addition to glucose metabolism and energetics (Casero and Pegg, 2009; Platten et al., 2012; Zhang and Du, 2012; Jeon and Hay, 2018). Therefore, targeting the energy metabolism of cancer cells, which takes advantage of the metabolic differences between cancer cells and normal cells opens the doorway to novel therapeutic interventions.

The TME endures biochemical alterations during the growth of the solid tumor, including depletion of glucose, bicarbonate, and oxygen (i.e., hypoxia and anoxia), high amounts of lactate and adenosine, and low pH value (Wang et al., 1995; Ke and Costa, 2006). Hypoxia, a prevalent characteristic of cancer especially solid tumors, is hypothesised to enhance tumor invasiveness and metastasis (Ke and Costa, 2006). Tumor hypoxia has been attributed to a variety of factors. First, angiogenesis inability to keep up with cancer growth, such as the need for the cancer cell mass "outstripping" the ability of blood vessels to carry oxygenated blood. Second, ischemia-induced by arteriovenous shunting or microvessel 'steal' syndromes induced by abnormal vessel arborization and aberrant vascular connections inside malignancies. Lastly, elevated hydrostatic pressure within the tumor, results in compression of the microvasculature (Heldin et al., 2004). Several mechanisms, notably the hypoxia-inducible factor-1 (HIF-1) pathway, which promotes the elevated expression of glycolytic enzymes, can govern the metabolic transition state above at the transcriptional level. As a result, tumor hypoxia and HIFs influence the majority of cancer "hallmarks", including cellular proliferation, apoptosis, metabolism, immunological responses, genomic instability, vascularization, neovascularization, invasion, and metastasis (Wigerup et al., 2016). Moreover, HIFs seem to impact chemo and radiation resistance through multiple pathways. Additionally, HIFs expression has been linked to poor prognosis and treatment relapse in clinical tumor samples (Sørensen and Horsman, 2020). Thus, HIFs appear to be critical therapeutic targets that can be used to enhance current cancer treatment for metastatic and treatment-resistant cancers.

The primary intent of this mini-review is to provide a brief overview of the metabolic processes that are regulated by a hypoxia-inducible factor. In this review, we outline the relevance of HIFs in glycolysis, cancer progression and the epithelial-mesenchymal transition (EMT). A further goal of the review is to overview the currently available therapeutic strategies.

Relevance of HIF-1 Stimulated Glycolysis in Hypoxia

Hypoxia affects metabolic pathways in a variety of ways. For example, by blocking the oxygen-dependent process of mitochondrial OXPHOS, hypoxia reduces ATP synthesis, and thus makes O_2-independent glycolysis a more important energy source (Denko, 2008; Frezza and Gottlieb, 2009). Increased glycolysis generates ATP quickly, but at the price of a substantial amount of glucose, as seen by elevated lactic acid levels. Intra-tumoral acidosis is mediated by the latter, in conjugation with mitochondria's impaired capacity to use protons in ATP synthesis (Zhou et al., 2006). Surprisingly, rather than being anti-cancer, the stress placed on cancer cells appears to promote the formation of more aggressive subclones with a greater ability to penetrate tissues and metastasis (Gatenby and Gillies, 2004; Gatenby et al., 2007). Hypoxia-induced events are mostly determined by the activity of the transcriptional regulators' hypoxia-inducible factor-1α (HIF-1α) and its partner HIF-1β.

HIF-1, a transcription factor, regulates the activation of several genes involved in glucose uptake and metabolism, cell survival/proliferation, angiogenesis, invasion, and metastasis (Semenza et al., 1994; Carmeliet et al., 1998). It is a heterodimer of HIF-1α and a constitutively expressed subunit HIF-1β which also forms a dimer with HIF-2α and regulates gene activation (Wang et al., 1995; Carmeliet et al., 1998). HIF-1α is generally targeted for ubiquitin-mediated destruction by proline hydroxylation and association with the Von Hippel-Lindau (VHL) tumor suppressor complex under normoxic conditions, but it is stabilised when the partial pressure of oxygen is low (**Figure 1**). Moreover, overexpression of HIF-1α is linked to a poor prognosis in various patients with human malignancies including breast, colon, gastric, lung, skin, ovarian, pancreatic, prostate, and renal cancer (Bos et al., 2001; Dales et al., 2005; Chen et al., 2007; Simiantonaki et al., 2008). Thus, HIF-1α significantly enhances our molecular understanding of cancer progression and metastasis which is discussed in detail in the following sections.

Hypoxic Tumor-Microenvironment: Leading to Cancer Progression and Epithelial-Mesenchymal Transition

Mammalian cancer cells within a Hypoxic tumor microenvironment (HTM) undergo tremendous alterations, eventually intensifying their malignant activity. As a result, emphasis has been laid on identifying processes involved in cancer cell adaptation to the HTM in order to identify targets for potential therapeutic treatments (Liu et al., 2011; Kogita et al., 2014; Yang et al., 2015). Basically, in hypoxia conditions, HIF-1α forms the HIF complex, which functions as a transcription factor in the activation of a wide range of genes, orchestrating major phenotypic alterations and eventually leading to EMT. Following EMT, cells lose their normal morphology and gain mesenchymal traits (Kalluri and Weinberg, 2009; Singh and Settleman, 2010), including the development of stemness (Sutherland, 1988), increased invasiveness, and metastasizing capacities (Vaupel, 2004). All of these alterations have been associated with poor prognosis and chemotherapy resistance in a variety of tumor types (Yang et al., 2008; Chou et al., 2012). EMT is characterised by the loss of cell adhesion protein (for instance E-cadherin) and
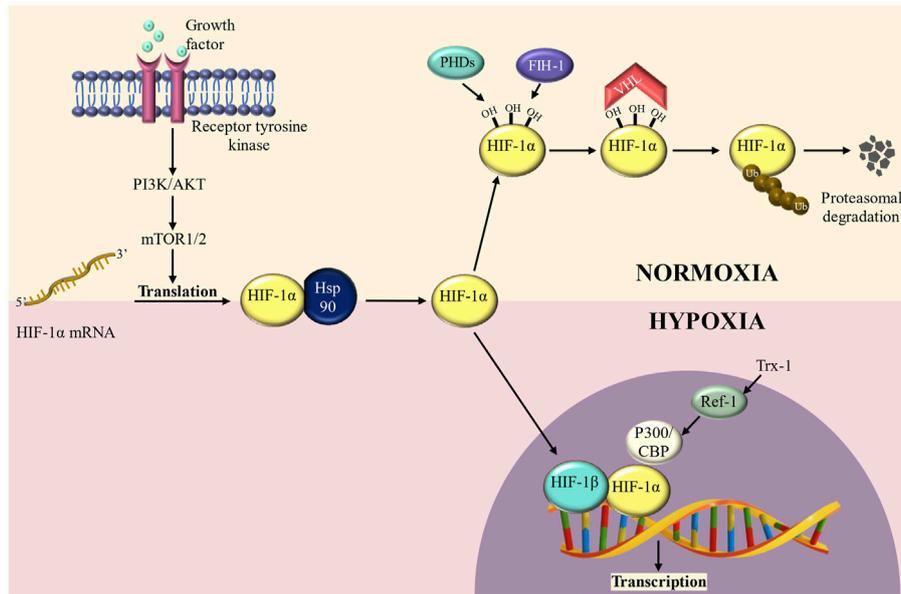
FIGURE 1 | HIF-1α regulation in normoxic and hypoxic conditions. HIF-1α is hydroxylated at conserved residue (Proline 564) under normoxic conditions, a process mediated by prolyl-4- hydroxylases (PHDs) and factor inhibiting HIF-1 (FIH-1) enzymes. PHD hydroxylation promotes HIF-1α protein destabilization, whereas FIH-1 hydroxylation inhibits transcriptional activity by preventing interaction with CBP/p300. HIF-degradation is mediated by a ubiquitin-dependent process carried out by the Von Hippel-Lindau (VHL) E3 ubiquitin ligase complex. Under hypoxic circumstances, inactivation of PHDs and FIH-1 causes HIF-stabilization, followed by translocation into the nucleus and dimerization with HIF-1/ARNT to create the HIF transcription factor. During hypoxia, HIFs, in collaboration with the coactivator CBP/p300, promote transcription of a wide range of target genes.

the elevated expression of mesenchymal-specific proteins such as SNAIL, Vimentin, and TWIST. As a matter of fact, this phenotypic shift has been highlighted as a major phase in the intricate process of developing distant metastasis (Chaffer and Weinberg, 2011; Valastyan and Weinberg, 2011).
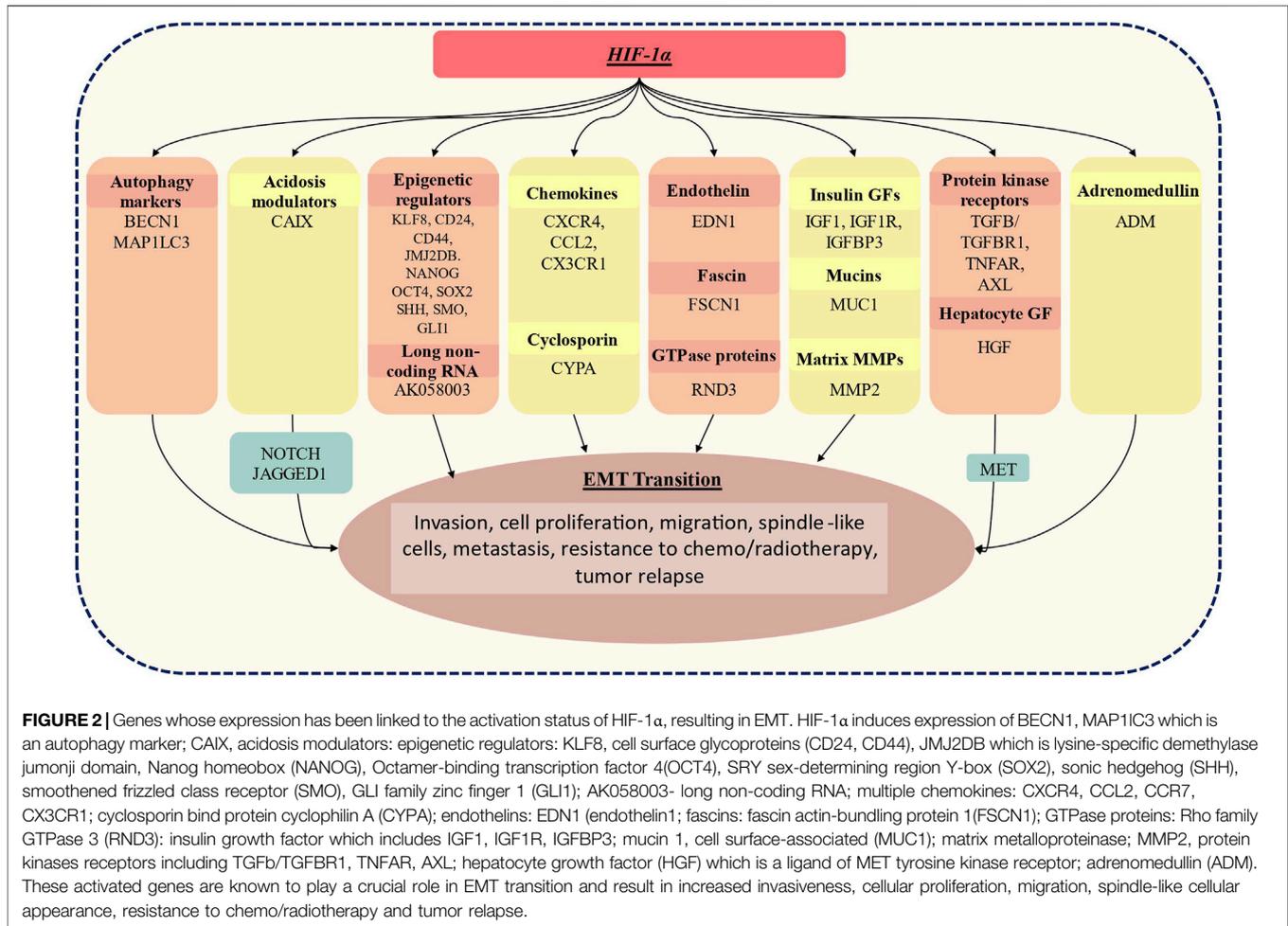
As represented in **Figure 2**, the HIF-1α complex activates a number of key genes that mediate hypoxia > HIF > EMT axis. This axis has been extensively investigated in many aggressive tumors including lung, triple-negative breast cancer (TNBC), pancreatic ductal adenocarcinoma (PDAC) and renal cell carcinoma (RCC). For instance, autophagy markers (BECN1 and MAP1LC3) are activated in lung and PDAC (Zhu et al., 2014; Zou et al., 2014); overexpression of CAIX, the acidosis modulator has been reported in TNBC and RCC (Tan et al., 2009); further overexpression of epigenetic regulator (DNA methyltransferase, histone acetyltransferases, chromatin-remodelling enzymes, etc) and long-non coding RNA has been reported in gastric cancer, TNBC and PDAC (Krishnamachary et al., 2012; Onishi et al., 2012; Fujikuni et al., 2014; Liu et al., 2014; Wang et al., 2014); the chemokines are overexpressed in gastric cancer and multiple myeloma (Azab et al., 2012; Oh et al., 2012; Tao et al., 2014). Similarly, overexpression of cyclosporin binding protein cyclophilin A (CYPA) in PDAC (Zhang et al., 2014), endothelin in melanoma (Spinella et al., 2014); fascin in PDAC (Zhao et al., 2014); MMPs in PDAC, lung and ovarian cancer cell lines (Quintero-Fabián et al., 2019); protein kinase receptors in gastric, RCC, melanoma cancer (Chuang et al., 2008; Marconi et al., 2013) has been reported. HIF-1α also activates another critical cell signaling pathway i.e., HGF/MET signaling.

Several studies suggest that MET, together with its ligand HGF, promotes cancer cell hallmarks including cell proliferation, survival, migration, angiogenesis in multiple mammalian cancer including hepatocellular carcinoma, head and neck cancer etc., (Goyal et al., 2013; Huang et al., 2020; Raj et al., 2022).

Additionally, in a positive feedback mechanism, ILK (Integrin Linked kinase) is activated by HIF-1α and is responsible for elevated HIF-1α expression through the regulatory loop (Matsuoka et al., 2013). Furthermore, E-cadherin, which was previously thought of as a tumor suppressor, was shown to have an unanticipated involvement in regulating genes involved in response to hypoxia and thus posing a potential role in metastatic breast cancer (Chu et al., 2013; Tam et al., 2020).

Moreover, intratumoral hypoxia alters the immune response of tumor in a variety of ways, all of which indicate an immunosuppressive impact (Palazón et al., 2012). HIF-1α, for example, can recruit myeloid-derived suppressor cells, regulatory T-cells, tumour-associated macrophages with immunosuppressive properties, as well as limit cytotoxic T-lymphocyte invasion (Corzo et al., 2010; Doedens et al., 2010; Imtiyaz et al., 2010; Barsoum et al., 2014). Besides that, HIF-1α stimulates the synthesis of the immunological checkpoint protein PD-L1(programmed death ligand-1), which aids in immune suppression and evasion (Noman et al., 2014; Abou Khouzam et al., 2021). As a result, the majority of the data implies that HIFs promote tumor growth through immunosuppression.

Collectively, these recent discoveries have motivated the scientific community to focus its efforts on developing novel drugs that can inhibit HIF-1α or its target genes. Further, we

FIGURE 2 | Genes whose expression has been linked to the activation status of HIF-1α, resulting in EMT. HIF-1α induces expression of BECN1, MAP1IC3 which is an autophagy marker; CAIX, acidosis modulators: epigenetic regulators: KLF8, cell surface glycoproteins (CD24, CD44), JMJ2DB which is lysine-specific demethylase jumonji domain, Nanog homeobox (NANOG), Octamer-binding transcription factor 4(OCT4), SRY sex-determining region Y-box (SOX2), sonic hedgehog (SHH), smoothened frizzled class receptor (SMO), GLI family zinc finger 1 (GLI1); AK058003- long non-coding RNA; multiple chemokines: CXCR4, CCL2, CCR7, CX3CR1; cyclosporin bind protein cyclophilin A (CYPA); endothelins: EDN1 (endothelin1; fascins: fascin actin-bundling protein 1(FSCN1); GTPase proteins: Rho family GTPase 3 (RND3): insulin growth factor which includes IGF1, IGF1R, IGFBP3; mucin 1, cell surface-associated (MUC1); matrix metalloproteinase; MMP2, protein kinases receptors including TGFb/TGFBR1, TNFAR, AXL; hepatocyte growth factor (HGF) which is a ligand of MET tyrosine kinase receptor; adrenomedullin (ADM). These activated genes are known to play a crucial role in EMT transition and result in increased invasiveness, cellular proliferation, migration, spindle-like cellular appearance, resistance to chemo/radiotherapy and tumor relapse.

have focused on the compounds that have been developed as HIF-1α inhibitors and are now undergoing clinical trials. These novel compounds may pave the way for more effective therapy and might improve the prognosis of aggressive cancer patients.

Advanced Clinical Trials Targeting the Adaption to Hypoxia Tumor Microenvironment Therapeutic Targets

The ability to specifically target cancer cells while causing minimal harm to normal cells is one of the "Holy Grail" of cancer therapy. The propensity to exploit abnormalities between normal and malignant cells has significantly aided the discovery of novel anti-cancer drugs. Various small compounds discovered have been briefly summarized in the following section, albeit the bulk of them are still in the early stages of clinical trials.

As discussed above, HIF-1α activation has been found to have a significant impact on cancer cell metabolism as it influences the expression of several genes leading to increased glycolysis and impaired mitochondrial function in tumor cells. Several anticancer drugs that modulate the activity or levels of HIF-1α in cells influence HIF-1 without directly targeting it.

Digoxin (DIG) (PubChem CID: 2724385), a cardiac glycoside, has been demonstrated to have an anti-cancer effect *in vitro* and *in vivo* in various solid tumors by inhibiting HIF-1α production (Newman et al., 2008; Zhang et al., 2008; Lin et al., 2009). DIG is now being studied in phase 2 clinical trial (https://clinicaltrials.gov/ct2/show/NCT01763931) as a new HIF-1α inhibitor in breast cancer. This clinical trial will also be valuable in evaluating adverse events, as well as the safety and tolerability of DIG in pre-surgical breast cancer patients using the Common Terminology Criteria for Adverse Events, version 4. Additionally, Ganetespib (PubChem CID: 135564985), (5-[2,4-dihyroxy-5-(1-methylethyl)phenyl]4-(1-methyl-1H-indol-5-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one) have been reported to increase the proteasome-mediated degradation of Hsp90. Hsp90, a chaperone, is implicated in tumor development, angiogenesis, and the generation of cancer stem cells (Pillai and Ramalingam, 2014; White et al., 2016). Its route triggers the activation of multiple oncogenic proteins including HIF-1α. Thus by targeting Hsp90, Ganetespib inhibits HIF-1α in TNBC mouse model (Xiang et al., 2014). Ganetespib is now being studies in a phase 3 trial in patients with advanced non-small cell lung cancer (NSCLC) in conjunction with docetaxel (https://www.clinicaltrials.gov/ct2/show/NCT01798485). This clinical trial

seeks to identify a potential synergism between ganetespib (150 mg/m^2) and docetaxel (75 mg/m^2) in order to suggest a more effective anti-cancer therapy than docetaxel alone.

Among multiple factors that influence hypoxia-induced tumor acidosis, CAIX is a hypoxia-inducible metal enzyme that promotes cancer cell survival/proliferation and invasion *via* HIF activation (Lock et al., 2013). It regulates cellular pH by catalyzing the reversible hydration of carbon dioxide to bicarbonate and protons. It is expressed exclusively on the cell surface of tumor cells, particularly CSCs (cancer stem cells), and is one of the key factors influencing cancer cell survival and metastasis (Lock et al., 2013). Moreover, CAIX is abundantly expressed in pancreatic ductal adenocarcinoma and breast cancer and has been implicated as a biomarker of poor prognosis for metastatic development and survival (Touisni et al., 2011; Lock et al., 2013). Additionally, research has proven a vital role for CAIX expression in the maintenance of the EMT phenotype, "stem cell" function, and hypoxia-induced tumor heterogeneity (Touisni et al., 2011; Ledaki et al., 2015). SLC-0111 (PubChem CID: 310360) is a small molecule that reaches the hypoxic niches and selectively binds and inhibits CAIX. Presently SLC-0111 is in phase I clinical trial (https://clinicaltrials.gov/ct2/show/NCT02215850) and the study focuses on its safety, tolerability, and pharmacokinetics, and efficacy in treating cancers. Similarly, another molecule DTP348 (PubChem CID: 57413968) namely 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethylsulfamide, is reported to target CIAX (Rami et al., 2013). Presently, this oral dual CAIX inhibitor/radiosensitizer is being researched in phase I clinical trial (https://clinicaltrials.gov/ct2/show/NCT02216669). This clinical study will consider the effects of DTP348 alone and in combination with radiation in patients with solid tumors to establish the appropriate phase II clinical trial dosage, safety, and tolerability.

Interestingly, HGF is the natural ligand of *MET*, a proto-oncogene. The HIF-1α induced HGF/MET pathway activation has been reported to induce EMT transition, resulting in a mesenchymal population that is more tumorigenic and chemoresistant than the preceding ones (Cañadas et al., 2014). Rilotumumab, Crizotinib/axitinib and cabozantinib are designed to effectively target HGF/MET pathway. Rilotumumab (PubChem SID: 135262715), is a human monoclonal antibody that is reported to significantly block the binding of HGF/SF to its MET receptor. Presently, it is being tested in phase 3 clinical trial (https://clinicaltrials.gov/ct2/show/NCT01697072) to evaluate if the treatment with epirubicin, cisplatin, and capecitabine in combination with rilotumumab results in better clinical outcomes in metastatic *MET* positive gastric cancers. Axitinib (PubChem CID: 6450551), with crizotinib (PubChem CID: 11626560), is currently being tested in a phase 1b clinical trial in patients with advanced solid tumors (https://clinicaltrials.gov/ct2/show/NCT01999972) (Kwak et al., 2010; Chen Y. et al., 2015). Moreover, cabozantinib is an oral inhibitor of *MET, RET, ROS1, NTRK1,* and AXL. It has been found to shrink tumor cells and significantly reduce cellular proliferation in medullary thyroid and prostate cancer. Cabozantinib (PubChem CID: 46830297), is currently being investigated to determine objective response rate (ORR), overall survival (OS) and progression-free survival (PFS) in advanced non-small cell lung cancer with *RET* fusions and those with *ROS1* or *NTRK1* fusions or elevated *MET* or *AXL* activity (https://clinicaltrials.gov/ct2/show/NCT01639508).

According to the current research, several phytocompounds also have been shown to play a significant role in cancer therapy and have numerous potential targets in tumorigenesis, including HIF-1 (Deng et al., 2019). Baicalein (PubChem CID: 5281605), (5,6,7- trihydroxyflavone), a flavonoid derived from *Scutellaria baicalensis* has been reported to have potent cytotoxic activity against a wide range of cancer (Bie et al., 2017; Dou et al., 2018; Wang et al., 2019). Surprisingly, baicalein when administered leads to the inhibition of hypoxia-induced Akt phosphorylation as a result of increased PTEN accumulation and decreased HIF-1α expression. Thus baicalein is a potential therapeutic sensitiser against gastric cancer since it inhibits glycolysis *via* PTEN/Akt/HIF-1α (Chen F. et al., 2015). Other investigations have corroborated the inhibitory effects of phytochemicals on HIF-1 in control of glucose metabolism. For instance, methylalpinumisoflavone (MF) (PubChem CID: 15596285), a flavonoid isolated from *Lanchocarpus glabrescens,* demonstrates a strong anti-cancer effect on T47D cells by suppressing HIF-1 and targets genes including CDKN1A, VEGF, and GLUT-1 in T47D cells (Liu et al., 2009). Moreover, oroxylin A (PubChem CID: 5320315) treatment has been linked to a reduction in cancer-related glycolysis *via* sirtuin-3 mediated destabilization of HIF-1 in MDA-MB-231 cells (Wei et al., 2015). Furthermore, EGCG (PubChem CID: 65064) is known to decrease the HIF-1α and glycolysis-related enzymes in T47D cells (Wei et al., 2018). Additionally, resveratrol (PubChem CID: 445154) has been shown to reduce the cellular uptake of glucose and induce glycolysis in cancer cell lines. Resveratrol inhibited intracellular reactive oxidative species (ROS) and hence lowered HIF-1 accumulation, decreased GLUT-1 expression, and induced glycolytic flow, according to measurements of cellular absorption of the glucose analogue 18F-fluorodeoxyglucose following resveratrol exposure (Jung et al., 2013).

Further using a combination of anti-cancer therapies is more likely to be successful than using a single drug (Maschek et al., 2004). Another concept has been proposed that takes the use of underlying metabolic variations between malignancies and healthy tissues (Payne, 2007). For instance, many tumors' reliance on glycolysis has been addressed using a variety of glycolytic pathway enzyme inhibitors that are also being evaluated as possible treatment drugs (Maher et al., 2004; Maschek et al., 2004; Xu et al., 2005; Pelicano et al., 2006; Gogvadze et al., 2009; Marín-Hernández et al., 2009; Mathupala et al., 2009). The major targets thus far have been glucose absorption (mediated mostly by GLUT-1), glucose retention (mediated by hexokinase) and lactate generation (catalyzed by lactate dehydrogenase-A). Unfortunately, inhibiting glycolysis has a significant complication; unlike organs that may easily utilise carbon sources other than glucose, the brain, retina, and testes are extremely glucose dependent. As a result, different metabolic targets such as specific glycolytic pathway enzyme isoforms which are transcriptionally overexpressed in response to HIF-1 elevations must be taken into account (Marín-Hernández et al., 2009).

Targeting proteins such as GLUTs, HK1, HKII, PFK-L, ALD-A, ALD-C, PGK1, ENO-α, PYK-M2, LDH-A, PFKFB-3 along with HIF-1α may be more trackable for drug development than HIF-1α itself. Identifying metabolic alterations that are specific to malignancies is inevitably a critical research goal.

CONCLUSION

Metabolic reprogramming is a frequent cancer cell mechanism for dealing with elevated energy demands. The growing interest in cancer metabolism has already resulted in a slew of novel potential therapeutics. In conclusion, several reports have shown that hypoxic cells may adapt to low oxygen levels by changing transcriptional and translational responses to increase glucose absorption and anaerobic catabolism. Since HIF-1 has been proven to be a master regulator of a wide range of proteins and enzymes involved in glucose metabolism and the glycolytic pathway. Thus modulation of the HIF-1 pathway is a promising therapeutic strategy. It is envisaged that a deeper insight into the molecular mechanisms involved in HIF-1 regulation and the Warburg effect in carcinogenesis would unlock new therapeutic interventions. Nonetheless, due to the present generation of agents' limited selectivity and specificity, there are possible challenges and concerns. Additionally, the recent metabolism-based therapeutics have shown some harmful effects on normal cells. Therefore, we propose combining the drugs to target distinct elements of cancer bioenergetics and hypoxia-induced factors in order to develop synergistic cancer treatments. Furthermore, directing these molecules to their targets would limit off-target effects while increasing efficacy.

AUTHOR CONTRIBUTIONS

AS: Conceptualization, Figures, Writing- original draft. SS: Writing- Revise and Editing. NS: Writing- Revise and Editing, Supervision. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: SS was employed by the company Kashiv Biosciences.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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GLOSSARY

ATP adenosine triphosphate

AXL AXL receptor tyrosine kinase

BECN1 beclin-1

CAIX carbonic anhydrase 9 precursor

CRC colorectal cancer

DIG digoxin

EGCG epigallocatechin gallate

EMT epithelial-mesenchymal transition

ENO-α alpha-enolase

GLUT glucose transporter

HIF 1α-hypoxia-inducible factor-1α

HIF-1 hypoxia-inducible factor-1

HGF hepatocyte growth factor

HK1 hexokinase-1

hsp90 heat shock protein 90

HTM hypoxic tumor microenvironment

ILK Integrin Linked kinase

LDH lactate dehydrogenase

MAP1LC3 microtubule-associated proteins 1A/1B light chain 3B

MF methylalpinumisoflavone

MET mesenchymal-epithelial transition

NTRK1 neurotrophic receptor tyrosine kinase 1

NSCLC non-small lung cancer

OXPHOS oxidative phosphorylation

PDAC pancreatic ductal adenocarcinoma

PD-L1 programmed death ligand-1

RCC renal cell carcinoma

RNA ribonucleic acid

RET rearranged during transfection

PGK1 phosphoglycerate kinase 1

PFKFB 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3

PFK Phosphofructokinase

PTEN phosphatase and tensin homolog

PYK M2-M2 isoform of pyruvate kinase

ROS1 ROS proto-oncogene 1

TME tumor microenvironment

TNBC triple-negative breast cancer

VEGF vascular endothelial growth factor

VHL Von Hippel-Lindau