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Review

Roles of hypoxia in tumor progression and novel strategies for cancer treatment

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ABSTRACT

The metabolic process of normal cells in general and of cancer cells in particular requires an important molecule—oxygen. In tumors, the oxygen level tends to decrease gradually from the outer layers to the central core, leading to a condition termed ``hypoxia.'' Changes in the oxygen level modify the signaling pathways and metabolic activities of cancer cells. Basically, tumor development is divided into three stages: initiation, promotion, and progression. Among them, the effects of hypoxia are most evident during tumor progression. In this review, we summarize previous findings on the mechanisms underlying hypoxia-induced alterations in the expression of genes and proteins associated with hypoxia-inducible factors (HIFs), which play a central role in the development of malignancy in many types of cancer. We also present the latest evidence on HIF-targeted cancer treatment that yields positive outcomes *in vitro* and *in vivo*.

Key words: HIF inhibitors, hypoxia, cancer cell, hypoxia-inducible factors, tumor progression

INTRODUCTION

Cancer is a group of diseases with a leading mortality rate and a high recurrence rate owing to the absence of effective targeted therapies. Therefore, in-depth understanding of its characteristics is crucial in treating this fatal disease.

Recently, hypoxia has emerged as a novel candidate in targeted therapy for cancer. Hypoxia exists in solid tumors (e.g., breast, pancreatic, liver, lung, cervical, ovarian, or colon cancer)[1] as well as liquid tumors (e.g., leukemia)[2]. It has been shown to influence the malignant properties of tumors and to induce resistance to cancer treatment[3]. Signaling pathways related to hypoxia-inducible factors (HIFs) play a central role in metabolism adaption of cancer cells[4], contribute to adaptive immune escape[5], regulate angiogenesis, and promote cell proliferation and survival and tumor progression[6]. Hence, hypoxia is considered to affect several hallmarks of cancer[7].

Maintaining the level of cellular oxygen is crucial to cell fat, since oxygen molecules act as terminal acceptors in the electron transmission chain to create ATPs during oxidative phosphorylation[8]. This process leads to reactive oxygen species production, consequently causing cell death owing to DNA damage and genomic instability[8,9].

The tumor oxygen level typically ranges from 0.3% to 2.2% in various types of cancer[10], and the oxygen level gradient reduces gradually from the periphery to the center of tumors (**Figure 1**)[11]. If an increased oxygen level is required in tumors, they may induce angiogenesis with dysfunctional blood vessels, consequently leading to different hypoxic statuses and tumor aggressiveness[8]. Rates of cell proliferation higher than those of new vessel formation in tumors lead to unequal perfusion and acute hypoxia among tumor regions. Gradually, strongly proliferative cancer cells accumulate and settle in areas unreachable by nutritive blood vessels, thereby causing chronic hypoxia. Both acute and chronic hypoxia can contribute to therapy resistance[12].

In the present review, we summarize several major roles of hypoxia in tumor development and provide the latest information on hypoxia-targeted cancer treatment.

HYPOXIA AND TUMOR INITIATION AND PROMOTION

Tumors are formed owing to an uncontrolled division of cells. This loss of control is caused by errors in genomes and chromosomes through chemical, physical, or biological agents. Defects largely due to DNA replication and repair lapses, oncogene mutations, chromosomal instabilities, and tumor suppressor gene mutations are fundamental for tumor initiation[13,14].

Several research has shown a relationship between chronic hypoxia and tumor initiation both *in vitro* and *in vivo*. HIF-1α reduces the ability to repair DNA damage and causes gene mutations in cells grown under hypoxic conditions. Under severe hypoxic conditions, replication is unstable, which may lead to some

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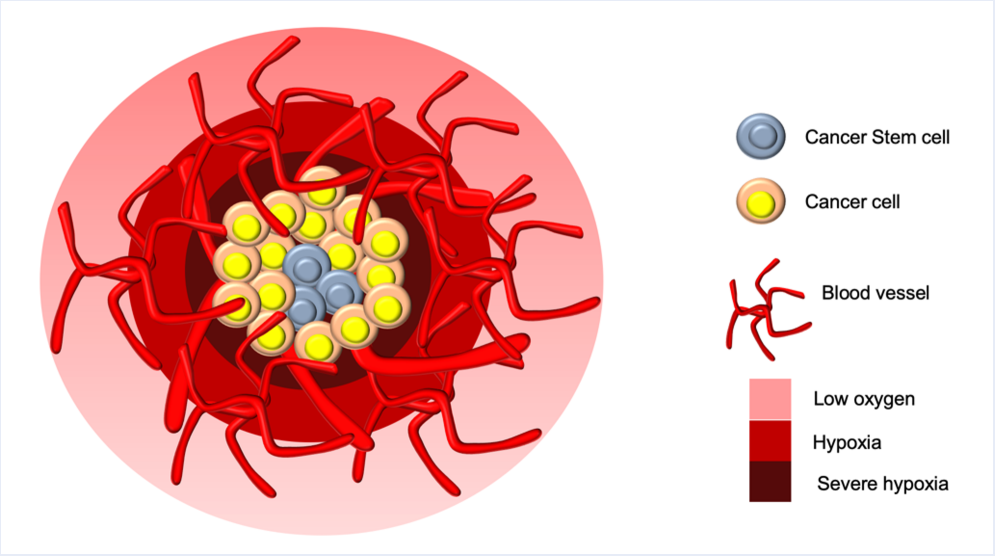

Figure 1: **Oxygen concentration-based partional structure in cancer tumors with possible niche for cancer stem cells in the center necrotic core.**

errors in DNA replication[15]. Previous studies have revealed genomic instability of prostate cancer cells cultured under hypoxic conditions, which substantially contributes to tumor initiation. HIF-1α also upregulates human telomerase reverse transcriptase to restore the telomere, leading to intractable cell proliferation and triggering tumor promotion and formation[16]. It is involved in the regulation of cell death through various mechanisms in many cell types[17]. Depending on the conditions of action, apoptosis is either activated or inactivated with the regulation of the expression of p53 or BCL-2 family signaling pathways[17,18]. Under chronic hypoxic conditions, HIF-1α upregulates p53 via various mechanisms but mostly inhibits apoptosis through indirect effects on MDM2 to inactivate this gene[18]. HIF-1α also inhibits BAX and activates BCL-2 to prevent mitochondrial *c*-cytochrome release and inactivate apoptosis[17]. Based on these correlational factors between hypoxic conditions and basic factors of tumor formation, hypoxia may induce tumor initiation.

HYPOXIA AND TUMOR PROGRESSION

Hypoxia and angiogenesis

To increase the intra-tumor oxygen level, primary tumors have to induce angiogenesis and form new vessels supplying oxygen-rich blood from the arteries for feeding. Angiogenesis is of great importance in tumor growth. In the absence of angiogenesis, defined as the process that creates new arteries and veins from preexisting blood, tumors remain dormant, maintaining an equal state between cell survival and death[19]. Genes associated with angiogenesis, such as vascular endothelial growth factor (VEGF), angiopoietin (ANG), and platelet-derived growth factor (PDGF), are some representative proteins in the downstream targets of HIFs[20].

VEGF has been isolated, identified, and studied *in vitro* and *in vivo* in mammals in the early 1990s. German scientists have claimed that VEGF mRNA is overexpressed during the formation of new blood vessels in mouse embryos, which indicates that VEGF and its receptors VEGF-R1 and VEGF-R2 are major factors in mammalian angiogenesis[21,22]. Previous studies suggest a link between HIF-1α and VEGF not only in cancer[23] but also in other diseases[24]. Under the phosphorylation of specific protein 1 (Sp1) and HIF subunit and recruitment of VEGF promoters, transcription is triggered under the effect of the Ras/MEK/extracellular signal-regulated kinase (ERK) pathway. The expression of VEGF-A mRNA can be increased by the PI3K/AKT pathway and modified by activator protein-1[25]. The phosphorylation of HIF-1α and coactivator p300 induces transcriptional activation via ERK, whose pathway attracts the connection between RNA polymerase II and VEGF promoters. At the other regulation levels, the transcription of VEGF mRNA is stabilized through stress-activated kinase p38[26]. At the translational level,

the internal ribosome entry site (IRES) sequences are inserted in the middle of the 5' non-coding regions of VEGF-A mRNA[27] and HIF-1α mRNA[28]. The interference of the IRES between these two components accounts for the translation under hypoxic conditions and nutrient deprivation. Normally, the cap-dependent translation often halts in such hypoxic and nutrient-deprived conditions. However, VEGF is considered an "existing" factor that continues to be translated under hypoxia[29]. Some studies have demonstrated the complementary roles of HIF-1α and HIF-2α in angiogenesis. In particular, HIF-1α enhances vessel growth, while HIF-2α promotes vessel maturation[30,31]. Recently, several new transcription factors, microRNAs (miRNAs), and RNA-binding proteins have been demonstrated to be crucial for axis HIF-1α/VEGF signaling in tumor progression. Zinc finger homeobox[32], Bcl-2-associated transcription factor 1[33], and miRNA-574-5b[34] are typical examples of factors that regulate the ability to induce angiogenesis under hypoxic conditions within tumors.

In addition to VEGF, the ANG protein family (ANG-1, ANG-2, and ANG-4) also contributes to many aspects of angiogenesis[35,36]. Early upregulation of ANG proteins has been observed in hepatocellular carcinoma[37], glioblastoma[38,39], and squamous cell carcinoma[40], in which their effect on tumor angiogenesis differs from that of VEGF during tumor progression. ANG-1 or ANG-4 and ANG-2 affect Tie-2 receptor, a tyrosine kinase receptor selectively expressed in the vascular endothelium[41], on opposite directions. While ANG-1 or ANG-4 binds to and phosphorylates Tie-2, resulting in vessel stabilization and remodeling, ANG-2 acts as an antagonist of Tie-2 to destabilize and regress the vessels[36]. However, this inhibitory effect of ANG-2 can be prevented under the presence of VEGF derived from avascular and hypoxic tumors owing to tumor vessel decline[41]. The ANG-1/ANG-2 ratio markedly contributes to physiological angiogenesis[42], since a reduction in this ratio under hypoxia with an increased level of VEGF results in tumor vessel formation[39,43]. ANG-2 secreted from human melanoma cells is also believed to be a prognostic marker for metastasis[44], indicating that it plays crucial roles not only in angiogenesis but also in other aspects during tumor progression. Thus, blocking the expressions of VEGF and ANG-2 is a new and effective strategy to lessen brain and lung metastases[45,46].

PDGF, which has been first identified in platelets, is an important factor in blood vessel regulation[47]. PDGF isoforms interact with their tyrosine kinase receptors to perform various physiological functions[48]. Gene mutations of PDGF receptors have been observed in different malignant tumors[48], which may lead to disturbances in related signaling pathways[49]. In osteosarcoma, an increased level of PDGF-BB and its receptor is transcriptionally dependent on HIF-1α to promote cell proliferation and migration under hypoxic conditions[50]. Overexpression of HIF-1α is related to an increased expression of PDGF-BB in invasive breast cancer cells[51], which contributes to lymphatic vessel density and lymph node metastasis[52]. The proportional relationship between HIF-1α and PDGF-BB is regulated by AKT, forming an autocrine loop that may increase cisplatin resistance in hepatocellular carcinoma[53]. Similarly, hypoxia was found to enhance the HIF-1α/PDGF-D/PDGFRα/AKT pathway, which accelerated cell growth and invasion in glioblastoma[54]. Only HIF-1α appears to play a central role in the regulation of PDGFs, since no studies have confirmed a link between other HIFs and PDGFs.

Hypoxia and epithelial–mesenchymal transition

Epithelial–mesenchymal transition (EMT) is crucial in the invasion and metastasis of tumors, as cells lose their epithelial differentiation to acquire the mesenchymal phenotype, which allows them to detach from primary tumors and disseminate into stromas[55]. Hypoxia is notably a hallmark of cancer and is believed to induce EMT via HIFs in various types of cancer[20,56–60]. HIF-1α or HIF-2α upregulates the Wnt/β-catenin signaling pathway to enhance the biological features related to EMT, which helps tumor cells survive and proliferate during hypoxia[56,58]. In contrast, HIF-3α isoform 2 binds to and destabilizes β-catenin to inhibit Wnt signaling, which is involved in stem cell renewal and tissue homeostasis[61].

Loss of E-cadherin and switching to N-cadherin are also considered a marker of EMT owing to their main role in cell–cell adhesion in epithelial cell membranes[62]. Twist[63], zinc finger E-box binding homebox (ZEB) 1/2[64,65], Snail[66], and Slug[67,68] are major transcription factors directly or indirectly responsible for this cadherin switch in metastatic cancer. Consequently, blocking these factors has been recently suggested as a new strategy for preventing metastatic cancer[69–72]. Their expressions seem to be affected by HIF-1 signaling. In hypoxic HeLa cervical cancer cells, the expression levels of miR-21 and miR-210 are increased, thus targeting and downregulating HECT domain E3 ubiquitin ligase 1 and consequently increasing Snail expression to attenuate the E-cadherin

level[73]. MiR-21, miR-210, and several other miRNAs act as downstream molecules of HIF-1α in relation to cancer cell viability and migration[74–76]. Slug is also an E-cadherin direct regulator, which is upregulated by dimethylation of lysine demethylase 3A or binding of OCT4B under hypoxic conditions[77,78]. Meanwhile, hypoxia enhances Bcl-2–Twist interaction by facilitating the binding of Bcl-2 to Twist, forming a protein complex and then targeting Bmi-1 to cause changes in EMT-related proteins in cancer cells[79,80]. Interestingly, HIF-2α stimulates Twist-2 to bind to the E-cadherin promoter through the P2 region and activates EMT in pancreatic cancer[81]. Additionally, HIF-1α directly inhibits E-cadherin via miR-421 signaling or miR-205/ASPP2 axis in cancer cells[82,83]. It also controls EMT and the stem cell-like phenotype of liver cancer cells via miR-191[84].

Transforming growth factor (TGF)-β, released by cancer cells, stromal fibroblasts, and other cells in the tumor microenvironment, has a key role in promoting EMT during cancer progression and metastasis[85]. The phosphorylation of the binding between TGF-β and its receptor TGFR1 and TGFR2 promotes the activation of Smad2 and Smad3, which form a trimer with Smad4. This complex then displaces into the nucleus, in which a synergic action of the DNA binding transcription factors SNAIL, ZEB, and TWIST connects to the regulation of the target genes of TGF-β[86]. The activity of EMT-related transcription factors can be increased during the combination of the Smad complex with any targeted effects[87]. The activation of co-bindings between Smad3 and Smad4 caused by TGF-β leads to several events, including the repression of E-cadherin and inhibition of the gene expression owing to the dual interaction with SNAIL1[88], increasing the expression of TWIST owing to the dual interaction between Smad3 and Smad4 originating from the interaction with activating transcription factor 3 to suppress the expression of ID1[89]. TGF-β1 triggers the downregulation of prolyl hydroxylase-2 via a Smad-dependent signaling pathway, leading to the accumulation of HIF-1α and EMT[90].

Notch is considered a major receptor involved in the induction of the EMT signaling pathway under hypoxia. During downstream regulation, Notch regulates SNAIL in two different synergistic methods: direct or indirect regulation. The recruitment of the Notch intracellular domain to the SNAIL promoter leads to direct upregulation of SNAIL with the combination of the transcriptional complex with HIF-1α and to indirect upregulation of SNAIL with an increase in the levels of LOX protein stemming from the combination of HIF-1α with the LOX promoter[91]. SNAIL and SLUG, the two transcriptional repressors involved in EMT, also aim at the Notch signaling pathway[92]. In breast cancer cells, an increase in the expression of SNAIL and SLUG, which follows the accumulation of HIF-1α and HIF-2α, reduces the expression of E-cadherin[93]. Notch activity has also been reported in lung cancer stem cells (CSCs) via the expression of spheroid growth in cell cultures, high rate of chemoresistance, and tumor formation in the cell injected to the CSCs of NOD/SCID mice[94]. In addition, the Notch signaling pathway can induce cell cycle arrest and apoptosis, which are key steps in carcinogenesis[95–97].

Hypoxia and tumor invasion and metastasis

Malignant cancer is characterized by the formation of secondary tumors through invasion and metastasis. Under hypoxic conditions, HIF-1α and HIF-2α, controlled by the c-Jun NH2-terminal kinase pathway, are involved in the migration of gastric cancer cells[98]; thereby, HIFs play a crucial role in this oncological process.

Changes in the HIF-1α level strongly induce the expression of mRNAs encoding for urokinase-type plasminogen-activator receptor, metalloproteinase-2 (MMP-2), and cathepsin D, proteins involved in the degradation of the extra-cellular matrix, and disrupt basement membrane invasion in colon cancer[99], esophageal carcinoma[100], and prostate cancer[101]. Via ZEB-2, HIF-1α downregulates EphrinB2, whose low expressions cause tumor invasiveness in human glioma[102]. Recently, the expression of other downstream targets of HIF-1α, including right open reading frame kinase-3 involved in the organization of actin cytoskeleton[103], v-maf musculoaponeurotic fibro-sarcoma oncogene homolog F[104], and SP1[105], has also been demonstrated to increase when cancer cells are exposed to low oxygen levels, which promotes cell invasion and metastasis. In breast cancer, hypoxia induces the upregulation of ADAM12, thereby activating EGFR/FAK signaling and inducing lung metastasis in SCID mice[106], which may be associated to poor outcomes. In hypoxic non-small-cell lung cancer, Twist not only inhibits E-cadherin expression but also directly increases the cancer cell motility rate[107]. Overexpression of Twist upregulates AKT2 in the late stages of breast cancer[108], inducing its aggressiveness, and enhances Tcf-4/Lef DNA binding, promoting invasion and cell migration in gastric cancer[109]. Such overexpression has been proven to be directly induced by the upregulation of HIF-1α under hypoxia[110].

HIF-2α also promotes invasion and metastasis of cancer cells via the upregulation of Twist and CXCR4 in papillary thyroid carcinoma [111]. In hepatocellular carcinoma, Wang *et al.* found that HIF-2α directly regulates the transcription of stem cell factor, increasing the expression of MMP-2 and promoting cancer cell invasion [112]. The E2F3 transcriptional regulatory pathway is considered to induce an overexpression of HIF-2α owing to many steps in cancer progression [113]. Furthermore, HIF-2α is found to be highly expressed compared with HIF-1α when ovarian cancer cell lines enter the hypoxic state and become more invasive [114]. Down- or upregulation of both HIF-1α and HIF-2α is related to a higher or lower expression of insulin-like growth factor binding protein-3, respectively [114], which has been demonstrated to suppress tumor angiogenesis and growth arrest [115]. HIFs can either affect or be affected by upstream and downstream factors to regulate the invasive and metastatic capabilities of cancer cells.

HIF-3α has recently been demonstrated to regulate pancreatic cancer invasion and metastasis via RhoC/ROCK1 signaling [116]. Further experiments are required to confirm the role of HIF-3α in cancer progression.

Hypoxia and immune escape from cancer

The immune system regulates tumor biology by inhibiting the malignant characteristics of tumors. Immune escape from cancer suppresses the effects of immune cells and allows resistance to the cytotoxicity of immune effectors, and hypoxia may contribute to this process [129]. Under hypoxic conditions, tumor cells release immunosuppressive molecules [129]. In hepatocellular carcinoma, hypoxia positively influences the expression of S100, heat shock proteins, and high-mobility group B1 in tumor cell-released autophagosomes, which induces the production of IL-10 and B-cells with the ability to hamper T-cell proliferation and function [130]. As T-cells can kill tumor cells by binding to their receptors [131], and they are considered main targets in cancer immunotherapy [132], their inhibition may decrease the effectiveness of cancer treatment. TGF-β, a multifunctional cytokine and T-cell proliferation suppressor [133], is also highly expressed in gastric cancer [134] and glioblastoma [135], along with HIF-1α. TGF-β converts naive T-cells to regulatory T-cells [136], thereby ameliorating the function of natural killer cells [137], and remarkably suppresses the maturation of dendritic cells [138], which may reduce the effectiveness of the antitumor activities of the immune system. Nevertheless, hypoxia sometimes supports T-cell development via stimulation of CD137 on the T-cell surface in patients with colon carcinoma [139] or in anti-VEGF-treated mice [140].

Hypoxia also alters cell surface molecules that may bind to immune checkpoints in T-cells to induce immune escape. Programmed cell death protein-1 and cytotoxic T lymphocyte-associated antigen-4 are two main immune checkpoints in T-cells that downregulate T-cell pathways when conjugated to their ligands (PD-L1 and PD-L2 or CD80 and CD86, respectively) [141]. Multiple drugs with the ability to inhibit these two molecules have been studied and developed to treat many types of cancer; these drugs include ipilimumab [142], nivolumab [143], pembrolizumab [144], atezolizumab [64,65,145,146], and tremelimumab [147]. Both HIF-1 and HIF-2α directly bind to hypoxia response element-4 in the PD-L1 proximal promoter, thereby upregulating the expression of this ligand in tumor cells and mediating the suppression of T-cells [148,149]. Enhancer of zeste homolog-2 potentially affects the expression of PD-L1 via HIF-1α [150]. HIF-1α-induced PD-L1 increases the resistance to cytotoxic T lymphocyte-mediated lysis and leads to T-cell apoptosis in cancer cells [5].

Hypoxia and therapy resistance

HIFs have been confirmed to be related to miRNAs in promoting cancer therapy. Many miRNAs control the transcriptional activity of HIFs. For instance, miR-199a is suggested to be a tumor suppressor, since its downregulation under hypoxic conditions results in an overexpression of HIF-1α and is associated with increased cisplatin resistance in osteosarcoma cell lines [151]. While hepatocellular cancer cells are resistant to 5-flourouracil, overexpression of miR-183 significantly reduces the expression of isocitrate dehydrogenase 2 or suppressor of cytokine signaling 6, which is related to the upstream signaling of HIF-1α [152]. On the contrary, upregulation of miR-21 may lead to an overexpression of HIF-1α and promote resistance to cisplatin in lung adenocarcinoma cell line A549 [66]. Further, miR-193a-3p negatively regulates the expression of SRSF2 via the hypoxia signaling pathway to promote radio-resistance among nasopharyngeal cancer cell lines [153]. In general, miRNAs either directly or indirectly increase the expression of HIFs, thereby causing therapy resistance in different cancer cell lines.

Conversely, some miRNAs have been reported to act as downstream factors of HIFs. In bladder cancer, cisplatin attacks and upregulates HIF-1α, increasing

Table 1: Hypoxia induces autophagy in cancer cells to adapt to cancer therapies

Type of cancer	Related hypoxia genes	Autophagy markers	Therapy-resistance	Referrence
Bladder cancer	HIF-1α	LC3-II	Gemcitabine	117
Bladder cancer	HIF-1α	Beclin-1	Cisplastin	118
Hepatocellular carcinoma	N/A	FOXO3a	Sorafenib	119
Hepatocellular carcinoma	N/A	LC3-II	Cisplastin Epirubicin Gemcitabine Mitomycin	120
Lung cancer	N/A	N/A	Cisplastin	121
Lung cancer	N/A	N/A	Radiotherapy	20
Lung cancer	HIF-1α	LC3-II Beclin-1 p62	Radiotherapy	122
Colon cancer	HIF-2α	N/A	5-flourouracil CCI-779	109
Colon cancer	HIF-1α	Beclin-1 Atg12 LC3-II	Radiotherapy	123
Ovarian cancer	HIF-1α	N/A	Cisplastin	124
Cervical cancer	HIF-1α	LC3-II Beclin-1, Atg12-Atg5 Atg7 p62	Paclitaxel	125
Breast cancer	N/A	Beclin-1 Atg12-Atg5 Atg7	Ionizing radiation	126
Osteosarcoma	HIF-1α	LC3	Radiotherapy	127
Glioblastoma	HIF-1α	Atg5	Temozolomide	128
Astrocytoma	HIF-1α	Atg5	Temozolomide	128

the level of miR-424. MiR-424 may mediate the suppression of UNC5B and SIRT, decreasing the number of apoptotic cancer cells induced by cisplatin [154]. In contrast, HIF-1α upregulated in hypoxic colorectal cancer cells directly inhibits miR-338-5p and activates the IL-6/STAT3/Bcl-2 pathway, consequently causing resistance to cisplatin [155]. Hypoxia also diminishes the efficacy of sorafenib in treating hepatocellular carcinoma by inhibiting the androgen receptor and miR-520f-3p to increase the expression of SOX9 and modulate the stem-like phenotype within liver cancer cells [156]. However, the link between hypoxia and miRNAs requires further clarification. Nonetheless, both are known to be involved in cancer therapy resistance.

Autophagy is another mechanism of hypoxia that mediates therapy resistance in cancer cells. Several studies have reported the effect of hypoxic conditions on the ability of cancer cells to resist therapy (***Table 1***). HIFs, mainly HIF-1α, either activate or inactivate transcription factors participating in autophagy. In glioblastoma and astrocytoma cells, HIF-1α negatively regulates miR-224-3p, thereby enhancing the expression of Atg5 and FIP200, inducing autophagy, and postponing chemosensitivity *in vitro* and *in vivo* [128,157]. Similar results were obtained in colorectal cancer cells and tissues. HIF-1α downregulates the expression of miR-20a to mediate hypoxia-induced autophagy via the upregulation of Atg5/FIP200 sig-

naling[158]. It also positively controls astrocyte elevated gene-1 in T-cell non-Hodgkin's lymphoma and promotes autophagy-induced chemoresistance under hypoxia[159]. Since chemotherapy and radiotherapy usually induce apoptosis[160,161], tumor cells activate autophagy to digest damaged cellular components. Hypoxia-induced autophagy either positively or negatively contributes to the regulation of immune escape from cancer[129].

TARGETING HIFS FOR CANCER TREATMENT

Owing to the crucial roles of HIFs, especially HIF-1α, in tumor development, cancer treatment has recently involved the use of HIF inhibitors. There are two types of HIF inhibitors: direct and indirect[162]. However, regardless of the type, the ultimate purpose of these inhibitors is to completely block HIF-related signaling pathways, thereby reducing the malignant properties of cancer tumors.

Temsirolimus and everolimus are examples of indirect HIF inhibitors clinically used in treating renal cell cancer[67]. These drugs inhibit the activity of mTORC1, thereby destabilizing HIFα signaling pathways[67]. Recently, natural compounds isolated from plants have been utilized in cancer drug development. For instance, cardamonin, a chalcone extracted from *Alpinia katsumadai*, inhibits HIF-1α activity and tumor angiogenesis in breast cancer xenograft models through the mTOR/P70S6K pathway[163]. Apigenin inhibits HIF-1α protein expression by downregulating the PI3K/AKT pathway and enhancing the stability of p53 in ovarian, prostate, and breast cancer cells[164]. Genipin, derived from *Gardenia jasminoides*, inhibits HIF-1α accumulation under hypoxic conditions in various cancer cell lines and prevents invasion of colon cancer cells by downregulating the ERK signaling pathway[68]. Even a short exposure to shikonin, extracted from *Lithospermum erythrorhizon*, suppresses NF-kB activity and thereby downregulates HIF-1α protein during lymphangiogenesis[165]. These suggest the great potential of using plant-derived compounds in cancer treatment targeting HIF signaling pathways.

Generally, direct HIF inhibitors downregulate the expression of HIFs by suppressing the transcriptional and translational activities or disrupting the connection with other proteins[67]. Instead of reducing the HIF-1α level, arylsulfonamide KCN1 interferes with the interaction between HIFs and p300/CBP to inhibit glioma growth *in vitro* and *in vivo*[69]. In a pilot trial, the use of EZN-2968 in 10 patients with different types of cancer yielded positive outcomes, since it decreased the HIF-1α mRNA and protein levels[166]. Hypoxia contributes to tumor malignancy by controlling downstream targets, with HIFs playing a central role. Aminoflavone (AF), which has been studied in phase II clinical trials on cancer treatment, also specifically inhibits HIF-1α transcriptional activity and avoids HIF-1α and HIF-2α in several cancer cell lines[167]. It diminishes tamoxifen resistance by suppressing α6-integrin and inducing BAX expression in tamoxifen-resistant breast cancer cells[168]. Belzutifan, an advanced pharmacologic agent blocking HIF-2α activity by allosterically interfering with its interaction with HIF-1[169], is safer and more effective for patients with von Hippel–Lindau disease-associated renal cell carcinoma[170]; it was approved by the United States Federal Drug Administration for use in patients with non-metastatic tumors[171]. Sanguinarine blocks HIF-1α translocation and reduces hypoxia-induced EMT marker and VEGF levels in hepatocellular carcinoma[172]. Panaxadiol, isolated from *Panax ginseng*, inhibits PD-L1 expression by blocking HIF-1α protein synthesis and restores T-cell activity to kill colon cancer cells in co-culture models[173]. These examples propose a novel strategy for drug combinations in futuristic cancer treatment (**Figure 2**).

CONCLUSION

Hypoxia plays a pivotal role in cancer progression. Regulation of HIFs under hypoxic conditions changes the expression of their target genes and related pathways to cause tumor aggressiveness, including angiogenesis, EMT, metastasis, immune escape, and therapy resistance. New methods developed to specifically inhibit HIFs and their signals have initially demonstrated their effects *in vitro* and *in vivo*. Further clinical trials are necessary to confirm the roles of these compounds in cancer treatment targeting hypoxia.

ABBREVIATIONS

AKT: Ak strain transforming, **ANG**: angiopoietin, **Atg**: autophagy-related gene, **BAX**: BCL-2-associated X, **BCL-2**: B-cell lymphoma 2, **CD**: cluster differentiation, **CSC**: cancer stem cell, **EMT**: Epithelial–mesenchymal transition, **ERK**: extracellular signal-regulated kinase, **HIF**: hypoxia-inducible factor, **IL**: interleukin, **LC3**: light chain 3, **MDM2**: Murine double minute 2, **miR**: microRNA, **mTOR**: mammalian target of rapamycin, **N/A**: not available, **NOD/SCID**: non-obese diabetic/Severe combined immunodeficiency, **PD-L1/2**: Programmed death-ligand $\frac{1}{2}$, **PDGF**: platelet-derived growth factor,

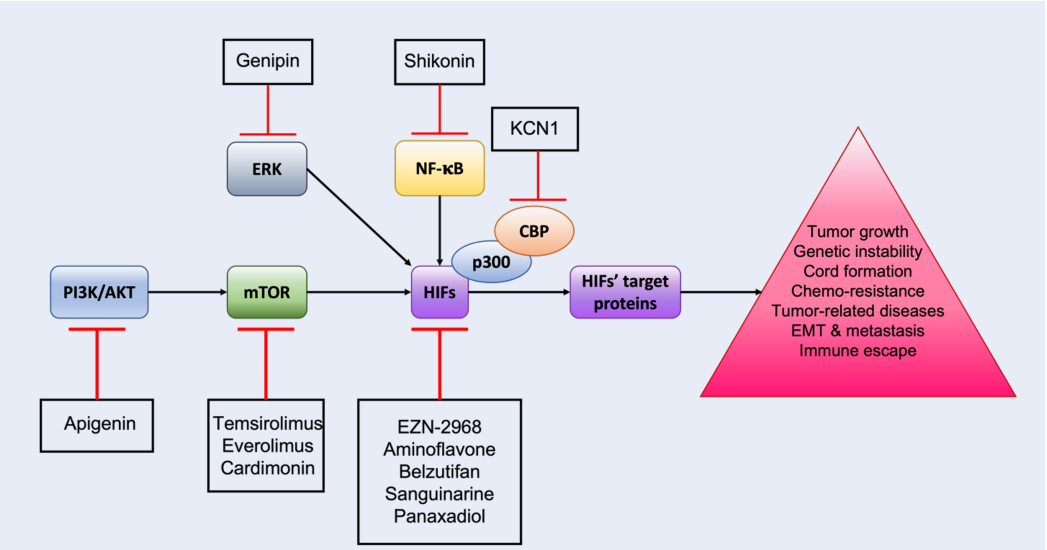

Figure 2: **New and novel strategies in drug development targeting HIFs in cancer treatment during last decade.**

PI3K: phosphoinositide 3-kinase, **TGF-beta**: transforming growth factor beta, **VEGF**: vascular endothelial growth factor, **ZEB**: zinc-finger E-box binding-homebox

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AUTHOR'S CONTRIBUTIONS

Bui Dinh Khan took the main responsibility for layout and content of the manuscript. Tran Ngo The Nhan, Hoang Nguyen Minh Chau and Nguyen Thi Yen Nhi equally contributed to this work. All authors read and approve the final version of the manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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