Emerging role of circRNAs in cancer under hypoxia (Review)

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Received March 30, 2022; Accepted August 12, 2022

DOI: 10.3892/ol.2022.13492

Abstract. Circular RNA (circRNA), a recently identified type of non-coding RNAs (ncRNAs), forms a covalently closed loop with neither a 5' cap structure nor a 3' polyadenylated tail. Due to their lack of free ends, circRNAs are not easily cleaved by RNase R, thus avoiding degradation and being more stable than linear RNAs. Recent studies have suggested that circRNAs play a crucial role in regulating gene expression by acting as microRNAs sponges, RNA binding protein sponges and translational regulators. Currently, circRNAs are hot research topics due to their close association with the development of cancer and other diseases. Hypoxia is the most common microenvironment during tumor growth, and hypoxia-inducible factors have different effects on tumor growth and influence important cancer characteristics, including cell proliferation, apoptosis, differentiation, vascularization/angiogenesis, genetic instability, tumor metabolism, tumor immune response, invasion and metastasis. The present review aimed to study the biogenesis and mechanisms of gene regulation of circRNAs in hypoxia, to summarize the latest studies on circRNAs as potential diagnostic and prognostic biomarkers in hypoxia, and to understand the role of circRNAs in the process of tumor drug resistance under hypoxia.

Contents

1. Introduction

Cancer is a major public health problem and one of the main causes of mortality worldwide (1). Although there are numerous treatment options available, including chemotherapy, surgery, radiotherapy, hormone therapy and immunotherapy, according to the World Health Organization, 19.3 million patients were diagnosed with cancer and 10 million succumbed to the disease in 2020 (1). There are multiple reasons for this, including lack of specific and effective tumor markers, late detection due to atypical early symptoms, rapid growth and metastasis of tumors, and drug resistance caused by tumor chemotherapy, which results in poor therapeutic effect (2-4). Circular RNAs (circRNAs) participate in the regulation of all principal hallmarks of malignancy, and are considered promising markers for predicting cancer diagnosis and prognosis (5).

2. Formation and function of circRNAs

circRNAs are endogenous RNA molecules that are widely present in mammalian transcriptomes and are involved in the regulation of gene expression, belonging to the family of non-coding RNAs (ncRNAs) (6,7). circRNAs are generated by a precursor mRNA through back-splicing or non-canonical splicing with no free end or polyadenylated tail. Compared with linear ncRNAs, circRNAs are more stable, since their circular structure protects them from degradation by the majority of RNA decay mechanisms (8,9). Based on the exons and introns that they contain from the parental genes, circRNAs can be divided into three categories: i) Exonic circRNAs (ecircRNA), which only contain back-spliced exons; ii) circular intronic RNAs (ciRNA) that come from introns; and iii) exon-intron circRNAs (EIciRNAs), which are circularized with both exons

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Key words: circular RNA, hypoxia, cancer, hypoxia-inducible factors, drug resistance

and introns (10). A schematic diagram of their structure is shown in Fig. 1.

circRNAs used to be considered to be a byproduct of splicing errors, with no biological function, and were considered junk RNAs in the past (11). With the widespread application of RNA sequencing and the rapid expansion of bioinformatics, the functions of additional circRNAs have been identified (12). circRNAs perform four main functions. First, they act as competing endogenous RNA (ceRNA) or microRNA (miRNA or miR) sponges (8). circRNAs can competitively bind to miRNAs, leading to a decrease in functional miRNA molecules and a subsequent upregulation of target miRNAs (8). Cerebellar degeneration-associated protein 1 antisense transcript (CDR1as) is the most representative miRNA sponge circRNA, and contains >70 miR-7-binding sites. CDR1as is a circular inhibitor of miR-7. When CDR1as is highly expressed, miR-7 activity is decreased, leading to increased expression of miR-7's target genes (8,13,14). Second, circRNAs interact with RNA binding proteins and mRNAs (15,16). For example, circ-Foxo3 can repress cell cycle progression by binding to the G_1 to S phase transition-related proteins CDK2 and p21 (15). circRNAs can interact with mRNAs, and circRNAs that contain a translation start site can act as mRNA traps and regulate protein translation of mRNA (16). Third, circRNAs regulate the expression of their parent genes, and circRNAs involved in gene regulation are enriched in the nucleus (17). EIciRNAs, such as EIciEIF3J and EIciPAIP2, can bind to nuclear ribonucleoprotein with U1 small nuclear RNA and RNA polymerase II in a cis-acting form to enhance the transcription of their parental genes (10). Fourth, circRNAs are involved in protein translation. Although circRNAs belong to ncRNAs, a number of these molecules have been reported to be translatable (18,19). Legnini *et al* (18) confirmed that circ-ZNF609 can be translated into a protein that participates in myogenesis (18). A previous study reported that upregulation of FBXW7-185aa, a novel protein encoded by circ-FBXW7, inhibits cell proliferation and cell cycle progression in glioblastoma, since it reduces the half-life of c-Myc (19).

Accumulating evidence shows that circRNAs play important roles in the development and progression of non-cancerous and cancerous diseases, such as neurological (20) and cardiovascular (21) diseases, as well as insulin secretion (22) and tumors [(including lung, breast and gastric cancer (GC)] (23-25). circRNAs regulate the apoptosis, proliferation, migration, invasion and angiogenesis of cancer cells, and lead to tumor drug resistance through the hypoxia-inducible factor (HIF) regulatory pathway under hypoxia (23-26). For example, circAGFG1 promotes the proliferation and invasion of non-small cell lung cancer (NSCLC) cells, and inhibits apoptosis by accelerating glycolysis via the miR-28-5p/HIF-1α axis (23).

3. Formation and function of HIFs

Accumulating evidence has shown that the hypoxic microenvironment, which is critical during cancer development, plays a key role in regulating cancer progression and metastasis. The effects of HIF, a master regulator of the hypoxic response, have been extensively studied during these processes (23-25).

HIFs are a family of three members, and they are heterodimers composed of an O2-sensitive α subunit (HIF-1α, HIF-2α or HIF-3α) and an O2-insensitive HIF-1β subunit (27). HIF-α is the most characteristic subtype of HIF and is a conditionally regulated transcription factor (28). HIF-1α promotes an acute response to hypoxia, while HIF-2α promotes a chronic response. The function of HIF-3α and its numerous splice variants is not known in detail (29,30). Under normal oxygen conditions, HIF-α is modified into a hydroxylated HIF-α subunit by HIF prolyl hydroxylases (PHDs) or factor inhibiting HIF (FIH) and then degraded or inactivated, as shown in Fig. 2A (31,32). Diminished PHD and FIH activity during periods of hypoxia stabilizes HIF-α and results in its translocation to the nucleus, where HIF-α and HIF-1β form a heterodimer, a structurally active transcription factor, as represented in Fig. 2B (28,31,32).

Hypoxia is one of the most common conditions encountered within the tumor microenvironment (29). Impairment in diffusion, abnormalities in tumor microvessels and altered microcirculation lead to deficient or even abolished oxygen supply in the tumor microenvironment (33,34). Therefore, the HIF signaling pathway plays an important role in tumors. First, HIF-1 is a key mediator of tumor metabolism. Specifically, HIF-1 is an important mediator of the tumor-associated metabolic switch, also known as the Warburg effect, in which tumor cells generate energy mainly by non-oxidative breakdown of glucose rather than conventional oxidative phosphorylation (24,35,36). Second, it regulates the tumor microenvironment and promotes tumor progression. Hypoxia is a critical parameter that modulates stromal and/or endothelial/tumor cell interactions, and intratumoral hypoxia leads to the release of factors that recruit tumor-associated macrophages, myelogenous suppressor cells and other immune cells, which arrive at the tumor site and secrete proinflammatory cytokines or other mediators to induce tumor angiogenesis, promote cancer cell metastasis or produce immunosuppression (37-40). Third, HIF-α promotes tumor metastasis through the epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs) (41-43). HIF-α-mediated EMT results in the enrichment of a stem-like side population of cells in thyroid cancer (42), and HIF-α promotes mammary tumor growth and metastasis, partly through the regulation of CSCs (43). Fourth, HIF is involved in tumor resistance. Previous studies have shown that HIF-1 and reactive oxygen species enhance the development of resistance to chemotherapeutics, such as doxorubicin and etoposide, in lung, cervical carcinoma and melanoma cell lines (44,45).

The circRNA and HIF regulatory pathways have been extensively studied in recent years. The present review focused on the biological functions (Table I) and mechanisms of action (Fig. 3) of circRNA in various tumors under hypoxia, and evaluated its potential as a new diagnostic and prognostic biomarker.

4. Role of circRNA in lung cancer under hypoxia

Lung cancer is the most commonly diagnosed cancer and the primary cause of cancer-associated mortality worldwide (1). Given the high mortality and markedly low survival rate of lung cancer, the determination of specific biomarkers for

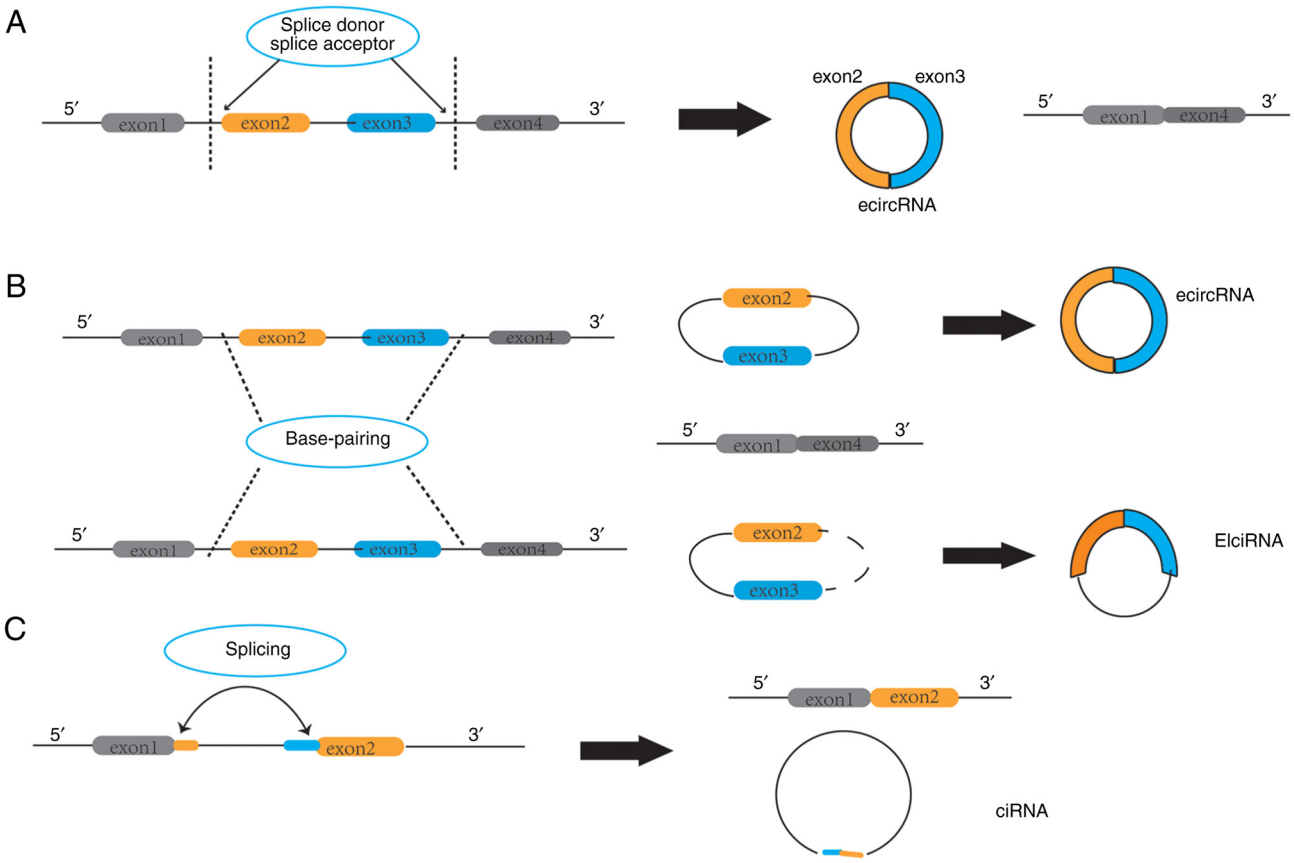

Figure 1. Possible models of circRNA biogenesis. (A) Lariat-driven circularization: Exon skipping event results in covalently splices from a 3' splice donor to a 5' splice acceptor, which forms a lariat structure containing exons 2 and 3, and a linear product of exons 1 and 4. The introns are removed by the spliceosome to form an ecircRNA. (B) Intron-pairing-driven circularization: Direct base-paring of complementary-sequence motifs (such as *Arthrobacter luteus* elements) forms a circular structure and a linear product. The introns are removed or retained to form an ecircRNA or an EIciRNA. (C) ciRNA: The intron lariat is generated from a splicing reaction. A GU-rich element near the 5' splice site (orange box) and a C-rich element near the branch point (blue box) makes it sufficiently stable to escape debranching. circRNA, circular RNA; ecircRNA, exonic circRNA; EIciRNA, exon-intron circRNA; ciRNA, circular intronic RNA.

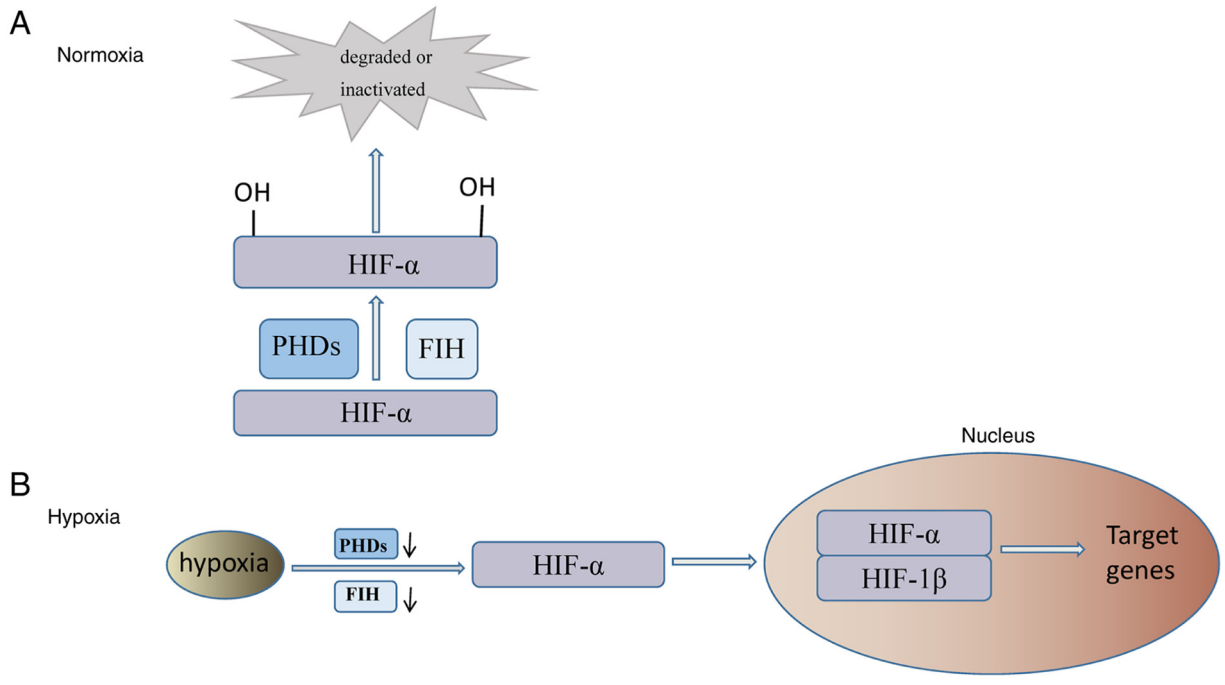

Figure 2. Regulation of HIF by oxygen. (A) Under normal oxygen conditions, HIF-α is converted into a hydroxylated HIF-α subunit by HIF PHDs or factor inhibiting HIF, and then degraded or inactivated. (B) Diminished PHDs and FIH activity during periods of hypoxia stabilizes HIF-α and results in its translocation to the nucleus, where HIF-α and HIF-1β form a heterodimer, a structurally active transcription factor that activates the transcription of HIF target genes. HIF, hypoxia inducible factor; PHD, prolyl hydroxylase; FIH, factor inhibiting HIF.

Table I. Functional characteristics of circRNAs in multiple human cancer types under hypoxia.

First author, year	Cancer type	circRNA name	Expression	Host gene name	Functional roles	Target miRNA	HIFs	Study model	(Refs.)
Ma *et al*, 2021	Lung cancer	circAGFG1	Upregulated	AGFG1	Viability (+) Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	miR-28-5p	HIF-1α	*In vivo/in vitro*	(23)
Feng *et al*, 2020	Lung cancer	hsa-circ-0000211	Upregulated	SFMBT2	Migration (+) Invasion (+)	miR-622	HIF-1α	*In vitro*	(47)
Chi *et al*, 2019	Lung cancer	circPIP5K1A	Upregulated	PIP5K1A	Proliferation (+) Migration (+)	miR-600	HIF-1α	*In vivo/in vitro*	(51)
Cao *et al*, 2020	Breast cancer	circRNF20	Upregulated	RNF20	Proliferation (+) Apoptosis (-)	miR-487a	HIF-1α	*In vivo/in vitro*	(24)
Liang *et al*, 2017	Breast cancer	circDENND4C	Upregulated	-	Proliferation (+)	-	HIF-1α	*In vitro*	(53)
Wang *et al*, 2020	Breast cancer	circPVT1	Upregulated	-	Proliferation (+) Migration (+) Invasion (+)	miR-29a-3p	HIF-1α	*In vivo/in vitro*	(54)
Darbeheshti *et al*, 2021	Breast cancer	circ_0047303	Upregulated	ZNF521	Proliferation (+) Invasion (+)	-	HIF-1	*In vitro*	(55)
Liu *et al*, 2020	Gastric cancer	circ-MAT2B	Upregulated	-	Proliferation (+)	miR-515-5p	HIF-1α	*In vivo/in vitro*	(25)
Darbeheshti *et al*, 2021	Gastric cancer	circHIPK3	Upregulated	HIPK3	Proliferation (+) Migration (+) Invasion (+)	miR-653-5p/ miR-338-3p-NRP1	HIF-2α	*In vivo/in vitro*	(55)
Zhai *et al*, 2019	Hepatocellular carcinoma	hsa-circ-0046600	Upregulated	B3GNTL1	Proliferation (+) Migration (+) Invasion (+)	miR-640	HIF-1α	*In vivo/in vitro*	(59)
Tu *et al*, 2021	Hepatocellular carcinoma	circ-0003006	Upregulated	FLNB	Proliferation (+) Migration (+) Invasion (+)	miR-542-3p	HIF-1α	*In vivo/in vitro*	(60)
Tan *et al*, 2019	Hepatocellular carcinoma	circ-EPHB4	Downregulated	EPHB4	Apoptosis (+) Migration (-) Invasion (-)	-	HIF-1α	*In vivo/in vitro*	(61)
Liu and Xu, 2021	Pancreatic cancer	circ_03955	Upregulated	-	Proliferation (+) Apoptosis (-)	miR-3662	HIF-1α	*In vivo/in vitro*	(64)
Ou *et al*, 2019	Pancreatic cancer	circ_0000977	Upregulated	NOL10	Immune escape (+)	miR-153	HIF-1α	*In vivo/in vitro*	(67)
Chen *et al*, 2020	Colorectal cancer	circ-ERBIN	Upregulated	-	Proliferation (+) Migration (+) Invasion (+)	miR-138-5p/ 4EBP-1	HIF-1α	*In vivo/in vitro*	(70)

Table I. Continued.

First author, year	Cancer type	circRNA name	Expression	Host gene name	Functional roles	Target miRNA	HIFs	Study model	(Refs.)
Zhou *et al*, 2020	Colorectal cancer	circRNA_100859	Upregulated	-	Proliferation (+) Apoptosis (-) Migration (+) Invasion (+)	miR-217	HIF-1α	*In vivo/in vitro*	(71)
Qian *et al*, 2020	Cervical cancer	circ-HIPK3	Upregulated	HIPK3	Proliferation (+) Migration (+)	miR-338-3p	HIF-1α	*In vivo/in vitro*	(72)
Chen *et al*, 2019	Cervical cancer	circRNA CDR1as	Downregulated	-	Proliferation (-) Migration (-) Invasion (-)	miR-135b-5p	HIF1AN	*In vivo/in vitro*	(73)
Su *et al*, 2019	Glioma	hsa_circ_0002142	Upregulated	DENND2A	Migration (+) Invasion (+)	miR-625-5p	HIF-1α	*In vitro*	(74)

circRNA, circular RNA; miR/miRNA, microRNA; HIF, hypoxia inducible factor; hsa, *Homo sapiens*.

the diagnosis and treatment of lung cancer remains critical. Previous studies found that, under hypoxia, circRNAs may become important biomarkers of lung cancer, since they participate in the malignant progression of lung cancer, including metastasis, cell proliferation, tumor growth and drug resistance) (23,46-48).

In lung cancer tissues, HIF-α expression was significantly elevated compared with that in adjacent normal lung control tissues, suggesting the existence of tumor hypoxia during the development of lung cancer (23,46,47). Li *et al* (49) determined the protein levels of HIF-1α and downstream target genes, such as pyruvate dehydrogenase kinase, glucose transporter 1, adrenomedullin vascular endothelial growth factor A and ribosomal protein L28, in hypoxic A549 cells, and they were significantly higher than those in normoxic A549 cells. Notably, there was no change in HIF-1α expression level, suggesting that hypoxia regulates HIF-1α at the translational level (46). Hypoxia is common in lung cancer with lymph node metastasis (50). Cheng *et al* (46) examined the circFAM120A levels in 11 paired tumor and adjacent non-cancer tissues from patients with lymph node-positive lung adenocarcinoma (LAC) using reverse transcription-quantitative PCR (RT-qPCR). The expression of circFAM120A was significantly reduced in all tumor specimens, suggesting that circFAM120A may be a potential marker of LAC hypoxia, and may be able to predict the risk of lung cancer metastasis.

Ma *et al* (23) found that miR-28-5p suppressed the proliferation, migration and invasion, and accelerated the apoptosis of NSCLC cells by targeting HIF-1α. In H1299 cells transfected with anti-miR-28-5p alone or in combination with si-circAGFG1, miR-28-5p interference elevated the expression of HIF-1α, and the introduction of small interfering RNA (siRNA) circAGFG1 reduced the expression of HIF-α, which confirmed that circAGFG1 enhanced the enrichment of HIF-1α via sponging miR-28-5p in NSCLC cells. circAGFG1 notably upregulated in NSCLC tumor tissues compared with the findings in adjacent normal tissues. circAGFG1 was significantly upregulated in NSCLC tumor tissues compared with the levels found in normal adjacent tissues. *In vivo* and *in vitro* experiments confirmed that circAGFG1 promoted the proliferation, migration and invasion of NSCLC cells, and accelerated cell apoptosis under hypoxia (23). Similarly, Feng *et al* (47) reported higher expression of hsa-circ-0000211 in LAC tissues than in normal tissues. hsa-circ-0000211 upregulated HIF-1α expression by targeting miR-622, and inhibition of hsa-circ-0000211 inhibited LAC migration and invasion. The mechanism of action is that hsa-circ-0000211 promotes LAC cell migration and invasion by regulating the miR-622/HIF-1α network. In addition, circPIP5K1A (hsa_circ_0014130) expression was increased in NSCLC cells (51). circPIP5K1A knockdown suppressed NSCLC cell metastasis and proliferation by promoting the expression of miR-600 (51). Overexpression of miR-600 inhibited the HIF-1α-mediated metastasis and proliferation of NSCLC cells by downregulating the EMT-related proteins, Snail and vimentin, and by upregulating E-cadherin (51). Regarding the mechanism of action, miR-600 was the circPIP5K1A target, and miR-600 interacted with the 3' untranslated region (UTR) of HIF-1α circPIP5K1A, which functioned as a miR-600 sponge to facilitate NSCLC proliferation and metastasis by promoting HIF-1α (51).

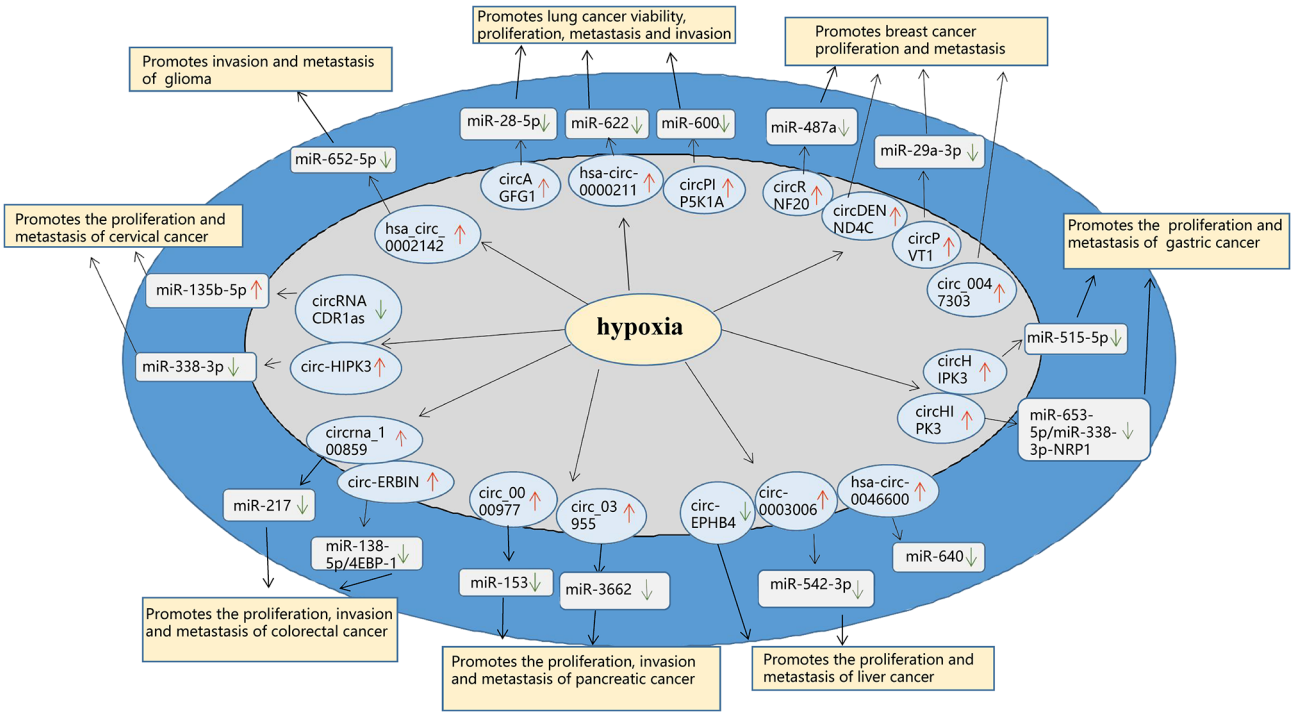

Figure 3. Under hypoxia, the role of circRNAs in different cancer types is mainly played by sponging miRNAs. circRNA, circular RNA; miR/miRNA, microRNA; hsa, *Homo sapiens*.

The above findings suggest that, in a hypoxic environment, circRNAs can promote lung cancer proliferation and metastasis through different pathways; thus, these circRNAs may become candidate markers and therapeutic targets for lung cancer.

5. Role of circRNA in breast cancer (BC) under hypoxia

BC is emerging as the leading cause of cancer-associated mortality, and the second highest cause of mortality in women worldwide (1,52). Compelling evidence has demonstrated the potential functions of circRNAs in BC tumorigenesis (24,53-55).

circDENND4C is a HIF1α-associated circRNA induced under hypoxia in BC cells (53). Liang *et al* (53) found that the expression of circDENND4C was increased after hypoxia induction or decreased after knocking down HIF-1α. Compared with that in the negative control group, silencing of circDENND4C or HIF-1α resulted in decreased proliferation of cancer cells under hypoxia (53). In addition, RT-qPCR showed that circDENND4C expression was higher in tumor tissues than in normal adjacent tissues, and the expression level of circDENND4C was positively correlated with the HIF-1α mRNA level. In addition, the circDENND4C level was correlated with tumor size, which suggested that the larger the tumor became, the more likely it was to suffer hypoxia-mediated injury (53). Using RT-qPCR, Cao *et al* (24) demonstrated that circRNF20 was overexpressed in BC tissues compared with its expression levels in normal tissue. Survival analysis conducted by Kaplan-Meier and log-rank test revealed that high circRNF20 expression was associated with a low survival rate in patients with BC. The RT-qPCR results showed that circRNF20 gene knockout increased the expression of miR-487a and downregulated the expression level of HIF-1α, while circRNF20 overexpression decreased the expression of miR-487a and enhanced the expression of HIF-1α. miR-487a overexpression decreased the HIF-1α level, while miR-487a silencing upregulated the HIF-1α level (24). Cell proliferation and flow cytometry assays showed that circRNF20 gene knockout inhibited cell proliferation and increased cell apoptosis, while circRNF20 overexpression had the opposite effects. Therefore, these findings indicate that circRNF20 promotes BC tumor growth and proliferation, and inhibits tumor cell apoptosis. Mechanistically, circRNF20 harbors miR-487a, acting as a miRNA sponge, and then miR-487a targets the 3' UTR of HIF-1α (24).

Wang *et al* (54) reported that circPVT1 was remarkably increased in BC tissues compared with its level in adjacent normal tissues, while the miR-29a-3p levels were considerably decreased. Kaplan-Meier analysis revealed that patients with BC with low miR-29A levels had a shorter median survival, and overexpressed circPVT1 was correlated with positive lymph node examination and tumor size. The authors also found that overexpression of circPVT1 or downregulation of miR-29a-3p significantly increased the anterior gradient 2 (AGR2) and HIF-1α levels, and promoted the proliferation, migration and invasion of BC cells. The mechanism of action is that circPVT1 acts as a BC oncogene, binds to miR-29a-3p, and promotes cell proliferation, invasion, migration, and inhibition of apoptosis through a miR-29a-3p-mediated AGR2-HIF-1α axis (54).

The aggressive and highly metastatic nature of triple-negative BC (TNBC) causes poor outcomes in patients with TNBC. The HIF-1 signaling pathway is a prominent pathway that contributes to angiogenesis and metastasis progression in

tumors (37). Darbeheshti *et al* (55) found that circ_0047303 was significantly upregulated in TNBC compared with its expression in normal adjacent tissues by fluorescence RT-qPCR. The results indicated that circ_0047303, the highest upregulated circRNA, could potentially sponge/inhibit multiple downstream miRNAs that function in the HIF-1 signaling pathway. Kaplan-Meier analysis suggested that patients with high circ_0047303 expression had shorter disease-free survival. By regulating the function of HIF-1, circ_0047303 expression was associated with the clinicopathological characteristics of the patients, and was positively correlated with tumor size, tumor stage and lymph node metastasis. Therefore, this circRNA was considered to have a prognostic value (55).

These findings suggest that circRNAs may be promising biomarkers for BC diagnosis, and even potential therapeutic targets for BC treatment through the HIF signaling pathway under hypoxic conditions.

6. Role of circRNA in GC under hypoxia

GC is a major public health problem worldwide, and is responsible for >1 million new cases and estimated 783,000 mortalities in 2018. GC is the fifth most commonly diagnosed type of cancer, and the third leading cause of cancer-associated mortality (1,56). Thus, it is crucial to study biomarkers and therapeutic targets for GC.

Liu *et al* (25) found that circ-MAT2B and HIF-1α circ-MAT2B gene knockout could significantly inhibit cell viability and DNA synthesis in GC cells. In addition, it could inhibit glucose uptake, lactic acid synthesis and tumor growth *in vivo*. Moreover, high expression of circ-MAT2B was positively correlated with tumor size, lymph node metastasis and TNM stage, and the overall survival (OS) and DFS of patients with high circ-MAT2B expression were shorter than those of patients with low circ-MAT2B expression (26). HIF-1α is a driver of glycolysis and uncontrolled proliferation of tumor cells, activating various oncogenic pathways (57). HIF-1α was upregulated in GC, which was due to the overexpression of circMAT2B. Exogenous expression of HIF-1α could effectively rescue the glycolysis reduction caused by circ-mat2b gene knockout, suggesting that HIF-1α is necessary for the function of circ-mat2b in GC (25). The mechanism of action is that circ-mat2b was predominantly located in the cytoplasm, and acted as a ceRNA to sponge miR-515-5p and increase HIF-1α-mediated silencing of miR-515-5p. In addition, overexpression of HIF-1α could rescue the attenuated aggressive phenotype of GC cells caused by circ-mat2b knockdown. Importantly, HIF-1α was able to directly bind to the circ-mat2b promoter and transcriptionally activate circ-mat2b, thus forming a positive feedback loop (25).

The role of circRNAs in GC metastasis under hypoxia is unclear. Previous results showed that the expression of HIF-2α was significantly upregulated in well-differentiated GC cells. HIF-2α gene knockdown reduced the expression of circHIPK3 in GC cells, and further overexpression of circHIPK3 enhanced the migration and invasion abilities of GC cells (55). These results suggest that HIF-2α mainly promotes the upregulation of circHIPK3 expression in GC cells under a long-term hypoxic microenvironment, thus promoting GC metastasis (55). The mechanism of action is that circHIPK3 induces the upregulation of neuropilin 1 (NRP1) expression in GC cells by using miR-653-5p and miR-338-3p sponges in a long-term hypoxic microenvironment. NRP1 may promote the migration and invasion of GC cells through the ERK/AKT signaling pathway. A previous study found that the OS of patients with GC with high expression of NPR1 was shorter than that of patients with GC with low expression of NPR1, which also indicated that NPR1 is upregulated by circHIPK3 and may lead to poor prognosis of patients with GC (55).

In conclusion, circRNA may be used as a potential biomarker of long-term hypoxia in GC, as well as a sensitive and specific indicator of diagnosis and prognosis.

7. Role of circRNA in hepatocellular carcinoma (HCC) under hypoxia

HCC is a malignant tumor with a high incidence. Despite the development of advanced diagnostic and treatment techniques for HCC, the outcomes remain unsatisfactory due to disease relapse, late diagnosis and drug resistance (1,58). Therefore, it is of great importance for patients with HCC to identify biomarkers associated with early diagnosis, therapeutic intervention and prognosis, and to study the molecular mechanism of HCC occurrence and metastasis.

Zhai *et al* (59) and Tu *et al* (60) found that the expression level of hsa-circ-0046600 and circ-0003006 in HCC tissues was significantly higher than that in adjacent normal tissues, and was positively correlated with tumor size, TNM stage, pathological vascular invasion and lymph node metastasis. Further experiments showed that hsa-circ-0046600 knockdown inhibited SK-HEP-1 cell migration, indicating that hsa-circ-0046600 was overexpressed in HCC cells and promoted the migration of these cells. The expression of miR-640 was significantly downregulated in HCC tissues, and the expression of hsa-circ-0046600 was negatively correlated with that of miR-640. HIF-1α was the downstream protein of hsa-circ-0046600. Therefore, the-circ-0046600 mainly affected the malignant biological behavior of HCC cells by competitively binding to miR-640 HCC by promoting hypoxia-induced expression of HIF-1α and other proteins (59). Similarly, circ-0003006 was demonstrated to promote HCC progression *in vitro* and *in vivo* by sponging miR-542-3p to release the inhibition of HIF-1α (60).

In HCC, the expression of circEPHB4 was downregulated, while the overexpression of circEPHB4 inhibited the survival of HCC cells, induced apoptosis, and inhibited cell migration and invasion (61). Tan *et al* (61) found that induced overexpression of circEPHB4 increased the apoptosis rate of HCC cells, inhibited cell proliferation and prevented HCC cell invasion. In addition, circ-EPHB4 levels were negatively correlated with tumor weight, size and metastasis *in vitro*, suggesting that circ-EPHB4 inhibits tumor genesis, development and metastasis. The results showed that circ-EPHB4 inhibited tumor genesis and metastasis by inhibiting HIF-1α expression, which in turn inhibited the HIF-1α PI3K-AKT signaling pathway and the HIF-1α/ZEB1 axis (61). These findings provide a novel perspective for the study of HCC, and suggest that circRNA has antitumor effects on HCC.

8. Role of circRNA in pancreatic cancer under hypoxia

Pancreatic cancer (PC) is a common malignant tumor worldwide that presents a serious threat to human health. PC's survival is the poorest amongst all solid cancer types, with a median survival duration of <6 months (62,63). Thereby, the identification of novel and effective biomarkers for PC diagnosis and therapeutic targets is urgently required.

Liu and Xu (64) showed that the upregulation of circ_03955 in PC was positively correlated with the adverse clinical outcome of patients with PC. *In vitro* and *in vivo* experiments showed that circ_03955 could promote the proliferation and inhibit the apoptosis of PC cells, as well as promote the Warburg effect. Its mechanism is as follows: circ_03955 acts as a sponge for miR-3662 to promote cancer through the miR3662/HIF-1α axis (64). Disruption of the circ_03955/miR-3662/HIF-1α loop may prevent the development and progression of PC.

Previous studies have shown that hypoxia can induce the upregulation of HIF1a, metalloproteinase ADAM10 and the downregulation of MHC class I chain-related molecule A, leading to the reduction of natural killer group 2D in natural killer (NK) cells, and tumor cell escaping immune surveillance and NK cell-mediated lysis (65,66). One of the reasons for the malignant progression of PC is the ability of tumor cells to evade immune-mediated lysis (67). Ou *et al* (67) found that HIF-1α mRNA expression was significantly upregulated in PC tissues compared with that in non-cancer tissues. Hypoxia has been considered an essential inducer of tumor cell resistance to immune effectors-mediated lysis (65). Hypoxia was reduced, whereas HIF-1α knockdown partially restored the killing effect of NK cells, suggesting that HIF-1α could modulate the immune resistance and immune escape of Panic-1 cells to NK cell-mediated lysis upon hypoxic conditions (67). The expression of circ_0000977 could be induced by hypoxia, and circ_0000977 knockdown enhanced the killing effect of NK cells on PC cells under hypoxia through HIF-1α and ADAM10. Therefore, circ_0000977 could regulate the HIF-1α-mediated immune escape of PC cells (67). The mechanism of action is that the circ_0000977/miR-153 axis modulates the HIF-1α-mediated immune escape of PC cells through the miR-153 downstream targets HIF-1α and ADAM10 (67). These findings indicate that the circ_0000977/miR-153/HIF1A/ADAM10 axis could potentially be used as an immune-sensitizer in the treatment and/or prevention of cancer.

9. Role of circRNA in colorectal cancer (CRC) under hypoxia

CRC is one of the most common gastrointestinal malignancies, and the incidence of the disease has rapidly increased in recent years (68). Although comprehensive therapies have been used, the prognosis of colon cancer remains poor, which may be due to the lack of early diagnosis and effective targeted therapy agents (69).

A previous study has shown that circ-Erbin was highly expressed in CRC cells, and circ-Erbin overexpression facilitated the proliferation, migration and metastasis of CRC *in vitro* and *in vivo* (70). Chen *et al* (70) found that circ-Erbin overexpression was promoted through angiogenesis by increasing the expression of HIF-1α in CRC (37,70). The main mechanism is that, as the sponge of miR-125A-5p and miR-138-5p, circ-Erbin mediates HIF-1α activation through the miR-125a-5p-5p/miR-138-5p/eukaryotic translation promoter 4E-binding protein 1 (4EBP-1) axis, and promotes the cap-independent protein translation of HIF-1α in CRC cells alonsgise targeted 4EBP-1. Similarly, another study identified that circRNA_100859 was overexpressed in colon cancer tissues and inhibited cell apoptosis (71). circRNA_100859 is a miR-217 sponge. miR-217 directly targets HIF-1α, and the circRNA_100859-miR-217-HIF-1α axis is associated with stage, histological grade and HIF-1α mutations in CRC (71). Thus, circRNA_100859 may be used as a new biomarker for the diagnosis and prognosis of CRC.

10. Role of circRNA in other cancer types under hypoxia

A number of previous studies have shown that circRNAs play an important role in gynecological tumors (72,73) and gliomas (74) under conditions of hypoxia.

Cervical cancer (CC) is the fourth most common malignancy and the second most frequent cause of cancer-associated death in women (1,75). The high mortality of CC is related to the molecular mechanism responsible for its occurrence and development. Qian *et al* (72) found that circ-HIPK3 expression was significantly elevated in CC cells and tissues. circ-HIPK3 silencing repressed tumor growth and metastasis, and induced apoptosis in CC cells. circ-HIPK3 sponged miR-338-3p and miR-338-3p to upregulate HIF-1α and CC progression. miR-338-3p silencing or HIF-1α overexpression rescued the circ-HIPK3 knockdown-mediated inhibition of CC malignant characteristics. Functionally, circ-HIPK3 promoted CC cell proliferation, clone formation, migration and invasion, while inhibited cell apoptosis by sponging miR-338-3p to upregulate HIF-1α expression, and contributed to EMT in CC cells. Mechanismly, circ-HIPK3 acts as a ceRNA of miR-338-3p to promote cell proliferation and metastasis in CC via regulating HIF-1α-mediated EMT (72). circRNAs and HIF1-α inhibitors (HIF1AN) are closely correlated with cancer. Chen *et al* (73) showed that CDR1as expression was significantly lower in ovarian cancer tissues than in normal ovarian tissues by using RT-qPCR (73). *In vitro* and *in vivo*, CDR1as overexpression inhibited the proliferation, invasion and migration of ovarian cancer cells. Silencing CDR1as increased the expression of miR-135b-5p, and decreased the expression of HIF1AN, thus increasing the proliferation capacity of ovarian cancer cells (73). Mechanistically, CDR1as, acting as a sponge of miR-135b-5p, promotes the expression of HIF1AN and therefore plays a role in tumor inhibition (73). These results provide new information for the diagnosis and treatment of ovarian cancer.

Glioma, which originates from glial cells, is the most prevalent and malignant tumor of the central nervous system (76). Despite the existence of potential treatments for glioma, glioma tumors are highly invasive and led to a high mortality rate (76,77). Therefore, it is necessary to conduct in-depth research on the pathological molecular mechanism of this disease to identify new treatment methods. circDENND2A (hsa_circ_0002142) has been suggested to be a hypoxia-responsive circRNA in glioma via

bioinformatic analysis (74). Hypoxia induced the expression of circDENND2A, and promoted the migration and invasion of glioma cells, which was achieved through the sponge action of miR-625-5p (74). Notably, glioma tissues overexpressing HIF-1α showed high expression of circDENND2A and low expression of miR-625-5p under hypoxia. These results suggest that there is a DENND2A/miR-625-5p axis in glioma tissues, which is associated with HIF-1α (74). Understanding the mechanism of this interaction may provide a promising target for the treatment of glioma metastasis in a hypoxic microenvironment.

11. Association of circRNA with tumor drug resistance under hypoxia

HIF, a marker of hypoxia, activates downstream oncogene transcription containing hypoxia response elements to regulate tumor metabolism and metastasis (78). HIF may also lead to chemotherapy and radiotherapy resistance through a variety of mechanisms (48,79). Therefore, in the clinic, HIF expression is associated with poor prognosis and treatment recurrence. In recent years, it has been found that therapeutic resistance induced by hypoxia can be reversed by circRNA intervention (Table II).

Platinum drugs are platinum compounds that are first-line drugs for the treatment of cancer, including lung cancer (26,80). However, platinum drug sensitivity is repressed with chemoresistance progression. Compared with that in normoxic cells, the expression of circASXL1 and crcAKT3 was upregulated, while the expression of miR-206 and miR-516B-5p was downregulated, in hypoxic lung cancer tissues and cells (48,81). Functionally, knocking out the circASXL1 and circAKT3 genes increased the sensitivity of cells to cisplatin (DDP), inhibited HIF-1α-dependent glycolysis, and weakened the increase in chemotherapy resistance in ASXL1 and AKT3-induced lung cancer cells. In terms of the mechanism, circASXL1 has binding sites for miR-206, while AKT3 has binding sites for miR-516b-5p. Notably, the knockdown-mediated inhibition of cisplatin resistance and glycolysis were reversed in lung cancer cells with inhibitors of miR-206 or miR-516b-5p. In addition, the circASXL1/miR-206 or miR-516B-5p/STAT3 axis could inhibit lung cancer growth *in vivo* (48,81). These results indicated that there may be multiple pathways leading to lung cancer drug resistance, and further research is necessary to completely reverse chemotherapy drug resistance under hypoxia. Similarly, circELP3 has been associated with disease progression and hypoxia-induced DDP resistance in BC (27). Decreasing the level of circELP3 via siRNA reduced the *in vitro* proliferation and DDP resistance of BC cells, and promoted cell apoptosis. Furthermore, interfering with circELP3 suppressed tumor xenograft growth in nude mice *in vivo* (27).

In a previous study, hypoxia induced the upregulation of circNRIP1 and reduced the sensitivity of GC cells to 5-fluorouracil (5-FU), as evidenced by the increase in multidrug resistance 1 gene, P-glycoprotein, HIF-1α and glucose-6-phosphate levels, glucose consumption, lactate production and cell survival (82). Silencing of circNRIP1 enhanced the sensitivity of GC cells to 5-FU under hypoxic conditions. The mechanism of action is that circNRIP1, as a miR138-5P sponge, regulates HIF-1α-dependent glycolysis through the circNRIP1/mir138-5P/

Table II. Mechanisms of drug resistance of circRNAs under hypoxia in various human cancer types.

First author, year	Cancer type	circRNA name	Expression	Host gene name	Resistance type	Target miRNA	HIF	Study model	(Refs.)
Yu *et al*, 2021	Lung cancer	circASXL1	Upregulated	ASXL1	Platinum resistance	miR-206	HIF-1α	*In vivo*	(48)
Xu *et al*, 2020	Lung cancer	circAKT3	Upregulated	AKT3	Platinum resistance	miR-516B-5p	HIF-1α	*In vivo*	(82)
Xu *et al*, 2020	Breast cancer	circELP3	Upregulated	ELP3	Platinum resistance	-	-	*In vivo*	(81)
Zeng *et al*, 2021	Gastric cancer	circNRIP1	Upregulated	NRIP1	Fluorouracil resistance	mir138-5P	HIF-1α	*In vivo*	(83)
Yang *et al*, 2017	Pancreatic cancer	circZNF91	Upregulated	-	Gemcitabine resistance	mir-23b-3p	HIF-1α	*In vivo*	(84)
Li *et al*,2018	Hepatocellular carcinoma	circRNA ZNF292 (CZNF292)	Upregulated	-	Radioinsensitivity	-	HIF-1α	*In vivo*	(80)

circRNA, circular RNA; miRNA, microRNA; HIF, hypoxia inducible factor.

HIF-1α axis to enhance hypoxia-induced 5-FU resistance (82). In PC, circZNF91 overexpression could significantly promote chemotherapy resistance in PC cells, while knockdown of circZNF91 retarded the hypoxic exosome-transmitted chemoresistance (83). Mechanistically, the hypoxia-induced extracellular domain ZNF91 can competitively bind to miR-23b-3p, which suppresses the inhibitory effect of miR-23b-3p on the expression of the deacetylase Sirtuin 1 (SIRT1). Therefore, upregulation of SIRT1 enhances the deacetylation-dependent stability of the HIF-1α protein, resulting in glycolysis and gemcitabine resistance in receptor PC cells. Therefore, the aforementioned signaling axis may be used in the future to treat tumor chemoresistance induced by hypoxia.

In HCC cells, cZNF292 was hypoxia-induced in a time-dependent manner, independently of HIF-1α (79). CZNF292 knockdown could enhance the radiosensitivity of hepatoma cells under hypoxic or normoxic conditions. CZNF292 gene knockout may lead to ataxia telangiectasia mutated phosphorylation and decreased DNA-PKCs kinase activity, which may reduce the DNA repair ability of HCC cells, which may be the main reason for their radiosensitization (79). These findings provide a theoretical and experimental foundation for the application of circRNAs as radiosensitizers in tumor radiotherapy.

12. Discussion

circRNAs mainly regulate tumor proliferation, metastasis, invasion and chemical resistance through the Wnt/β-catenin, MAPK/ERK, PI3K/AKT pathways (84). Hypoxia is one of the most common characteristics of the tumor microenvironment. Whereas transient or acute hypoxia occurs in tumors with inadequate blood perfusion, chronic hypoxia, which limits oxygen diffusion, occurs in enlarged tumors (85). Under hypoxia, HIFs regulate tumor metabolism through the mTOR-HIF-1α signaling pathway, which is a key mediator of Warburg metabolism (86,87). HIF-1 induces mesenchymal transformation from epithelial tumor cells via the Wnt/β-catenin and Wnt/HIF-catenin signaling pathways (88,89). Tumor inflammation is regulated by NF-κB, signal transduction and STAT3 (87,90). Therefore, circRNAs and HIFs have multiple overlapping pathways that jointly promote tumor proliferation, metastasis, angiogenesis and drug resistance under hypoxia. Further investigation of such common pathways should aim to explore tumor prevention and targeted therapy.

The impact of hypoxia on chemoresistance can be attributed to several factors. First, due to the low drug concentration in hypoxic cells, as it accumulates in areas away from functioning blood vessels (4). Second, the majority of anticancer drugs target proliferating cells; however, hypoxic cells experience nutrient starvation and impaired cell proliferation compared with aerobic cells, and thus they have less effect on hypoxic cells (91,92). Besides knocking down relevant circRNA target genes or adding downstream miRNA inhibitors to reverse tumor resistance, HIFs-targeted tumor therapy has the potential to improve therapeutic efficacy. Different strategies targeting hypoxic cancer cells and/or HIF include hypoxic-activated precursor drugs and inhibition of HIF dimerization, mRNA or protein expression, DNA binding ability and transcriptional activity (93). Recent advances in clinical immunotherapy and studies on the regulation of tumor immune response by HIF suggest that combined immunotherapy and inhibition of HIF may be an effective treatment (28,93).

In conclusion, circRNAs and HIFs act together to form signaling pathway axes, and promote tumor growth, proliferation, metastasis and chemical resistance under hypoxic conditions. Further studies should be conducted to identify key targets in their interactions that can inhibit tumor growth and, most importantly, reverse tumor resistance. The interactions between circRNAs and HIFs are complex, and there are numerous cross-pathway interferences, which increases the difficulty of future studies. Further in-depth investigation is required.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Key Science and Technology Project of Zigong City, Sichuan Province (grant no. 2021ZCYKY11).

Availability of data and materials

Not applicable.

Authors' contributions

QL performed the literature search and selection. ZD was responsible for the conception, analysis and design of the study. QL and WL were major contributors to the writing of the manuscript. HP and SX participated in the coordination of the study and reviewed the manuscript. QL and WL were responsible for the revision of the manuscript. HW and SX were responsible for the literature search and assisted in the design of the study. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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