The role of HIF-1 α in chemo-/radioresistant tumors

Yu Xia¹

Lixia Jiang²

Tianyu Zhong²

¹The Graduate School, Gannan Medical University, Ganzhou, People's Republic of China; ²Department of Laboratory Medicine, First Affiliated Hospital of Gannan Medical University, Ganzhou, People's Republic of China

Abstract: Chemo-/radioresistance is a major obstacle in clinical oncology. The precise failure mechanisms of chemo-/radioresistance are multifactorial failures. It is now widely accepted that a tumor hypoxia microenvironment contributes significantly to chemo-/radioresistance. Hypoxia is the most common and obvious neoplastic microenvironment and is due to the rapid proliferation of tumor cells. HIF-1 α is a principal molecular mediator of adaptability to hypoxia in tumor cells. HIF-1 α activation leads to the transcription of a plethora of target genes that promote physiological changes associated with chemo-/radioresistance, including increasing the ability of DNA repair, the inhibition of apoptosis, and alterations of the cellular metabolism. Moreover, recent findings suggest that HIF-1 α -activated autophagy is a crucial factor in the promotion of cell survival under the distressed microenvironment, thereby leading to the chemo-/radioresistance. This chapter presents an overview of the role of HIF-1 α in chemo-/radioresistance of tumor cells.

Keywords: HIF-1 α , chemo-/radioresistance, cancer

Introduction

In recent years, cancer has become a major threat to public health due to the increase in both morbidity and mortality of malignancies.¹ Torre et al identified the mortality rates. In 2012, 14.1 million new cancer cases occurred and 8.2 million cancer deaths occurred. Breast cancer is the leading killer at 25% among females, and lung cancer is both the leading killer at 19.6% among males and 13% of all cancer deaths for both males and females.

The main methods of antitumor therapy currently are surgery, chemotherapy, radiotherapy, and targeted therapy. Normally, patients with a malignant tumor need to have the tumor removed first by surgical resection, followed by chemotherapy, and radiotherapy at different times;² however, cancer treatments with either drugs or radiation are seriously limited by chemo-/radioresistance of tumors.³ Both Rueff and Rodrigues⁴ and Gatti and Zunino⁵ reported that chemo-/radioresistance is the primary cause for treatment failure in the majority of patients with malignant carcinoma. Thus, both how to overcome the resistance of chemo-/radiotherapy and how to improve the curative effect of cancer treatment are pressing problems to be solved.

The precise failure mechanisms of chemo-/radioresistance are multifactorial failures and can be classified broadly into the following two categories: tumor cell intrinsic resistance, which is largely due to the germinal genetic makeup according to Kartal-Yandim et al,⁶ and due to tumor microenvironment-related factors according to Gottesman.⁷ In recent years, Prasad et al³ identified three tumor cell intrinsic resistance mechanisms, the high expression of *MDR1* (multidrug resistance gene)

Correspondence: Lixia Jiang;
Tianyu Zhong
Department of Laboratory Medicine, First Affiliated Hospital of Gannan Medical University, 23 Qingnian Road, Ganzhou, Jiangxi Province 341000, People's Republic of China
Tel +86 797 828 3947
Email jlx7310@163.com;
zhongtianyu@gmail.com

in tumor cells, alterations in drug metabolism, and drug transport. Moreover, Verduzco et al, Muz et al, and others now widely accept that the alteration in tumor microenvironment during chemo-/radiotherapy leads to the expression of tumor-microenvironment-related factors, which contribute significantly to chemo-/radioresistance.^{8–11}

Hypoxia is the most common and obvious neoplastic microenvironment in solid tumors and is due to the rapid proliferation of tumor cells.¹² Moreover, Verduzco et al⁸ and Muz et al⁹ reported that the hypoxia tumor microenvironment is an independent prognostic factor in a diverse range of solid human tumors; HIF-1 α , a nuclear transcription factor, is a biomarker of the hypoxia microenvironment.¹² Both Wu et al¹³ and Lixia et al¹⁴ reported that HIF-1 α protein expression has been detected in most types of solid tumors and is associated with increased tumor growth, vascularization, and metastasis. In addition, HIF-1 α activation has an emerging role in increasing resistance to current cancer therapies.^{10,11} Moreover, both Dong et al¹⁵ and Greco and Scott¹⁶ reported that many mechanisms are involved in the roles of HIF-1 α during the promotion of the survival of tumor cells under chemo-/radiotherapy and chemo-/radioresistance.

Constitutive activation of HIF-1 α is observed in a broad spectrum of solid tumors, and HIF-1 α has an emerging role in tumorigenesis and chemo-/radioresistance. As a result, inhibiting the HIF-1 α activity may represent a valuable anticancer therapeutic strategy. This review gives an overview of recent observations regarding the effects of HIF-1 α on chemo-/radioresistance with special emphasis on the underlying molecular mechanisms.

HIF-1 α promotes chemo-/radioresistance in tumor cells

A hypoxia microenvironment forms easily in the process of the rapid proliferation of cells in a tumor, and the hypoxia microenvironment is a common feature of malignant solid tumors. Both Verduzco et al⁸ and Muz et al⁹ identified that hypoxia has an emerging role in chemo-/radioresistance of solid tumors because the activity of chemotherapeutic agents decreases or even disappears in the hypoxia microenvironment. HIF-1 α is a biomarker of hypoxia microenvironment. Muz et al⁹ identified HIF-1 α as a principal molecular mediator of adaptability to hypoxia in tumor cells, and HIF-1 α mediates cell proliferation, apoptosis, metabolism, immune responses, genomic instability, vascularization, invasion, and metastasis. Li et al¹⁷ and others demonstrated that HIF-1 α is both highly expressed in most of the solid

tumors such as in cervical cancer,¹⁸ breast cancer,¹⁹ colorectal cancer,²⁰ and gastric cancer²¹ and is tightly associated with the occurrence and development of tumors. Readers interested in the detailed information on the role of HIF-1 α in tumor tumorigenesis should read two recent reviews on this topic, because this article mainly focuses on the chemo-/radioresistance roles of HIF-1 α .^{22,23}

Recent findings by Li et al and others demonstrated that the high expression of HIF-1 α is not only related to malignant progression^{17,18} but also has an important effect on the treatment outcome of tumors.²⁴ Moreover, Zhao et al and others wrote that a contribution of HIF-1 α to drug resistance has been observed in a wide spectrum of clinical tumor samples such as gastric,²⁴ pancreatic,²⁵ and gall bladder types²⁶ and HIF-1 α expression is associated with both poor prognoses and relapses during treatment. Furthermore, Zhao et al and others noted that HIF-1 α appears to be a crucial molecular target that can be exploited to improve on the current treatment of metastatic and treatment-resistant tumors of the stomach, pancreas, and gall bladder.^{24–26} These data suggested that HIF-1 α plays important roles in treatment-resistant tumors.

The mechanisms of chemo-/radioresistance are complex and may change during different stages in tumors. According to Takasaki et al,²⁷ Meijer et al,²⁸ and Unruh et al,²⁹ at least three mechanisms are involved in the roles of HIF-1 α in promotion of chemo-/radioresistance: HIF-1 α -mediated apoptosis, increased ability of DNA-repair, and induced alterations of cellular metabolism. Moreover, Feng et al³⁰ suggested that HIF-1 α -activated autophagy is a crucial factor in the promotion of cell survival under the distressed microenvironment, thereby leading to the therapy resistance. The overall conclusion of Takasaki et al's,²⁷ Meijer et al's,²⁸ Unruh et al's,²⁹ and Feng et al's³⁰ observations is that HIF-1 α promotes chemo-/radioresistance of cancer cells and mechanisms are complex and varied. The following section outlines general molecular mechanisms that have been shown in the roles of HIF-1 α in chemo-/radioresistance (Table 1).

HIF-1 α -mediated activation of DNA repair pathway

DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. DNA damage is the mainstay of cancer treatment. For instance, chemo-/radiotherapy could lead to tumor cell death by inducing DNA damage. However, Wang et al¹¹ reported that tumor cells such as glioblastoma cells could initiate DNA damage repair, thereby causing the inhibition

Table 1 Overview of HIF-1 α -mediated chemo-/radioresistance mechanisms

Resistance phenotype	Molecular basis (if known)	Cell model	Therapies	Reference
DNA repair pathway activation	XPA	Lung cancer cells	Cisplatin	36
DNA repair pathway activation	DNA-PK	Mouse embryonic fibroblasts	Etoposide	40
DNA repair pathway activation	XPA	Germ cell tumors	Cisplatin	41
DNA repair pathway activation		Hepatocellular carcinoma cells	Radiotherapy	42
DNA repair pathway activation		Gastric cancer cells	Chemo-/radiotherapy	43
DNA repair pathway activation	DNA-PK, H2AX	Mouse mesenchymal stromal cells	Radiotherapy	44
Metabolic reprogramming	GLUT1	Lung cancer cells	Cisplatin	47
Metabolic reprogramming	GLUT1	Colorectal cancer cells	RIP-dependent necroptosis	51
Metabolic reprogramming	LDHA	Multiple myeloma cells	Bortezomib	53
Apoptosis inhibition	STAT3, TCF4	Colon cancer cells	Chemo-/radiotherapy	58
Apoptosis inhibition	P53	Gastric cancer cells	5-Fluorouracil	59
Apoptosis inhibition	Survivin, Bax, caspase 3/8	Gastric cancer cells	Chemo-/radiotherapy	60
Autophagy activation	MIRNA20, Bcl2	Colon cancer cells	Radiotherapy	70
Autophagy activation	BNIP3, Beclin-1	Lung cancer cells	Cisplatin	71
Autophagy activation	Beclin-1, c-Jun	Lung cancer cells	Radiotherapy	72
Autophagy activation	LC3II	Osteosarcoma cells	Radiotherapy	30
Autophagy activation		Lung cancer cells	Silver nanoparticle	73
Autophagy activation	mTOR/PI3K	Mouse mesenchymal stromal cells	Radiotherapy	74

Abbreviations: DNA-PK, DNA-dependent protein kinase; RIP, receptor-interacting protein.

of DNA damage induced by chemo-/radiotherapy. Also, Yang et al³¹ reported that the hepatocarcinoma cells exhibited higher activity of DNA damage repair pathway than normal cells and Stover et al³² reported that activated DNA repair pathway is a significant cause of chemo-/radioresistance in tumor cells. Thus, after exposure to chemotherapeutic drugs and radiation, many cancer cells could avoid death through the activation of DNA repair pathway.

Fortini et al³³ reported that chemo-/radiotherapy may induce single-stranded DNA breaks (SSBs) or double-stranded DNA breaks (DSBs), which must be repaired or must start apoptosis. The repair of SSBs is carried out by major pathways: base excision repair (BER), poly-ADP-ribose polymerase (PARP-1), and both XPA and XPD are the key molecules in the BER process. DSBs are more harmful on cell survival than SSBs and are strong activators of apoptosis because cell death could be induced by the persistence of DSBs if not repaired. To preserve genomic stability and survival, cells have developed DNA damage response (DDR) to handle DSBs according to Fortini et al.³³ Fortini et al³³ also observed that cells respond to DSBs quickly and accurately, that three steps could be necessary: first, the damage must be detected by both ataxia telangiectasia mutated (ATM) and ataxia telangiectasia RED3 related (ATR); second, damaged proteins must fit into the transmembrane proteins of the cells; and finally, cells react to repair DSBs under the function of the DNA-dependent protein kinase (DNA-PK) and histone H2AX,

when the DNA repair is failed, Li et al³⁴ proposed that the ATM/ATR complex activates P53, its downstream molecule, which induces apoptosis.

A large number of studies showed that HIF-1 α could increase the ability of DNA damage repair through the regulation of DNA repair pathway, thus leading to the chemo-/radioresistance in tumor cells. For instance, Um et al³⁵ identified that HIF-1 α contributed to resistance to ionizing radiation and anticancer drug therapy through the upregulation of DNA-PK in hypoxia tumor cells. Liu et al³⁶ identified that HIF-1 α contributed to cisplatin resistance in lung cancer through regulation of DNA repair pathway (Table 1). Wrann et al³⁷ and Logsdon et al³⁸ concluded that generally HIF-1 α increases the ability of DNA damage repair through the regulation of DNA repair system in liver cancer,³⁷ breast cancer,³⁷ osteosarcoma,³⁷ and pancreatic ductal adenocarcinoma cells.³⁸

Most of molecules in DNA repair pathway are regulated by HIF-1 α . For example, HIF-1 α mediates the overexpression of PARP-1, XPA, and XPD.³⁹ These three proteins could have an effect on the BER process, and Li et al³⁴ identified that BER is associated with resistance to some chemotherapeutic drugs in non-small-cell lung cancer (NSCLC) cells. In addition, Stover et al³² identified that the activities of ATM, DNA-PK, and H2AX in the DSBs repair pathway are also regulated by HIF-1 α . Earlier, Wirthner et al⁴⁰ suggested that an increased number of DSBs occurred in etoposide-treated HIF-1 α -deficient mouse embryonic fibroblasts (MEFs). When Wirthner et al⁴⁰ studied

the potential molecular mechanism, markedly reduced protein expression of DNA-PK was found in HIF-1 α -deficient MEFs. This study demonstrated that etoposide treatment in HIF-1 α -deficient MEFs both reduced the protein expression of DNA-PK and increased the susceptibility to DNA repair (Table 1). Shenoy et al⁴¹ showed that HIF-1 α enhanced DNA repair through upregulating XPA, which leads to cisplatin resistance in testicular germ cell tumors (Table 1). In a study about the mechanism of chemo-/radioresistance in hepatocellular carcinoma, Jin et al⁴² (Table 1) demonstrated that HIF-1 α inhibited the formation of both radiotherapy-induced DSBs and SSBs. Klein et al⁴³ (Table 1) suggested that the HIF-1 α -activated DNA damage repair pathway also has an emerging role in chemo-/radioresistance in gastric cancer. In addition, Sugrue et al⁴⁴ suggested that the expressions of both DNA-PK and H2AX were positively correlated with the expression of HIF-1 α in radiation-treated mouse mesenchymal stromal cells (MSCs) and showed that after knockdown of HIF-1 α in MSCs, the MSC's ability to repair DNA was impaired and that radiation-induced apoptosis in MSCs was increased. Consistent with previous outcomes, the study of Segrue et al⁴⁴ suggested that HIF-1 α promoted radioresistance in MSCs through enhancing the ability of DNA repair (Table 1). The collective research supported HIF-1 α role to promote DNA repair and HIF-1 α 's emerging role in chemo-/radioresistance in a variety of tumor cells.

HIF-1 α -mediated alterations in cellular metabolism

Reprogramming of energy metabolism is another hallmark of cancer. Tan et al⁴⁵ summarized that targeting metabolic pathways may increase sensitivity to either standard chemotherapy or radiotherapy. In addition, Gatenby and Gillies⁴⁶ reported that the upregulation of enzymes involved in glycolysis has an emerging role in chemo-/radioresistance in various malignant tumors such as esophageal, gastric, breast, and colorectal malignant tumors. The first rate-limiting step of glucose metabolism is the transport of glucose across the plasma membrane, and GLUT1 is the transport membrane protein in this process. Using the xenograft model, Liu et al⁴⁷ demonstrated that the inhibition of GLUT1 increased cisplatin-induced lung cancer cell death (Table 1). Pyruvate dehydrogenase kinase (PDK) 3 is responsible for the conversion of pyruvate to acetyl-coenzyme A, which enters the tricarboxylic acid cycle to produce ATP. Lu et al⁴⁸ reported that knockdown of PDK3 both inhibited hypoxia-induced glycolysis and increased the sensitivity of colon cancer cell lines to chemotherapeutic agents such as cisplatin, paclitaxel,

and oxaliplatin. Zhou et al reported the following two observations: first, LDHA catalyzes the final three steps in the glycolytic pathway, such as the conversion of pyruvate, the reduction of nicotinamide adenine dinucleotide (NAD) to lactate, and the oxidization of NAD, and second, LDHA has a critical role in tumor maintenance. A further study by Zhou et al⁴⁹ reported that the knockdown of LDHA reduced survival under hypoxic conditions in breast cancer cell lines. Luo and Semenza⁵⁰ reported the following three observations: first, PKM2 is the last rate-limiting enzyme in the glycolytic pathway, second, PKM2 is expressed predominantly in tumor cells, and third, PKM2 is important for both cancer metabolism and tumor growth. Moreover, the study suggested that the chemical inhibition of PKM2 could sensitize hypoxic tumors to radio-/chemotherapy. All these data indicated that the alterations in PKM2 metabolism and LDHA metabolism have a critical role in the therapy resistance of tumors, and targeting metabolic reprogramming represents promising novel anticancer strategies.

HIF-1 α affects chemo-/radiosensitivity via regulation of genes related to metabolic pathways. For example, Meijer et al²⁸ showed that HIF-1 α inhibition results in the following metabolic changes: decreased rate of glucose uptake, decreased lactate production, increased oxygen consumption, and increased production of reactive oxygen species (ROS), which could enhance the therapeutic efficacy of radiotherapy. Meijer et al hypothesized that HIF-1 α is also a critical regulator of many of the genes responsible for alterations in glycolysis of the tumor, which drives therapeutic resistance. For example, Meijer et al²⁸ observed that HIF-1 α -mediated upregulation of GLUT-1 increased intracellular ATP, pyruvate, and lactate levels and, thus, induced glycolysis. Moreover, a study of Huang et al⁵¹ reported that this metabolic shift enhanced both the production of ATP through mechanisms that are independent of the mitochondria and confers resistance to receptor-interacting protein-dependent necroptosis in colorectal cancer cells (Table 1). Kim et al⁵² reported that HIF-1 α has been shown to both bind to the promoter of PDK3, the most active isoform of the PDK family, and to induce PDK3 expression levels, resulting in a switch from mitochondrial respiration to glycolysis. Furthermore, Lu et al⁴⁸ reported that HIF-1 α -mediated PDK3 upregulation both significantly inhibited cell apoptosis and increased resistance to either cisplatin or paclitaxel. According to previous studies, switching from mitochondrial respiration to glycolysis promotes tumor cells' survival; thus, these studies demonstrated that HIF-1 α could promote chemoresistance via the upregulation of PDK3. Maiso et al⁵³

recently demonstrated that HIF-1 α increased the expression of LDHA and glucose uptake and that specific inhibition of *LDHA* and *HIF1A* can restore sensitivity to therapeutic agents such as bortezomib in multiple myeloma cells (Table 1). This study confirmed that HIF-1 α reduced the efficacy of chemotherapeutic drugs by increasing the expression of LDHA. Luo et al⁵⁰ reported that PKM2 is also a transcriptional target of HIF-1 α and attaches directly with the HIF-1 α subunit and proposed that the inhibition of PKM2 could be used to sensitize hypoxic tumors to radio-/chemotherapy. In addition, Mazure et al⁵⁴ reported recently, HIF-1 α either blocked mitochondrial respiration or destroyed mitochondria via activation of PDK1, thus enhancing the cellular glycolytic metabolism and inducing cellular resistance to apoptosis. In conclusion, these findings indicated that HIF-1 α mediated alterations in cellular metabolism via regulating the activity of enzymes in the metabolic pathway, which plays a critical role in radio-/chemoresistance of tumor cells.

HIF-1 α -mediated inhibition of apoptosis in tumor cells under chemo-/radiotherapy

In regard to therapeutic resistance, Zhao et al⁵⁵ reported that chemo-/radiotherapy can induce cell apoptosis, which is considered a major mechanism in chemo-/radiotherapy's induced cell death. Thus, Zhao et al argues both that apoptosis impairment represents a key cause of chemo-/radioresistance and that apoptosis activation relies on distinct signaling pathways, which mainly refer to the extrinsic pathway and the intrinsic pathway. Krakstad and Chekenya⁵⁶ add that the extrinsic apoptosis pathway is activated upon ligand binding to death receptors (DR4/5, DcR2, and Fas), but the intrinsic pathway is triggered by signals such as DNA damage, oxidative stress, and growth factor deprivation, which are mainly regulated by the tissue trauma interactions by both proapoptotic and antiapoptotic proteins. Mohammad et al⁵⁷ proposed that both these pathways, extrinsic and intrinsic, are always highly deregulated in cancers and pathway deregulation could allow cancer cells to escape apoptosis resulting in both tumor survival and chemo-/radioresistance. These above observations confirmed that either defective apoptosis or changes in cell cycle regulation have a crucial role in chemo-/radioresistance in tumor cells.

HIF-1 α 's activation can elicit both pro- and antiapoptotic effects depending on the cellular context. Takasaki et al, in regard to therapeutic resistance, demonstrated that HIF-1 α both inhibited proapoptotic proteins and activated antiapoptotic proteins to inhibit the intrinsic cell death pathway. The

inhibited proapoptotic proteins and activated antiapoptotic proteins promote the survival of tumor cells under the chemo-/radiotherapy. For example, Takasaki et al reported that HIF-1 α induced the expression of both c-myc and survivin, which are two of many antiapoptotic proteins. Takasaki et al²⁷ reported that both c-myc and survivin, thereby, inhibited the apoptosis of lung cancer cells. Nishimoto et al⁵⁸ suggested about colon cancer that HIF-1 α inhibited the chemo-/radiotherapy-induced apoptosis of tumor cells through the promotion of antiapoptotic proteins (STAT3 and TCF4; Table 1). Rohwer et al, in a gastric cancer study, showed that HIF-1 α -mediated suppression of p53 activation occurred in response to the chemotherapeutic agent 5-fluorouracil. HIF-1 α -mediated suppression of p53 provides an interesting new angle as the suppressive effect of HIF-1 α on chemotherapy-induced apoptosis was dependent on a functional p53 pathway (Table 1).⁵⁹ Zhao et al recently, in a gastric cancer study, showed that after knockdown of HIF-1 α in gastric cancer cells, both the decreased expression of survivin and the increased expression of proapoptotic proteins (notably, Bax and caspase 3/8) were found. Furthermore, Zhao et al⁶⁰ proposed that chemo-/radiotherapy-induced apoptosis of tumor cells was significantly increased (Table 1). In addition, in human colon cancer cells, Pei et al reported that HIF-1 α decreased proapoptotic signaling by inhibiting the extrinsic cell death pathway, which allows cells to tolerate higher levels of chemotherapeutic injury before activating cellular death pathways. For example, Pei et al⁶¹ reported that HIF-1 α reduced the expression of proapoptotic signaling factors, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Taken together, the overall conclusion of these observations demonstrated that HIF-1 α is an important mediator of chemo-/radioresistance in solid tumors through regulating the cell apoptosis and indicated the function of HIF-1 α as an antagonist of apoptosis.

HIF-1 α -mediated activation of autophagy

Besides apoptosis, the process of autophagy is increasingly recognized as an important regulator in cell death. According to both Dalby et al⁶² and Song et al,⁶³ autophagy is a metabolic process in response to both hypoxia and metabolic stress, can produce ATP to avoid necrotic or apoptotic cell death, and has an emerging role in promoting the survival of tumor cells. Both Fang et al⁶⁴ and Li et al⁶⁵ wrote that similar to apoptosis, autophagy is also highly regulated and that multiple proteins are involved in the regulation of autophagy. For example, autophagy-related protein (ATG) is an important family of

proteins involved in autophagy regulation, the activation of autophagy is induced mainly by ATG1, ULK1, ATG13, and Beclin-1, and the formation of the autophagosome is induced by some other ATG proteins such as ATG6, ATG9, and LC3. Furthermore, Paggetti et al⁶⁶ reported that the activation of the mTOR/PI3K pair participates during the inhibition of autophagy. Sannigrahi et al⁶⁷ and Lei et al⁶⁸ reported that the activation of autophagy has an emerging role in inducing the therapy resistance in tumors. For example, Liu et al⁶⁹ reported that the functional inactivation of autophagy pathways results in significantly enhanced efficacy of chemo-/radiotherapy in melanoma cells. This study confirmed that the activation of autophagy plays an important role in the promotion of cell survival under the distressed microenvironment. HIF-1 α had primarily been characterized as a central regulator of hypoxia-induced autophagy; hypoxia-induced autophagy promotes the survival of tumor cells in a cytotoxic microenvironment, which is another crucial mechanism of chemo-/radioresistance in tumors.

A large number of studies demonstrated that HIF-1 α -mediated activation of autophagy is a crucial cause for the chemo-/radioresistance in tumor cells. For example, as BCL2 inhibits autophagy through interacting with Beclin-1. Sun et al's research suggested that HIF-1 α inhibited the expression of BCL2 through upregulating the expression of miRNA210 in colon cancer cells. The miRNA210 upregulation induced the activation of autophagy resulting in radioresistance (Table 1).⁷⁰ Recently, Wu et al wrote about the mechanism of resistance to cisplatin in lung cancer. Wu et al showed that HIF-1 α activated autophagy through increasing the expression of BNIP3 and Beclin-1 in lung cancer cells. Furthermore, Wu et al reported that when HIF-1 α inhibited the autophagy by using autophagy inhibitor 3-MA, the cisplatin-induced apoptosis of tumor cells was significantly increased. Wu et al's⁷¹ results suggested that HIF-1 α -mediated activation of autophagy can induce the resistance to cisplatin in lung cancer (Table 1). Consistent with previous outcomes, Zou et al⁷² reported that HIF-1 α also increased the expression of Beclin-1 through activation of the c-Jun pathway and suggested that the activated autophagy inhibits the radiotherapy-induced ROS in lung cancer cells (Table 1). Feng et al reported that the activity of autophagy was markedly enhanced in hypoxic osteosarcoma cells and reported that both the significantly increased expression of both HIF-1 α and LC3II were found and that a significant positive correlation between HIF-1 α and LC3II was observed (Table 1). Moreover, Feng et al³⁰ reported that HIF-1 α -activated autophagy inhibited radiotherapy-produced ROS,

which inhibited apoptosis of osteosarcoma cells. Jeong et al reported about the treatment of lung cancer with silver nanoparticles and drew similar conclusions. Jeong et al reported that HIF-1 α -induced autophagy had a role in the removal of ROS produced by silver nanoparticles in lung cancer cells. Jeong et al⁷³ reported the inhibited silver nanoparticle-induced death of tumor cells (Table 1). In addition, Lv et al⁷⁴ showed that the overexpression of the HIF-1 α activated autophagy through inhibiting mTOR/PI3K pathway in MSCs promotes survival of the MSCs under radiotherapy (Table 1). Most of the data above suggested that HIF-1 α -induced autophagy may play a crucially important role in promotion of tumor cells' survival under radiotherapy. Collectively, all these studies supported that HIF-1 α activates autophagy through the regulation of a variety of autophagy-related proteins, which has an important role in chemo-/radioresistance of tumor cells.

Table 1 shows that multiple mechanisms participate in HIF-1 α -induced chemo-/radioresistance in tumor cells; chemo-/radioresistance is a crucial problem in antineoplastic therapy. Many references in this review showed that HIF-1 α induced chemo-/radioresistance, not only through the regulation of DNA repair pathway, cellular metabolism, apoptosis, and autophagy, but also through enhanced expression of *MDR1*, thereby promoting multiple-drug resistance in tumors.¹⁵ Therefore, inhibiting the expression of HIF-1 α by targeted therapeutics is of great significance for improving chemo-/radiosensitivity in tumors.

Conclusion and prospects

Despite significant advances in recent years, therapy resistance and the consequential need for both superior medicines and novel therapeutic approaches remain the main obstacles in clinical antineoplastic therapy. Studies showed that microenvironment-related factors of tumor cells are the main cause for chemo-/radioresistance. Hypoxia is the most common and the most obvious feature in a solid tumor; HIF-1 α is a biomarker of the hypoxia microenvironment in a solid tumor. HIF-1 α protein expression has been detected in most types of solid tumors and is associated with increased tumor growth, vascularization, and metastasis. Furthermore, a large number studies showed that HIF-1 α has an emerging role in the chemo-/radioresistance of tumors and the mechanisms are complex. Recently, HIF-1 α -activated autophagy has been increasingly recognized as an important cause for chemo-/radioresistance of tumors. The research about autophagy enriches the cognition of the role of HIF-1 α in chemo-/radioresistance.

As HIF-1 α plays different roles in different organs and cancers under various stimuli, most of the studies demonstrated that the mechanisms of the roles of HIF-1 α in chemo-/radioresistance are different upon different treatments. However, some studies about lung cancer suggested that the mechanisms of HIF-1 α in the promotion of cells' survival under the same treatment (cisplatin) are also different. This observation illustrates that the chemo-/radioresistance–HIF-1 α -related network is complex and not quite clear, which require in-depth study. At least, it is now extensively accepted that HIF-1 α plays a central role in chemo-/radioresistance and HIF-1 α inhibition provides effective anticancer advantages that can reverse chemo-/radioresistance. Therefore, pharmacological HIF-1 α inhibition is necessary for reversing chemo-/radioresistance in tumors. However, whether the inhibition of HIF-1 α in tumor cells turns out to be beneficial for tumor therapy has still not been reported. Future research and more tumor models in immunocompetent animals are needed for testing the inhibition of HIF-1 α in clinical antitumor therapeutics.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, vJemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
- Cao W, Gu Y, Meineck M, Xu H. The combination of chemotherapy and radiotherapy towards more efficient drug delivery. *Chem Asian J*. 2014;9(1):48–57.
- Prasad NR, Muthusamy G, Shanmugam M, Ambudkar SV. South Asian medicinal compounds as modulators of resistance to chemotherapy and radiotherapy. *Cancers (Basel)*. 2016;8(3):E32.
- Rueff J, Rodrigues AS. Cancer drug resistance. A brief overview from a genetic viewpoint. *Methods Mol Biol*. 2016;1395:1–18.
- Gatti L, Zunino F. Overview of tumor cell chemoresistance mechanisms. *Methods Mol Med*. 2005;111:127–148.
- Kartal-Yandim M, Adan-Gokbulut A, Baran Y. Molecular mechanisms of drug resistance and its reversal in cancer. *Crit Rev Biotechnol*. 2016; 36(4):716–726.
- Gottesman MM. Mechanisms of cancer drug resistance. *Annu Rev Med*. 2002;53(1):615–627.
- Verduzco D, Lloyd M, Xu L, et al. Intermittent hypoxia selects for genotypes and phenotypes that increase survival, invasion, and therapy resistance. *PLoS One*. 2015;10(3):e0120958.
- Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia (Auckl)*. 2015;3:83–92.
- Liang Y, Zheng T, Song R, et al. Hypoxia-mediated sorafenib resistance can be overcome by EF24 through Von Hippel-Lindau tumor suppressor-dependent HIF-1 α inhibition in hepatocellular carcinoma. *Hepatology*. 2013;57(5):1847–1857.
- Wang G, Wang JJ, Fu XL, Guang R, To ST. Advances in the targeting of HIF-1 α and future therapeutic strategies for glioblastoma multiforme (review). *Oncol Rep*. 2017;37(2):657–670.
- Ding Z, Yang L, Xie X, et al. Expression and significance of hypoxia-inducible factor-1 alpha and MDR1/P-glycoprotein in human colon carcinoma tissue and cells. *J Cancer Res Clin Oncol*. 2010;136(11): 1697–1707.
- Wu D, Potluri N, Lu J, Kim Y, Rastinejad F. Structural integration in hypoxia-inducible factors. *Nature*. 2015;524(7565):303–308.
- Lixia J, Shaohua S, Qiaofa S, Feng L, Sijun L. Expression and correlation of hypoxia inducible factor HIF-1 α and HIF-2 α in cervical carcinoma. *J Pract Med*. 2012;28:1942–1943.
- Dong ZZ, Yao M, Wang L, Wu W, Gu X, Yao DF. Hypoxia-inducible factor-1alpha: molecular-targeted therapy for hepatocellular carcinoma. *Mini Rev Med Chem*. 2013;13(9):1295–1304.
- Greco O, Scott S. Tumor hypoxia and targeted gene therapy. *Int Rev Cytol*. 2007;257:181–212.
- Li Y, Li C, Shi H, Lou L, Liu P. The association between the rs11549465 polymorphism in the hif-1 α gene and cancer risk: a meta-analysis. *Int J Clin Exp Med*. 2015;8(2):1561–1574.
- Jiang LX, Shi QF, Shi SH, Li F, Liu SJ. Expression of hypoxia inducible factor-2 alpha in cervical squamous cell carcinoma and their clinical significance. *Lab Med*. 2012;27:819–821.
- Liu ZJ, Semenza GL, Zhang HF. Hypoxia-inducible factor 1 and breast cancer metastasis. *J Zhejiang Univ Sci B*. 2015;16(1):32–43.
- Zhang W, Shi X, Peng Y, et al. HIF-1 α promotes epithelial-mesenchymal transition and metastasis through direct regulation of ZEB1 in colorectal cancer. *PLoS One*. 2015;10(6):e0129603.
- Chen L, Shi Y, Yuan J, et al. HIF-1 alpha overexpression correlates with poor overall survival and disease-free survival in gastric cancer patients post-gastrectomy. *PLoS One*. 2014;9(3):e90678.
- Ioannou M, Paraskeva E, Baxevanidou K, et al. HIF-1 α in colorectal carcinoma: review of the literature. *J BUON*. 2015;20(3):680–689.
- Rezvani HR, Ali N, Nissen LJ, et al. HIF-1 α in epidermis: oxygen sensing, cutaneous angiogenesis, cancer, and non-cancer disorders. *J Invest Dermatol*. 2011;131(9):1793–1805.
- Zhao Q, Li Y, Tan BB, Fan LQ, Yang PG, Tian Y. HIF-1 α induces multidrug resistance in gastric cancer cells by inducing MiR-27a. *PLoS One*. 2015;10(8):e0132746.
- Wang R, Cheng L, Xia J, Wang Z, Wu Q, Wang Z. Gemcitabine resistance is associated with epithelial-mesenchymal transition and induction of HIF-1 α in pancreatic cancer cells. *Curr Cancer Drug Targets*. 2014;14(4):407–417.
- Gao H, Xie J, Peng J, et al. Hispidulin inhibits proliferation and enhances chemosensitivity of gallbladder cancer cells by targeting HIF-1 α . *Exp Cell Res*. 2015;332(2):236–246.
- Takasaki C, Kobayashi M, Ishibashi H, Akashi T, Okubo K. Expression of hypoxia-inducible factor-1 α affects tumor proliferation and antiapoptosis in surgically resected lung cancer. *Mol Clin Oncol*. 2016;5(2):295–300.
- Meijer TW, Kaanders JH, Span PN, Bussink J. Targeting hypoxia, HIF-1, and tumor glucose metabolism to improve radiotherapy efficacy. *Clin Cancer Res*. 2012;18(20):5585–5594.

29. Unruh A, Ressel A, Mohamed HG, et al. The hypoxia-inducible factor-1 alpha is a negative factor for tumor therapy. *Oncogene*. 2003;22(21):3213–3220.
30. Feng H, Wang J, Chen W, et al. Hypoxia-induced autophagy as an additional mechanism in human osteosarcoma radioresistance. *J Bone Oncol*. 2016;5(2):67–73.
31. Yang SF, Chang CW, Wei RJ, Shiue YL, Wang SN, Yeh YT. Involvement of DNA damage response pathways in hepatocellular carcinoma. *Biomed Res Int*. 2014;1:153867.
32. Stover EH, Konstantinopoulos PA, Matulonis UA, Swisher EM. Biomarkers of response and resistance to DNA repair targeted therapies. *Clin Cancer Res*. 2016;22(23):5651–5660.
33. Fortini P, Ferretti C, Dogliotti E. The response to DNA damage during differentiation: pathways and consequences. *Mutat Res*. 2013;743–744(341):160–168.
34. Li L, Zhu T, Gao YF, et al. Targeting DNA damage response in the radio(chemo)therapy of non-small cell lung cancer. *Int J Mol Sci*. 2016;17(6):E839.
35. Um JH, Kang CD, Bae JH, et al. Association of DNA-dependent protein kinase with hypoxia inducible factor-1 and its implication in resistance to anticancer drugs in hypoxic tumor cells. *Exp Mol Med*. 2004;36(3):233–242.
36. Liu Y, Bernauer AM, Yingling CM, Belinsky SA. HIF1 α regulated expression of XPA contributes to cisplatin resistance in lung cancer. *Carcinogenesis*. 2012;33(6):1187–1192.
37. Wrann S, Kaufmann MR, Wirthner R, Stiehl DP, Wenger RH. HIF mediated and DNA damage independent histone H2AX phosphorylation in chronic hypoxia. *Biol Chem*. 2013;394(4):519–528.
38. Logsdon DP, Grimard M, Luo M, et al. Regulation of HIF1 α under hypoxia by APE1/Ref-1 impacts CA9 expression: dual targeting in patient-derived 3D pancreatic cancer models. *Mol Cancer Ther*. 2016;15(11):2722–2732.
39. Rezaeian AH, Wang YH, Lin HK. DNA damage players are linked to HIF-1 α /hypoxia signaling. *Cell Cycle*. 2017;16(8):725–726.
40. Wirthner R, Wrann S, Balamurugan K, Wenger RH, Stiehl DP. Impaired DNA double-strand break repair contributes to chemoresistance in HIF-1 alpha-deficient mouse embryonic fibroblasts. *Carcinogenesis*. 2008;29(12):2306–2316.
41. Shenoy N, Dronca R, Quevedo F, et al. Low hypoxia inducible factor-1 α (HIF-1 α) expression in testicular germ cell tumors – a major reason for enhanced chemosensitivity? *Chin J Cancer Res*. 2017;29(4):374–378.
42. Jin W, Wang J, Xu S, et al. Radioprotective effect on HepG2 cells of low concentrations of cobalt chloride: induction of hypoxia-inducible factor-1 alpha and clearance of reactive oxygen species. *J Radiat Res*. 2012;54(2):203–209.
43. Klein O, Rohwer N, de Molina KF, et al. Application of two-dimensional gel-based mass spectrometry to functionally dissect resistance to targeted cancer therapy. *Proteomics Clin Appl*. 2013;7(11–12):813–824.
44. Sugrue T, Lowndes NF, Ceredig R. Hypoxia enhances the radioresistance of mouse mesenchymal stromal cells. *Stem Cells*. 2014;32(8):2188–2200.
45. Tan W, Zhong Z, Wang S, et al. The typical metabolic modifiers conferring improvement in cancer resistance. *Curr Med Chem*. 2017;24(34):3698–3710.
46. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? *Nat Rev Cancer*. 2004;4(11):891–899.
47. Liu Y, Cao Y, Zhang W, et al. A small-molecule inhibitor of glucose transporter 1 downregulates glycolysis, induces cell-cycle arrest, and inhibits cancer cell growth in vitro and in vivo. *Mol Cancer Ther*. 2012;11(8):1672–1682.
48. Lu CW, Lin SC, Chien CW, et al. Overexpression of pyruvate dehydrogenase kinase 3 increases drug resistance and early recurrence in colon cancer. *Am J Pathol*. 2011;179(3):1405–1414.
49. Zhou M, Zhao Y, Ding Y, et al. Warburg effect in chemosensitivity: targeting lactate dehydrogenase-A re-sensitizes taxol-resistant cancer cells to taxol. *Mol Cancer*. 2010;9:33.
50. Luo W, Semenza GL. Emerging roles of PKM2 in cell metabolism and cancer progression. *Trends Endocrinol Metab*. 2012;23(11):560–566.
51. Huang CY, Kuo WT, Huang YC, Lee TC, Yu LC. Resistance to hypoxia-induced necroptosis is conferred by glycolytic pyruvate scavenging of mitochondrial superoxide in colorectal cancer cells. *Cell Death Dis*. 2013;4:e622.
52. Kim J, Tchermyshev I, Semenza GL, Dang CV. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab*. 2006;3(3):177–185.
53. Maiso P, Huynh D, Moschetta M, et al. Metabolic signature identifies novel targets for drug resistance in multiple myeloma. *Cancer Res*. 2015;75(10):2071–2082.
54. Mazure NM, Brahimi MC, Pouyssegur J. Hypoxic mitochondria: accomplices in resistance. *Bull Cancer*. 2011;98(5):40–46.
55. Zhao J, Feng D, Yang L, Shen G, Zheng F, Xu B. The emerging role of hypoxia-inducible factor-2 involved in chemo/radioresistance in solid tumors. *Cancer Treat Rev*. 2015;41(7):623–633.
56. Krakstad C, Chekenya M. Survival signalling and apoptosis resistance in glioblastomas: opportunities for targeted therapeutics. *Mol Cancer*. 2010;9(1):135.
57. Mohammad RM, Muqbil I, Lowe L, et al. Broad targeting of resistance to apoptosis in cancer. *Semin Cancer Biol*. 2015;35(Suppl):S78–S103.
58. Nishimoto A, Kugimiya N, Hosoyama T, Enoki T, Li TS, Hamano K. HIF-1 α activation under glucose deprivation plays a central role in the acquisition of anti-apoptosis in human colon cancer cells. *Int J Oncol*. 2014;44(6):2077–2084.
59. Rohwer N, Dame C, Haugstetter A, et al. Hypoxia-inducible factor 1alpha determines gastric cancer chemosensitivity via modulation of p53 and NF-kappaB. *PLoS One*. 2010;5(8):e12038.
60. Zhao Q, Tan BB, Li Y, Fan LQ, Yang PG, Tian Y. Enhancement of drug sensitivity by knockdown of HIF-1 α in gastric carcinoma cells. *Oncol Res*. 2016;23:129–136.
61. Pei GT, Wu CW, Lin WW. Hypoxia-induced decoy receptor 2 gene expression is regulated via a hypoxia-inducible factor 1alpha-mediated mechanism. *Biochem Biophys Res Commun*. 2010;391(2):1274–1279.
62. Dalby KN, Tekedereli I, Lopez-Berestein G, Ozpolat B. Targeting the prodeath and prosurvival functions of autophagy as novel therapeutic strategies in cancer. *Autophagy*. 2010;6(3):322–329.
63. Song L, Liu S, Liang Z, et al. MiR-21 modulates radiosensitivity of cervical cancer through inhibiting autophagy via the PTEN/Akt/HIF-1 α feedback loop and the Akt-mTOR signaling pathway. *Tumour Biol*. 2016;37(9):12161–12168.
64. Fang Y, Tan J, Zhang Q. Signaling pathways and mechanisms of hypoxia-induced autophagy in the animal cells. *Cell Biol Int*. 2015;39(8):891–898.
65. Li ZY, Yang Y, Ming M, Liu B. Mitochondrial ROS generation for regulation of autophagic pathways in cancer. *Biochem Biophys Res Commun*. 2011;414(1):5–8.
66. Paggetti J, Viry E, Berchem G, Moussay E, Janji B. Hypoxia-induced autophagy in tumor cells: a key target for improving cancer immunotherapy. *Cancer Cell Microenviron*. 2014;1:e213.
67. Sannigrahi MK, Singh V, Sharma R, Panda NK, Khullar M. Role of autophagy in head and neck cancer and therapeutic resistance. *Oral Dis*. 2015;21(3):283–291.
68. Lei Y, Zhang D, Yu J, Dong H, Zhang J, Yang S. Targeting autophagy in cancer stem cells as an anticancer therapy. *Cancer Lett*. 2017;393:33–39.
69. Liu H, He Z, Simon HU. Targeting autophagy as a potential therapeutic approach for melanoma therapy. *Semin Cancer Bio*. 2013;23(5):352–360.
70. Sun Y, Xing X, Liu Q, et al. Hypoxia-induced autophagy reduces radiosensitivity by the HIF-1 α /miR-210/Bcl-2 pathway in colon cancer cells. *Int J Oncol*. 2015;46(2):750–756.
71. Wu HM, Jiang ZF, Ding PS, Shao LJ, Liu RY. Hypoxia-induced autophagy mediates cisplatin resistance in lung cancer cells. *Sci Rep*. 2015;5:12291.

72. Zou YM, Hu GY, Zhao XQ, et al. Hypoxia-induced autophagy contributes to radioresistance via c-Jun-mediated Beclin1 expression in lung cancer cells. *J Huazhong Univ Sci Technolog Med Sci.* 2014; 34(5):761–767.
73. Jeong JK, Gurunathan S, Kang MH, et al. Hypoxia-mediated autophagic flux inhibits silver nanoparticle-triggered apoptosis in human lung cancer cells. *Sci Rep.* 2016;6:21688.
74. Lv B, Hua T, Li F, et al. Hypoxia-inducible factor 1 α protects mesenchymal stem cells against oxygen-glucose deprivation-induced injury via autophagy induction and PI3K/AKT/mTOR signaling pathway. *Am J Transl Res.* 2017;9(5):2492–2499.

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