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Review

Role of tumor hypoxia in acquisition of resistance to microtubule-stabilizing drugs

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ABSTRACT

Microtubules, an important cytoskeletal protein involved in mitotic and non-mitotic functions of cells, are important targets in cancer therapy. Microtubule-stabilizing drugs like the taxanes are critical adjuvant and palliative first-line therapies for the treatment of early, advanced and metastatic solid tumors of different lineages. Their adverse on- and off-target effects and high susceptibility to multidrug resistance, however, are major challenges encountered in the clinic in the treatment of solid cancers. Although biochemical resistance to microtubule-stabilizing drugs has been well characterized, molecular mechanisms that contribute to clinical resistance to taxanes in solid tumors still remain poorly understood and uncontrolled. The heterogeneous tumor microenvironment leads to greater diversity of resistance mechanisms to taxanes. Tumor hypoxia, a prominent feature of solid tumors, results in a broad range of effects on a number of cellular pathways and is one of the major contributors to the development of resistance to not only microtubule-stabilizing drugs but also other anticancer drugs. In this review, we highlight the potential role of hypoxia in the development of resistance to taxanes through mechanisms that involve altering the cell cycle, changing the properties of microtubules, and inducing the overexpression of gene products that contribute to drug resistance. Hypoxia-induced challenges described in this review are not limited to microtubule-stabilizing drugs alone, but in many cases also impact on treatment with non-microtubule-targeting anticancer drugs.

Contents

Abbreviations: 2-ME, 2-methoxyestradiol; CAIX, carbonic anhydrase IX; CSC, cancer stem cell; Dtx, docetaxel; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FIH-1, factor inhibiting HIF-1; GSCs, glioma stem cells; HIF-1, hypoxia-inducible factor-1; HRE, hypoxia response element; MDR, multidrug resistance; miRNA, microRNA; MMAE, monomethyl auristatin E; MT, microtubule; MSA, microtubule-stabilizing agent; MTA, microtubule-targeting agent; mTOR, mammalian target of rapamycin; PHD, prolylhydroxylase domain; pHe, extracellular pH; pHi, intracellular pH; P-gp, P-glycoprotein; Ptx, paclitaxel; Sirt2, sirtuin 2; TUBB3, class βIII-tubulin; VEGF, vascular endothelial growth factor

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1. Introduction

Microtubules (MTs) are ubiquitous, hollow cylindrical cytoskeletal protein polymers that have diverse roles in eukaryotic cells. Due to their pivotal position in mitotic and non-mitotic functions of cells, they are one of the most important targets in cancer therapy. Classical MT-stabilizing agents (MSAs) like the taxanes are adjuvant and palliative therapies for the treatment of early, advanced and metastatic cancers of the breast, ovary, lung, and head and neck, as well as other solid tumors [1,2]. Although MSAs have proven to be useful in the clinic, their dose-limiting toxicities and high susceptibility to multidrug resistance (MDR) are major challenges to improve MSA-based chemotherapy.

The biochemical mechanisms that contribute to taxane resistance under normoxic conditions have been well characterized in cancer cells. These mechanisms include overexpression of drug efflux pumps, metabolism or conjugation of drugs, switching of expression to tubulin isotypes that are less susceptible, especially βIII-tubulin (TUBB3), altered interactions with MT-associated proteins such as tau, stathmin, MAP2, and MAP4, mutations in taxane binding sites, and changes to cytoskeletal structures [3–8]. In solid tumors, even greater diversity of resistance mechanisms exists, presumably stemming from the heterogeneous tumor microenvironment [9]. Accordingly, molecular mechanisms of clinical resistance to taxanes still remain poorly understood and uncontrolled [10].

The abnormal vasculature of solid tumors and the resulting limited supply of nutrition and oxygen create hypoxic regions that affect cancer progression and contribute to the resistance to chemotherapy and radiotherapy [11,12]. Tumor hypoxia has a broad effect on a number of cellular pathways and is one of the major contributors to the development of resistance to MT-targeting drugs (MTAs) and other anticancer drugs [13]. Herein, we review the potential role of hypoxia in the development of resistance to taxanes through mechanisms that involve altering the cell cycle, changing the properties of MTs, and inducing the overexpression of gene products that contribute to drug resistance. Hypoxia-induced challenges described in this review are not limited to taxanes alone, but in many cases also impact on treatment with non-MT targeting anticancer drugs.

2. Tumor hypoxia and hypoxia-inducible factor-1

Responses to hypoxia are mediated by hypoxia-inducible factor-1 (HIF-1), a protein heterodimer overexpressed in over 50% of solid tumors as a result of the hypoxic conditions inside the tumor (Table 1) [14,15]. Accordingly, HIF-1-positive patients in the clinic show significantly low 5-year survival rates compared to HIF-1-negative patients [14]. Necrotic regions of tumors show high levels of HIF-1α, indicating HIF-1α levels are regulated by tumor oxygenation (Fig. 1).

HIF-1 consists of two subunits, a constitutively expressed HIF-1β and an oxygen-sensitive HIF-1α. At low oxygen concentrations, HIF-1α dimerizes with HIF-1β, and the heterodimer acts as a hypoxic transcription factor, binding to the hypoxia response element (HRE) and activating or inhibiting multiple pathways that assist the cell to survive in a hypoxic environment [27,28] (Fig. 2). The coactivators, E1A binding protein p300 (P300) and CREB-binding protein (CBP), also interact with the HIF-1 heterodimer to activate transcription. Under normoxic conditions, HIF-1α is maintained at low levels by degradation in the proteasome, a process controlled by prolylhydroxylase domain (PHD) and factor inhibiting HIF-1 (FIH-1) proteins. PHD proteins act as oxygen sensors, hydroxylating the oxygen-dependent degradation domain of HIF-1α in normoxia and allowing VHL E3 ligase (von Hippel–Lindau E3 ligase tumor suppressor) to tag the protein for destruction [28]. A major theme of HIF-1α action is to reduce metabolism to protect cells under low oxygen conditions. Thus, HIF-1α translocates to the nucleus, forms a heterodimer with HIF-1β and inhibits ribosomal protein synthesis and mTOR (mammalian target of rapamycin) activation and its downstream effects, a protective response that also occurs in nutrient-limiting conditions [27]. AMP-activated protein kinase is stimulated by HIF-1 and plays an important role in altering metabolism during starvation to prevent the death of the cell. Targets of HIF-1, among many others, include glucose transporter genes, vascular endothelial growth factor (VEGF), platelet-derived growth factor, erythropoietin, and carbonic anhydrase IX (CAIX) [29–31].

In addition to the metabolic changes seen in response to HIF-1, the HIF-1 heterodimer also triggers the transcription of gene products that are associated with resistance to anticancer agents [32]. HIF-1α overexpression is associated with resistance to paclitaxel (Ptx), although another taxane, docetaxel (Dtx), downregulates the expression of HIF-1α in cancer cells [33]. Thus, Dtx, as an anti-HIF-1α agent and MSA, has been used to treat advanced hormone-refractory prostate tumors that show overexpression of HIF-1α [33]. Overexpression of HIF-1α in laryngeal cancer cells increases resistance to taxane-induced apoptosis through development of the MDR phenotype [34]. Downregulation of HIF-1α by siRNA improves accumulation and retention of doxorubicin, a non-MTA, DNA-damaging agent that, like taxanes, is also susceptible to MDR.

Altered expression of microRNA (miRNA) is known to play a significant role in the development of resistance to taxanes in the clinic [35,36]. Interestingly, a number of miRNAs are induced by HIF-1α in hypoxic conditions [37,38]. In addition to miRNA, tumor-infiltrating immune cells in the tumor microenvironment are also associated with resistance to anticancer agents in the clinic. Recent evidence suggests that hypoxia modulates the function and activity of immune cells, potentially implicating hypoxia-immune cell interactions in the development of resistance to anticancer drugs in solid tumors [39].

Expression of HIF-1α is not limited to hypoxic conditions since MAPK and PI3K pathway-mediated expression of HIF-1α has also been reported in normoxic conditions [40]. Transient overexpression of HIF-1α increases the invasive potential of melanoma that normally express low levels of endogenous HIF-1α. In contrast, siRNA downregulation of HIF-1α decreases anchorage-independent growth and Matrigel® invasion of highly metastatic melanoma cells that overexpress HIF-1α in normoxic conditions. The mechanisms by which HIF-1α signaling leads to acquisition of resistance to MSAs remain highly debatable; however, it is clear that HIF-1α-mediated activation of downstream pathways plays a significant role in development of MDR in the clinic [41].

Table 1
Expression of HIF-1α in various solid tumors.

Tumor type	HIF-1α level	References
Oropharyngeal	94%	[16]
Cervical	94%	[17]
Borderline ovarian	88%	[18]
Early-stage invasive cervical	81%	[19]
Oligodendroglioma	80%	[20]
Breast, lymph node-positive	76%	[21]
Ovarian	69%	[18]
Non-small cell lung cancer	62%	[22]
Breast	57%	[23]
Endometrial	49%	[24]
Head and neck	47%	[23]
Bladder	38%	[23]
Gastrointestinal stromal	32%	[25]

3. Altered MT dynamics and expression of class III β-tubulin in MSA-resistant hypoxic cells

There is evidence that hypoxia has significant effects on the changes in MT dynamics induced by an MSA. This effect may be due to conformational changes in tubulin that alter its susceptibility to MSAs. For example, hypoxia stabilizes MTs in tumor cells and increases their resistance to vincristine-induced disassembly via an early growth response 1

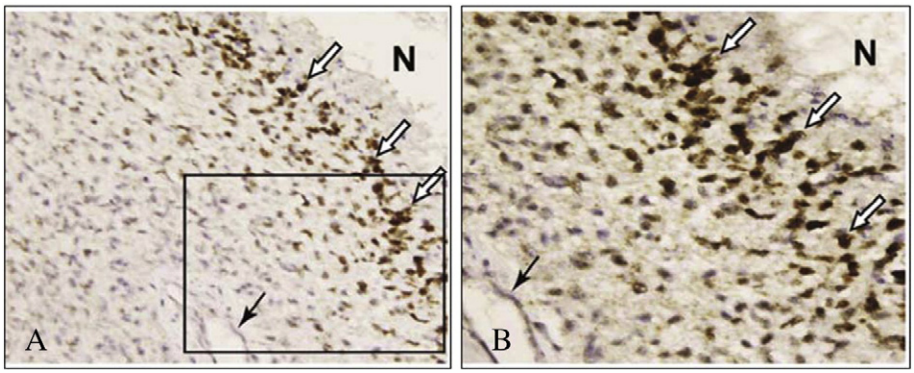

Fig. 1. HIF-1α expression in glioblastoma. Immunohistochemistry sections of human glioblastoma multiforme (A) showing high expression of HIF-1α near necrotic areas (white arrows) with pseudopalisading tumor cells, suggesting HIF-1α expression levels are modified by oxygenation of the tumor. Hyperplastic vessels indicated by black arrows are unstained with HIF-1α. (B) Shows the magnified area outlined by the box in A. 'N' indicates necrotic areas. A, ×100 and B, ×400. Images have been reproduced with modifications from Zagzag et al. [26] with permission.

(Egr-1)-dependent pathway [42]. Hypoxia-induced transcription of Egr-1 is known to be involved in drug resistance in a variety of cancers. Additionally, hypoxia-induced inhibition of glycogen synthase kinase-3 in MDA-MB-231 cells causes hyperstabilization of MTs and results in defective intracellular trafficking [43]. The hyperstabilized MTs confer resistance to MT-destabilizing agents like vinblastine and vincristine. Moreover, these hyperstabilized MTs in the tumor cells affect invasive and metastatic behavior of cells by inhibiting the MT functions required for cell migration.

In the clinic, overexpression of TUBB3 is indicative of highly metastatic tumors that are resistant to treatment with MTAs like Ptx, Dtx, and vinorelbine [44–47]. These changes in βIII-tubulin are clinically relevant [6], and patient survival rate is much higher in gastric cancers with low levels of TUBB3 [47]. In addition to resistance to MSAs, TUBB3 overexpression also makes cells resistant to DNA damaging drugs like cisplatin and doxorubicin [48]. Under hypoxic conditions, cells recruit Pim-1, a serine/threonine-protein kinase proto-oncogene, into the cytoskeleton and trigger signaling cascades for cell survival and drug resistance. In

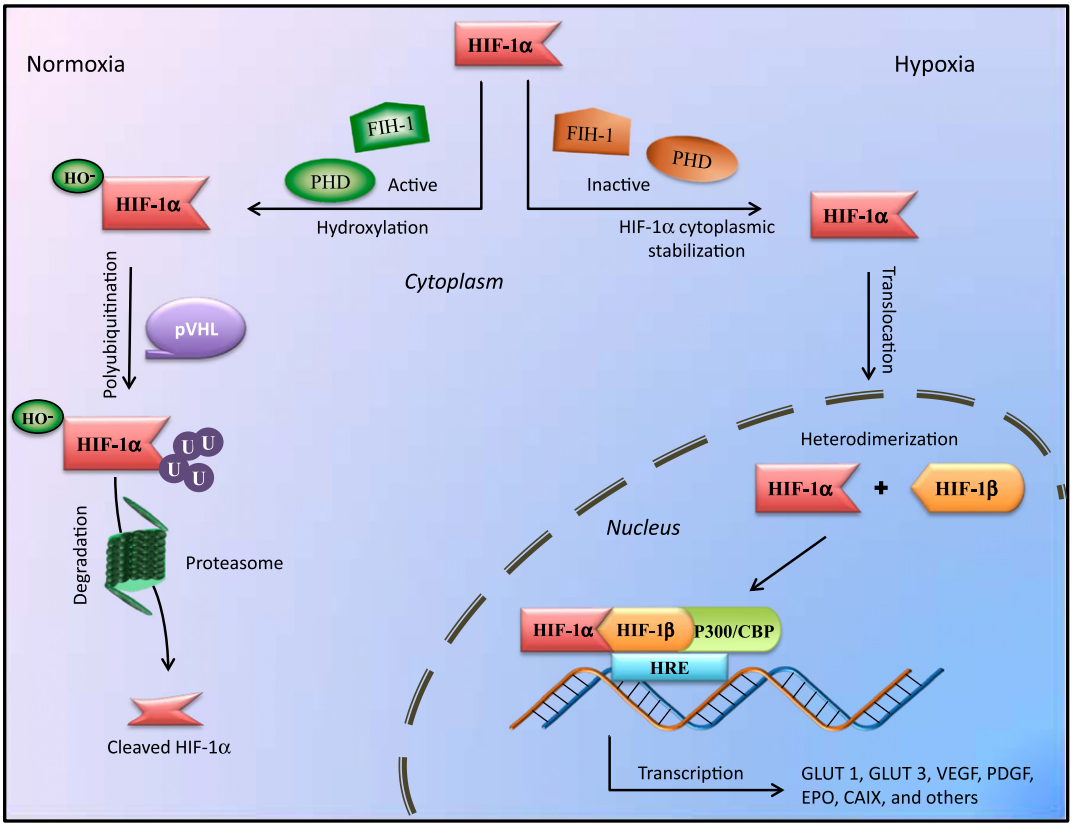

Fig. 2. HIF-1α pathway in normal and hypoxic conditions. HIF-1 consists of two subunits, a constitutively expressed HIF-1β and an oxygen-sensitive HIF-1α. In hypoxia, inactive HIF hydroxylases result in HIF-1α cytoplasmic stabilization and translocation to the nucleus. In the nucleus, HIF-1α heterodimerizes with HIF-1β and binds to the hypoxia response element (HRE) in the presence of p300-CBP transcription coactivator. This activates or inhibits multiple pathways that assist the cell to survive in the hypoxic environment. Under normoxic conditions, HIF-1α is maintained at low levels by degradation in the proteasome. Prolylhydroxylase domain (PHD) and factor inhibiting HIF-1 (FIH-1) proteins act as oxygen sensors and hydroxylate the oxygen-dependent degradation domain of HIF-1α. Following hydroxylation, VHL E3 ligase (pVHL)-mediated polyubiquitination of HIF-1α results in proteasomal degradation.

fact, TUBB3/Pim-1 negative patients respond to treatment; whereas, TUBB3/Pim-1 positive patients do not [49]. Studies with cells isolated from primary tumors clearly show that tumors expressing high levels of TUBB3 are less sensitive to taxane- and vinorelbine-based therapies [45,47,50,51]. Hypoxia increases expression of TUBB3 at both the protein and mRNA levels in ovarian and prostate cancer cells, and these changes are associated with a corresponding resistance to taxanes [52,53]. In support of this, it was shown that tubulin isolated from cells pre-exposed to hypoxia are resistant to Ptx-induced tubulin polymerization *in vitro* [53]. CpG methylation of the HRE blocked transcription factor binding, causing downregulation of TUBB3 expression and increased sensitivity to Ptx [53]. The effect of HIF-1α on cancer cell sensitivity to Ptx also occurs in normoxic conditions. Ptx-sensitive lung cancer cells in normoxia become resistant to Ptx when HIF-1α is overexpressed [54].

HIF-1α can indirectly regulate MT dynamics through its activity on HIF-1 downstream targets like Myc-nick and survivin. It has been reported that Myc-nick, an inactive c-Myc cleavage product of calpin proteolysis, interacts with both α- and β-tubulin and directly regulates α-tubulin acetylation by recruiting Gcn5 histone acetyltransferase to MTs [55]. Under hypoxic conditions, Myc-nick-induced α-tubulin acetylation makes MTs resistant to destabilization by nocodazole [56]. In addition to Myc-nick, the antiapoptotic protein survivin is also implicated in a direct modulation of MT dynamics and regulates key mitotic events like spindle and interphase MT organization, assembly of the spindle checkpoint, and cytokinesis [57]. Bearing in mind the multifaceted effects of HIF-1α, it can be speculated that hypoxia-regulated induction of HIF-1α, which triggers survivin expression and cleavage of Myc to Myc-nick, indirectly regulates MT dynamics and the cell's response to MSAs in hypoxia.

4. The role of cell cycle and autophagy in MSA resistance in hypoxia

Although inhibition of non-mitotic functions by MSAs in solid tumors is now being considered as one of the alternative routes to cell death [58,59], most studies have investigated the prominent antimitotic effect of MSAs on rapidly dividing cancer cells [60]. An immediate effect of hypoxia is the cessation of normal metabolic activities, resulting in G_1 cell cycle arrest [61–63] (Fig. 3). Solid tumors with a hypoxic core consist mainly of proliferation-arrested cells that are resistant to cell cycle-specific drugs but not drugs like bortezomib or doxorubicin that work independently of the cell cycle [64]. G_1-arrested melanoma cells that are quiescent under hypoxia can evade the cytotoxic effects of MAPK inhibitors, later switching to actively dividing cells upon return to normoxic conditions [62].

Huang et al. [65] showed that A2780 ovarian cancer cells when exposed to hypoxic conditions are less sensitive to Ptx due to HIF-1α-induced arrest of cells in G_0/G_1 phase of the cell cycle. Knockdown of HIF-1 reverses hypoxia-induced cell cycle arrest and resistance to Ptx, suggesting that hypoxia alters pathways that affect the mitotic route of Ptx-induced cytotoxicity [65,66]. Dong et al. [67] found that in human MCF7 breast cancer cells, hypoxia decreased the extent of Ptx-induced arrest in G_2/M phase by inhibiting Ptx-induced tubulin polymerization and expression of cyclin B1, a cell cycle protein involved in G_2/M progression. Upregulation of cyclin B1 blocked these hypoxia-induced effects of Ptx. Similarly, HIF-1α-induced downregulation of cyclin D1 and a corresponding inhibition of G_1/S transition make lung cancer cells resistant to 5-fluorouracil-mediated apoptosis and assist in survival in hypoxic conditions [68]. With hypoxia, a switch from apoptosis to autophagy, corresponding to a G_1/S arrest, contributes to

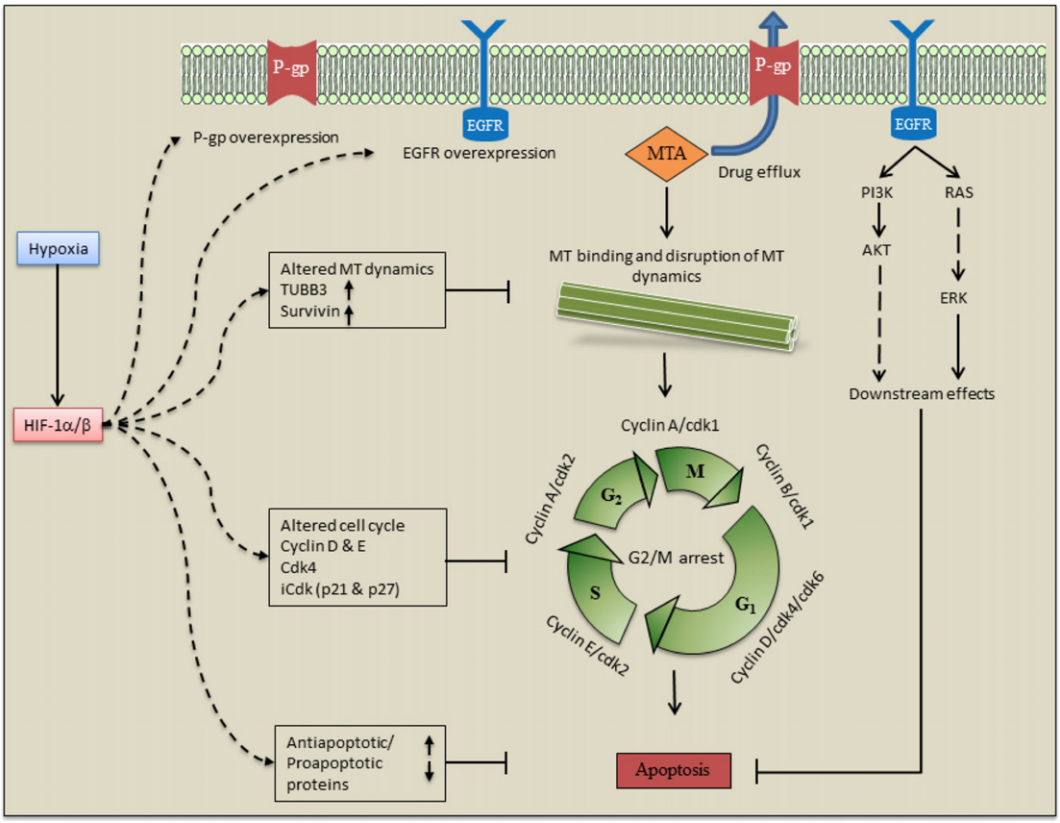

Fig. 3. HIF-1α-mediated cell resistance pathways. HIF-1α is a master regulator of numerous pathways that directly or indirectly trigger cell resistance to MTAs. HIF-1α-induced altered expression of P-gp, TUBB3, survivin, and pro- and antiapoptotic proteins directly alter the response of cancer cells to MTAs in hypoxia. Overexpression of EGFR in hypoxia modulates drug sensitivity in hypoxic cancer cells by downstream effects that alter apoptotic and cell survival pathways in response to MTAs. iCdk is inhibitor of Cdk.

cell survival following Ptx treatment [69]. Interestingly, some cell types appear to maintain proliferative activity under hypoxic conditions; however, the precise mechanism by which cells continue to divide in hypoxia remains unresolved [70]. One of the views is that HIF-1α interacts with cyclin-dependent kinases (cdk) and blocks cdk1-mediated-lysosomal degradation of HIF-1α during G_1 to S phase transition in the cell cycle (Fig. 3). Blocking lysosomal degradation of HIF-1α results in hypoxia-induced cell cycle arrest, suggesting that cells under hypoxic conditions maintain proliferation through the lysosomal pathway of HIF-1α degradation [70].

Autophagy, an alternative to apoptosis in cell cycle-arrested hypoxic cells, has been closely associated with development of resistance to chemotherapeutic drugs like Ptx and cisplatin [69,71–73]. Under nutrient-deprived conditions, autophagy provides energy for cells to survive and directs them away from caspase-mediated apoptotic pathways. Cases of reduced caspase expression, especially caspase 3, may be linked to the switch to an autophagy pattern of cell death. MDA-MB-231 human breast cancer cells treated with Ptx activate autophagy as a protective measure to prevent cell death. Notte et al. [69] showed that in normoxic conditions, the autophagy response can become saturated or maximal, resulting in apoptosis. However, in hypoxic conditions, autophagy continues without the switch to apoptosis, resulting in protection of the MDA-MB-231 cells to Ptx-induced killing. Treatment of glioblastoma xenografts in mice with the anti-VEGF drug bevacizumab on its own results in induction of autophagy due to hypoxia. If bevacizumab is given in combination with the autophagy inhibitor chloroquine, it significantly reduces tumor growth [74].

These findings implicate the autophagy-lysosomal degradation pathway in cancer cells as a potential drug target for the treatment of hypoxic tumors. Inhibitors of autophagy and/or inhibition of pathways that activate autophagy will improve therapeutic outcomes of MSA therapy in hypoxic tumors that respond poorly to an MSA on its own, and in which increased autophagy is a therapeutic challenge [75].

5. Expression of hypoxia-induced gene products and MSA resistance

In the clinic, expression levels of the drug efflux pump P-glycoprotein (P-gp) are associated with a reduced response to MSAs, although P-gp expression levels do not form the basis for selection of patients for MSA-based therapy [60]. Hypoxia-induced increased expression of HIF-1α is one of the main driving forces for overexpression of P-gp, a member of the MDR-1 gene family [76]. Ovarian cancer cell spheroid cultures expressing high levels of P-gp and another MDR protein, p27, are significantly resistant to Ptx compared to monolayer cell cultures [77]. Selective knockdown of P-gp in spheroids reverses the resistance. In spheroids, translocation of HIF-1α to the nucleus to form the HIF-1 heterodimer results in the upregulation of P-gp and a corresponding resistance to even non-MSAs like doxorubicin [13].

P-gp overexpression significantly reduces the accumulation of MSA in cells and presumably also within the tumor [78]. For example, accumulation and distribution of the fluorescently-tagged Ptx BODIPY-Taxol differ between wild-type MCF7 spheroids with no P-gp expression and those overexpressing P-gp [78]. Inhibition of P-gp with nicardipine in mutant cell spheroids results in a similar distribution pattern of BODIPY-Taxol to wild type spheroids. Although the precise role of P-gp and other drug efflux pumps in resistance to MSAs and their pharmacokinetics in the clinic remains debatable; nevertheless, P-gp-mediated drug resistance in tumors is a major clinical challenge in MSA-based therapy [79].

In addition to upregulation of P-gp, overexpression of oncogenic forms of members of the epidermal growth factor receptor (EGFR) family in wide spectrum solid tumors is also associated with resistance to MSAs [80]. Under hypoxic conditions, overexpression of EGFR in epidermoid carcinoma A431, breast adenocarcinoma MDA-MB-231, and non-small cell lung cancer NCI-H358 cell lines increases resistance to Ptx [81]. Interestingly, under the same conditions, the same cells respond positively to Dtx, indicating an unusual difference between Ptx and Dtx responses in EFGR overexpressing cells [81]. In advanced non-small cell lung HIF-1-induced overexpression of VEGF, in addition to P-gp overexpression, decreases the sensitivity of patients to combined Dtx and carboplatin-based therapy [82]. It has been reported that VEGF can induce the expression of P-gp in tumor endothelial cells and potentially cause resistance to Ptx [83]. Interestingly, low concentrations of Ptx are known to inhibit VEGF-A expression in human ovarian cancer cell lines and carcinoma tissue samples from patients [84]. Downregulation of HIF-1α by nitroglycerin reverses the resistance to chemotherapy and radiation [85]. Accordingly, nitroglycerin is an important agent undergoing clinical development for the treatment of solid tumors (see Table 2 for summary of clinical and preclinical hypoxia-directed therapies).

The interplay between HIF-1 and oncoproteins is known to regulate molecular pathways that help cancer cells evade hypoxia-induced cell death and the cytotoxic effects of drugs. One such interaction occurs between HIF-1 and c-Myc, an oncoprotein implicated in many cancers [108,109]. Interestingly, under hypoxic stress, calpin-mediated proteolysis of c-Myc into its inactive cytoplasmic cleavage product, Myc-nick, enables cancer cells to evade cell death, as discussed before [56]. Additionally, transient expression of Myc-nick in colon cancer cells promotes anchorage-independent cell growth and cell survival in hypoxia by promoting autophagy. Furthermore, Myc-nick facilitates tumor metastasis by triggering the expression of the actin-bundling protein fascin, presumably through facilitation of filopodia formation and cell motility [56]. Not surprisingly, high levels of Myc-nick are found in hypoxic colon tumors, and this increased expression confers resistance to anticancer drugs such as etoposide, cisplatin, oxaliplatin and imatinib. Altered Myc-nick expression in hypoxic tumors that are resistant to the front line drugs provides another new avenue for the development of treatment strategies for combination therapy with MSAs.

6. Role of changes in apoptosis proteins in hypoxia in MSA resistance

Altered expression of pro- and antiapoptotic proteins is a survival strategy in cancer cells to evade cell death under conditions of various stresses, including hypoxia. HIF-1 induces upregulation of the antiapoptosis proteins survivin [57,110], Bcl-2 and Bcl-XL [69,111], and downregulation of the pro-apoptotic proteins Bid, Bad, and Bax [112] (Fig. 3). However, hypoxia-mediated changes in expression of pro- and antiapoptotic proteins also occur independently of HIF-1 [111,112]. Intriguingly, cellular responses to hypoxia are cell-type dependent and can induce resistance to Ptx in one cell type but not others. For example, hypoxia protects HepG2 hepatocarcinoma and MDA-MB-231 breast cancer cells from Ptx-induced cell death, but has little effect on A549 lung adenocarcinoma, MCF7 breast carcinoma, or HepB3 hepatocarcinoma cells [113]. In the HepG2 cells, hypoxia downregulates the expression of and posttranslationally modifies pro-apoptotic Bcl-2 proteins.

The antiapoptotic protein survivin, coded for by the gene BIRC5, contributes to cell resistance not only to taxanes but also to non-MSAs and radiotherapy [114–118]. Patients with low to moderate survivin expression levels show a high overall survival rate in the clinic [114,118]. Levels of survivin expression correlate with expression levels of HIF-1α under hypoxic conditions, and, in line with this, downregulation of HIF-1α inhibits survivin expression [115,119]. HIF-1α regulates survivin transcriptional activity by binding to its promoter region; thus, mutations in the survivin promoter that interfere with HIF-1α binding decrease survivin transcription [115]. Ptx treatment has also been reported to induce survivin expression; however, the survivin induction is independent of Ptx-induced G_2/M cell cycle arrest [120]. Inhibiting survivin expression significantly augments Ptx- and non-MSA-mediated cell death in resistant and sensitive cells [117,120,121].

Mitotic deregulation that results in a faster exit of cells from M phase is another route for acquisition of Ptx resistance in cancer cells. In breast cancer cells, activation of the PI3K/Akt/Src pathway leads to overexpression of HER2 receptor tyrosine kinase, which, in turn, upregulates

Table 2
Selected hypoxia-directed therapeutic strategies in various stages of clinical or preclinical development for the treatment of solid tumors.

Strategies	Therapy	Stage	References
Hypoxia-activated prodrugs	Banoxantrone, mitomycin C, nitroglycerin, PR-104, TH-302, tirapazamine	Clinical	[85–88]
Anemia correction	Recombinant human erythropoietin, epoetin alfa/ESA therapy, PHD inhibitors	Clinical	[89–93]
Oxygen therapy	Hyperbaric oxygen, accelerated radiotherapy, carbogen and nicotinamide	Clinical	[94–96]
Lactate transporter (monocarboxylate transporter 1) inhibitor	AZD3965, α-cyano-4-hydroxycinnamate	Early clinical/preclinical	[97,98]
Radiosensitizers	Doranidazole, nitroimidazoles	Clinical/preclinical	[99,100]
Survivin inhibitors	Antisense oligonucleotides (EZO-3042), sepantronium bromide (YM155), terameprocol	Early clinical	[101–103]
HIF-1α inhibitors	Naphthalene derivative (CL67)	Preclinical	[104]
CAIX inhibitors	CAI17, BAY 79-4620, girentuximab	Preclinical	[99,105–107]

survivin expression [122]. Altered survivin expression together with deregulated mitosis results in Ptx resistance. Survivin inactivates caspase 3 and 9, and silencing of BIRC5 leads to P53 activation [116]. Gastric cancer cells treated with increasing concentrations of cisplatin show HIF-1α-mediated phosphorylation of Akt and subsequent upregulation of survivin [117]. Specific inhibition of phosphorylated Akt reduces HIF-1α expression and in turn reduces HIF-1α-induced survivin expression, improving therapeutic responses to cisplatin. The link between HIF-1α-induced overexpression of survivin and subsequent drug resistance is not limited to hypoxia alone. Under normoxic conditions, cross-talk between epidermal growth factor (EGF) and HIF-1α in breast cancer cells results in resistance to Dtx-induced apoptosis by overexpression of survivin. Activated EGF in normoxic cancer cells upregulates the expression of HIF-1α through the PI3K/AKT pathway [123].

7. Hypoxia-inducible carbonic anhydrase IX in cancer metastasis and resistance

The metabolic shift to glycolysis (Warburg effect) in tumors in an unfavorable hypoxic environment generates excessive glycolytic byproducts that result in intracellular acidosis [124]. To maintain intracellular pH homeostasis in hypoxia, cancer cells upregulate the expression of CAIX, a metalloenzyme that catalyzes the reversible hydration of CO_2 to bicarbonate and a proton [31,125]. CAIX is a transmembrane isoform of the carbonic anhydrase gene family that is overexpressed in a majority of solid tumors in response to hypoxia. CAIX overexpression alters intra- and extracellular pH and results in tumor metastasis and resistance to weakly basic anticancer drugs [126–128] (Fig. 4).

An optimal microenvironmental pH is essential for normal cell physiology and the active and passive transport of small molecules through the cell membrane [129]. A shift in intracellular pH (pH_i) to a more basic pH increases cell proliferation [130]; whereas, an acidic extracellular pH (pH_e) induces tumor metastasis and resistance to anticancer drugs [127,128]. As a non-ionizable drug, Ptx is unlikely to be affected in a major way by altered pH within tumors [131]. Nevertheless, given the fact that altered cell pH regulates a number of signaling and transport pathways, it is likely that some MSA resistance may occur in tumors via pathways that are triggered by altered intra-tumoral pH. For example, extracellular acidosis elevates the activity of P-gp and deactivates tumor suppressor genes, with both effects presumably contributing to tumor progression and drug resistance in solid tumors [128].

In breast tumors, cancer stem cells (CSCs) have been associated with acquired resistance to taxanes through induction of pathways that contribute to cell survival [see review by Wang [132] for detailed pathways]. CSC phenotypes are regulated and maintained in the hypoxic tumor microenvironment. Acidic pH promotes the growth of glioma stem cells (GSC) and growth of tumors by inducing the expression of angiogenic factors and HIF-2α [133]. Increasing low tumor pH to normal inhibits acidic stress-induced GSC growth. Interestingly, CAIX contributes to the survival and progression of breast CSCs in a hypoxic environment, and selective inhibition of CAIX eradicates the CSC population [134]. In a mouse model of breast cancer, a CSC-enriched population

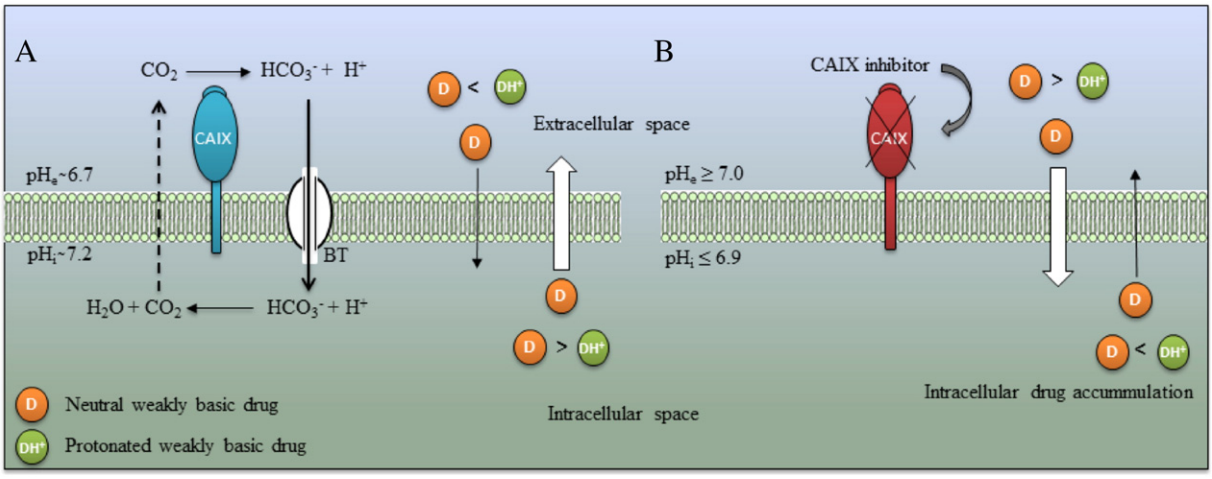

Fig. 4. Cellular uptake of weakly basic anticancer drugs in CAIX-overexpressing cells. Hypoxia-induced overexpression of CAIX results in neutralization and acidification of pH_i and pH_e, respectively, via hydration of CO_2 to bicarbonate (HCO_3^-) and a proton (H^+) and transport of bicarbonates across the cytoplasm via a bicarbonate transporter (BT). Weakly basic drugs that are neutral at physiological pH can easily enter the cell to induce cytotoxic effects. However, an acidic extracellular space due to CAIX overexpression results in protonation of these weakly basic drugs, reducing their intracellular uptake and causing accumulation in the extracellular space. Excessive accumulation of drugs in the extracellular space is presumably the cause of the systemic toxicity seen in the clinic. (B) CAIX inhibition results in intracellular acidosis ($pH \leq 6.9$) and an increased pH_e. At neutral or basic pH_e (≥ 7.0), weakly basic drugs remain unprotonated and easily pass through the cell membrane to accumulate intracellularly. Inside the cell, acidic pH_i (≤ 6.9) prevents escape of protonated drugs through the membrane, maintaining their high intracellular cytotoxic concentrations.

is resistant to Ptx therapy on its own; however, Ptx in combination with a CAIX inhibitor reduces tumor growth and obliterates secondary cancer metastases in the lungs [134]. Clinically, CAIX expression is predicted to serve as a prognostic marker for neoadjuvant therapy of triple-negative breast cancer patients treated with anthracyclines and taxanes, and for doxorubicin resistance in early stage breast cancer [135,136].

8. Potential avenues to overcome hypoxia-induced MSA resistance in the clinic

8.1. Direct inhibition of HIF-1α

The striking upregulation of HIF-1α in various tumors and the extensive cellular responses to HIF-1α that contribute to drug resistance make HIF-1α a primary drug target for the treatment of solid tumors [137]. Approaches to inhibit HIF responses to hypoxia can involve direct inhibition of HIF-1α by treatment with antisense RNA, blockade of dimerization of the α and β HIF-1 subunits, and use of anticancer agents that are known to inhibit components of the PI3K/AKT/HIF-1α pathway [104,138]. Investigation of disubstituted naphthalene derivatives like CL67 that bind to a G-quadruplex structure in the HIF promoter has shown that CL67 inhibits HIF-1α downstream signaling in renal carcinoma cell lines and mouse xenograft models of renal cancer [104]. Renal cancers are particularly susceptible to HIF-1α because they often have an inactivated VHL E3 ligase and thus are unable to properly degrade HIF-1α. Presence of multiple HIF-1α isoforms and HIF-1α expression in non-cancerous cells in normoxic conditions, however, raises a concern for off-target effects of direct inhibition of HIF-1α [139].

8.2. HIF-1α proteolysis and hypoxia-activated prodrugs

In hypoxic tumors, use of drugs that trigger the activation of the HIF-1α degradation pathway holds potential for the clearance of overexpressed HIF-1α and the improvement of MSA sensitivity. Treatment of hypoxic cells with rapamycin, for example, results in HIF-1α degradation which in turn leads to inhibition of survivin expression and increased apoptosis in lung cancer cells [140]. Likewise, inhibitors of Hsp90 that cause HIF-1α ubiquitination and degradation via Rack1 even in the absence of VHL hold promise as potential anti-HIF candidates [141].

Sirtuin 2 (Sirt2)-induced deacetylation and the subsequent hydroxylation are also known to result in destabilization of HIF-1α and inhibition of its transcriptional activity in hypoxic cells [142]. The Sirt2-mediated posttranslational degradation of HIF-1α in hypoxic conditions is highly dependent on the intracellular balance of NAD^+/NADH. An altered balance between NAD^+ and NADH due to dysfunctional mitochondria present in tumors can inactivate Sirt2 and facilitate HIF-1α-induced tumor progression and resistance to anticancer agents [143]. Restoring a normal NAD^+/NADH ratio using NAD^+ precursors is reported to have therapeutic benefits in mouse xenograft models of breast cancer [143]. Alternatively, small molecules that target pathways that normalize the NAD^+/NADH ratio and facilitate Sirt2-mediated proteolysis of HIF-1α might serve to improve solid tumor responses to MSAs.

Additionally, combining MSA therapy with hypoxic cytotoxins presents another approach for inhibition of solid tumor growth in hypoxic microenvironments. For example, tirapazamine, which specifically targets hypoxic cells by being activated to a toxic radical by reductases only in hypoxic conditions, augments the cytotoxicity of taxanes and cisplatin [144]. A significant number of hypoxia-activated prodrugs are now in clinical trials for the treatment of solid tumors (Table 2) [86-88].

8.3. Survivin and CAIX inhibitors

Hypoxic tumors that are resistant to MSAs due to HIF-1α-mediated upregulation of survivin will benefit from agents that downregulate survivin. A number of survivin inhibitors are now in early clinical trials, and their effects in combination with other anticancer agents are being evaluated (Table 2) [101-103]. Drugs that induce proteasome-mediated degradation of HIF-1α and downregulation of survivin are potential candidates for the treatment of survivin-expressing, MSA-resistant hypoxic tumors [145]. In one study, co-delivery of Ptx and survivin siRNA in polymeric micelles to Ptx-resistant cells significantly enhanced Ptx-induced inhibition of cell proliferation. Sequential treatment of cells with siRNA and Ptx was less effective [121].

Specific inhibition of CAIX expression or its activity may enhance therapeutic outcomes with MSAs and other anticancer modalities in solid tumors that overexpress CAIX (Table 2) [99,105-107,146,147]. BAY79-4620, a CAIX-specific monoclonal antibody, in combination with a tubulin-targeting agent, monomethyl auristatin E (MMAE), shows significant anti-tumor effects in mouse xenografts of human cervical, prostate, colorectal, gastric, and lung tumors cells [107]. MMAE by itself is highly cytotoxic by preventing tubulin polymerization; however, in conjugation with the CAIX-specific monoclonal antibody has reduced systemic cytotoxicity and improved antitumor effects. In a patient-derived lung tumor model with heterogeneous CAIX expression, carboplatin and Ptx therapy have only limited efficacy compared to BAY 79-4620-mediated therapy [107]. Interestingly, BAY79-4620-induced tubulin disruption and antitumor activity is specific to CAIX-expressing tumors and predominant only in cells that are susceptible to tubulin disruption. In addition to antibodies, sulfonamide-based inhibitors that specifically target CAIX are currently being developed as potential antitumor agents [148]. Lately, more potent secondary and tertiary aryl sulfonamides have been developed that selectively inhibit CAIX in the nanomolar range [149] (Table 2).

Novel drug delivery strategies are being developed to efficiently deliver anticancer drugs into tumors with low pH_e using pH-sensitive vectors [150]. CAIX-directed immunoliposomes enter cells via endocytosis following CAIX antibody binding to the cell surface, resulting in increased drug accumulation specifically in the CAIX-expressing cells [151]. Moreover, endosome-mediated evasion of liposomal drugs from efflux by P-gp pumps results in accumulation of drugs in the perinuclear region from which they are transported into the nucleus [131,151]. CAIX-directed Dtx-entrapped immuno-liposomes have greater antiproliferative effects than nontargeted liposomes in CAIX-positive lung cancer cells [151].

8.4. Improved MSAs and their enhanced delivery in hypoxic cancer cells

MTs are indispensable for the transcriptional activity of HIF-1, as HIF-1α associates with polymerized MTs and translocates to the nucleus via dynein motor proteins [152,153]. Thus, regulating HIF-1α translocation to the nucleus via MTs might hold promise for inhibition of downstream pathways of HIF-1α associated with MSA resistance. Interestingly, all MTAs irrespective of binding site, chemical structure, or mode of action on MTs inhibit HIF-1α translation without altering HIF-1α mRNA levels [33]. For example, both Ptx and the MT destabilizing agent 2-methoxyestradiol (2-ME) suppress HIF-1α protein translation by inhibiting the MT-mediated translocation of cytoplasmic HIF-1α to the nucleus [152]. While MT disruption for shorter intervals results in inhibition of HIF-1α nuclear translocation, longer intervals trigger HIF-1α translation inhibitory signals [152]. Interestingly, in addition to inhibiting HIF-1α translocation to the nucleus, 2-ME also upregulates expression of proapoptotic Bid protein, and sensitizes cells to Ptx-induced apoptosis [154]. In conditions of hypoxia in which taxanes administered on their own result in a poor outcome, combined therapy between Ptx and 2-ME induces synergistic effects in tumor xenografts of head and neck squamous cell carcinoma [154]. Although it is known that both Ptx and 2ME-induced apoptosis partly result from Bcl-xL phosphorylation and inhibition [155], it is also plausible that their synergy could result from their effect on HIF-1α. Topoisomerase inhibitors, such as topotecan and camptothecin, and anthracyclines, like doxorubicin and daunorubicin, are known inhibitors of HIF-1 [156,157]. Therefore,

Table 3
Selected MSA formulations for potential treatment of hypoxic tumors with MDR phenotype.

Therapy	Properties	References
Cellax™	– PEGylated-Dtx – Increased tumor uptake – Endocytosis-mediated cellular accumulation – Sustained release of Dtx – Evade P-gp-mediated efflux – Longer circulating half-life – High plasma area under the curve – Effective in MDR tumors – Increased radiosensitization with Cellax™	[158–162]
PM060184	– Novel β-tubulin binding site – High MT binding affinity – P-gp insensitive	[163]
ABRAXANE® (Abraxis BioScience and AstraZeneca)	– Albumin-bound Ptx – Well-tolerated, no hypersensitivity reactions – Faster infusion, high intratumoral accumulation – High plasma accumulation – High anti-angiogenic activity – More effective in SPARC overexpressing tumors – Risk of neutropenia correlates with aging	[164–166]
Triazolopyrimidines and phenylpyrimidines	– MT stabilizers – Brain-penetrant – No effect on P-gp	[167]
Patupilone, ixabepilone	– Epothilones – More cytotoxic than Ptx – Poor substrate of P-gp and MRP1 – Highly effective in tumors with p53 mutation – Potent radiosensitizer – Myelosuppression predominant toxic effect	[168–170]
EndoTAG®-1 (Medigene)/Lipusu® (Luye Pharma Group)/LEP-ETU (NeoPharm)	– Liposomal Ptx – Targets activated endothelial cells – Selectively targets endothelial cells – Prolonged elimination half-life than Ptx – More accumulation in tissue than Ptx – Greater safety profile than Ptx	[171–173]
Paclitaxel poliglumex	– Polyglutamic acid-linked paclitaxel – Shorter infusion time – Reduced systemic exposure to high concentrations of paclitaxel – Less grade 3 or 4 neutropenia and febrile neutropenia – Neuropathy only in paclitaxel poliglumex arm – Pre-hypersensitivity test not required – Interacts with estrogen	[174]

combination therapy between these anticancer agents and MSAs is another potential strategy for the treatment of hypoxic tumors with MSAs.

Therapeutic strategies that effectively deliver MSAs and evade the P-gp efflux pump hold promise for the treatment of hypoxic cancers, taking into account the direct effects of MSAs on HIF-1α (Table 3). For example, resistance can be overcome in hypoxic tumors by using polymeric Dtx and liposomal Ptx, both of which accumulate in cancer cells by endocytosis and sustainably release drug in hypoxic conditions [160].

MSAs that can overcome P-gp-mediated drug efflux are also promising in the treatment of hypoxic and Ptx-resistant tumors. PM060184, an MSA that binds to tubulin at a novel β-tubulin site, overcomes P-gp-mediated drug efflux in tumor xenografts [163]. This property of PM060184 to overcome P-gp-mediated efflux is a result of its high binding affinity for MTs compared to other MTAs like Ptx and vinblastine. Similarly, epothilones that are poor substrates of P-gp and inhibit HIF-1α may effectively overcome hypoxia-induced resistance in solid tumors [33].

Cellular responses to hypoxia are extensive and cell-type dependent, and understanding such response heterogeneity will help overcome some of the resistance to chemotherapy seen in the clinic, in particular taxane resistance in tumors of different lineages. Currently, several strategies are in preclinical and clinical trials for the treatment of hypoxic tumors (Table 2). Additionally, MSA-mediated therapies are being developed for effective treatment of MDR hypoxic tumors (Table 3). Nevertheless, more options for control of the hypoxic environment and HIF-1α signaling pathways would be welcome additions to the clinical treatment of solid tumors with not only MSAs but also non-MT-mediated drugs.

Competing interests

All authors declare that they have no competing interests.

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