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REVIEW ARTICLE

HIF REGULATION IN TUMOR PROGRESSION AND ANGIOGENESIS AND POTENTIAL THERAPEUTIC AGENTS

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SUMMARY

The key transcription regulator hypoxia-inducible factor (HIF) is commonly overexpressed in a variety of human malignancies, including multiple myeloma. It regulates the transcription of a broad range of genes involved not only in tumor angiogenesis, but also in other aspects of cancer biology. Most of our knowledge of HIF derives from studies investigating a role for HIF under hypoxic conditions; however, HIF-1α stabilization is also found under normoxic conditions. HIF therefore evolved as a promising target for cancer therapies during the last decade. Ongoing efforts aim to identify derived HIF inhibitors and test their preclinical and clinical activity.

INTRODUCTION

Since the discovery of the hypoxia-inducible factor (HIF) in 1992 (1) and the first report of its overexpression in a variety of primary cancers, a multitude of studies have defined a pathophysiological role for HIF in tumorigenesis. HIF is a key factor not only in tumor angiogenesis, but also in tumor cell survival and proliferation, migration, invasion, pH regulation, metabolism, drug and radiation resistance, immune evasion and genetic stability. Besides intratumoral hypoxia, genetic alterations and activation of signaling pathways within the tumor microenvironment trigger HIF expression, stability and degradation (2). Here we review recent insights into the regulation and function of HIF and summarize derived targeted therapies.

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HIF AND ITS REGULATORS

HIF is composed of an oxygen-regulated α-subunit and a constitutively expressed β-subunit. Within the nucleus, one of three HIF-α subunits (HIF-1α, HIF-2α/EPAS-1 and HIF-3α/IPAS) dimerizes with one of two isoforms of the β-subunit through the basic helix–loop–helix (bHLH) and PER-ARNT-SIM (PAS) A and B domains located in the *N*-terminal region of each subunit (3, 4). These dimers bind to specific DNA sequences within the promoter, intron and/or enhancer regions of target genes called hypoxia response elements (HREs), which are composed of 5′-RCGTG-3′ and recruit coactivators (5). Under normal conditions, HIF-2α and HIF-3α are specifically expressed in endothelial cells, type II pneumocytes, renal interstitial cells, liver parenchymal cells and cells of the myeloid lineage. In contrast, HIF-1α is expressed ubiquitously. Both, HIF-1α and HIF-2α are overexpressed in common human cancers and their metastases (6). Importantly, increased levels of HIF-1α or HIF-2α are correlated with adverse prognosis in breast, cervical and endometrial cancer, but also colorectal, non-small cell lung cancer (NSCLC), ovarian, rectal, pancreatic and prostate cancers (7-13).

HIF-1α level is regulated via modulation of its synthesis and protein stability. Under normoxia, HIF expression is finely balanced between constitutive synthesis and proteasomal degradation (14-17). Expression and activity of HIF-α proteins are regulated via post-translational prolyl hydroxylase domain-containing protein (PHD1, PHD2, PHD3)-mediated prolyl hydroxylation of the oxygen-dependent degradation domain (ODDD) and factor inhibiting HIF (FIH)-mediated asparaginyl hydroxylation of the *C*-terminal end of HIF-1α and HIF-2α subunits (18-21). Specifically, hydroxylation on proline residue 402 and/or 564 of HIF-1α by PHD2 mediates HIF interaction with the Von Hippel-Lindau disease tumor suppressor protein (VHL) (22-26). In turn, VHL protein recruits an E3 ubiquitin-protein ligase and catalyzes polyubiquitination of HIF-1α, thereby triggering its inactivation by proteasomal degradation (27, 28). Asparaginyl hydroxylation of HIF-1α and HIF-2α prevents binding of coactivators p300 and CREB-binding protein, thereby inhibiting HIF activity (29-31). Hydroxylation is dependent on the presence of oxygen, 2-oxoglutarate (α-ketoglutarate) and cofactor Fe^{2+}. Under hypoxia, reduced oxygen inhibits PHD and FIH activity and stabilizes HIF-α proteins by increasing mitochondrial reactive oxygen species (ROS) release, as well as inhibiting pro-

teasome-mediated degradation and nuclear accumulation (32-34). In addition to hypoxia, factors that inhibit PHD and FIH and result in HIF-α stabilization include fumarate, succinate and 2-hydroxyglutarate (35-37). Conversely, inactivating homozygous mutations in fumarate hydratase and succinate dehydrogenase trigger HIF-1α expression in human tumors (38). Mutant isocitrate dehydrogenase increases 2-hydroxygluturate levels, which are associated with glioblastoma and acute myeloid leukemia (39). Promising therapeutic approaches to target HIF sequelae include inhibition of HIF synthesis, HIF degradation, HIF dimerization, the HIF–PHD interaction, as well as the HIF–p300 interaction.

Furthermore, the transcriptional-activation domains (TADs) N-TAD and C-TAD in the *C*-terminus of HIF-1α and HIF-2α subunits regulate the HIF transcriptional activity. Importantly, in contrast to N-TAD, C-TAD is inhibited by FIH hydroxylation, allowing bifunctional transcriptional activity of HIF-1α.

Recent data demonstrate a functional role for the stress-responsive family of NAD-dependent deacetylases, the sirtuins (40), in HIF-α regulation (41-44). Specifically, SIRT1 forms complexes with and deacetylates both HIF-1α (42) and HIF-2α (41), and thereby represses HIF-1α but activates HIF-2α transcriptional activity. Conversely, under hypoxia, decreased NAD^+ downregulates SIRT1, thereby increasing HIF-1α acetylation and promoting the expression of HIF-1α-induced target genes. Similar to SIRT1, SIRT6 enhances deacetylation of histones associated with HIF-1α-regulated glycolytic genes, consistent with transcriptional repression (44). Based on these recent findings, potential therapeutic approaches to indirectly target HIF-α include inhibition of mitochondrial ROS production by targeting components of the electron transport chain, inhibition of constitutively activated cellular metabolites, blockade of TADs and modulation of sirtuin activity.

In addition to hypoxia, HIF activation is triggered oxygen-independently by autocrine growth factor stimulation, including cytokines, lipopolysaccharides, epidermal growth factor (EGF), heparin-binding growth factor 2 (HBGF-2), insulin-like growth factor (IGF), loss of tumor suppressor function (LOF), including inhibitor of growth protein 4 (ING4), p53, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN and VHL, gain of oncogene function (GOF), including Ras, RAF proto-oncogene serine/threonine-protein kinase, proto-oncogene tyrosine-protein kinase Src, phosphoinositide 3-kinase (PI3K)/protein kinase Akt, serine/threonine-protein kinase mTOR and Myc proto-oncogene protein (6, 27, 45-47), as well as ROS and reactive nitrogen species (48-50).

HIF FUNCTIONS

HIF regulates a broad range of genes associated with tumor angiogenesis, tumor cell survival and proliferation, migration, pH regulation, metabolism, drug and radiation resistance, immune evasion and genetic stability. These genes include *VEGF*, *TGFA* and *TGFB*, *IGF2*, *EPO*, *WAF1*, *CCNG2*, *MET*, *LRP1*, *CA9*, *HK1*, *HK2*, *SLC2A1* (*GLUT1*), *GAPDH*, *LDHA*, *TGM2*, *TFR*, *TF*, *CP*, *ABCB1* (*MDR1*) and others (47).

Moreover, HIF-1α induces tumor invasion in renal cell carcinoma via loss of the epithelial-to-mesenchymal transition (EMT) regulator E-cadherin (51), tumor invasion and metastasis in head and neck squamous cell cancer via direct regulation of twist-related protein 1 (*TWIST1*) transcription (52), prostate cancer progression via VEGF-dependent zinc finger protein SNAI1 nuclear translocation (53), and tumor invasion and metastasis in breast cancer via the extracellular matrix remodeling enzyme lysyl oxidase (LOX) (54). Interestingly, HIF not only regulates gene expression in tumor and endothelial cells, but also in stem cells and tumor-associated macrophages (TAMs). For example, HIF-2α expression in TAMs correlates with unfavorable prognosis in cervical cancer and breast cancer (55, 56), as well as hepatocellular cancer (57). Therapeutic approaches include inhibition of HIF binding to DNA, as well as targeting VEGF, IGF and TGF.

An important role for HIF-1α and bone marrow hypoxia was also suggested in multiple myeloma progression (58). Given the importance of the bone marrow microenvironment and angiogenesis in multiple myeloma pathogenesis, our own group investigated the potential pathophysiological role of HIF-1α in triggering multiple myeloma bone marrow angiogenesis (59). The particular novelty of our data was the demonstration that HIF-1α protein level and activity in multiple myeloma cells under normoxic conditions is regulated by oncogenic c-Myc to influence VEGF secretion and angiogenic activity. These data are consistent with previous studies in other tumor models (46, 49, 60-62). However, in contrast to previous data (63-65), our data demonstrate a c-Myc-dependent regulation of HIF-1α rather than HIF-1α-dependent c-Myc regulation. In addition, our study identified c-Myc, HIF-1α, and the collaboration between both as potential new therapeutic targets in multiple myeloma. Using a drug screen, we defined bortezomib, lenalidomide, adaphostin and enzastaurin to decrease HIF-1α levels and VEGF, dependent on c-Myc. Prior studies found that bortezomib inhibits tumor adaptation by stimulating FIH (66), and that ING4 suppresses HIF-1α activity and angiogenesis under hypoxic conditions (67).

THERAPEUTIC APPROACHES TO TARGET HIF

High-throughput screening assays have identified a variety of HIF inhibitors (68-70). Based on recent insights on the pathophysiological role of HIF in tumorigenesis during the last decade, therapeutic approaches to target HIF include inhibition of HIF expression, protein translation, stability, dimerization, DNA binding and transcriptional activity, as well as inhibition of proteins encoded by HIF target genes in response to hypoxia or other HIF-inducing factors. Ongoing clinical trials are evaluating HIF inhibitors alone or in combination with other novel or conventional therapies (Table I).

Conventional and novel therapies with anti-HIF activity

A multitude of conventional and novel therapies inhibit HIF-1α activity by decreasing HIF-1α mRNA levels (e.g., GL-331 [71]) or HIF-1α protein levels. Specifically, decreased HIF-1α synthesis results from targeting tumor-induced signaling pathways, including PI3K/Akt/mTOR and Ras/RAF pathways. Agents include the BCR-ABL inhibitor imatinib (72, 73), the EGFR inhibitors gefitinib, erlotinib and cetuximab (74, 75), the HER2/Neu inhibitor trastuzumab (45), the mTOR inhibitors rapamycin, temsirolimus, everolimus and CCI-779 (45, 76-78), the farnesyltransferase inhibitor SCH-66336 (79), genistein (80), the MEK inhibitor PD-98059 (81), as well as the

Table I. *Targeting HIF for cancer therapy.*

Conventional and novel therapies with anti-HIF activity			
Targets		Inhibitors	Clinical development
		Decreasing HIF-1 mRNA levels	
		GL-331	Preclinical
		Decreasing HIF-1 protein levels	
PI3K/Akt			
		LY-294002	Preclinical
		Wortmannin	Preclinical
		Nelfinavir	Phase I, II
		Silybin/silibinin	Phase II
mTOR		Rapamycin	Phase I
		Temsirolimus/CCI-779	Phase I, II; approved
		Everolimus	Phase I,II; approved
Ras/RAF			
	BCR-ABL	Imatinib	Approved
	EGFR	Gefitinib	Approved
		Erlotinib	Approved
		Cetuximab	Approved
	HER2/Neu	Trastuzumab	Approved
	Farnesyltransferase	SCH-66336/Genistein	Phase II
	MEK	PD-98059	Preclinical
COX-2		NS-398	Observational
		Ibuprofen	Phase II (in cancer)
		Celecoxib	Phase II, III (in cancer)
HSP 90		Geldanamycin/17-AAG/Tanespimycin	Phase I-III
		17-DMAG/Alvespimycin	Phase I, II
		Apigenin	Phase II
Topoisomerase	Topoisomerase I	Topotecan	Phase I-III, approved
	Topoisomerase II	NSC-644221	Preclinical
		EZN-2208/Pegylated SN-38	Phase I, II
Microtubule		Taxotere	Approved
		2-ME	Phase I, II
		Epothilone B/Patupilone	Phase I, II
		Curcumin	Phase I-III
		Vincristine	Approved
		ENMD-1198	Preclinical
		EF-24	Preclinical
HD		NVP-LAQ824/Dacinostat	Preclinical
		FK-228/Romidepsin	Phase II
		SAHA	Phase I, II
		Trichostatin A	Preclinical
		HDACi	Phase I, II
Proteasome		Bortezomib	Phase II-III, approved
Thioredoxin		Pleurotin	Preclinical
		PX-12	Phase I-II
CDK		Flavopiridol/Alvocidib	Phase I, II
		Decreasing transcriptional activity of HIF-1	
Cardiac glycosides		Digoxin	Phase I, II (in cancer)
		Ouabain	Preclinical
		Proscillaridin	Preclinical
Decoy oligodeoxynucleotides			

Continued

Table I. *(Cont.) Targeting HIF for cancer therapy.*

Agents with more specific anti-HIF activity		
Targets	Inhibitors	Clinical development
	Stabilization of HIF-1α ubiquitination	
Unknown	PX-478	Phase I
Soluble guanylate cyclase	YC-1	Preclinical
	Targeting DNA–RNA interaction	
	EZN-2968	Phase I
	RX-0047	Preclinical
	Targeting HIF–PHD interaction	
	FG-2216	Phase II
	FG-4592	Phase I, II
	Targeting HIF-1 transcriptional activity	
	Polyamide	Preclinical (in cancer)
	Targeting PAS-A domains of HIF-1α and HIF-1β	
	NSC-50352	Preclinical
	Targeting interaction between HIF-1α and HIF-1β under hypoxic conditions	
	Acriflavine	Preclinical
	Rolitetracycline	Preclinical
	Disrupter of HIF binding to the coactivator p300	
	Chetomin	Preclinical
	TH-302	Phase I, II
	Rapid degradation	
Unknown	Berberine	Preclinical (in cancer)
	Pseudolaric acid B	Preclinical (in cancer)
	Bisphenol A	Observational
	103D5R	Preclinical
	Targeting binding of HIF-1 to DNA	
	Echinomycin	Preclinical
	Polyamides	Preclinical (in cancer)
	DJ-12	Preclinical (in cancer)
	Doxorubicin	Phase I-III, approved
	Daunorubicin	Phase I-III, approved
	Cisplatin	Phase I-III, approved

PI3K, phosphatidylinositide 3-kinase; Akt, protein kinase Akt; HD, histone deacetylase; CDK, cyclin-dependent kinase.

cyclooxygenase-2 (COX-2) inhibitors NS-398, ibuprofen and celecoxib (82). Additional compounds modifying HIF-1 protein levels include doxorubicin and daunorubicin (83), the HSP 90 inhibitors geldanamycin/17-AAG, 17-DMAG and apigenin (84-86), docetaxel, 2-methoxyestradiol and epothilone B (87, 88), the topoisomerase inhibitors topotecan (89, 90), NSC-644221 (91) and EZN-2208 (92), as well as histone deacetylase inhibitors (93-96), the proteasome inhibitor bortezomib (97) and the thioredoxin inhibitors 1-methylpropyl 2-imidazolyl disulfide and pleurotin (98).

Both temsirolimus and everolimus have now been approved for the treatment of advanced renal cell carcinoma. A clinical trial evaluating the role of low-dose administration of topotecan in patients with metastatic or unresectable solid tumors is ongoing (ClinicalTrials.gov ID: NCT00182676). Similarly, EZN-2208, a pegylated form of SN-38, the active component of CPT-11 (irinotecan) (92, 99-101), is currently being evaluated in two phase II clinical trials in patients with metastatic colorectal cancer and metastatic breast cancer, respectively.

Interestingly, Zhang et al. also suggest a role for cardiac glycosides, including digoxin, ouabain and proscillaridin, for HIF inhibition (102). A phase II clinical trial testing the anticancer activity of digoxin in recurrent prostate cancer is ongoing (ClinicalTrials.gov ID: NCT01162135).

Agents with more specific anti-HIF activity

More specific HIF-1 inhibitors include **PX-478**, **lificiguat** (YC-1), EZN-2968, FG-2216 and FG-4592, a **polyamide**, **rolitetracycline** (NSC-50352), **acriflavine**, **chetomin** and **TH-302**.

PX-478 (103, 104) and lificiguat (105-110) inhibit HIF-1α expression. Specifically, PX-478 stabilizes HIF-1α ubiquitination, thereby leading to increased degradation of polyubiquitinated HIF-1α, reduction of HIF-1α mRNA expression and inhibition of HIF-1α translation (104). PX-478 provides radiosensitization to cancer cells, including glioma, squamous cell, prostate and pancreatic adenocarcinoma cell lines, in vivo (111-113). A phase I clinical trial using PX-478 in advanced solid tumors or lymphoma and advanced solid tumors with metastasis has now been completed (ClinicalTrials.gov ID: NCT00522652).

EZN-2968 is a highly specific antisense oligonucleotide that binds to HIF-1α mRNA, consequently reducing HIF-1α protein levels (114). A phase I clinical trial using EZN-2968 weekly in patients with advanced solid tumors or lymphoma and a phase I clinical trial using EZN-2968 in patients with advanced solid tumors with liver metastasis have been initiated (ClinicalTrials.gov ID: NCT00466583 and NCT01120288). Preliminary data show that EZN-2968 is well tolerated in previously treated patients with advanced malignancies. Durable stable disease has been observed (115).

FG-2216 and FG-4592 inhibit the HIF–PHD interaction (116, 117) and are being investigated for the treatment of anemia in the oncology setting. Due to the death of a trial participant from fulminant hepatitis, these agents were suspended temporarily in May 2007. The hold was lifted in early 2008.

The polyamide inhibits DNA binding and HIF-1α transcriptional activity by binding to the promoter of the HIF-1α target gene *VEGF* with nanomolar affinity (118, 119).

A screen of compounds recently identified rolitetracycline, which blocks binding between the PAS-A domains of HIF-1α and HIF-1β (120). Acriflavine, an antimicrobial used in World War II, similar to rolitetracycline, decreases the interaction between endogenous HIF-1α and HIF-1β under hypoxic conditions (121).

The small molecule chetomin is a disrupter of HIF binding to the coactivator p300. Systemic administration of chetomin inhibited hypoxia-inducible transcription within tumors and tumor growth (122).

TH-302 is a new hypoxia-activated prodrug. TH-302 induces G_0/G_1 cell cycle arrest by downregulating cyclin D1/2/3, cyclin-dependent kinase CDK4/6, cyclin-dependent kinase inhibitor 1, cyclin-dependent kinase inhibitor 1B and retinoblastoma-associated protein (pRb) expression, and triggers apoptosis in multiple myeloma cells by upregulating cleaved proapoptotic caspase-3, -8, and -9 and poly(ADP-ribose)polymerase (123).

Further agents include **berberine** (124), **pseudolaric acid B** (125), **bisphenol A** (126) and **103D5R** (127), which trigger HIF-1α degradation, and **KRH-102053**, which triggers rapid degradation of HIF-1α via a new activator of HIF-prolyl hydroxylase 2 (128).

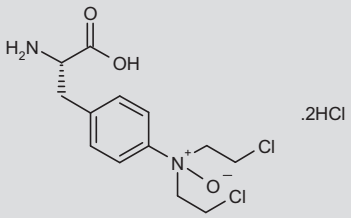
Agents targeting the c-Myc and HIF collaboration

In many tumors, c-Myc collaborates with HIF-1 to confer metabolic advantages to tumor cells (46, 129). Based on c-Myc/HIF-1-associated metabolic differences between normal and cancer cells induced by the Warburg effect, L-lactate dehydrogenase A chain (LDH-A) and PDK1 have been identified as additional potential novel therapeutic targets (130-133). Growth inhibition was also triggered by inhibition of another c-Myc/HIF-1 target gene, the transferrin receptor protein 1 gene (*TFRC*) (134, 135), and echinomycin, which, in addition to inhibiting DNA binding and transcriptional activity of HIF-1, also inhibits DNA binding of c-Myc/max (136, 137). Promising results were additionally observed by targeting HIF-1/c-Myc-dependent glutamine metabolism by antisense mRNA against glutaminase, acivicin and BPTES (138-140). Supporting our own data, inhibition of HIF-1 function by echinomycin or small interfering RNA (siRNA) against HIF-1 resulted in enhanced sensitivity to melphalan in multiple myeloma cells (141). Taken together, these studies strongly indicate a potential therapeutic role for targeting the c-Myc/HIF-1 pathway in multiple myeloma and other solid and hematological malignancies.

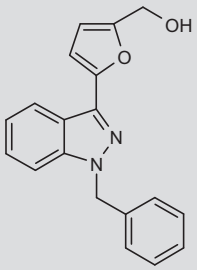
CONCLUSIONS

Adaptation of cancer cells to their microenvironment and hypoxia in particular represents a key event in tumorigenesis. The main transcriptional regulator of mechanisms mediating adaptive responses to reduced O_2 is HIF. Since HIF regulates more than 200 genes associated with tumorigenesis, it represents a promising target in cancer therapy. Although most of the current studies are evaluating antitumor effects of HIF-1α inhibition, ongoing preclinical and clinical trials are also investigating the potential role of HIF-2α inhibition in cancer treatment.

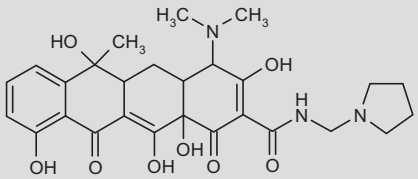
Based on our increased knowledge of HIF-1 synthesis, stabilization, degradation and function in tumor biology during the last decade, a multitude of derived targeted therapies have been identified. Among these agents are also conventional chemotherapeutics, including anthracyclines, which, at least in part, mediate their anticancer activity via HIF inhibition. While some of the new HIF inhibitors have already demonstrated preclinical activity and are now in early clinical testing, the growing list of pharmacological HIF inhibitors and their varied targets also mirrors the complex molecular role of HIF in tumorigenesis. Indeed, HIF function, and therefore the efficacy of HIF inhibitors, is dependent on tumor type, organ and the tumor microenvironment, and might vary due to the heterogeneity of cancer, even within the same patient over time and space. Moreover, most of the knowledge of HIF derives from studies investigating a role for HIF under hypoxic conditions; however, HIF-1α stabilization is also found under normoxic conditions. Given the broad range of client proteins, e.g., HSP 90 inhibitors or histone deacetylase inhibitors, it is difficult to determine the extent of antitumor activity due to HIF-1 inhibition. Validation of HIF inhibition is currently restricted to IHC, Western blot analysis, mRNA expression of HIF-1 and HIF-1 target genes, and more indirectly, angiogenesis. Importantly, measurements to assess HIF inhibition should not be based on antitumor activity, since it is difficult to envision how HIF-1 inhibition may be associated with marked tumor shrinkage under heterogeneous conditions of HIF-1 expression (69). Therefore, more stringent biomarkers consistently associated with HIF inhibition in tumor tissue are urgently needed.



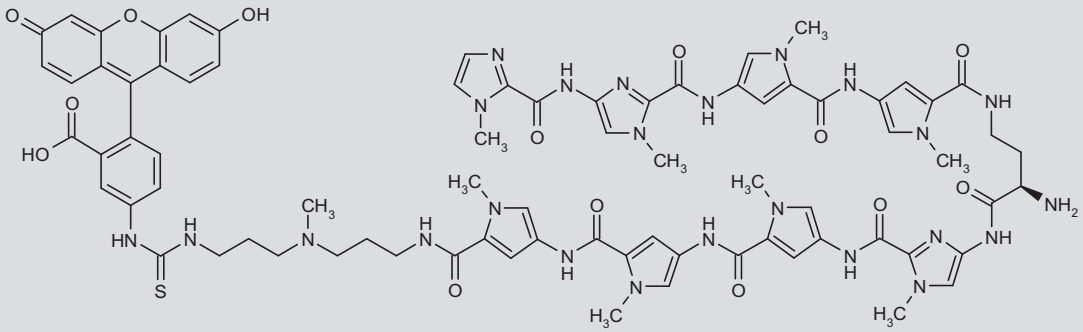
PX-478



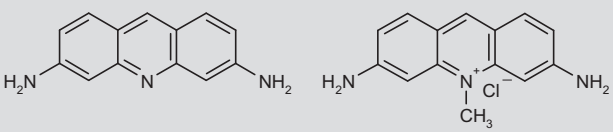
Lificiguat (YC-1)



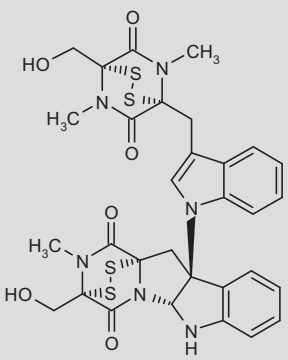
Rolitetracycline



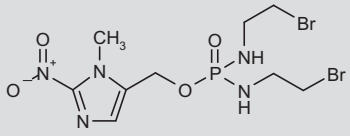
Polyamide



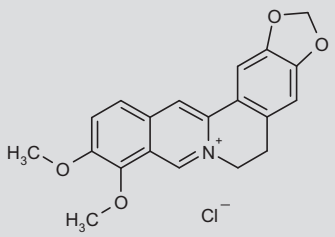
Acriflavine



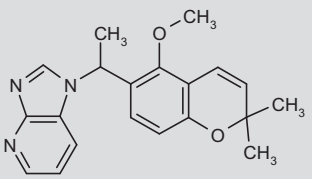
Chetomin



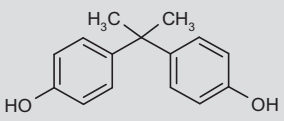
TH-302



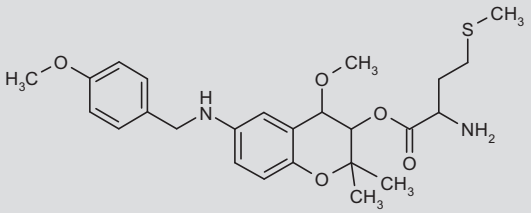
Berberine



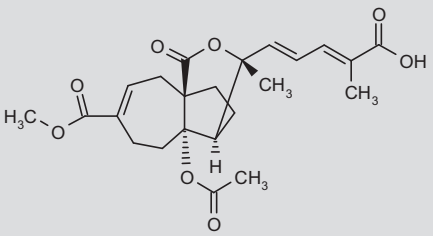
103D5R (127)



Bisphenol A



KRH-102053



Pseudolaric acid B

Although HIF is predominantly associated with tumor progression and poor clinical outcome, recent studies demonstrate that HIF-1α might also have tumor suppressive activity, further highlighting the complexity of associated pathophysiological mechanisms. Indeed, in a variety of cancers, including NSCLC, head and neck squamous cell carcinoma and neuroblastoma, HIF-1α, but not HIF-2α, expression correlates with lower cancer stage (2, 35). Moreover, constitutive expression of HIF-1α renders pancreatic cancer cells resistant to apoptosis induced by hypoxia and nutrient deprivation (142). One explanation could be that HIF-1α induces mir-210 in both normoxic and hypoxic cells, followed by tumor suppression. Indeed, overexpression of mir-210 in pancreatic and head and neck cancer cell lines delays tumor cell growth in a murine xenograft model (143). Similarly, Noguera et al. recently showed that high HIF-1α levels correlate negatively with advanced clinical stage and tumor vascularization in neuroblastoma (144). An explanation for the opposing effects of HIF-1α and HIF-2α on tumor behavior might be the antagonist effect of HIF-1α versus the agonist effect of HIF-2α on c-Myc activity (129). Specifically, under physiological conditions, HIF-1α inhibits c-Myc activity by direct interaction, induction of Max-interacting protein 1 and stimulation of a proteasome-dependent pathway (129, 145, 146), but it also accentuates Myc/Max-mediated transcriptional activation via HIF-2α-induced stabilization of Myc/Max. By increasing c-Myc/Max interactions, HIF-2α promotes c-Myc-mediated activation of cyclin D2 and triggers the repression of p21 and p27 (129, 147). When deregulated during tumorigenesis, (oncogenic) c-Myc paradoxically collaborates with HIF-1α in inducing the expression of PDK1 and hexokinase-2, followed by aerobic glycolysis (Warburg effect) (46, 129, 148, 149), and VEGF (angiogenesis) (46, 150).

Another explanation for the different effects of HIF-1α and HIF-2α on tumor behavior is their opposing regulation of the tumor suppressor protein p53. Specifically, HIF-1α stabilizes p53 and hypoxia-induced cell death. In contrast, HIF-2α indirectly suppresses p53 activity, thereby promoting radioresistance and chemoresistance (63, 151). An even more complex role for HIF-2α was recently demonstrated: whereas HIF-2α overexpression contributed to lung cancer progression, therapeutic inhibition of HIF-2α below a critical threshold paradoxically promoted tumor growth by reducing expression of tumor suppressor genes, including *SCGB3A1* (152, 153).

In summary, although there is an increasing amount of data suggesting the benefits of targeting HIF for tumor treatment, further studies to delineate the functional sequelae of HIF in tumorigenesis are urgently needed. Ongoing studies aim to identify more specific

HIF inhibitors for personalized therapy regimens alone or in combination with other agents in order to increase patient survival.

DISCLOSURES

The author states no conflicts of interest.

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