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From tumor hypoxia to cancer progression: the implications of hypoxia-inducible factor-1 expression in cancers

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Abstract: Hypoxia, defined as a decrease of tissue oxygen levels, represents a fundamental pathophysiological condition in the microenvironment of solid tumors. Tumor hypoxia is known to be associated with radio/chemo-resistance and metastasis that eventually lead to cancer progression contributing to poor prognosis in cancer patients. Among transcription factors that accumulated under hypoxic conditions, hypoxia-inducible factor-1 (HIF-1) is a master transcription factor that has received the most intense attention in this field of research due to its capacity to modulate several hundred genes. With a clearer understanding of the HIF-1 pathway, efforts are directed at manipulation of this complex genetic process in order to ultimately decrease cellular HIF-1 levels. Some novel agents have been shown to have HIF-1 inhibition activity through a variety of molecular mechanisms and have provided promising results in the preclinical setting.

Introduction

To grow beyond a diameter of approximately 1 mm, newly developing tumors must form their own vascular network and blood supply [1]. Angiogenesis is an adaptive response to tissue hypoxia [2]. Compared with the regular, ordered vasculature of normal tissues, blood vessels in tumors are often highly abnormal, with distended capillaries, leaky walls, and sluggish flow [3]. Tissue hypoxia results when supply of oxygen from the bloodstream does not meet demand from the cells in the tissue [4]. Protection against hypoxia in solid tumors is an important step in tumor development and progression [5].

The beginnings of hypoxia research in tumor biology can be traced back to observations made in the early 20th century by Otto Warburg, who demonstrated that, unlike normal cells, tumor cells favor glycolysis, independent of cellular oxygenation levels [6].

Physiologists and clinicians define hypoxia as a state of reduced O_2 availability or decreased O_2 partial pressures below critical thresholds, thus restricting or even abolishing the function of organs, tissues, or cells [7]. Other investigators define hypoxia as areas with O_2 tensions (pO_2 values)≤2.5 mm Hg [8].

Hypoxia was initially studied because of its effects on responses to radiotherapy. Radiation treatment requires free radicals from oxygen to destroy target cells, and cells in hypoxic areas were found to be resistant to radiation-induced cell death [9]. Hypoxia alters the behavior of tumor cells through a number of O_2-sensitive pathways and the best understood pathway is that mediated by the hypoxia-inducible factor family of transcription factors (HIFs) [10]. Activation of HIF in cancer has been shown to contribute

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to the classical tumor phenotypes of upregulated glycolysis and angiogenesis, leading to widespread interest in the HIF system as a target in cancer therapeutics [11]. Furthermore, studies indicate that hypoxia promotes genetic instability that leads to tumor progression [12]. Putra et al. [13] has provided evidence that functional polymorphisms in the HIF-1α gene may have an important impact on lung carcinogenesis, especially in adenocarcinomas, possibly by increasing genomic instability.

Hypoxia-Inducible Factors Family

To date, three HIFs (HIF-1, HIF-2, and HIF-3) have been identified as regulating transcriptional programs in response to low oxygen levels [14]. HIF-1α is expressed ubiquitously in all cells, whereas HIF-2α and HIF-3α are selectively expressed in certain tissues, including vascular endothelial cells, type II pneumocytes, renal interstitial cells, liver parenchymal cells, and cells of the myeloid lineage [15].

HIF-1 is a heterodimeric protein that is composed of HIF-1α and HIF-1β subunits. The amino terminal half of each subunit consists of basic helix-loop-helix and Per-ARNT-Sim (PAS) domains that mediate heterodimerization and DNA binding [16]. HIF-1α is subjected to O_2-dependent hydroxylation on proline residue 402 and/or 564 by prolyl hydroxylase domain protein 2 and this modification creates an interface for interaction with the von Hippel-Lindau tumor suppressor protein, which recruits an E3 ubiquitin-protein ligase that catalyzes polyubiquitination of HIF-1α, thereby targeting it for proteasomal degradation [17]. During hypoxia, HIF-1α is stabilized and dimerized with HIF-1β, and the complex is translocated into the nucleus where it binds to hypoxia-responsive elements in the promoters or enhancers of the target genes, such as the genes encoding erythropoetin, glucose transporters, glycolytic enzymes, hemeoxygenase-1, inducible nitric oxide synthase, transferrin, and vascular endothelial growth factor (VEGF) [18]. HIF-1α protein expression is likely to be particularly sensitive to changes in the rate of synthesis because of its extremely short half-life under non-hypoxic conditions [19].

HIF-2α has been associated with, and appears to promote, an undifferentiated phenotype in pluripotential cells [20]. HIF-2α (also known as EPAS-1, HLF) facilitates oxygen delivery and cellular adaptation to hypoxia by stimulating erythropoiesis, angiogenesis, and anaerobic glucose metabolism [21]. It has been shown that HIF-2α binds

to the Oct-4 promoter and induces Oct-4 expression and transcriptional activity, thereby contributing to impaired development in homozygous HIF-2α KI/KI embryos, defective hematopoietic stem cell differentiation in embryoid bodies, and large embryonic stem cell-derived tumors characterized by altered cellular differentiation [22]. Furthermore, tumor hypoxia/HIF2α activation elicits an increase in epidermal growth factor receptor (EGFR) protein synthesis, and hence receptor expression, that is required for tumor cell growth autonomy [23].

HIF-3α is expressed abundantly in lung epithelial cells, and the transcriptional induction of HIF-3α plays an important role in the response to hypoxia *in vitro* [24]. Moderate hypoxia induced mRNA transcription of HIF-3α whereas HIF-1α and HIF-2α mRNA levels remained unchanged [25]. As a very sensitive and rapidly reacting component of the HIF system, HIF-3α may therefore contribute to protection during early intervals of hypoxia and/or moderate hypoxia, while, in contrast, HIF-1α and HIF-2α may confer protection against severe and/or prolonged hypoxia [25].

Hypoxia and HIF-1α

Tumor hypoxia has two sides. On the one hand, tissue O_2 concentrations of <1% (pO_2<7 mm Hg) exert anti-proliferative effects, restrict cell proliferation, promote differentiation, and may induce apoptosis and necrosis [26]. On the other hand, hypoxia is known to promote aggressive phenotypes of tumor and induces their invasiveness and metastasis [27]. When PC-3 cells and prostate cancer cell lines were exposed to 1% oxygen (hypoxia) for various periods of time, chronic hypoxia (≥24 hours) decreased cell proliferation and induced cell death. In contrast, the prostate cancer cells exposed to acute hypoxia (≤6 hours) displayed increased motility, clonogenic survival, and invasive capacity [28].

The upregulation of HIF-1 is considered the molecular "switch" or "event" that is turned on by hypoxia [29]. However, stimulation of cells with a variety of growth factors and cytokines, including epidermal growth factor, fibroblast growth factor-2, heregulin, insulin, insulin-like growth factor 1 and 2, and interleukin-1b also induce the expression of HIF-1α protein, HIF-1 DNA-binding activity, and HIF-1 target gene expression under non-hypoxic conditions [30].

As HIF-1 is a central transcription factor, once it is being upregulated, it will subsequently modulate the expression of many genes involved in cell metabolism, proliferation,

apoptosis, and angiogenesis [31]. Recently, large-scale microarray approaches indicate that HIF-1 activates hundreds of target genes [32]. Activating HIF-1 usually means increased nuclear-HIF-1α expression. Although nuclear-HIF-1α expression has been reported to be the master of transcription factor, some study also revealed the importance of cytoplasmic-HIF-1α expression [33].

Role of HIF-1 in Metastasis and Therapy Resistance

Severe and prolonged hypoxia may initiate apoptosis, whereas under acute and mild hypoxia, cells may adapt to this environmental stress and will survive [34]. Mounting evidence also suggests that hypoxic induces metastasis of hypoxia-surviving cancer cells. Cancer metastasis is mediated by the epithelial mesenchymal transition (EMT) process, by which cancer cells loss its epithelial markers and gain its mesencymal markers [35]. Loss or reduction of E-cadherin, an epithelial marker, expression is frequently observed at the invasive front of many advanced-stage human carcinomas [36]. Several lines of evidence suggest that hypoxia may be an important factor contributing to the loss of E-cadherin in solid tumors [37].

Hypoxia has also led to therapeutic resistance through: 1) direct effects due to a lack of O_2 which some drugs and radiation require to be maximally cytotoxic; 2) indirect effects via altered cellular metabolism which decreases drug cytotoxicity, and; 3) enhanced genetic instability which can lead to more rapid development of drug resistant tumor cells [38]. The chemoresistance of hypoxic regions is a consequence, at least in part, of the low accessibility of the drug to these areas due to their poor vascularization [39]. As for radiotherapy, the biological effect of radiation depends on the degree of oxygenation, and hypoxic cells are approximately three-fold more resistant than well-oxygenated cells [40]. In one study, it has been demonstrated that hypoxia-induced chemoresistance to cisplatin and doxorubicin in non-small cell lung cancer (NSCLC) cells is through the HIF pathway and silencing of the HIF-1α gene reverses these drugs' resistance [41].

HIF and Cancer Stem Cells

Recently, HIFs have been shown to activate specific signaling pathways such as Notch and activate the expression of transcription factors such as Oct-4 that control stem cell self-renewal and multipotency [42]. It has been reported that embryonal carcinoma cell lines showed faster proliferation when the culture was carried out under hypoxic (5% O_2) vs. normal (21% O_2) conditions [43].

Using a novel cycling hypoxia-selected subpopulation from human breast cancer cell lines, Louie et al. [44] demonstrated that a stem-like breast cancer cell subpopulation could be expanded through repetitive hypoxia/reoxygenation cycles without genetic manipulation. They also discovered that cells derived from this subpopulation can form colonies readily, are highly tumorigenic in immune-deficient mice, and exhibit both stem-like and EMT phenotypes [44].

HIF-1α-Targeted Therapy

With a clearer understanding of the HIF-1 pathway, efforts are directed at manipulation of this complex genetic process in order to ultimately decrease cellular HIF-1 levels. Inhibition of HIF-1 in animal model systems manifests decrease in tumorigenesis and increase in survival [45]. As HIF-1 has been found to regulate the shift within the tumor cells to anaerobic metabolism and to activate VEGF and angiogenesis, downregulation of the HIF-1 complex may suppress cancer progression [46]. Many approaches have been made to inhibit the expression or the transcriptional activity of HIF-1, such as genetic approaches and pharmacological approaches [47]. Meanwhile, there is a group of hypoxia-activated prodrugs, which preferentially form cytotoxic and DNA-damaging free radicals under hypoxia, thus selectively eradicating hypoxic cells [48]. According to their putative mechanism of action, HIF-1 inhibitors could be tentatively divided into agents that modulate: 1) HIF-1α DNA binding; 2) HIF-1α mRNA expression; 3) HIF-1α protein degradation; 4) HIF-1α transcriptional activity; and 5) HIF-1α protein translation [49].

HIF-1α DNA Binding Inhibition

Doxorubicin is known to have HIF-1 inhibition activity by blocking its binding to DNA [50]. Wang et al. [51] proposed a complex drug delivery system consisting of liposomes as a nano-carrier, doxorubicin as a cell death inducer, and antisense oligonucleotides targeted to HIF-1α mRNA as a suppressor of cellular resistance and angiogenesis. The system effectively delivers active ingredients into tumor cells,

multiplies the cell death signal initiated by doxorubicin, and inhibits cellular defensive mechanisms and angiogenesis.

HIF-1α mRNA Expression Inhibition

EZN-2968 is a RNA antagonist composed of a third-generation oligonucleotide that specifically binds and inhibits the expression of HIF-1α mRNA [52]. EZN-2968 has been reported to induce a potent, selective, and durable antagonism of HIF-1 mRNA and protein expression (IC50, 1-5 nmol/L) under normoxic and hypoxic conditions associated with inhibition of tumor cell growth [52]. Another agent that disrupts HIF-1α mRNA expression is aminoflavone. Aminoflavone is a ligand of the aryl hydrocarbon receptor that has been shown to inhibit HIF-1α mRNA expression by ~50% [53].

HIF-1α Protein Degradation

EGFR tyrosine kinase inhibitor, gefitinib, has been shown to circumvent hypoxia-induced drug (cisplatin, paclitaxel and gemcitabine) resistance via the regulation of HIF-1α expression [54]. This action of gefitinib was caused by reduced protein stability without any change in the level of HIF-1α mRNA. Interestingly, downregulation of HIF-1α has also been associated with positive therapeutic responses of cancer cells to EGFR-targeted therapy [55].

Inhibition of HIF-1α Transcriptional Activity

Rapamycin has been shown to induce apoptosis in NSCLC cell lines through downregulation of survivin under hypoxic condition [56]. Pretreatment of PC-3 cells and prostate cancer cell lines with the rapamycin inhibited both the accumulation of HIF-1α and HIF-1-dependent transcriptional activity [57]. Another active substance that might fall into this 'transcription-inhibition category' is chetomin. Chetomin, a dithiodiketopiperazine metabolite of the fungus *Chaetomium* species, was known to have antimicrobial activity [58]. Systemic administration of chetomin inhibited hypoxia-inducible transcription within tumors and inhibited tumor growth [59]. Meanwhile P3155, an HIF-1α inhibitor with antiangiogenic activity, showed specific HIF-1α inhibition with IC50 of 1.4 μM under hypoxia [60]. It suppressed HIF-1α expression as well as the phosphatidylinositol-3-kinase/Akt pathway and abrogated expression of the HIF-1-inducible gene [60].

HIF-1α Translation Inhibition

Selective inhibition of HIF-1 activation by using HIF-1α-targeted siRNA treatment reduces hypoxic radioresistance *in vitro* as effectively as a pharmacologic approach with chetomin as a small molecule blocking the HIF pathway [61]. In another study, HIF-1α siRNA-transfected glioma cell lines have decreased growth both *in vitro* and *in vivo* as well as proliferative index [62].

Inhibition of HIF-1 has not always about therapeutic domain. Some studies have also investigated the possible benefit of HIF-1 inhibition for cancer prevention. Several natural products (e.g., resveratrol, genistein, apigenin, and berberin) have also been found to inhibit the activity of HIF-1 [63]. However, the use of HIF-1 inhibitors in cancer chemoprevention might be associated with toxicity [63].

Conclusion

Hypoxia is a common pathophysiological occurrence with a profound impact on the cellular transcriptome [64], and is undoubtedly an important mechanism of HIF activation in tumors [65]. HIF-1 is a master regulator of various target genes that plays critical roles in a multitude of pathways involved in the progression of cancer. The discovery of HIF-1 has increased enthusiasm for the investigation and development of targeted therapies modulating the cancer cell's response to the hypoxic microenvironment. Despite further needs of preclinical and clinical validation, HIF-1-targeted therapies, combined with radiotherapy and chemotherapy, are expected to be included in an integrated approach to cancer therapy in the future.

References

1. Vaupel P. The role of hypoxia-induced factors in tumor progression. Oncologist 2004;9 Suppl 5:10-7.
2. Fong GH. Mechanisms of adaptive angiogenesis to tissue hypoxia. Angiogenesis 2008;11:121-40.
3. Menon C, Polin GM, Prabakaran I, Hsi A, Cheung C, Culver JP, Pingpank JF, Sehgal CS, Yodh AG, Buerk DG, Fraker DL. An integrated approach to measuring tumor oxygen status using human melanoma xenografts as a model. Cancer Res 2003;63:7232-40.
4. Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC. HIF-

1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. Cell Metab 2006;3:187-97.

5. Fillies T, Werkmeister R, van Diest PJ, Brandt B, Joos U, Buerger H. HIF1-alpha overexpression indicates a good prognosis in early stage squamous cell carcinomas of the oral floor. BMC Cancer 2005;5:84.

6. Bertout JA, Patel SA, Simon MC. The impact of O2 availability on human cancer. Nat Rev Cancer 2008;8:967-75.

7. Höckel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. J Natl Cancer Inst 2001;93:266-76.

8. Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev 2007;26:225-39.

9. Harris AL. Hypoxia: a key regulatory factor in tumour growth. Nat Rev Cancer 2002;2:38-47.

10. Wouters BG, Koritzinsky M. Hypoxia signalling through mTOR and the unfolded protein response in cancer. Nat Rev Cancer 2008;8:851-64.

11. Raval RR, Lau KW, Tran MG, Sowter HM, Mandriota SJ, Li JL, Pugh CW, Maxwell PH, Harris AL, Ratcliffe PJ. Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. Mol Cell Biol 2005;25:5675-86.

12. Huang LE, Bindra RS, Glazer PM, Harris AL. Hypoxia-induced genetic instability: a calculated mechanism underlying tumor progression. J Mol Med (Berl) 2007;85:139-48.

13. Putra AC, Tanimoto K, Arifin M, Hiyama K. Hypoxia-inducible factor-1alpha polymorphisms are associated with genetic aberrations in lung cancer. Respirology 2011;16:796-802.

14. Rankin EB, Giaccia AJ. The role of hypoxia-inducible factors in tumorigenesis. Cell Death Differ 2008;15:678-85.

15. Majmundar AJ, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell 2010;40:294-309.

16. Semenza GL. Hydroxylation of HIF-1: oxygen sensing at the molecular level. Physiology (Bethesda) 2004;19:176-82.

17. Semenza GL. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene 2010;29:625-34.

18. Mojsilovic-Petrovic J, Callaghan D, Cui H, Dean C, Stanimirovic DB, Zhang W. Hypoxia-inducible factor-1 (HIF-1) is involved in the regulation of hypoxia-stimulated expression of monocyte chemoattractant protein-1 (MCP-1/CCL2) and MCP-5 (Ccl12) in astrocytes. J Neuroinflammation 2007;4:12.

19. Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003;3:721-32.

20. Ratcliffe PJ. HIF-1 and HIF-2: working alone or together in hypoxia? J Clin Invest 2007;117:862-5.

21. Rankin EB, Biju MP, Liu Q, Unger TL, Rha J, Johnson RS, Simon MC, Keith B, Haase VH. Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin *in vivo*. J Clin Invest 2007;117:1068-77.

22. Covello KL, Kehler J, Yu H, Gordan JD, Arsham AM, Hu CJ, Labosky PA, Simon MC, Keith B. HIF-2alpha regulates Oct-4: effects of hypoxia on stem cell function, embryonic development,

and tumor growth. Genes Dev 2006;20:557-70.

23. Franovic A, Gunaratnam L, Smith K, Robert I, Patten D, Lee S. Translational up-regulation of the EGFR by tumor hypoxia provides a nonmutational explanation for its overexpression in human cancer. Proc Natl Acad Sci U S A 2007;104:13092-7.

24. Li QF, Wang XR, Yang YW, Lin H. Hypoxia upregulates hypoxia inducible factor (HIF)-3alpha expression in lung epithelial cells: characterization and comparison with HIF-1alpha. Cell Res 2006;16:548-58.

25. Heidbreder M, Fröhlich F, Jöhren O, Dendorfer A, Qadri F, Dominiak P. Hypoxia rapidly activates HIF-3alpha mRNA expression. FASEB J 2003;17:1541-3.

26. Vaupel P. Hypoxia and aggressive tumor phenotype: implications for therapy and prognosis. Oncologist 2008;13 Suppl 3:21-6.

27. Xing F, Okuda H, Watabe M, Kobayashi A, Pai SK, Liu W, Pandey PR, Fukuda K, Hirota S, Sugai T, Wakabayshi G, Koeda K, Kashiwaba M, Suzuki K, Chiba T, Endo M, Mo YY, Watabe K. Hypoxia-induced Jagged2 promotes breast cancer metastasis and self-renewal of cancer stem-like cells. Oncogene 2011;30:4075-86.

28. Dai Y, Bae K, Siemann DW. Impact of hypoxia on the metastatic potential of human prostate cancer cells. Int J Radiat Oncol Biol Phys 2011;81:521-8.

29. Wen B, Burgman P, Zanzonico P, O'Donoghue J, Cai S, Finn R, Serganova I, Blasberg R, Gelovani J, Li GC, Ling CC. A preclinical model for noninvasive imaging of hypoxia-induced gene expression; comparison with an exogenous marker of tumor hypoxia. Eur J Nucl Med Mol Imaging 2004;31:1530-8.

30. Semenza G. Signal transduction to hypoxia-inducible factor 1. Biochem Pharmacol 2002;64:993-8.

31. Fan LF, Dong WG, Jiang CQ, Qian Q, Yu QF. Role of Hypoxia-inducible factor-1 alpha and Survivin in colorectal carcinoma progression. Int J Colorectal Dis 2008;23:1057-64.

32. Millonig G, Hegedusch S, Becker L, Seitz HK, Schuppan D, Mueller S. Hypoxia-inducible factor 1 alpha under rapid enzymatic hypoxia: cells sense decrements of oxygen but not hypoxia per se. Free Radic Biol Med 2009;46:182-91.

33. Dorević G, Matusan-Ilijas K, Babarović E, Hadzisejdić I, Grahovac M, Grahovac B, Jonjić N. Hypoxia inducible factor-1alpha correlates with vascular endothelial growth factor A and C indicating worse prognosis in clear cell renal cell carcinoma. J Exp Clin Cancer Res 2009;28:40.

34. Greijer AE, van der Wall E. The role of hypoxia inducible factor 1 (HIF-1) in hypoxia induced apoptosis. J Clin Pathol 2004;57:1009-14.

35. Voulgari A, Pintzas A. Epithelial-mesenchymal transition in cancer metastasis: mechanisms, markers and strategies to overcome drug resistance in the clinic. Biochim Biophys Acta 2009;1796:75-90.

36. Schmalhofer O, Brabletz S, Brabletz T. E-cadherin, beta-catenin, and ZEB1 in malignant progression of cancer. Cancer Metastasis Rev 2009;28:151-66.

37. Sullivan R, Graham CH. Hypoxia-driven selection of the metastatic phenotype. Cancer Metastasis Rev 2007;26:319-31.

38. Teicher BA. Hypoxia and drug resistance. Cancer Metastasis Rev 1994;13:139-68.
39. del Peso L. Hypoxia-inducible factors and cancer. Clin Transl Oncol 2004;6:3-11.
40. Isa AY, Ward TH, West CM, Slevin NJ, Homer JJ. Hypoxia in head and neck cancer. Br J Radiol 2006;79:791-8.
41. Song X, Liu X, Chi W, Liu Y, Wei L, Wang X, Yu J. Hypoxia-induced resistance to cisplatin and doxorubicin in non-small cell lung cancer is inhibited by silencing of HIF-1alpha gene. Cancer Chemother Pharmacol 2006;58:776-84.
42. Keith B, Simon MC. Hypoxia-inducible factors, stem cells, and cancer. Cell 2007;129:465-72.
43. Silván U, Díez-Torre A, Arluzea J, Andrade R, Silió M, Aréchaga J. Hypoxia and pluripotency in embryonic and embryonal carcinoma stem cell biology. Differentiation 2009;78:159-68.
44. Louie E, Nik S, Chen JS, Schmidt M, Song B, Pacson C, Chen XF, Park S, Ju J, Chen EI. Identification of a stem-like cell population by exposing metastatic breast cancer cell lines to repetitive cycles of hypoxia and reoxygenation. Breast Cancer Res 2010;12:R94.
45. Kim JW, Gao P, Dang CV. Effects of hypoxia on tumor metabolism. Cancer Metastasis Rev 2007;26:291-8.
46. Ziello JE, Jovin IS, Huang Y. Hypoxia-Inducible Factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia. Yale J Biol Med 2007;80:51-60.
47. Yeo EJ, Chun YS, Park JW. New anticancer strategies targeting HIF-1. Biochem Pharmacol 2004;68:1061-9.
48. Hong B, Lui VW, Hui EP, Ng MH, Cheng SH, Sung FL, Tsang CM, Tsao SW, Chan AT. Hypoxia-targeting by tirapazamine (TPZ) induces preferential growth inhibition of nasopharyngeal carcinoma cells with Chk1/2 activation. Invest New Drugs 2011;29:401-10.
49. Onnis B, Rapisarda A, Melillo G. Development of HIF-1 inhibitors for cancer therapy. J Cell Mol Med 2009;13:2780-6.
50. Lee K, Qian DZ, Rey S, Wei H, Liu JO, Semenza GL. Anthracycline chemotherapy inhibits HIF-1 transcriptional activity and tumor-induced mobilization of circulating angiogenic cells. Proc Natl Acad Sci U S A 2009;106:2353-8.
51. Wang Y, Saad M, Pakunlu RI, Khandare JJ, Garbuzenko OB, Vetcher AA, Soldatenkov VA, Pozharov VP, Minko T. Nonviral nanoscale-based delivery of antisense oligonucleotides targeted to hypoxia-inducible factor 1 alpha enhances the efficacy of chemotherapy in drug-resistant tumor. Clin Cancer Res 2008;14:3607-16.
52. Greenberger LM, Horak ID, Filpula D, Sapra P, Westergaard M, Frydenlund HF, Albaek C, Schrøder H, Ørum H. A RNA antagonist of hypoxia-inducible factor-1alpha, EZN-2968, inhibits tumor cell growth. Mol Cancer Ther 2008;7:3598-608.
53. Terzuoli E, Puppo M, Rapisarda A, Uranchimeg B, Cao L, Burger AM, Ziche M, Melillo G. Aminoflavone, a ligand of the aryl hydrocarbon receptor, inhibits HIF-1alpha expression in an AhR-independent fashion. Cancer Res 2010;70:6837-48.
54. Rho JK, Choi YJ, Lee JK, Ryoo BY, Na, II, Yang SH, Kim CH, Yoo YD, Lee JC. Gefitinib circumvents hypoxia-induced drug resistance by the modulation of HIF-1alpha. Oncol Rep 2009; 21:801-7.
55. Lu Y, Liang K, Li X, Fan Z. Responses of cancer cells with wild-type or tyrosine kinase domain-mutated epidermal growth factor receptor (EGFR) to EGFR-targeted therapy are linked to downregulation of hypoxia-inducible factor-1alpha. Mol Cancer 2007;6:63.
56. Chen B, Yuping S, Ni J. Rapamycin decreases survivin expression to induce NSCLC cell apoptosis under hypoxia through inhibiting HIF-1alpha induction. Mol Biol Rep 2012;39:185-91.
57. Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT. Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. Mol Cell Biol 2002;22:7004-14.
58. Melillo G. Targeting hypoxia cell signaling for cancer therapy. Cancer Metastasis Rev 2007;26:341-52.
59. Kung AL, Zabludoff SD, France DS, Freedman SJ, Tanner EA, Vieira A, Cornell-Kennon S, Lee J, Wang B, Wang J, Memmert K, Naegeli HU, Petersen F, Eck MJ, Bair KW, Wood AW, Livingston DM. Small molecule blockade of transcriptional coactivation of the hypoxia-inducible factor pathway. Cancer Cell 2004;6:33-43.
60. Manohar SM, Padgaonkar AA, Jalota-Badhwar A, Sonawane V, Rathos MJ, Kumar S, Joshi KS. A novel inhibitor of hypoxia-inducible factor-1alpha P3155 also modulates PI3K pathway and inhibits growth of prostate cancer cells. BMC Cancer 2011;11:338.
61. Staab A, Fleischer M, Loeffler J, Said HM, Katzer A, Plathow C, Einsele H, Flentje M, Vordermark D. Small interfering RNA targeting HIF-1alpha reduces hypoxia-dependent transcription and radiosensitizes hypoxic HT 1080 human fibrosarcoma cells in vitro. Strahlenther Onkol 2011;187:252-9.
62. Jensen RL, Ragel BT, Whang K, Gillespie D. Inhibition of hypoxia inducible factor-1alpha (HIF-1alpha) decreases vascular endothelial growth factor (VEGF) secretion and tumor growth in malignant gliomas. J Neurooncol 2006;78:233-47.
63. López-Lázaro M. Hypoxia-inducible factor 1 as a possible target for cancer chemoprevention. Cancer Epidemiol Biomarkers Prev 2006;15:2332-5.
64. Cummins EP, Taylor CT. Hypoxia-responsive transcription factors. Pflugers Arch 2005;450:363-71.
65. Maxwell PH, Pugh CW, Ratcliffe PJ. Activation of the HIF pathway in cancer. Curr Opin Genet Dev 2001;11:293-9.