Molecular-targeted therapy hypoxia in head and neck squamous cell carcinoma patients (Review)

MAKOTO ADACHI and LIGY THOMAS

Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Received July 9, 2012; Accepted August 21, 2012

DOI: 10.3892/mco.2012.17

Abstract. Despite advances in surgical techniques, radiotherapy, and chemotherapy, 5-year survival in patients with late-stage head and neck squamous cell carcinoma (HNSCC) have not improved significantly over the past decades. HNSCC tumors are commonly associated with hypoxia, which is characterized by an acute and/or chronic decline in oxygen tension. Hypoxia is an important cancer-aggravating microenvironmental factor that contributes to malignant behaviors such as acquisition of antiapoptotic ability by cancer cells and tumor progression, invasion, metastasis, and resistance to chemotherapy and radiotherapy. Numerous studies have assessed tumor hypoxia and identified molecular markers that are promising therapeutic targets in HNSCC cases. Moreover, investigators have suggested a number of molecular strategies to target cell processes critical to hypoxia development in HNSCC patients via the direct or indirect regulation of hypoxia-inducible factor-1α expression in cancer cells. In this review, we described recent advances in the identification and development of molecular-targeted therapy targeting hypoxia in HNSCC patients.

Contents

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the eighth most common cancer in the United States, accounting for approximately 3% of all cancers. In 2010, physicians diagnosed approximately 49,260 new cases of HNSCC and 11,480 patients succumbed to the disease in the United States (1). Despite advances in surgical techniques, radiotherapy, and chemotherapy, 5-year survival rates in patients with late-stage HNSCC have not improved significantly over the past decades. In particular, the 3- to 5-year survival rates in patients with T3 or T4 HNSCC have remained poor (20-30%) (2). Given this poor survival rate, current intensive research is directed towards improving outcomes of HNSCC by combining alternative molecular-targeted therapy with conventional therapy.

Hypoxia is common in HNSCC cells and is an important cancer-aggravating microenvironmental factor that contributes to malignant behaviors such as the acquisition of antiapoptotic ability by cancer cells, as well as tumor progression, invasion, metastasis, and resistance to chemotherapy and radiotherapy (3). It has been reported that hypoxic HNSCC cells are approximately three times more radioresistant than well-oxygenated cells as radiation damage is mainly induced by the generation of highly reactive free radicals in the presence of oxygen, causing DNA damage and, consequently, cell death. Mottram (4) first described the radioresistance of hypoxic cells, and Thomlinson and Gray (5) confirmed this resistance. Specifically, in the latter study, the authors suggested that the presence of quiescent but viable hypoxic cancer cells is able to limit the success of radiotherapy. Therefore, tumor hypoxia may be a prognostic indicator for HNSCC and may play a role in selection of therapeutic strategies for this cancer.

2. Measuring HNSCC hypoxia

Numerous studies have focused on the role of tumor hypoxia in various types of cancer. Methods used to measure tumor hypoxia include direct placement of intratumoral oxygen microelectrodes, the comet assay, and the systemic administration of drugs followed by histopathologic analysis of tumor samples. In particular, oxygen microelectrodes measure intratumoral oxygen tension, with a pO_2 value less than 2.5 mmHg considered to be clinically significant and associated with poor local control of hypoxia (6). However, pO_2 results can be misleading, as readings vary according to the location of the microelectrodes inside the tumor. Additionally, these microelectrodes can only be placed in accessible tumors. The advantage of the comet assay

Correspondence to: Dr Makoto Adachi, Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit-0123, Houston, TX 77030, USA
E-mail: madachi_dds_phd@yahoo.co.jp

Key words: head and neck cancer, hypoxia, molecular-targeted therapy

is its ability to measure DNA damage due to irradiation in hypoxic cells. Although a correlation exists between necrosis and hypoxia, the number of viable hypoxic cells has greater prognostic significance than the number of necrotic cells. The systemic administration of drugs such as nitroimidazoles, which diffuse easily into hypoxic cells due to drug solubility and low metabolism in tumor cells prior to biopsy or resection, can be used to quantify hypoxic HNSCC cells. Hypoxic cells are then identified using immunofluorescence assays or flow cytometry.

The imaging modalities used to identify hypoxia include ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), detection of radiolabeled nitroimidazoles using single-photon emission computed tomography, and dynamic contrast-enhanced magnetic resonance imaging. Studies examining the ability of ^{18}F-FDG PET to detect tumor hypoxia have had mixed results (7,8). Tracers used in PET instead of ^{18}F-FDG include metal-labeled markers such as copper-labeled diacetyl-bis(N^4methylthiosemicarbazone). Dynamic contrast-enhanced magnetic resonance imaging can also be used to assess tumor perfusion and, thus, indirectly assess tumor oxygenation. Evidence regarding its usefulness in predicting response to cervical cancer and HNSCC to radiotherapy has been reported (9,10).

3. Molecular markers of hypoxia

Recent studies have identified molecular markers of hypoxia that are promising therapeutic targets in HNSCC patients (11). Endogenous molecular markers include hypoxia-inducible factor (HIF)-1α, HIF-2α, glucose transporter 1 (Glut-1), and carbonic anhydrase IX. HIF-1α and HIF-2α are transcription factors that mediate the cell response to hypoxia and are highly expressed in solid tumors containing hypoxic regions (12). These two factors upregulate the expression of vascular endothelial growth factor, Glut-1, and carbonic anhydrase IX, causing their intracellular levels to increase within 2 min of exposure to hypoxia. Overexpression of HIF-1α in HNSCC cells is positively correlated with local tumor aggressiveness, increased tumor angiogenesis, poor prognosis (13,14), and resistance to radiotherapy and chemotherapy (15,16). The correlation between the expression of HIF-1α and resistance to chemotherapy may be explained by the results of *in vivo* studies showing that the sensitivity of tumors to alkylating agents may depend on Glut-1 expression in cancer cells (17).

4. Strategies for modifying tumor hypoxia

A number of hypoxia-modifying strategies have been examined, with little to moderate success, including the use of hyperbaric oxygen therapy, carbogen, nicotinamide with radiotherapy, tirapazamine (a bioreductive agent with selective cytotoxicity in hypoxic cells) with chemoradiation, and radiosensitizers including nimorazole with radiotherapy (18).

Several molecular strategies have been suggested in the targeting of cell processes for the modification of hypoxia through the direct or indirect regulation of HIF-1α expression in tumor cells (19). Investigators pursuing direct regulation have identified and investigated small molecular targets, HIF-1α, and examined their use as therapeutic agents for hypoxia. One of these molecules, S-2-amino-3-(4'-N,N,-bis[2-chloroethyl] amino)phenyl propionic acid N-oxide dihydrochloride (PX-478), reduces the constitutive and hypoxia-induced expression of HIF-1α in cancer cells and inhibits the expression of vascular endothelial growth factor and Glut-1. Inhibition of tumor growth induced by treatment with this molecule appears to correlate with the inhibition of glucose metabolism rather than of angiogenesis (20). Thus, PX-478 has been assessed in phase 1 studies (21).

Currently, topotecan is used in chemotherapy for small-cell lung cancer and ovarian cancer (21). However, combination of the HIF-1α inhibitor with conventional chemotherapeutic agents or with an emerging molecular-targeted agent may have greater clinical efficacy against hypoxia than either therapy alone (13). Investigators studying the indirect regulation of HIF-1α expression in cancer cells have reported that hypoxia-responsive transcription factors and signaling mechanisms that lead to activation of these factors, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling axis and Janus kinase/signal transducer and activator of transcription (STAT) signaling pathway, may be targets for hypoxia therapy (13). STAT3 and HIF-1 activate the vascular endothelial growth factor (VEGF) gene in response to PI3K/Akt/mTOR signaling pathways. For example, the STAT3 inhibitor Stattic has been reported to inhibit STAT3 activation induced by the phosphorylation and concurrent HIF-1 expression in HNSCC cells, leading to tumor supression and enhanced tumor radiosensitivity (22). Therefore, STAT3 is a potential molecular therapeutic target for HNSCC, particularly in hypoxic environments.

5. Conclusion

Hypoxia in HNSCC must be addressed to improve treatment efficacy. Increased knowledge of the molecular biology of hypoxia is likely to enhance its detection, assessment of its relevance, and overcoming its negative influence in treatment of HNSCC.

Acknowledgements

Makoto Adachi is funded by the Uehara Memorial Foundation Postdoctoral Fellowship and the Japan Society for the Promotion of Science Postdoctoral Fellowship for Research Abroad. This review is funded in part by the MD Anderson Cancer Center Support Grant CA016672.

References

1. Jemal A, Siegel R, Xu J and Ward E: Cancer statistics. CA Cancer J Clin 60: 277-300, 2010.
2. Choong N and Vokes E: Expanding role of the medical oncologist in the management of head and neck cancer. CA Cancer J Clin 58: 32-53, 2008.
3. Karar J and Maity A: Modulating the tumor microenvironment to increase radiation responsiveness. Cancer Biol Ther 8: 1994-2001, 2009.
4. Mottram JC: A factor of importance in the radio sensitivity of tumours. Br J Radiol 9: 606-614, 1936.
5. Thomlinson RH and Gray LH: The histological structure of some human lung cancers and the possible implications for radiotherapy. Br J Cancer 9: 539-549, 1955.

6. Nordsmark M, Overgaard M and Overgaard J: Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. Radiother Oncol 41: 31-39, 1996.
7. Rajendran JG, Mankoff DA, O'Sullivan F, *et al*: Hypoxia and glucose metabolism in malignant tumors: evaluation by [18F] fluoromisonidazole and [18F]fluorodeoxyglucose positron emission tomography imaging. Clin Cancer Res 10: 2245-2252, 2004.
8. Bentzen L, Keiding S, Horsman MR, Falborg L, Hansen SB and Overgaard J: Feasibility of detecting hypoxia in experimental mouse tumours with 18F-fluorinated tracers and positron emission tomography - a study evaluating [18F]fluoro-2-deoxy-D-glucose. Acta Oncol 39: 629-637, 2000.
9. Cooper RA, Carrington BM, Loncaster JA, *et al*: Tumour oxygenation levels correlate with dynamic contrast-enhanced magnetic resonance imaging parameters in carcinoma of the cervix. Radiother Oncol 57: 53-59, 2000.
10. Hoskin PJ, Saunders MI, Goodchild K, Powell ME, Taylor NJ and Baddeley H: Dynamic contrast enhanced magnetic resonance scanning as a predictor of response to accelerated radiotherapy for advanced head and neck cancer. Br J Radiol 72: 1093-1098, 1999.
11. Ferreira MB, De Souza JA and Cohen EE: Role of molecular markers in the management of head and neck cancers. Curr Opin Oncol 23: 259-264, 2011.
12. Melillo G: Inhibiting hypoxia-inducible factor 1 for cancer therapy. Mol Cancer Res 4: 601-605, 2006.
13. Aebersold DM, Burri P, Beer KT, *et al*: Expression of hypoxia-inducible factor-1alpha: a novel predictive and prognostic parameter in the radiotherapy of oropharyngeal cancer. Cancer Res 61: 2911-2916, 2001.
14. Yeo EJ, Chun YS and Park JW: New anticancer strategies targeting HIF-1. Biochem Pharmacol 68: 1061-1069, 2004.
15. Semenza GL: Intratumoral hypoxia, radiation resistance, and HIF-1. Cancer Cell 5: 405-406, 2004.
16. Rohwer N, Lobitz S, Daskalow K, *et al*: HIF-1alpha determines the metastatic potential of gastric cancer cells. Br J Cancer 100: 772-781, 2009.
17. Airley RE, Phillips RM, Evans AE, *et al*: Hypoxia-regulated glucose transporter Glut-1 may influence chemosensitivity to some alkylating agents: Results of EORTC (First Translational Award) study of the relevance of tumour hypoxia to the outcome of chemotherapy in human tumour-derived xenografts. Int J Oncol 26: 1477-1484, 2005.
18. Isa AY, Ward TH, West CM, Slevin NJ and Homer JJ: Hypoxia in head and neck cancer. Br J Radiol 79: 791-798, 2006.
19. Semenza GL: Targeting HIF-1 for cancer therapy. Nat Rev Cancer 3: 721-732, 2003.
20. Welsh S, Williams R, Kirkpatrick L, Paine-Murrieta G and Powis G: Antitumor activity and pharmacodynamic properties of PX-478, an inhibitor of hypoxia-inducible factor-1alpha. Mol Cancer Ther 3: 233-244, 2004.
21. Xia Y, Choi HK and Lee K: Recent advances in hypoxia-inducible factor (HIF)-1 inhibitors. Eur J Med Chem 49: 24-40, 2012.
22. Adachi M, Cui C, Dodge CT, Bhayani MK and Lai SY: Targeting STAT3 inhibits growth and enhances radiosensitivity in head and neck squamous cell carcinoma. Oral Oncol: Jul 6, 2012 (E-pub ahead of print).