The Korean Journal of Hepatology 2010;16:278-279
DOI: 10.3350/kjhep.2010.16.3.278

Editorial

Hypoxia-inducible factor 1, hepatocellular carcinoma and angiogenesis

Jin-Wook Kim

Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

See Article on Page 280

Angiogenesis is essential for tumor growth,[1] and it has been shown that anti-angiogenic therapy has been proven to be effective in several cancers such as colorectal cancer[2,3] and hepatocellular carcinoma (HCC).[4] Currently available anti-angiogenic cancer chemotherapy targets the vascular endothelial growth factor (VEGF) pathway by VEGF monoclonal antibody (bevacizumab)[3] or multi-targeted receptor tyrosine kinase inhibitors (sorafenib).[4] Hypoxia-inducible factor 1 (HIF-1) is a heterodimer protein which is composed of oxygen-regulated HIF-1α subunit and constitutively expressed HIF-1β subunit.[5,6] Under normoxic condition, the degradation of HIF-1α subunit is facilitated by ubiquitination following the hydroxylation of proline residue(s). However, under hypoxic condition, stability of HIF-1α increases due to suppressed proline hydroxylation, leading to increased transcription of genes associated with adaptive homeostatic response to hypoxia such as erythropoiesis, glucose metabolism and angiogenesis.[7] In addition to intratumoral hypoxia, loss of function of tumor-suppressor genes also contributes to over-expression of HIF-1α in various human cancers.[6] HIF-1 is a key regulatory factor for angiogenesis in response to hypoxia: it induces expression of angiogenic growth factors such as VEGF, stromal derived factor 1, angiopoietin 2, placental growth factor, platelet-derived growth factor B and stem cell factor.[8] Many human cancers over-express HIF-1α, and expression of HIF-1α is associated with poor prognosis.[6,9] In hepatitis B virus-associated HCC, high expression of HIF-1α is found in half of tumor specimens and correlated with venous invasion and lymph node invasion.[10] These findings suggest the possibility of HIF-1α as a novel therapeutic target in HCC.

In the current issue, Choi et al. suppressed HIF-1α by adenovirus-mediated small hairpin RNA and observed that proliferation of hepatoma cell lines was suppressed and the new vessel formation by vascular endothelial cells was inhibited.[11] This suppressive effect against hepatoma cells is concordant with the report by WeiXing et al. which knocked down HIF-1α by antisense oligonucleotide.[12] In the current study, however, the mechanisms by which HIF-1α directly inhibits the proliferation of hepatoma cell lines were not examined. In hypoxic state, HIF-1 can either induce or inhibit apoptosis.[13] Moreover, a recent report shows that knock-down of HIF-1α causes reciprocal increase of HIF-2α and vice versa, leading to attenuated apoptosis in HepG2 cells.[14] Therefore, further studies are warranted to examine the effects of HIF-1α on the apoptosis and proliferation of HCC in hypoxic state.

Recent reports including this study by Choi et al. have demonstrated that knock-down of HIF-1α by small interfering RNA[15] or short hairpin RNA can disrupt angiogenesis by HUVEC cells. However, the therapeutic potential of anti-angiogenic effect by targeting HIF-1 needs to be further validated in animal HCC models. One recent study targeting HIF-1α showed suppressed tumor growth and microvessel density in a murine subcutaneous HCC model.[16] However, two reports assessing the effect of HIF-1α on the tumor growth in orthotopic hepatoma models showed conflicting results.[17,18] These results imply that

Keywords: Hypoxia-inducible factor 1; Hepatocellular carcinoma; Angiogenesis

Corresponding author: Jin-Wook Kim
Department of Internal Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam 463-707, Korea
Tel. +82-31-787-7009, Fax. +82-31-787-4051, E-mail; kimjw@snubh.org

the action of HIF-1 may be influenced by the types of tumor cells and/or the stromal components of the tumor.[9] Further animal studies are also warranted to examine the efficacy of combination therapy that includes HIF-1α targeting and conventional types of anti-cancer drugs.

REFERENCES

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971;285:1182-1186.
2. Wagner AD, Arnold D, Grothey AA, Haerting J, Unverzagt S. Anti-angiogenic therapies for metastatic colorectal cancer. Cochrane Database Syst Rev 2009;3:CD005392.
3. Reinacher-Schick A, Pohl M, Schmiegel W. Drug insight: antiangiogenic therapies for gastrointestinal cancers-focus on monoclonal antibodies. Nat Clin Pract Gastroenterol Hepatol 2008;5:250-267.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359:378-390.
5. Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci USA 1995;92:5510-5514.
6. Semenza GL. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene 2010;29:625-634.
7. Semenza GL. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. Physiology (Bethesda) 2009;24:97-106.
8. Rey S, Semenza GL. Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling. Cardiovasc Res 2010; 86:236-242.
9. Melillo G. Inhibiting hypoxia-inducible factor 1 for cancer therapy. Mol Cancer Res 2006;4:601-605.
10. Xie H, Song J, Liu K, Ji H, Shen H, Hu S, et al. The expression of hypoxia-inducible factor-1alpha in hepatitis B virus-related hepatocellular carcinoma: correlation with patients' prognosis and hepatitis B virus X protein. Dig Dis Sci 2008;53:3225-3233.
11. Choi SH, Shin HW, Park JY, Yoo JY, Kim DY, Rho WS, et al. Effects of the knockdown of hypoxia-inducible factor-1alpha expression by adenovirus-mediated shRNA on angiogenesis and tumor growth inhibition in hepatocellular carcinoma cell lines. Korean J Hepatol 2010;16:280-287.
12. WeiXing C, Tiantian H, Qun N, Chaohui Y, Ping X. Inhibitory effect of hypoxia inducible factor-1 antisense oligonucleotide on growth of human hepatocellular carcinoma cells. Med Oncol 2008;25:88-92.
13. Greijer AE, van der Wall E. The role of hypoxia inducible factor 1 (HIF-1) in hypoxia induced apoptosis. J Clin Pathol 2004;57:1009-1014.
14. Menrad H, Werno C, Schmid T, Copanaki E, Deller T, Dehne N, et al. Roles of hypoxia-inducible factor-1alpha (HIF-1alpha) versus HIF-2alpha in the survival of hepatocellular tumor spheroids. Hepatology 2010;51:2183-2192.
15. Jiang J, Xia XB, Xu HZ, Xiong Y, Song WT, Xiong SQ, et al. Inhibition of retinal neovascularization by gene transfer of small interfering RNA targeting HIF-1alpha and VEGF. J Cell Physiol 2009;218:66-74.
16. Liu F, Wang P, Jiang X, Tan G, Qiao H, Jiang H, et al. Antisense hypoxia-inducible factor 1alpha gene therapy enhances the therapeutic efficacy of doxorubicin to combat hepatocellular carcinoma. Cancer Sci 2008;99:2055-2061.
17. Sun X, Jiang H, Jiang X, Tan H, Meng Q, Sun B, et al. Antisense hypoxia-inducible factor-1alpha augments transcatheter arterial embolization in the treatment of hepatocellular carcinomas in rats. Hum Gene Ther 2009;20:314-324.
18. Daskalow K, Rohwer N, Raskopf E, Dupuy E, Kuhl A, Loddenkemper C, et al. Role of hypoxia-inducible transcription factor 1 alpha for progression and chemosensitivity of murine hepatocellular carcinoma. J Mol Med 2010;88:817-827.