Author's response to reviews

Title: Expressions of HIF-1alpha and VEGF in colorectal cancer: correlations with clinical outcomes and prognostic implications

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Author's response to reviews: see over
Dear editors:

Here is a manuscript by Dan Cao, Mei Hou, Yong-song Guan, Ming Jiang, Yu Yang, and Hong-feng Gou, entitled “Expression of HIF-1alpha and VEGF in colorectal cancer: association with clinical outcomes and prognostic implications”. It’s submitted to be considered for publication in BMC Cancer as a research article. This paper is new, neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal. The manuscript has been extensively revised with the help of medical experts with excellent written English.

We believe that this research may be of particular interest to the readers of your journal. Although HIF-1 alpha and VEGF were reported to be expressed in many types of cancers, up until now, few studies have been carried out to investigate the prognostic role of these factors in solid tumors, in particular, in human colorectal cancer. The aim of this study was to evaluate the immunohistochemical reactivity of HIF-1α and VEGF in CRC biopsies, and to analyze the association of these two factors with some clinical and histological characteristics, and with patients’ survival. HIF-1α and VEGF could be used as biomarkers indicating tumor infiltration and poor prognosis in colorectal cancer. HIF-1α inhibition might be a promising targeted therapy in CRC to exhibit its potential to improve outcomes in future perspective, just as VEGF targeting has proved to be.

All authors have given their approval for the submission of the paper.

Correspondence and phone calls about the paper should be directed to Dr. Mei Hou at the following address, phone, and e-mail address:

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Response to reviewers’ comments:

**Dear Reviewer1:**

Thank you for your second answer. We think our study is novel in aspect of association between tumor hypoxic biology and clinical features including clinicopathological factors and patients’ survival. Although HIF-1α and VEGF were reported to be expressed in many types of cancers, few studies have been carried out to analyze whether expression of these two factors is associated with clinical outcomes and prognostic implications in human colorectal cancer. The aim of our study was to investigate the effects of HIF-1α and VEGF expression on clinicohistological features and prognosis in human colorectal cancer, and the correlation between HIF-1α and VEGF. And our results suggest that HIF-1α and VEGF are important regulators of angiogenesis and closely related. HIF-1α and VEGF could be used as biomarkers indicating tumor infiltration and poor prognosis in colorectal cancer. HIF-1α inhibition might be a promising targeted therapy in CRC to exhibit its potential to improve outcomes in future perspective.

The written language has been revised extensively by scholars of medical English carefully.

**Dear Associate Editor:**

Thank you for your valuable advice. We think that the interests of the two articles you mentioned are different from our paper in some aspects.

1. About the article by Cleven et al (Cell Oncol. 2007; 29(3):229-40):

   The article aimed to examine the role of protein expression of hypoxia-inducible factor (HIF)-1alpha, HIF-2alpha, carbonic anhydrase 9 (CA9) and glucose transporter 1 (GLUT1) in patients with colorectal adenocarcinomas. The results showed stromal HIF-2alpha expression was an independent prognostic factor for survival, not HIF-1alpha. As we know from current studies, HIF-1alpha and VEGF play more important roles in angiogenesis. The aim of this study was to evaluate the effects of HIF-1 alpha and VEGF expression on clinical outcomes and prognosis in human colorectal cancer, and the correlation between HIF-1 alpha and VEGF.

2. About the article by Rasheed et al (Br J Cancer)
We had finished our paper before the article was published. Now the article was used as cited reference in our paper. This study investigated hypoxia-inducible factor-1alpha (HIF-1alpha) and HIF-2alpha protein expression in relation to rectal cancer recurrence and cancer-specific survival. But our study was about colorectal carcinoma patients, not only rectal cancer. As HIF-1α and VEGF are important regulators of angiogenesis, understanding association of tumor biology and clinical features is crucial for the development of antiangiogenic therapy. The aim of our study was to investigate the effects of HIF-1α and VEGF expression on clinical outcomes and prognostic implications, and correlation between these factors in human colorectal carcinoma.

We think that our study is novel in exploring the association between tumor biology in hypoxic condition and clinical features, and evaluating the effects of HIF-1α and VEGF expression on clinical outcomes and prognosis in human colorectal cancer and the correlation between HIF-1α and VEGF. Our results showed that the expression of HIF-1α and VEGF implied advanced stage and poor prognosis, and HIF-1α was positively correlative to VEGF in colorectal cancer. It was concluded that HIF-1α and VEGF could be used as biomarkers of indicating tumor infiltration and poor prognosis in colorectal cancer. HIF-1α inhibition might be a promising targeted therapy in CRC, which has the potential to improve outcomes in future perspective, just as VEGF targeting has proved to be. The clinical value of the two factors were initially identified, further research is anticipated.

The paper has been rewritten extensively with grammatical as well as typographical errors corrected carefully. We hope that this version will be easy reading with facts and ideas stated clearly. Yong-Song Guan helped to write, organize and correct the paper.