

February 8, 2015

Dear editor,

Please find enclosed the edited manuscript in Word format(file name: 15359-article.doc).

**Title:** Alternative splicing of VEGFA, APP and NUMB genes in colorectal cancer

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 15359

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated.
2. Revisions have been made according to the suggestions of the reviewer and highlighted in red.
  - (1) Stylistic changes and language correction have been made according to the suggestions of reviewers in order to increase the clarity of text.
  - (2) Description and biological significance of alternative splicing of VEGFA, APP and NUMB have been added in introduction and the paragraphs in discussion were properly shortened.
  - (3) We have revised the first three paragraphs of the discussion to focus on biological significance of the present data and explain the possible pathways. And the relative content has been added in the manuscript.
  - (4) Why we focused on the VEGFA165, 121 and 206 among all the isoforms has been added in the first paragraph of discussion. VEGFA121a/b is unable to bind to heparin, while VEGFA165a/b and VEGFA206a/b are heparin-binding isoforms. As previous studies demonstrated that VEGFA121a/b, VEGFA165a/b and VEGFA206a/b are closely associated with various cancers, our study mainly focuses on the expression of these

isoforms in CRC

(5) The protocol of PCR-RFLP has been provide in the revised manuscript in detailed in the section of "MATERIALS AND METHODS" on page 6-7 according to the reviewers' suggestion..

(6) We have performed qRT-PCR and PCR-RFLP analyses to detect the matched normal and tumor tissues of another 20 CRC patients from our sample database, and used statistical methods to analyze all the data.

(7)We have been rearranged and reedited these figures, combined the original Fig 4-6 into a new Fig 5, and added a new Figure 4 "Electrophoregram of alternative splicing variants in VEGFA, APP and NUMB" to make the presentation of our results more rational.

(8) Due to the case number has been up to 40, six cases had synchronous hepatic metastases, the primary tumor and hepatic tumors were simultaneously resected during surgery. Postoperative pathology confirmed that all CRC and hepatic metastases samples were tubular adenocarcinoma.

(9) Related literatures have been added and adjusted in the revised manuscript and highlighted in red.

(10) The explanation of the result about relationship between the expression of VEGFA, APP and NUMB mRNA with depth of tumor infiltration, the presence of lymph node metastasis and TNM stages, has been added in the discussion

(11) " $*P < 0.05$ " has been changed into " $**P < 0.01$ " in the presentation of Fig 1-3 and " $**P < 0.01$ " has been changed into " $***P < 0.001$ " in Fig 6.

(12) All of the figures have been adjusted according to the "Revision Policies" in order to meet the requirement which figures should be 85mm in height and 126mm in width, and at a resolution of 300dpi.

(13) The spelling of the author's name "Qin-Chao Zhu" has been revised into "Qing-Chao Zhu".

(14) The statistical methods of this study were reviewed by Yi-Jun Zhao, Hua-Zhong Han, Chen-Zhang Shi, Qing-Chao Zhu and Jun Yang, from Department of Surgery, Sixth People's Hospital affiliated to Shanghai Jiao Tong University

(15) Grammatical and spelling errors have been revised by a professional English language editing company of jingyunma-editing office, and a recommendation certificate have been provided(Verification Code: 2015-02-38).

3. References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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