Dear Editors and Reviewers:
Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Overexpression of CREPT confers colorectal cancer sensitivity to Fluorouracil" (Manuscript NO.: 36554). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1 (code: 01207047):
We appreciate the reviewers' careful and professional review. We are grateful that the reviewers' classification of our paper was "grade B (Very good)". Considering the given comments and suggestions, we made the following responses:

1- The pathologic terms, "high differentiation, medium and low differentiation are not suitable. Instead it will be better to use, "well differentiated, moderately differentiated and poorly differentiated".

   We have made correction according to the Reviewer's comments.

2- It will be nice to add a pathologist to their author list.

   The second author, Yi Wang, who is a pathology doctor, contributed significantly to the analysis of the IHC samples.

3- Results part: what does they mean with margin? Is it tumor margin or benign stromal tissue at the tumor periphery?

   We are very sorry for our vague definition of margin, we have added specifically statement in the manuscript that margin is the benign stromal tissue at the tumor periphery.

4- Results part: which pathologic type did show positive association with high CREPT expression? Please explain in the text.

   As is shown in Tab.1&2, high CREPT expression is detected in malignant tumor and high differentiation tumors. Compared to well differentiation samples, relatively less moderate and poorly differentiation samples were included. Further study is needed.

5- Figure 1 A: The tissue seems like normal colonic mucosa not an adenoma.

   Considering the Reviewer's question, we have re-conferred the pathology

diagnosis of that patient and the result is adenoma.

6- Figure 2B: In Kaplan-Meier graphics please indicate which lines do belong to patients with high Level of CREPT and patients with low level of CREPT. And in the results part please mention about The Kaplan-Meier graphic results.

We have made correction according to the Reviewer's comments. And we has modification of the Kaplan-Meier results in the result part.

7- Figure 2A: I think there is an error about differentiation. In pathology highly differentiated tumor means well differentiated. So CREPT level should be low. Low differentiation means poorly differentiated tumor and CREPT level should be high.

As is mentioned in the Result part:" Abundant expression of CREPT is observed in well differentiation tumors compared to moderately and poorly differentiation tumors (Figure 2A and Table 2)." In this research, our data indicates CREPT level is higher in well differentiated tumor compared to poor differentiated tumor.

Reviewer #2 (code: 03478911) :
We thank the reviewer's carefully reading and significative comments. Considering your comments, we made the following responses.

Major points:

1. There are a lot of reports about the relationship between CREPT expression and colorectal cancer progression (eg. Zheng G., et., al. 2016), however the authors did not describe what is different point with the previous reports.

   We appreciated the reviewer's serious comment. Compared to bought tissue microarray, samples in this study are first-hand samples from our hospital. We have confidence in our data. Besides, our research focuses on drug resistance analysis instead of clinicopathological features exploitation.

2. Please consider this point. Increased CREPT is a sign of poor prognosis, and it is contradictory that 5-FU will be treated to such patients. If not, please describe the authors' opinion in the discussion part.

   Considering the reviewer's suggestion, we have described in the result part that CRC patients with abundant CREPT expression are more likely to benefit from 5-FU-based chemotherapy. However, further study is needed to address which has greater impact on patients' clinical outcomes.

3. Is the purpose of this paper to simply exploring the CREPT for diagnostic purposes to enhance 5-FU efficacy? If not so, this reviewer though that it would be appropriate to treat 5-FU in patients with increased CREPT and concomitant therapy to reduce CREPT will be processed.

   The reviewer gave us an ingenious comment. Whether it is appropriate to treat 5-FU in patients with increased CREPT requires further randomized controlled trial and we are planning to perform the trail in the next step. Besides, according to our pervious study, CREPT is a nucleoprotein. To our knowledge, therapies targeting nucleoprotein is still under research, but it is a promising research area.

Minor points:

1. It will need to abide by the rules for using abbreviations.

   Thank you for your comment, we have made corrections in the manuscript.

2. There are a lot of grammatical errors.

   Thank you for your comment, we have the manuscript reviewed by an

native English speaker and made some corrections to the errors.

Reviewer #3 (code: 03505493):
Thank you for you earnestly careful review and we were pleased to receive that your classification of our paper was "grade C (Good)". Considering your detailed comments and suggestions, we made the following responses.

Major points:

1. Summarize in 1 or max 2 sentences this last part of the introduction, since it is too long and inappropriate in this place: "Here we set out to systematically determine the expression of CREPT in either CRC clinical samples or the established colorectal cell lines. Moreover, the relationship between CREPT expression and tumor progression has been comprehensively analyzed. The indispensable roles of CREPT in CRC was evaluated with manipulation the expression of CREPT. Most importantly, the potential role of CRETP expression in modulation of 5-FU sensitivity in CRC cell line was elucidated in our system. Based on all these results, we suggested that fundamental role of CREPT in tumorigenesis of CRC via inducing proliferation and stimulating cell cycle. Contradictorily, the over-expression of CREPT rendered cell sensitivity to chemotherapeutic drug 5-FU as well, which reinforced the apoptotic response. We proposed the prognostic biomarker function of CREPT for clinical application of 5-FU in addition to its conventional view as an oncogene". Please use 1 or 2 sentences, this is not acceptable as part of introduction, it seems a part of results mixed with discussion.

   It is true as Reviewer suggested that this part of introduction is long-winded and we have make some simplify and correction about this part.

2. Method: "The proportion of positive cancer cell staining was classified on a scale of 3 grades: (-), no positive cells; (1+), < 25%; (2+), 25-75%; (3+) >75%.". This scale has 4 grades and not three: first grade: (-) = no positive cells; second grade (1+) <25%; third grade 25-75%, 4th grade >75%. Please correct this point. Also please explain the choice of this peculiar score. Please indicate better the protocol of immunohistochemical analysis, the Source (manufacturer) and the method in a specific way (antigen retrival, incubation,…)

   We are very sorry for our negligence and have made correction according to your comments. As the reviewer suggested, the detailed protocol is added to the manuscript. Our score is based on our pre-experiments. Since the CREPT antibody is raised in our lab, related research of our publications on carcinomas used this score system, therefore, we followed this routine.

3. 5-FU is used also in other cancer types. Please discuss this point and write a comment indicating if your data may be translated for other cancer types or may address future research.

   This is a valuable and helpful comment, and we have discussed on this point and added to the discussion part.

4. In the text you have used the terms of "benign adenoma": please remove benign, since adenoma are precancerous lesions, benign may indicate that they are not invasive but this word is formally incorrect in this context.

   We are very sorry for our incorrect writing and correction has been made.

Minor points:

1. Introduction: "Colorectal cancer (CRC) is a malignance disease with apparent signs or symptoms such as blood in the stool, aberrance in bowel movement and weight loss [1]." Malignance or malignant? Please use correct words.

   We are very sorry for our incorrect writing and correction has been made.

2. Introduction: "Globally, colorectal cancer is the third most common malignance". Please use malignancy or tumor, malignance is not a good word in a scientific paper.

   We are very sorry for our incorrect writing and correction has been made.

3. I see a part of Fig.4 overlapped on figure 4 legend, please correct overlapping if it is due to your error, if not it will be corrected by the journal.

   We are sorry for our carelessness and correction has been made.

Other changes:

1. Result Part: ″ A significant increase of CREPT was detected in the CRC tissues in comparison with benign tissues (77% vs 46%, Figure 1A, B)″ ,″Table 1″ was add.
2. Figure 1D was moved because it was overlapped by other figures
3. Figure 4D, we remove this figure legend because it was mistakenly added.
4. Table 1&2: "*" was added to indicate there is significant difference.

All the changes are marked in red and/or noted in the manuscript, we tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.

We appreciate for Editors and Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.