Dear Dr. Ma and reviewers:

We must thank you and all reviewers for the critical feedback. We feel lucky that our manuscript went to these reviewers as the valuable comments from them not only helped us with the improvement of our manuscript, but suggested some neat ideas for future studies. Please do forward our heartfelt thanks to these experts.

Based on the comments we received, careful modifications have been made to the manuscript. Revised portion are marked in blue in the paper.

We hope that these revisions are satisfactory and that the revised version will be acceptable for publication in “World Journal of Gastroenterology". If you have any queries, please don’t hesitate to contact me. Below you will find our point-by-point responses to the reviewers' comments/ questions:

Reviewers' comments:

REVIEWER 1 EVALUATION

This study is in general well planned and performed. I have only one major suggestion and a few minor comments to improve the manuscript.

1. Major: it would be helpful to check the correlation between important molecular features (subtype, BRAF, KRAS and/or P53 mutations, MSI Status CIMP Status) and CASC19 and CEMIP expression.

Response: Thank you very much for your valuable suggestion. In fact, our team is performing genome-wide sequencing of some tumor tissues, mRNA expression in the same tissue sample, and expression of non-coding RNA in the same tissue sample. In the present study, we mainly focused on the regulation of colon cancer cells by CASC19 and the possible mechanisms of its action. Your suggestion gives us new ideas and directions. In future studies, we will further analyze gene mutations and the relationship between microsatellite status and non-coding RNA. Thank you very much.

2. Minor: the term chemotherapy is not suited to describe a targeting of CEMIP or CASC19. "Frozen in liquid nitrogen at -80°C" in materials and methods is incorrect.

Response: Thank you very much for your valuable comment.
I am sorry for our mistakes, we have made corrections in accordance with the advice you have given. The term “chemotherapy” has been changed to “therapy”. The sentence “Frozen in liquid nitrogen at -80°C” has been changed to “Frozen in liquid nitrogen and stored at -80°C”.

REVIEWER 2 EVALUATION

Wang and co-workers examine the mechanism by which the long non-coding RNA CASC19 regulates proliferation and metastasis in CCR. They found that CASC19 positively regulated CEMIP expression and epithelial-to-mesenchymal transition through targeting of miR-140-5p. The state-of-the art is adequate as well as the methodology used. The conclusions are in concordance with the results obtained. The paper can be published in its actual format.

Response: Thank you for your recognition of our research. We have re-examined the entire document and the research content, and have made some changes to some of the misnomers. In the future research work, we will be more serious and hard work.

REVIEWER 3 EVALUATION

1. Some of the methods is described with some inaccuracies. For example: - Paragraph "Wound-healing and transwell assay": How has been the wound healing assay evaluated and quantified? The Authors must describe this detail . Paragraph "CASC19 promoted CRC cell migration and invasion in vitro": Pg. 7 lane 46 "percent wound closure (%) ". How has been calculated this %?

Response: Thank you very much for your valuable comment. The method of "percent wound closure (%)" have been described in the Paragraph "Wound-healing and transwell assay" as follows: The area of open wound covered by cells was described in terms of "percent wound closure (%)" ((Scratch distance $_{0h}$- Scratch distance $_{24h}$)/ Scratch distance $_{0h}$×100%, the distances were measured by Image J).

2. Paragraph "Immunohistochemistry assay", pg 6, lanes 17-29: The method is described in a confusing manner, since the English is not fluent. I suggest modifying the text as following: "The Immunohistochemistry assay determined CEMIP expression in CRC tissues and adjacent normal colon mucosa tissues as described in our previous study [37]. Briefly, tissue samples were fixed in 4% paraformaldehyde, embedded in paraffin and sliced into 4 μm sections. Dehydration was carried out with xylene and a gradient of ethanol solution before the endogenous peroxidase blocking with a 3% H2O2 solution. The antigen retrieval was performed with heated sodium citrate solution (92°C–95°C, 10 nM, pH 6.0) for 5 minutes and 1% goat serum was added to the sections at room temperature for 2 minutes to block the sections. Rabbit anti-human CEMIP antibody (1:150; CST, USA) was applied onto the sections and left overnight to incubate at 4°C. After incubation with the secondary antibody 1h at RT, freshly prepared diaminobenzidine was then added to the sections that were then stained with hematoxylin. A light microscope (Leica

Microsystems, Wetzlar, Germany) was used to visualize slides and brown particles in the cytoplasm or cytomembranes were taken to indicate positive staining."

Response: Thank you very much for your valuable comment. We have corrected manuscript by native speakers of English.

3. Pg. 6, Lane 46: " Concurrently , the CASC19 expression in CRC cell lines was markedly elevated...." The term "Concurrently" is not appropriate: "Consistently" or "Coherently" should be more adequate.
Pg. 7 lane 5: " based on whether the patient had lymph node or liver metastasis"..." based on whether the patient had or not lymph node or liver metastasis"
Paragraph "CASC19 promoted CEMIP expression by targeting miR-140-5p", pg. 8 lane 34: "A luciferase reporter assay was carried out to determine if miR-140-5p could directly target miR-140-5p". Perhaps it should be "A luciferase reporter assay was carried out to determine if CASC19 could directly target miR-140-5p." - Paragraph "MiR-140-5p reverses the promoting effect of CASC19 on the proliferation and metastasis of CRC cells".
It is not proper to use the term "metastasis " in an in vitro systems… "metastasizing ability" should be more appropriate. This should be also modified in other points of the manuscript (same paragraph, pg. 9 lane 16; INTRODUCTION, pg.3 lane 33; CONCLUSION, pg. 9 lane 38)
DISCUSSION - pg. 9 lane 29: "Currently, in our study,…" should be: "In our study,…" - pg. 9 lane 31: "…research results…" should be only "…results...": "research" is redundant - pg.10 lane 8: "...there was an endogenous reaction between these two molecules..."should be "...there was an endogenous interaction between these two molecules..."

Response: Thank you very much for your valuable comment. We have corrected manuscript by native speakers of English.

4. Pg 7, lanes 1-2: "For further in vitro studies, HCT-116 and SW480 cell lines were used…" I suggest to replace with: " and this was confirmed for all the four cell line used (HCT-116 and SW480 SW620 and LOVO cells)".

Response: Thank you very much for your valuable comment. In the subsequent experiments, we followed the experimental principle and selected two kinds of cells as the main research objects. Although the relative mRNA expression of CEMIP and relative miR-140-5p were measured in all 4 cell lines, not all experiments were validated in 4 cell lines. So we propose that "For further *in vitro* studies, HCT-116 and SW480 cell lines were used".

5. In Table 1 TNM stages are not legible

Response: Thank you very much for your valuable comment. In our study, patients were staged in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis classification. Patients in the early stage (TNM stage Ⅰ and Ⅱ) and patients in the advanced stage (TNM stage Ⅲ and Ⅳ) were divided into 2 cohorts. We aimed to study the different CASC19 expression the early and advanced stage of patients with colorectal cancer because we think that CASC19 may associate with tumor progression. Then we analyzed CASC19 expression in TNM stage Ⅰ to Ⅳ separately, as shown in the figure below, CASC 19 expressions were not significantly different in TNM stage Ⅰ and Ⅱ (*P*=0.646), TNM stage Ⅲ and Ⅳ(*P*=0.270). However, compared with stage Ⅱ, tumor samples from patients in stage Ⅲ showed a higher CASC19 expression. According to the CASC19 expression, patients with TNM stage Ⅰ and Ⅱ or TNM stage Ⅲ and Ⅳ CRC were divided into one cohort.

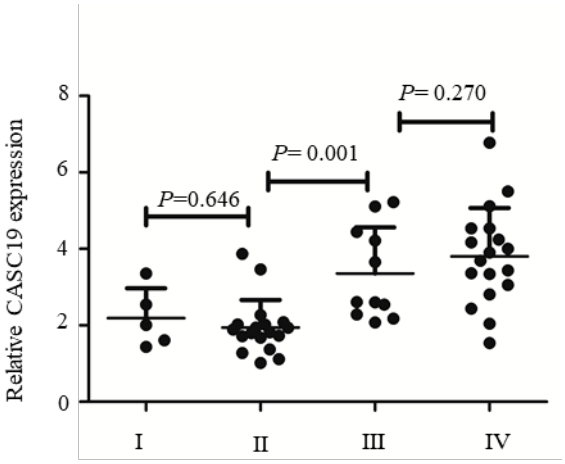

Figure S1 CASC19 expression in TNM stage Ⅰ to Ⅳ.

Based on your comments, we further analyzed the relationship between CASC19 expression and local invasion (T1+T2 and T3+T4) and we modified Table 1. As shown in Table 1. CASC19 was not associated with T stage (*P*=0.585).

Table 1 Associations of cancer susceptibility 19 with the clinical pathology features of patients with colorectal cancer

Features	Total	CASC19 expression		*P*-value
	N=52	High	Low	
Gender				
Male	25	10	15	0.483
Female	27	12	15	
Age, year				
≤ 60	13	5	8	0.503

>60	39	17	22	
Tumor size				
≤5cm	22	9	13	0.379
>5cm	30	13	17	
TNM stage				
Ⅰ-Ⅱ	23	6	17	0.019[a]
Ⅲ-Ⅳ	29	16	13	
Local invasion				
T1+T2	9	4	5	0.585
T3+T4	43	18	25	
Lymphatic metastasis				
Yes	22	14	8	0.008[b]
No	30	8	22	
Liver metastasis				
Yes	18	13	5	0.001[b]
NO	34	8	26	

Note: CASC19, cancer susceptibility 19; CRC, colorectal carcinoma. a, $P < 0.05$, b, $P < 0.01$.

6. Figure 1E: In Figure 6E it should be an error in the legend of the bar graph, since the nuclear marker U6 seems to be predominantly in the cytosol (about 80% in the cytosol vs about 20% in the nucleus), while that cytoplasmic marker GAPDH seems to be predominantly in the nucleus (about 15% in the cytosol vs about 85% in the nucleus)… Check this point accurately and correct it - Figure 2D: The % of early and late apoptotic cells reported in Figure 2D are not well legible: increase the font size.

Response: Thank you very much for your valuable comment. I am sorry for our mistakes. We have adjusted the image according to your suggestions.

Other responses:

1. Verify the accuracy of general information of our manuscript:

Response: Thank you very much. We have checked the general information and confirmed that the information is accurate.

2. Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).

Response: Thank you very much. The language certificate letter by professional English language editing companies has been provided.

3. In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final

acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information. The accepted formats are mp3 or wma.

Response: Thank you very much. The audio file has been provided.

4. Please provide the decomposable figure of all the figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. - image files.ppt" on the system. Make sure that the layers in the PPT file are fully editable. For figures, use distinct colors with comparable visibility and consider colorblind individuals by avoiding the use of red and green for contrast.

Response: Thank you very much. The PowerPoint file has been provided.

5. Your manuscript should be prepared with Word-processing Software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.

Response: Thank you very much. The manuscript has been modified.

6. **Please note that the author list and affiliations, author contributions, and funding information are not allowed to be modified after a manuscript's formal acceptance.**

Response: Thank you very much. Author contributions have been modified.

I greatly appreciate both your help and that of the referees concerning improvement to this paper. I hope that the revised manuscript is now suitable for publication.

Thank you very much.

Yours sincerely,

Feng Qi

Address：An-Shan Road， He-Ping Distrct, Department of General Surgery, Tianjin Medical University General Hospital

City: Tianjin

Post code: 300052

Country: China

Tel : +86 137 5211 5987

Email : qifengtmu2017@163.com