Dear Editor and Reviewers:

Thank you very much for your letter and for the reviewers' comments concerning our manuscript "Changes in extracellular matrix in different stages of colorectal cancer and their effects on the proliferation of cancer cells" (No.50639). Those comments are all valuable and very helpful for revising and improving our paper. We have studied the comments carefully and tried our best to revise and improve the manuscript. The main corrections in the paper and the responds to the reviewers' comments are as following:

(1) Comments from reviewer 1: 1. Authors investigated just the amount of type 1, 2, 3, and 4 collagens in tumor tissues. They didn't analyze other components of extracellular matrix including several types of proteins. Please consider performing proteomics analysis to reveal whole constituents of ECM. At least, authors should evaluate proteins which have a role for ECM formation, e.g. matrix metalloprotease. 2. ECM contains several types of biologically active substance. Some of them deactivated by the stabilization for ECM, and some of them were still active after it. However, authors didn't assess the deactivation by the stabilization for ECM.

Response:

1. This is a very good suggestion. According to the suggestion, we have supplemented the experiments. We used proteomics to analyze the differential expression of proteins in normal colorectal tissue and colorectal cancer tissue, and some of them were selected for analysis in every stage of colorectal cancer by western blot (this part is highlighted in yellow in page 9).

2. We add the discussion of the deactivation of component of ECM and this part is highlighted in yellow in page 11.

(2) Comments from reviewer 2: Good clinical consequences possible.

Response: Thank you.

(3) Comments from reviewer 3: 1. This topic is not the most novel as it has been studied before. The science behind the relationship between MMP2 and ECM is not very well understood. It is an important limiting step for the

haematogenous spread of colorectal cancer rather than it's isolated proliferation. The methodology is very good (use both in vitro and in vivo techniques) and the analysis is comprehensive using 2 separate assessment tools - MTT and WB. 2. I would value a little more on the purpose of the ECM in colorectal cancer: local invasion rather than proliferation in the background. 3.The discussion should include the pharmacological implication or even the clinical impact of such implication. Afterall, these scientific experiments are intended to improve oncological outcome. I would also discuss the use of cellular migration studies such as matrgel invasion chamber studies etc. Overall, this manuscript is well written and the experiments well conducted.

Response: Thank you for your nice comments.

1. We add further explanation about the relationship between MMP2 and ECM in the discussion and this is highlighted in yellow in page 11. MMP2 and other MMPs could degrade the ECM. The remodeled ECM became stiffer and high porosity. And this could affect the proliferation of cancer cells.

2. In this article, we mainly focused on the changes in extracellular matrix in different stages of colorectal cancer and their effects on the proliferation of cancer cells, so we do not place more emphasis on the invasion. However, this is a very good suggestion and this is also what we shall do next.

3. We have added the discussion of clinical impact into the paper and this is highlighted in yellow in page 11.

Thank you and all the reviewers for the kind advice.

Sincerely yours,

Zhu-Lin Li, Zhen-Jun Wang, Guang-Hui Wei, Yang Yong, Xiao-Wan Wang