30th December 2016

Dear Editor:

We appreciate the valuable comments and suggestions from the reviewers on our submitted manuscript "Combined Expression of CRM1 and CDK5 Displayed Higher Prognostic Accuracy for Gastric Cancer" (ESPS Manuscript NO: 31198) and have made modifications and corrections accordingly. Our responses to each advice have been listed below in red. Should you need any more information, please do not hesitate to contact me.

Best Regards

Yao Lin

On behalf of all the co-authors

**COMMENTS FOR THE AUTHOR:**

**Reviewer:**

In their paper Sun et al investigate the prognostic value of combined expression of CRM1 and CDK5 for Gastric Cancer. Expressions of CRM1respectively Cdk5 alone have already been published by the same group. Now, the authors investigate whether combined expression of Cdk5 and CRM1 correlates with clinic-pathological parameters in gastric cancer. The manuscript is sound and the experiments/correlations are well-performed, however, there are some points that need to be addressed: In their previous study, the authors showed that Cdk5 had a tumor-suppressor function. However, in other cancers (liver, pancreas, prostate, lung, breast, thyroid), Cdk5 had a tumor-promoting function. As well, the authors describe CRM1 as tumor suppressor in gastric cancer. In contrast, in other cancers, CRM1 exerts oncogenic functions. How do the authors explain the different function of Cdk5 and CRM1 in gastric cancer? In their previous study, the authors showed that the nuclear localization of Cdk5 was crucial for its tumor suppressing function. Also in the neuronal system as well as in other tumor entities, Cdk5 localization is crucial for its functions. CRM1 regulates Cdk5 localization. Thus, there might be a correlation with CRM1 expression, Cdk5 localization and gastric cancer prognosis/clinical parameters. The authors should investigate Cdk5 localization in relation to CRM1 expression in gastric cancer and correlate it with clinic-pathological parameters.

Response: Our previous work have demonstrated that the nuclear localization of CDK5 was critical for its tumor suppressor function in gastric cancer（Cyclin-Dependent Kinase 5 Decreases in Gastric Cancer and Its Nuclear Accumulation Suppresses Gastric Tumorigenesis. Clin Cancer Res; 21(6); 1419–28.）. Recently we found that CDK5RAP3 (a binding protein of the CDK5 activator p35) negatively regulates the β-catenin signaling pathway by repressing GSK-3β phosphorylation and acts as a tumor suppressor in gastric cancer (CDK5RAP3 acts as a tumor suppressor in gastric cancer through inhibition of β-catenin signaling. Cancer Lett. 2017 Jan 28; 385:188-197.). All our work demonstrated that CDK5 plays a tumor-suppressor role in gastric cancer, but the mechanism has not been completely clarified. We fully agree with the reviewer that it will be very interesting and informative to investigate the localization of CDK5 and CRM1 in patient samples. However, given that karyoplasm localization of CDK5 is dynamic in gastric cancer, it is difficult to obtain convincing quantitative results on CDK5 and CRM1 localization from the IHC images of gastric cancer patient samples. We will continue to investigate this question in our future research. The discussion on this issue has been added in the discussion section.