Author’s response to reviews

Title: Immunogenomic Pathways Associated with Cytotoxic Lymphocyte Infiltration and Survival in Colorectal Cancer.

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Ozgur Kutuk
Editor
BMC Cancer

Dear Professor Kutuk:

We would like to thank you for the opportunity to revise and resubmit our manuscript entitled “Immunogenomic Pathways Associated with Cytotoxic Lymphocyte Infiltration and Survival in Colorectal Cancer” by Yuanyuan Shen, Yue Guan, Justin Hummel, Chi-Ren Shyu, and Jonathan B. Mitchem. Please see our comments below for responses to the most recent review.

Deborah Wood Neklason (Reviewer 1): The authors have done a very nice job of addressing the concerns and I am satisfied. I have no suggested changes. It is a very interesting and well written manuscript.

Maarit Tiirikainen (Reviewer 2): I'm pleased to see that the authors have carefully addressed my concerns and made the appropriate corrections.

Thank you both for your comments. We appreciate your thoughtful input, which has significantly improved our work.

1) “…I still have problems accepting the conclusion "we found the immunoregulatory interactions....pathway was the MOST enriched pathway included at all sites and stages”. If the
"most" was replaced by "one of the most enriched", that would better reflect the actual results in Figure 2.”

In this revision, we have attempted to be more specific per the reviewer’s suggestion. To achieve this we have changed the Figure 2 legend to state:

“This analysis showed that the ‘immunoregulatory interactions between a lymphoid and a non-lymphoid cell’ was the most highly enriched pathway in early and local patients at all sites. Additionally, this was the most highly enriched pathway in patients with metastatic right-sided cancer. This pathway was also among the top pathways enriched among patients with metastatic left-sided colon cancer and rectal cancer. (Input data included in Supplemental File)”

In the abstract, the statement regarding this pathway was changed to read:

“We identified one pathway, “immunoregulatory interactions between a lymphoid and non-lymphoid cell”, that was highly enriched and included in all tumor locations and stages.

In the results section, the text was also altered to be more specific:

“Using the p value adjusted for false discovery rate and the ratio of differentially expressed genes in each pathway, we found that the “immunoregulatory interactions between a lymphoid and a non-lymphoid cell” was the most highly enriched pathway in early and local patients at all tumor locations. Additionally, this was the most highly enriched pathway in patients with metastatic right-sided cancer. This pathway was also among the top pathways enriched among patients with metastatic left-sided colon cancer and rectal cancer (Figure 2, Input data included in Supplemental File).”

We hope that this makes our analysis more clear. It is not our intent to mislead the reader or overstate our findings.

2) It also seems odd to show stages I+II (early) as well as stages I+II+III in this same figure, giving an impression that these are independent data. Having both on this same figure as results seems to support the conclusion I’m bothered by, but it is caused by overlapping data.

We agree with the reviewer that there is overlap between “early” and “localized”, as was stated by reviewer 1 in the first revision. The following statement in the discussion was included to help address this:

“One limitation of this study is related to patient numbers and clinical data available, as with many database studies. Due to patient numbers, we included patients in Stage I and II in the analysis for both “early” and “local” disease. This was done to increase patient numbers assigned to each group and improve our analysis. Based on our results, we felt this helped to support findings in the “early” stage patients as the Stage III patients contributed 40-60% of “local” patients depending on disease location.”
Additionally, we have attempted to be very transparent in labeling the figure and outlining the method such that there is no confusion regarding what we did in this analysis and why we felt this was important enough to include.

3) Furthermore, if one would look at colon cancer only, the immunoregulatory pathway would clearly not be the top one.

We have attempted to address the concerns of the reviewer by being more specific in the text regarding the “immunoregulatory interactions between a lymphoid and a non-lymphoid cell” pathway. This has been changed in the text of the paper to be more clear as outlined above in point 1. This pathway was the most highly enriched pathway for all patients with colon or rectal cancer without metastatic disease (Stages I-III) and the most highly enriched pathway for patients with metastatic right-sided colon cancer. The only patient groups where this was not the most highly enriched pathway were in patients with metastatic left-sided colon cancer and rectal cancer. The primary data from the pathway enrichment analysis is included in the supplementary files and this is now noted in both the legend for Figure 2 as well as in the results section.

Again, we thank the editor and reviewers for the opportunity to continue to improve our work and resubmit for publication.

Sincerely,

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