Peer Review File

Article information: http://dx.doi.org/10.21037/tcr-22-398

Review Comments:

Comment 1: Figure 3 contains analyses across multiple cancer types and are not only for renal carcinoma. The relevance of analyses on cancers other than kidney cancers should be stated. What type of kidney cancers were referred here?

Reply 1：Many thanks to the Reviewer's comments, we have noticed the confusion. Oncomine integrates RNA and DNA-SEQ data from sources such as GEO, TCGA and published literature. We provide this figure to illustrate the increased expression of collagen family members previously screened in various tumor tissues, as well as in kidney cancers tissues. The results may also shed light on the role of collagen family members in cancer progression. Since the Oncomine database has been shut down, we could not provide detailed data on the kidney cancer data set, but we also obtained consistent conclusions through TCGA and GEO database analysis. (please see Page 9, line 184- 188).

Changes in the text: We have explained the relevance of analyses on cancers other than kidney cancers. We have added "The collagen family members we screened showed elevated expression levels in various tumor tissues, as well as in renal cancer tissues. These results suggest that members of the collagen family may play a role in cancer progression."

Comment 2: Figure 5 and Supplement Figure 2 – Please indicate the type of renal cancer and the cutoff points used for the stratifications.

Reply 2：Thank you for your professional comment. We used RNAseq data from KIRC project in TCGA database for survival analysis. Patients were divided by the medium value of gene expression. The p value of genes less than .05 in survival analysis was identified as prognosis- related genes.(please see Page 10, line 204-205).

Changes in the text: We have added "We used RNAseq data from KIRC project in TCGA database for survival analysis. Patients were divided by the medium value of gene expression. "

Comment 3: Figure 7 is for which type of kidney cancer? The same applies for Fig 8 and other figures, for instance Supplement Fig 1.

Reply 3：Thank you for your comment sincerely. We used kidney renal clear cell

carcinoma data from MethSurv, TIMER, and cBioPortal databases for gene methylation analysis, immune correlation analysis, and gene mutation analysis.(please see Page 9, line 195, Page 11, line 233-235, Page 12, line 248).

Changes in the text:We have added “By analyzing the renal clear cell carcinoma data of cBioPortal,” “We used TCGA KIRC methylation data contained in MethSurv to perform survival analysis of CPGs located near collagen family genes.” “We used the kidney renal clear cell carcinoma data from TIMER database to detect the correlation between collagen family members’ expression levels and the infiltration levels of tumor-immune infiltrating cells (TIICs).”

Comment 4: Guo et al presented SFig 1 for mutations in the collagen genes. But the figure also contains gene expression, and the rate of gene expression alterations is much more prevalent compared the rate of gene mutation. Not sure what purpose does this figure serve.

Reply 4：We are very sorry for the exaggerated conclusions. We have corrected the text according to the Reviewer’s comments.(please see Page 10, line 199-202).

Changes in the text: We have added “We also found that altered expression of collagen family genes is also common in renal cancer, suggesting that mutations and altered expression of collagen family members play a role in renal cancer.”

Comment 5: Table 2 in line 179 is for the content of Table 3. The concept of using COL1A2 as an independent prognostic factor is troubling. In univariate analysis, its CpG methylation (which one?) is associated with poor OS but in multivariate Cox analysis the methylation is correlated with better survival. Which factors were included in multivariate analyses?

Reply 5：Considering the Reviewer’s comments, we are very sorry for our confusion of using COL1A2 as an independent prognostic factor. COL1A2 CPG island methylation levels in cg08695855, cg09146903, cg16872226, cg23348014, and ch.7.1973356R were associated with poor prognosis of tumors but in multivariate Cox analysis the COL1A2 is correlated with better survival. Univariate analysis was conducted to screen the differentially expressed collagen members significantly associating with OS of the TCGA KIRC patients. Then, the differentially expressed collagen members with p value of less than .05 were further identified by multivariate Cox proportional hazard regression. Considering the inconsistency of the two results and the need for more evidence to prove the relationship between COL1A2 methylation and tumor prognosis, we abandoned the use of COL1A2 as an independent prognostic factor of tumor. (please see Page 2, line 35, Page 11, line 221-225, line 186-194, Page 15, line 323, Figure6, SFigure 3).

Changes in the text: We have modified our text as advised. We removed descriptions

of COL1A2 as an independent prognostic factor.