Peer Review File

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Reviewer A

The study was conducted using TCGA LUAD database to differential expression (480 LUAD and 54 normal) of CCND1 correlated with overall survival and using TIMER database and CIBERSORTx algorithm to define correlation between CCND2 expression and tumor immune microenvironment (TIME) including T/B cell, macrophage, neutrophil and dendritic cell. The author reported that CCND2 could predict prognosis and involved TIME.

Comment 1: Table 2, please add information CCND2 expression whether down-regulate vs. up-regulated or vice versa associated with prognosis outcome. Moreover, the factors integrated in the model seem lack important prognosis information such as line of treatment (> 2 vs. < 2 lines), oncogene mutation i.e. KRAS, EGFR (presence vs. absent). I understand that oncogenic mutation data (level 3) could be retrieved from TCGA database. Furthermore, all of information according to the factors (xx vs. xx) should be added.

Reply: We appreciate the reviewer's suggestions. We added the result of the Deseq 2 in the table 2.

In present study, we only studied the underlining correlation between the expression of CCND2 and LUAD, the influence of the mutation of CCND2 on LUAD and line of treatment we will study in the future studies.

Changes in the text: table 2

2、CCND2 could be targeted by miR-464 and miR-4371, however the author stated that miR-17 was only the significantly down-expression in LUAD. Conflicting consequence of miR-17 expression and CCND2 expression was shown in line 202 and 204. If CCND2 could not be targeted by miR-17, then the correlation might be by chance? The author should add up a discussion section according to these issues (miR-

464, miR-4371 and miR-17). MiRNA is not the only mechanism of epigenetic silencing, what about the methylation effect of CCND2? Furthermore, Information according to gene list of Figure 3 should be added in the supplement file.

Reply: We thank you for your suggestions. We have modified our text as advised (see page 8, line 202-207, highlighted sentences). We wrote miR-646 to miR-464, and we had modified this error in page 4 line 83. We also added the discussion as advised (see page 8, line 213-221, highlighted sentences). We added the gene list of Figure 3 in the supplement table.

Changes in the text: page 8, line 202-207, line 213-221 and supplement table (page 6 line 155).

3、CCND2 was known as oncogene. The potential explanation why down-regulation of CCND expression is correlated with the prognosis.

Reply: We appreciate the reviewer's suggestions. We added a discussion section in page 10 line 263-277 (highlighted sentences).

Changes in the text: page 10 line 263-277.

4、Lastly, there are conflicting results according to TIMER database and CIBERSORTx algorithm. As TIMER showed positive correlation with CCND2 expression and all TIME (B-cell, CD8 T cell, CD4 T cell, macrophage, neutrophil and dendritic cell) but CIBERSORTx algorithm shown contradict results. The proportions of naive B cell, resting dendritic cells, and macrophages M1 were higher in the low CCND2 expression level group; whereas the proportions of macrophages M1, activated NK cells, and resting CD4+ memory cells were lower (line 194-196). What is the explanation that author proposed?

Reply: We thanks for the reviewer's suggestions. We added the discussion in page 9-10 line 250-261 (highlighted sentences).

Changes in the text: page 9-10 line 250-261.

Reviewer B

The results described are based on databases, it should be stressed that they need confirmation in a prospective patient study. The correlations are not clear and need a better description; obviously TIMER reports a Spearman`s correlation index; such an index indicates a non-existent to low correlation between values 0 to < 04, although beeing statistically significant therefore, the real impact of such values need to be discussed.

Reply: We appreciate the reviewer's suggestions. We discussion the Spwarman's correlation index in page 10 line 258-261 (highlighted sentences).

Changes in the text: page 10 line 258-261.