Peer Review File

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Reviewer A

The original work entitled: "Cadherin dysregulation in gastric cancer: insights into gene expression, pathways, and prognosis" is interesting and presents new information.
There are few previous works that have addressed the study of cadherins as a family and their relationship with cancer (1. Berx G, van Roy F. Involvement of members of the cadherin superfamily in cancer. Cold Spring Harb Perspect Biol. 2009 Dec;1(6):a003129. doi: 10.1101/cshperspect.a003129. Epub 2009 Sep 23. PMID: 20457567; PMCID: PMC2882122. and 2. van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. Nat Rev Cancer. 2014 Feb;14(2):121-34. doi: 10.1038/nrc3647. Epub 2014 Jan 20. PMID: 24442140.)
Response: We thank the reviewer for appreciating our work. We have already cited both these references in the Introduction section of our manuscript. The first reference (PMID: 20457567) is cited as reference #19 in the submitted version of the manuscript, whereas the second reference (PMID: 24442140) is cited as reference #14 in our manuscript.

The authors used all the existing and currently available information with a large number of data, for which I consider to be of greater relevance. However, I believe it is important to point out that cadherins have been given a contradictory role in the literature, since they can sometimes act as tumor suppressors and other times as oncogenes, depending on the context or type of cancer.
Response: Thank you for this suggestion. We have now included a few sentences regarding the contradictory role of cadherins in the Introduction of the revised manuscript (lines 89-99).

The E-cadherin protein (encoded by the CDH1 gene) is one of the molecules of this family that has been widely studied in gastric cancer, and it has been reported that its low expression is related to greater invasion and a less differentiated state of the cells. through the TEM process, which is linked to a poor prognosis for patients (Bure IV, Nemtsova MV, Zaletaev DV. Roles of E-cadherin and Noncoding RNAs in the Epithelial-mesenchymal Transition and Progression in Gastric Cancer. Int J Mol Sci 2019 Jun 12;20(12):2870. doi: 10.3390/ijms20122870. PMID: 31212809; PMCID: PMC6627057.), for this reason it strikes me that in the results of this work the authors found a greater expression of this molecule in Gastric cancer (Figure 1). Did the authors

perform further analyzes on the type of gastric cancer or the stage that could explain this situation?

Response: We thank the reviewer for this comment. We used TCGA data through GEPIA2 to identify differential genes between gastric cancer and normal samples (as indicated in the methods section). In literature, CDH1 has been reported to be up-/down-regulated depending upon the gastric cancer histology. For instance, CDH1 is upregulated in the intestinal type of gastric cancer, whereas it is downregulated in diffuse type adenocarcinoma owing to mutation and epigenetic modifications (*Tanabe S, Komatsu M, Aoyagi K, Yokozaki H, Sasaki H. Implications of epithelial-mesenchymal transition in gastric cancer. Transl Gastrointest Cancer 2015;4(4):258-264. doi: 10.3978/j.issn.2224-4778.2015.07.04; Tanabe S, Aoyagi K, Yokozaki H, Sasaki H. Gene expression signatures for identifying diffuse-type gastric cancer associated with epithelial-mesenchymal transition. Int J Oncol. 2014;44(6):1955-1970. doi:10.3892/ijo.2014.2387*). This could be the reason for the upregulation of CDH1 in our study. We confirmed this by downloading the sample details of stomach adenocarcinoma (STAD) patients from TCGA portal. Of the total 478 primary tumor samples, the histological subtype information was available for 450 samples. Among these, 41% (186 samples) belong to intestinal type, whereas only 16% (71 samples) belong to the diffuse type. Thus, a higher percentage of intestinal subtype in the TCGA-STAD sample pool could explain the upregulation of CDH1 in our study. We have now discussed this aspect in the Discussion section of the revised manuscript (lines 413-421).

Reviewer B

The authors study the expression, mutational status, survival rate of cadherins and also microRNAs targeting cadherins and immune cell infiltration associated with cadherin genes in gastric cancer by mining data from multiple databases and bioinformatic analysis.

1- Reading the manuscript is made difficult by the repetitive use of some formulas such as "play a role" which are often useless as they have a vague meaning. It is clear to everyone that every protein or other biological factor has a function to be revealed.

Response: We have now minimized the use of such repetitive words/sentences throughout the manuscript.

2- The repeated statement that the meaning of a finding in GC requires further

investigation is pleonastic. The specific comment may be clarified in the Discussion.
Response: We have now modified this in the Discussion section and replaced it with a more specific comment.

3- Regarding the results, I suggest adding the P value where necessary to distinguish statistically supported evidence from observations and descriptions.
Response: We have now included the specific p-values/p-value threshold in Results, wherever required.

4- Line 295-298: "Interestingly, 11% of the genomic changes in PCDH17 were single base mutations, whereas in the case of FAT1, they represented 8% of the total aberrations. However, CDH17 harbored CNVs in 3% of samples as compared to single nucleotide polymorphisms (SNPs) in 2.3% of patient samples….."
These observations should be explained better. Overall, it is unclear what the differences mean.
Response: This statement refers to the percentage of patients harboring SNPs/CNVs in different cadherin genes. We have now modified the sentences for better clarity (lines 289-292).

5- Make sure that the results reported in the figures are clearly explained in the text. In particular, Figure 3A needs further explanation as text added to the figure and in the manuscript text. How many samples and what percentage of the total cases are shown in Figure 3A on the left and right?
Response: We have now included the details on the number of GC patients with genomic aberrations and those with SNP and CNV/SV data in the Figure 3A legend as well as to some extent in the Results text discussing Figure 3A (lines 277-278 & 281-283).

6- The Discussion should be more concise. Comment on the main results in a single chapter, avoiding generic statements.
Response: We have now removed the redundant sentences/words and generic statements in the Discussion section at multiple stances.

7- When downloading figures from databases, the source must be indicated in the figure legend.
Response: We have now indicated the source database name and URL for the downloaded figures, wherever applicable.

8- Make sure the text in the figures is legible.

Response: We have now modified the figures for better clarity, specifically Figures 3, 5 and 6.

9- Lines 449-451, modify the sentence.

Response: The sentence has been modified for better clarity (lines 433-435).

This manuscript provides an overview of the molecular evidence on cadherin family proteins in the gastric cancer series available in TCGA. The manuscript consists mainly of descriptive findings and some bioinformatic processing. The main quality of the manuscript is completeness. The text needs to be restructured and simplified by eliminating repetitive statements.

Response: We have now revised the manuscript for better clarity.