

Point-by-point reply to reviewers.

Reviewer #1:

Specific Comments to Authors: *TBX3 is a gene belonging to the T-box family that plays an important role in embryonic, muscle and bone development. In recent years, many studies have found that TBX3 plays an important role in the development of breast cancer and melanoma through EMT, indicating that TBX3 may be a key gene for tumorigenesis. However, there are few studies on its relationship with gastric cancer. This manuscript reviews the functions and regulations of TBX3, as well as its application in breast cancer, melanoma, hepatocellular carcinoma, colorectal cancer, pancreatic cancer and gastric cancer was conducted and the possibility of it being a tumor therapy target was discussed. It is interesting to note the importance of TBX3 gene in future cancer research.*

The authors would like to thank the reviewer for taking his/her time and reviewing our manuscript.

Major concerns:

1. More literature needs to be analyzed in order to provide the relationship between TBX3 and tumor heterogeneity as a potential tumor therapy target. For example, in breast cancer, TBX3 promotes tumor progression by inhibiting cellular senescence and promoting EMT, but in melanoma, the overexpression of TBX3 is sufficient to promote tumor formation and invasion.

The authors would like to thank the reviewer for his/her comments. This discrepancy between breast cancers and melanomas are described in the main text (P. 11 L.8-12).

2. The literature on the relationship between TBX3 and gastric cancer is not sufficient. It seems that TBX3 promotes the progression and invasion of gastric cancer by inhibiting aging and enhancing EMT, but at the same time, TBX3 is an important gene that leads to the progression from low-grade intraepithelial neoplasia to high-level intraepithelial neoplasia, indicating that TBX3 may be involved in the early stage of gastric cancer. More evidence is needed to explain the expression of TBX3 in gastric cancer of different causes, such as alcohol consumption and nitrite.

The authors would like to thank the reviewer for his/her comments. We agree with the reviewer that the expression of TBX3 in gastric cancers of different causes should be clarified. However, currently, there are only limited numbers of reports regarding the correlation between TBX3 and gastric cancers (Pubmed search only gives 7 results; 2 of which are not related to gastric cancers), and we hope this will be answered by the future studies. That said, we have added some details in "TBX3 in gastric cancers" section of the revised manuscript.

3. Although the existing literature strongly suggests that TBX3 plays a key role in the carcinogenesis related to aging and the progress of gastric cancer, the existing methods and literature are still insufficient, and the content also needs to be further focused.

The authors would like to thank the reviewer for his/her comments. We have added a sentence that futures studies are awaited to elucidate the role of TBX3 in aging-related gastric carcinogenesis (P.15L.16-P.16L.1).

Reviewer #2:

Specific Comments to Authors:

1. The authors list the relations between TBX3 and cancers, which were reported in many papers, but the content of authors' own opinion about this review seems a little thin.

The authors would like to thank the reviewer for his/her comments. We have added some details and our opinion in "TBX3 in gastric cancers" section of the revised manuscript.

2. To finish a good review needs to read lots of papers, but the majority of references cited in the article are preferring the recent 5 years publishing. It's my own opinion.

The authors would like to thank the reviewer for his/her comments. We have added Muller's Nature paper published in 1997 (Ref. #10) in the revised manuscript.

3. The Figure 1 is good, but a bit simple, I think.

The authors would like to thank the reviewer for his/her comments. We have modified Figure 1.

4. The title is "The role of TBX3 in gastric cancers", but the content concerns many other cancers, and the gastric cancer is a bit short

The authors would like to thank the reviewer for his/her comments. TBX3 has been intensively studied in breast cancers and melanomas, but there are only limited number of reports investigating the correlation between TBX3 and gastric cancers. Therefore, we were not able to add more references regarding TBX3 and gastric cancers. However, we have added some details and our opinion in "TBX3 in gastric cancers" section of the revised manuscript.