

Peer Review File

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Reviewer A

I agree with the authors that the role of m6A methylation in TME is not negligible, and m6A methylation in tumor

cells will affect the infiltration, activation, and efficacy of immune cells in TME.

This manuscript provides useful references for scholars focusing on WTAP and probably new insights for WTAP as a prognostic evaluation and immunotherapy for tumors in the future. Here the authors should delineate how this could be useful for pediatric and, separately, for adult tumors. The figures have a relatively low resolution. They need to be provided at the highest quality!

Reply : Thank you very much for your acknowledgment and warm suggestions for our work. WTAP is important for future prognostic assessment and immunotherapy of tumors. By studying the expression level, function, and relationship with prognosis of WTAP in pediatric and adult tumors, its potential as a prognostic assessment of tumors can be explored, which will help clinicians to formulate better individualized therapeutic regimens, and to improve therapeutic efficacy and survival rates of pediatric and adult tumors. And we have improved the clarity of the images, especially Figures 1, 2, 8, 9, 10 and 11, and also adjusted the layout of the corresponding images.

Changes in the text: we have modified our text as advised (see Page 19-20, line 532-543).

Reviewer B

The paper titled “WTAP-mediated abnormal m6A modification promotes cancer progression by remodeling the tumor microenvironment: Bibliometric and database analyses” is interesting. From the bibliometric and database analyses on the researches on WTAP protein, it is suggested that up-regulated WTAP in cancers may promote cancer progression by mediating abnormal m6A modifications to reshape the tumor microenvironment, thereby affecting the survival prognosis of the patients. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) This study is based on the analysis and summary of the literatures. It is suggested to add clinical experimental research, which may be more meaningful.

Reply 1: Thank you very much for your acknowledgment and warm suggestions for our work. This study was conducted on the basis of analyzing and summarizing the literature, adding clinical experimental research is indeed more meaningful and will greatly improve the quality and level of the article, but at present, the hospital's clinical experimental conditions are limited, and it is not possible to collect enough research subjects to satisfy the conditions, but subsequently, after the hospital's conditions have been improved, we will carry out both basic experimental research and clinical experimental research on WTAP.

2) There are many databases. Why did the author only select WoSCC database in this study for searching? Please explain the reason.

Reply 2: Thank you very much for your acknowledgment and warm suggestions for our work. The Web of Science Core Collection (WoSCC) database is considered the most influential database, and we chose it because it can provide comprehensive information bibliometric software needs.

Changes in the text: we have modified our text as advised (see Page6, line124-126).

3) What is the correlation between m6A RNA and the immune microenvironment? What are the possible goals of future drug development? It is recommended to add relevant content to the discussion.

Reply 3: Thank you very much for your acknowledgment and warm suggestions for our work. We added relevant content to the discussion. On the one hand, m6A can not only regulate the differentiation and function of immune cells in the immune microenvironment, such as

macrophage polarization and T-cell activation, but also regulate the expression of immune cytokines, such as the production of interferon and tumor necrosis factor to influence immune-cell interactions and immune regulatory processes. On the other hand, m6A can also directly regulate the transcription and translation of immune-related genes, affecting the immune response. The application of WTAP-related targeted drugs, as well as the research and development of small-molecule inhibitors targeting m6A-regulated proteins and their novel drugs in combination with immune checkpoint blockers are bound to play an important value in the future.

Changes in the text: we have modified our text as advised (see Page 18-20, line 487-493, 544-547).

4) The method section of this study is relatively limited and it is recommended to add more.

Reply 4: Thank you very much for your acknowledgment and warm suggestions for our work. We have added a description of the methods section as per your request, including formatting requirements for literature downloads, software data handling, etc.

Changes in the text: we have modified our text as advised (see Page 6, line 130-131, 132-135, 147-149).

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Identification of prognostic genes and tumor-infiltrating immune cells in the tumor microenvironment of esophageal squamous cell carcinoma and esophageal adenocarcinoma, *Transl Cancer Res*, PMID: 35116502”. It is recommended to quote the articles.

Reply 5: Thank you very much for your acknowledgment and warm suggestions for our work. We have added the introductory section. We have added the introductory section and cited the above article.

Changes in the text: we have modified our text as advised (see Page 4-5, line 69-78, 84-94, 694-696).

6) What are roles of m6A in cancer pathogenesis? It is recommended to add relevant content.

Reply 6: Thank you very much for your acknowledgment and warm suggestions for our work. We have added the role of m6A in the pathogenesis of cancer as you requested. m6A

modification plays an important role in the pathogenesis of glioblastoma, hepatocellular carcinoma, renal cell carcinoma, breast cancer and acute myeloid leukemia. m6A promotes or suppresses tumor cells by regulating the expression of mRNAs of relevant oncogenes or oncogenes, and the level of m6A expression often directly determines the pathological process of the tumor.

Changes in the text: we have modified our text as advised (see Page 4-5, line 69-78).

7) It may be more meaningful to suggest to increase the functional research of WTAP.

Reply 7: Thank you very much for your acknowledgment and warm suggestions for our work. As a regulatory subunit essential for methyltransferase activity, WTAP not only plays a key role in the transcriptional regulation of RNA metabolism, but also can be involved in the onset and progression of numerous diseases by modulating m6A modifications. WTAP expression is upregulated in most tumor cells and correlates with poor prognosis. In terms of mechanism, WTAP mainly affects the expression level of m6A on mRNA of target genes, thus regulating the expression of target genes and activating or inhibiting related pathways to affect tumor progression. In addition, WTAP also plays the function of AS, regulating gene transcription and directly or indirectly affecting embryonic development. The current study of the mechanism of WTAP-mediated m6A in different tumors and its biological function, as well as the clinical protocols of WTAP as a potential therapeutic target are of great significance.

Changes in the text: we have modified our text as advised (see Page 4-5, line74-83).