Peer Review File

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Reviewer Comments

Comment 1: The gliomas evaluated as LGG in this study were containing IDH wild type tumors that might be classified into grade 4 gliomas in the WHO classification in 2021. IDH wild-type glioma should be excluded from the evaluation, when the authors were intended to analyze LGG in this article.

Reply 1: After re-examining the classification criteria for gliomas, we applied the new criteria for our study. Considering that IDH wild-type gliomas were classified as grade 4 gliomas, we excluded IDH wild-type gliomas for subsequent differential analysis.

Changes in the text: We have removed the content related to IDH mutations. (see Page 2, line 83; Page 3, line 114; Page 6, line 262; Page 7, line 273).

Comment 2: In Figure 3A, many of DNMT3A-highly expressing gliomas appeared to be coexisting 1p19q co-deletion. Were there any differences in the expression levels of DNMT3A between oligodendrogliomas and astrocytomas? The authors should discuss about this contradiction, because oligodendrogliomas had a better therapeutic sensitivity and prognosis than astrocytomas.

Reply 2: Considering that 1p19q co deletion is a common basic feature of gliomas, some 1p19q co deletions are present in both oligodendroglioma and astrocytoma. We searched for glioma types in three public databases and examined the expression of DNMT3A protein in the two types of gliomas, revealing significant differences in DNMT3A expression among different types of gliomas. Given the latest changes in glioma classification, we used a redefined glioma grading standard for analysis.

Changes in the text: See Page 6, line 262-264; Figure 3.

Comment 3: The explanation about nomogram shown in Figure 5A was poor. The author should explain in more detail how to use the nomogram.

Reply 3: We have re-organize the construction and content of the Nomogram diagram and made corresponding modifications in the text. More comprehensive explanation of the content of the Nomogram diagram.

Changes in the text: See Page 6, line 277-280.

Comment 4: The graphics in Figure 6 were same as those in Figure 7. Figure 6A-C have been missing.

Reply 4: We apologize for uploading the wrong image. We have uploaded the correct paper image.

Changes in the text: See Figure 6.

Comment 5: The authors tried to show a direct effect of DNMT3A for suppression of antitumor immune response in Figure 7, but this seems to be an expanded interpretation of the results. It has already been known that glioma cases exhibit poor prognosis when the tumors create

suppressive microenvironment for tumor immunity. It may appear to be associated with the suppressive immune microenvironment of gliomas shown in Figure 7, since high expression of DNMT3A is associated with poor prognosis, even if it is for reasons other than immunity. The authors did not show any direct effect of DNM3A on immunity. They should not be emphasized it too much.

Reply 5: We attempted to reveal the relationship between DNMT3A and tumor immunity through bioinformatics analysis, and found that DNMT3A plays an important role in maintaining tumor immunity and improving the efficiency of immunotherapy response. We validated the role of DNMT3A in regulating malignant progression of glioma cells through the TNF-α/NF-κB signaling pathway based on enrichment analysis results. We added relevant experimental content and validation in the main text.

Changes in the text: We have added some experimental content to verify that DNMT3A affects tumor progression through the TNF-α/NF-κB signaling pathway. (See Page 1, line 29-30; Page 5, line 186-192;Page 9, line 365-375; Figure 8 G, H).