N6-methylation of adenosine (m6A) is one of the most frequent chemical modifications in eukaryotic RNAs and plays a vital role in tumorigenesis and progression. Emerging studies have shown that m6A modification by ALKBH5 has been associated with immunotherapy response in various types of cancer. However, whether m6A demethylases ALKBH5 participate in regulating the tumor immune microenvironment and immunotherapy's efficacy in glioblastoma remains unknown.

Tang et al. found that deletion of ALKBH5 significantly inhibited glioma growth allografts, rescued the antitumoral immune response, and increased cytotoxic lymphocyte infiltration and proinflammatory cytokines in CSF while significantly suppressing PD-L1 protein expression. m6A-methylated RNA immunoprecipitation sequencing and RNA sequencing identify ZDDHC3 as the direct target of ALKBH5. Mechanically, ALKBH5 deficiency impairs the YTHDF2-mediated stability of ZDHHC3 mRNA, thereby suppressing PD-L1 expression by accelerating PD-L1 degradation in glioma. In addition, genetic deletion or pharmacological inhibition of ALKBH5 with IOX1 enhances the therapeutic efficacy of anti-PD-1 treatment in preclinical mice models. These data suggest that the combination of anti-PD-1 therapy and ALKBH5 inhibition may be a promising treatment strategy in glioma [1].

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Tang W, Xu N, Zhou J, He Z, Lenahan C, Wang C, Ji H, Liu B, Zou Y, Zeng H, Guo H. ALKBH5 promotes PD-L1-mediated immune escape through m6A modification of ZDHHC3 in glioma. Cell Death Discov. 2022 Dec 24;8(1):497. doi: 10.1038/s41420-022-01286-w. PMID: 36566230.