KDM1A

Efficient DNA repair in response to standard chemo and radiation therapies often contribute to GBM therapy resistance. Understanding the mechanisms of therapy resistance and identifying the drugs that enhance the therapeutic efficacy of standard therapies may extend the survival of GBM patients. In this study, we investigated the role of KDM1A/LSD1 in DNA double strand break (DSB) repair and combination of KDM1A inhibitor and TMZ in vitro and in vivo using patient derived GSCs.

Methods: Brain-bioavailability of the KDM1A inhibitor (NCD38) was established using LS-MS/MS. Effect of combination of KDM1A knockdown or inhibition with TMZ was studied using cell viability and self-renewal assays. Mechanistic studies were conducted using CUT&Tag-seq, RNA-seq, RT-qPCR, Western blot, HR and NHEJ reporter, immunofluorescence, and comet assays. Orthotopic murine models were used to study efficacy in vivo.

Results: TCGA analysis showed KDM1A is highly expressed in TMZ treated GBM patients. Knockdown or knockout or inhibition of KDM1A enhanced TMZ efficacy in reducing the viability and selfrenewal of GSCs. Pharmacokinetic studies established that NCD38 readily crosses the BBB. CUT&Tag-seq studies showed that KDM1A is enriched at the promoters of DNA repair genes and RNA-seq studies confirmed that KDM1A inhibition reduced their expression. Knockdown or inhibition of KDM1A attenuated HR and NHEJ-mediated DNA repair capacity and enhanced TMZ mediated DNA damage. Combination of KDM1A knockdown or inhibition and TMZ treatment significantly enhanced survival of tumor bearing mice.

Conclusions: Our results provide evidence that KDM1A inhibition sensitizes GBM to TMZ via attenuation of DNA DSB repair pathways [1)].

1)
Alejo S, Palacios BE, Venkata PP, He Y, Li W, Johnson JD, Yihong C, Jayamohan S, Pratap UP, Clarke K, Zou Y, Lv Y, Weldon K, Viswanadhapalli S, Lai Z, Ye Z, Chen Y, Gilbert AR, Suzuki T, Tekmal RR, Zhao W, Zheng S, Vadlamudi RK, Brenner AJ, Sareddy GR. Lysine-specific histone demethylase 1A (KDM1A/LSD1) inhibition attenuates DNA double strand break repair and augments efficacy of temozolomide in glioblastoma. Neuro Oncol. 2023 Jan 18:noad018. doi: 10.1093/neuonc/noad018. Epub ahead of print. PMID: 36652263.