POSTER PRESENTATION

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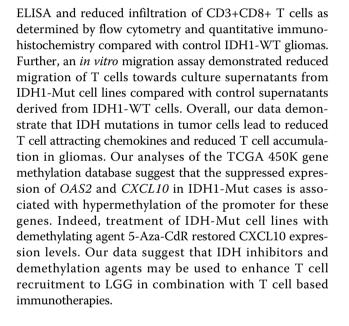
IDH mutation-induced suppression of type-1 anti-glioma immune response

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Isocitrate dehydrogenase (IDH) mutations are the first mutations that occur during the oncogenic process of lower-grade glioma (LGG) and confers a novel gain-offunction activity by converting α -ketoglutarate (α KG) to 2-hydroxyglutarate (2HG), promoting DNA hypermethylation. Our analysis of LGG cases from The Cancer Genome Atlas (TCGA) database revealed that IDHmutant (IDH-Mut) cases exhibit decreased expression of type-1 effector T cell response-related genes, which are critical for anti-glioma immunity, including: CD8A, IFNG, OAS2, GZMA, EOMES, CXCL9 and CXCL10, compared with IDH-wild type (IDH-WT) cases. On the other hand, type-2 and regulatory T cell responserelated genes, such as IL5 and TGFB1, are not significantly different between IDH-Mut vs. WT cases, indicating that the observed down-regulation of type-1 response-related genes does not merely represent a possible global gene suppression. Furthermore, IDH-Mut cases exhibit increased CXCL10 promotor methylation compared with WT cases. We thus hypothesized that IDH mutation-mediated tumor intrinsic mechanisms occurring within glioma cells may inhibit anti-tumor immunity to promote tumor growth. In vitro, a normal human astrocyte (NHA) cell line transfected with IDH1-Mut cDNA expressed lower levels of CXCL10 compared to NHA cells transfected with WT IDH1. Consistently, C57Bl/6 mouse-syngeneic astrocyte and glioma cell lines transfected with IDH1-Mut expressed lower levels of CXCL10 gene and protein, compared to control cells transfected with IDH-WT, which was restored following 30 day treatment of the cells with the IDH1 inhibitor, IDH-C35. Furthermore, in vivo orthotopic IDH1-Mut gliomas at 21 days post-intracranial injection in syngeneic mice expressed lower levels of T cell chemokines CXCL9 and CXCL10 as determined by RT-PCR and

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