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In Vivo Validation of Decitabine Immunotherapy Against IDH Mutant Gliomas

Xiaoran Zhang MD, MS; Wajin Jason Kim; Aparna Rao PhD; Nduka M. Amankulor MD

Introduction

Isocitrate Dehydrogenase (IDH) mutations are found in over 80% of low-grade gliomas and vast majority of secondary glioblastomas. Mutation in IDH leads to aberrant production of an oncogenic metabolite that promotes epigenetic dysregulation by inducing hypermethylation to suppress transcription of various tumor suppressor genes. Hypermethylation in IDHmut gliomas leads to transcriptional repression of NKG2D ligands, especially ULBP-1 and ULBP-3, and subsequent evasion of natural killer cell mediated lysis. 5-aza-2'deoxycytodine (Decitabine) is a DNA methyltransferase 1 inhibitor that prevents hypermethylation and is capable of restoring NKG2D ligand expression in IDHmut gliomas to re-sensitize them to natural killer cells.

Methods

Xenograft models of IDHwt and IDHmut gliomas were established in athymic-nude mice. mice were either treated with decitabine or DMSO intraperitoneally every 7 days. Tumor sizes were measured every 2-3 days. After the animals were sacrificed, xenografts were harvested and analyzed for the following: tumor expression of NKG2D ligands, tumor susceptibility to human and murine NK-cells, immunohistochemistry for NK infiltration and tumor infiltrating lymphocyte characterization.

Results

Decitabine was able to significantly inhibit the growth of IDHmut xenografts in the athymic nude mice. This effect was abrogated when natural killer cells were depleted. Ex vivo analysis of tumor cells from harvested xenografts confirmed that decitabine increased ULBP-1 and ULBP-3 expressions and susceptibility to both human and murine NK cells in IDHmut gliomas. Immunohistochemical analysis of the xenografts indicated that IDHmut gliomas had higher level of NK infiltration into the tumor compared to negative control. Finally, decitabine was able to alter the tumor infiltrating lymphocyte landscape in IDHmut glioma xenograft by increasing NK-cells, dendritic cells, macrophages but decrease monocytes and myeloid derived suppressor cell infiltration.

Conclusions

Decitabine is an effective immunotherapeutic agent to inhibit the growth of IDHmut glioma xenograft in an athymic nude mouse model. Decitabine is able to significantly alter the tumor-immune landscape in IDHmut gliomas to a pro-inflammatory state.

Learning Objectives

Describe mechanism of IDH mutant glioma immune escape

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