5-Azacytidine

5-Azacytidine was first synthesized almost 40 years ago. It was demonstrated to have a wide range of anti-metabolic activities when tested against cultured cancer cells and to be an effective chemotherapy for acute myeloid leukemia. However, because of 5-azacytidine's general toxicity, other nucleoside analogs were favored as therapeutics. The finding that 5-azacytidine was incorporated into DNA and that, when present in DNA, it inhibited DNA methylation, led to widespread use of 5-azacytidine and 5-aza-2'-deoxycytidine (Decitabine) to demonstrate the correlation between loss of methylation in specific gene regions and activation of the associated genes. There is now a revived interest in the use of Decitabine as a therapeutic agent for cancers in which epigenetic silencing of critical regulatory genes has occurred [1].

Human IDH1 WT and IDH1R132H cell lines and patient-derived xenografts (PDX) were used to evaluate the FDA-approved DNA demethylating agent 5-Azacytidine (5-Aza). Cell growth, protein and gene expression, chromatin immunoprecipitation, and nucleosome position assays were performed in 5-Aza treated cells. To evaluate antitumor activity in vivo, 5-Aza was administered alone and in combination with Temozolomide (TMZ) in a patient-derived xenograft (PDX) glioma models harboring IDH1R132H mutation.

5-Aza treatment has been found to reduce cell growth and increase Glial Fibrillary Acid Protein expression. Chromatin immunoprecipitation and nucleosome position assay showed that the mechanism of increased GFAP expression induction is associated with histone modification and nucleosome repositioning of the GFAP promoter, respectively. In vivo, 5-Aza treatment extended survival in IDH1R132H mutant, but not in an IDH1 WT glioma model. Additionally, 5-Aza enhances the therapeutic effect of DNA damaging agent TMZ in both subcutaneous and orthotopic PDX models of IDH1R132H mutant glioma [2].

Treatment of HCMV- infected D324 cells and HUVECs with the methylation inhibitor 5-Azacytidine (5AZA), significantly increased HCMV-IE and HCMV-gB gene transcription and protein expression. Immunohistochemical staining of DNMT-1 and HCMV proteins in MB cancer tissue sections revealed both nuclear and cytoplasmic DNMT-1 localization. In conclusion, DNMT-1 resides in the cytoplasm of HCMV-gB-expressing HUVECs and D324 cells. Increased viral protein synthesis in 5AZA-treated cells suggests that HCMV replication may benefit from a DNA methyltransferase-free cellular environment. Our findings emphasize the importance of assessing potential viral activation in the treatment of MB patients with epigenetic drugs [3].

1)
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2)
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3)

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