Targeting the Cancer Epigenome: Synergistic Therapy With KDM4 and BET Inhibitors

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Histone Lysine Demethylase 4 (KDM4) and Mammalian Bromodomain and Extra-Terminal Domain (BET) are proteins that are highly dysregulated in multiple kinds of cancers. This study researched the use of a KDM4 and BET inhibitor on cancer cell lines GIST-T1, KTC2, HepG2, HCT-116, and A549. The primary goal of this research was to see if the combined treatment of KDM4-IN-4 (a KDM4 inhibitor) and ABBV-75 (a BET inhibitor) would lead to anti-tumor synergy in the cell lines listed. Experiments were completed by culturing cells, conducting single and combination drug dose outs in triplicate, and the use of cell viability assays. CyQuant was the viability assay kit that was used. Cells were split every week, and three biological replicates of the drug dose outs were preformed to test for consistency and accuracy within results. A western blot was conducted to test for protein expression. Synergy was calculated via software CompuSyn using the Chou-Talaylay method, and the graphs were created using GraphPad. The western blot was analyzed using the software Image J. Dose out results show CI (combination index) values that are below one at multiple different concentrations among all five cell lines. Western blot results provide quantitative data on protein bands that correlate with protein expression following a drug treatment. These findings suggest that synergy does exist between ABBV-75 and KDM4-IN-4 in combination in all 5 cancer cell lines. This study also finds that protein expression of c-KIT and ETV1 was attenuated in GIST-T cells after a 24-hour drug treatment with the combined drugs at its IC50. This can lead to life saving novel therapies, and the synergistic behavior between these two drugs may be a universal result when using these two inhibiting drugs in combination.

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