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A Combination of Vitamin C with DNA methylation inhibitor Decitabine Preserves the Colon Immunogenicity and Overcomes the Chemo-resistance †

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Abstract: Decitabine (DAC) is an anti-cancer hypomethylating drug which is able to activate silenced genes by promoter demethylation. DAC upregulates the expression of the New York esophageal squamous cell carcinoma (NY-ESO-1), a highly immunogenic cancer testis antigen known to induce both humoral and cellular immune responses. However, DAC also upregulates the expression of Programmed Death Ligand-1 (PD-L1) in tumor cells leading to resistance to cancer therapy. Vitamin C (Vit-C) is a novel epigenetic regulator of DNA demethylation and is capable of downregulating transcription factors involved in the modulation of PD-L1 expression. Therefore, our major aim is to investigate whether Vit-C could improve the effect of DAC by reducing PD-L1 and to determine the effect of a combination of Vit-C and DAC in colorectal cancer cells. We treated the HCT-116 colon cancer cell line with DAC (20 μM) and Vit-C (1 mM) alone or in combination for 48h, then cell proliferation was assessed using the CCK-8 assay. The differential expression of immune-regulatory and pro-apoptotic markers was quantified using western blotting and quantitative real-time polymerase chain reaction (PCR). Additionally, we analyzed cell apoptosis and cell cycle profile using flow cytometry (FACS). Treatment of HCT-116 cells with DAC alone induces the expression of NY-ESO-1 and upregulates the expression of PD-L1 at mRNA and protein levels compared to untreated cells. Interestingly, the combination of Vit-C with DAC significantly decreased PD-L1 expression compared to DAC alone. Further, the cytotoxic effect of DAC was primarily linked to apoptosis confirmed by the overexpression of caspase 8 and cleavage of PARP and caspase 3. This apoptotic effect was confirmed by FACS and was enhanced when Vit-C was used in combination with DAC. Vit-C prevented the upregulation of PD-L1 and enhanced the cytotoxic effect of the chemotherapeutic drug DAC. Our findings suggest Vit-C as an attractive adjuvant therapy that will promote the immune response and help to overcome immune resistance to DAC in colon cancer patients.

Keywords: Vitamin C; Decitabine; cancer; chemoresistance; immune regulation; immune checkpoints

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