“Combinatorial Application of Tocotrienols and Chemotherapeutic Drugs as a Chemosensitization Strategy in Colorectal Cancer”

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5-Fluorouracil (5FU)-based chemotherapy remains as the most common treatment approach for advanced colorectal cancer despite of its poor response rate. Hence, the current study attempted to enhance 5FU therapeutic outcome by combining this drug with delta-tocotrienol (δT3, a minor constituent of vitamin E family) which serves as a chemosensitization strategy. The growth inhibitory effects of combined and single treatments of δT3 and/or 5FU on a panel of colorectal cell lines were determined by a highly robust bioluminescence cell viability assay. Colony formation assay was performed to study the combinatory effects on the *in vitro* cell survival. The prospective synergistic combination of treatment was investigated morphologically via phase-contrast and fluorescence microscopic observations. Flow cytometric cell cycle profiling and cell apoptosis detection were performed to identify the involvement of cell cycle perturbation and apoptosis induction in the combined treatment. In order to understand the underlying proapoptotic mechanisms, apoptosis array was conducted to study the biomarkers that are potentially involved. The results were further validated by Western immunoblotting. Current results demonstrated that the combined treatment significantly reduced the required concentrations of 5FU by 16 folds on Caco-2 and 4 folds on SW48 colon adenocarcinoma cell lines and effectively declined the cell survival as compared to the single treatments. Morphological assessments on cancer cells revealed that combined treatment caused an extensive cellular stress, displaying nuclear condensation, cytoplasmic vacuolation and cytoplasmic extension. The combined treatment led to a modest, but with a significant increment in apoptosis. Apoptosis array suggested that the combined treatment may exert an anticancer effect via the suppression of cell survival pathways by which Bcl-2, XIAP, cIAP-2 and Livin were down-regulated. Caspase-8 and caspase-3 activations were enhanced by the combined treatment, suggesting an involvement of extrinsic apoptotic pathway. In conclusion, the combined treatment of δT3 and 5FU could be a prospective strategy to chemosensitize colorectal cancer cells towards apoptosis.

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