INDUCTION OF COLON CANCER CELL DEATH BY CRANBERRY PROANTHOCYANIDINS VIA MAPK PATHWAY

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The potential ability of dietary cranberry to inhibit colon carcinogenesis is under investigation. Compounds isolated from locally grown cranberry fruit (*Vaccinium macrocarpon*) have been shown *in vitro* to decrease proliferation of colon cancer cells, in part by induction of apoptosis. These compounds include oligomeric polyphenols known as proanthocyanidins (PACs) containing two or more epicatechin units with different types of linkages. To further elucidate the mechanism by which PACs induce cell death, we transcriptionally profiled cells treated with PACs. HCT116 and HT29 colon cancer cells were exposed to a cranberry proanthocyanidin (PACs) fraction isolated from Early Black variety cranberry fruit, at time intervals of 6, 12, 18 and 24 hours. Total RNA was extracted from PAC-treated and untreated control cells. Transcriptional profiling was performed using an Illumina microarray bead system. Microarray results revealed that expression of several members of the mitogen activated protein kinase family (MAPK) was significantly altered in the presence of PACs, leading to decreased transcription of genes in the nucleus and decreased tumor cell growth. Quantitative (Q)-PCR was used to confirm microarray data showing gene expression changes in some key apoptotic pathways. Western blotting was used to confirm the up- regulation or down-regulation of key proteins involved in the MAPK pathway. Significant changes in p53, APAF and VEGF protein expression were seen as early as eighteen hours. Flow cytometry was employed to identify changes in the cell cycle due to exposure to PACs. HCT116 and HT29 colon cancer cells showed a significant change in granularity and a significant increase in G_2 arrest compared to control when exposed to PACs for as little as six hours. This study has provided insight into mechanisms by which cranberry PACs may inhibit colon cancer.