Different Molecular Events Account for Butyrate-Induced Apoptosis in Two Human Colon Cancer Cell Lines[1]

Carmel Avivi-Green,* Sylvie Polak-Charcon,† Zecharia Madar* and Betty Schwartz*[2]

*Institute of Biochemistry, Food Science and Nutrition, Faculty of Agricultural, Food and Environmental Quality Sciences, The Hebrew University of Jerusalem, Rehovot 76100, Israel; and †Institute of Pathology, Sheba Medical Center, Tel-Hashomer, Israel

ABSTRACT We studied the molecular events underlying butyrate-induced apoptosis in two different colon cancer cell lines: Caco-2, a well defined cancer cell and RSB, a cell line obtained from a colonic tumor of an ulcerative colitis patient. Caco-2 and RSB cells were exposed to 2, 5 and 10 mmol/L butyrate for 48 h. Caspase-1 was cleaved in Caco-2-cells at all butyrate concentrations, whereas in RSB-cells caspase-1 expression was undetectable. In RSB cells, butyrate dose-dependently induced caspase-3 cleavage, whereas in Caco-2-cells, butyrate up-regulated expression of the caspase-3 active subunit. Caspase-3-specific activity, cytoplasmic nucleosome concentration and growth were directly correlated with butyrate doses in both cell lines; however, the response was more pronounced in Caco-2 than in RSB cells. Expression of the cleaved poly(ADP-ribose) polymerase (PARP) product was elevated in both cell lines at the highest butyrate concentration. Bak expression gradually increased as a function of butyrate concentrations in both cell lines. At 10 mmol/L butyrate, expression increased by fivefold and sevenfold in Caco-2 and RSB cells, respectively. The highest expression of Bcl-2 was observed in control Caco-2 cells, and expression decreased with increasing butyrate concentration. This effect was not observed in RSB cells. Inactivation of caspase-1 with Z-YVAD-FMK abrogated butyrate-induced apoptosis in Caco-2 but not in RSB cells. Inactivation of caspase-3 with Z-DVED-FMK completely inhibited butyrate-induced apoptosis in RSB cells whereas this effect was less pronounced in Caco-2 cells. Our data demonstrate that butyrate-induced apoptosis is activated via different apoptotic pathways in diversely stratified colon cancers. J. Nutr. 132: 1812–1818, 2002.

KEY WORDS: • *apoptosis* • *butyrate* • *caspases* • *colon cancer*