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Apoptotic Effects of Selected Strains of Lactic Acid Bacteria on a Human T Leukemia Cell Line Are Associated With Bacterial Arginine Deiminase and/or Sphingomyelinase Activities

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Abstract: *The aim of the present work was, first, to analyze the apoptotic effect in vitro of sonicated preparations of selected strains of lactic acid bacteria on normal and tumor human lymphocytes. Incubation with bacterial samples led to a relevant time-dependent apoptotic cell death of Jurkat cells but not normal human peripheral blood lymphocytes.* Lactobacillus brevis *(CD2) samples were more efficient in inducing apoptosis of Jurkat cells than were samples of* Streptococcus thermophilus *(S244). In an attempt to characterize the mechanisms underlying these effects, we found that the apoptotic death-inducing ability of S244 preparations could be attributed to the ability of high levels of neutral sphingomyelinase activity to generate relevant amounts of ceramide, a known apoptotic death messenger, in Jurkat cells. On the other hand, our results indicate that apoptosis induced by CD2 samples could also be associated with high levels of arginine deiminase activity, which in turn was able to downregulate polyamine synthesis in Jurkat cells.*

Introduction

Lactic acid bacteria (LAB) belong to a variety of genera used to effect milk fermentation. The primary metabolic end product from carbohydrate metabolism of most of these bacteria is lactic acid, which in turn serves to preserve milk and to achieve syneresis and desired functional characteristics (1). It is known that LAB and their products have beneficial effects on the health of animals and humans, i.e., protection against enteric infections, use as an oral adjuvant, immunopotentiation in malnutrition, and prevention of chemically induced tumors (2,3). Several experimental studies indicate antitumor effects of LAB in vitro or in vivo (4,5), but the mechanisms are unclear. Some of these effects have been attributed to inhibition of mutagenic activity and decrease of several enzymes involved in the generation of carcinogens, mutagens, or tumor-promoting agents (6–8). On the other hand, specific cellular components in LAB strains seem to induce strong adjuvant effects, including modulation of cell-mediated immune responses, activation of the reticuloendothelial system, and regulation of several cytokines (9,10). *Lactobacillus casei* has been reported to exert antitumoral activity, mediated by the stimulation of cellular defense mechanisms, against various murine (Yac-1, P815, Ehrlich ascites tumor, and mammary carcinoma) and human (K562 and KB) tumor cell lines (11). Fichera and Giese (11) suggest that *L. casei* and its derivative peptidoglycan stimulate activity in normal cells and inhibit activity in tumor cells. Moreover, the suppressive effects of *L. casei* on the incidence of spontaneous thymic lymphoma in AKR mice have been reported by Watanabe (12). Mean survival age of AKR/J mice was significantly prolonged, enlargement of the thymus was markedly suppressed, and proliferation of ecotropic and recombinant murine leukemia viruses was markedly inhibited when animals were injected intraperitoneally with heat-killed *L. casei* cells; these effects were attributed to the immunostimulating activities of the bacterium (12). Recently, Kato et al. (13) reported the ability of *L. casei* to induce production of interleukin (IL)-12 and interferon (IFN)-γ in murine splenocytes in vitro. Moreover, Tejada-Simon et al. (14) recently evaluated the effects of exposure to eight different LAB in mice on ex vivo cytokine and nitric oxide (NO) production in leukocyte cultures. Their results indicate that *Lactobacillus acidophilus* and *L. casei* were able to potentiate IL-6 and IL-12 production by peritoneal cells, whereas *L. acidophilus* upregulated IFN-γ and NO. In contrast, *Lactobacillus helveticus*, *Lactobacillus gasseri*, *Lactobacillus reuteri*, and *Bifidobacterium* attenuated the production of IL-6, IFN-γ, and NO by peritoneal cells. They conclude that prior oral exposure to LAB could differentially potentiate or attenuate subsequent cytokine and NO production by peritoneal cells. Thus, according to data available in the literature, LAB-induced antimutagenic effects and immune regulation are considered the potential indirect causes of their antitumoral activity.

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