



Probiotic Modulation of Intestinal Cell Apoptosis in Inflammatory Bowel Disease and Colon Cancer

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Abstract

Probiotic bacteria have been proposed as a therapeutic strategy for chronic intestinal inflammation and colon cancer. One of the mechanisms of action by which probiotics exert their effects is the modulation of apoptosis in intestinal immune and/or epithelial cells. Therefore, the knowledge of how probiotics modulate cell apoptosis provide additional information in the therapeutic strategy of these intestinal disorders. The objective of this commentary is to highlight the most relevant studies focused on pro- and anti-apoptotic effects of probiotics in intestinal cells in order to gain insight into their mechanisms of action.

Keywords: Probiotic; Apoptosis; Inflammatory bowel disease; Colon cancer

Commentary

Nowadays, the use of probiotics has been proposed as a potential therapeutic strategy of inflammatory diseases and cancer in human medicine, including the treatment of intestinal pathologies, such as inflammatory bowel disease (IBD) and colon cancer. The interest in understanding the mechanisms of action by which probiotics exert their effects has increased during the last years. One of the mechanisms of action reported is the modulation of apoptosis in intestinal immune and/or epithelial cells, but the number of studies focused on this mechanism is limited. The knowledge of how probiotics modulate cell apoptosis provide additional information and could help in the therapeutic strategy of these intestinal disorders, reducing the mucosal inflammation or tumor growth. Therefore, this commentary aims to highlight the most relevant studies focused on pro- and anti-apoptotic effects of probiotics in intestinal cells in order to gain insight into their mechanisms of action.

Apoptosis signaling can be induced through the extrinsic and intrinsic pathways. The extrinsic pathway is mediated by several receptors, including first apoptosis signal (FAS; also called CD95 or APO-1), tumor necrosis factor receptor 1 (TNFR1), TNF-related apoptosis-inducing ligand (TRAIL) receptor 1 (TRAIL-R1 or DR4) and TRAIL receptor 2 (TRAIL-R2 or DR5), which are activated by extracellular ligands initiating a protein-protein interaction at cell membranes that active an intracellular caspase cascade [1,2]. On the other hand, the intrinsic pathway is initiated by several stimuli (*e.g.*, DNA damage, starvation, oxidative stress and chemotherapeutic drugs) which involve mitochondrial outer membrane permeabilization and mitochondria-to-cytosol translocation of (i) cytochrome c that forms the apoptosome complex with the apoptotic protease-activating factor-1 (Apaf-1) and activates caspase-9, which subsequently triggers caspase-3; (ii) inhibitors of apoptosis proteins (IAPs), such as Smac/Diablo and Omi/HtrA2, which enhance caspase activation, or (iii) apoptosis-inducing factor (AIF), which causes nuclear chromatin condensation and facilitates DNA fragmentation by the nuclease Endo

G (caspase-independent pathway) [1-3]. Pro- and anti-apoptotic effects have been described as beneficial features of probiotics in intestinal pathologies. In this sense, the activation of the cell programmed death could suppress the number of active monocytes and lymphocytes in chronic inflammatory diseases [4] and could limit the number of carcinogenic cells in tumors [5]. However, the anti-apoptotic effect of probiotics in epithelial intestinal cells could reduce the colonic barrier disruption in chemical-induced colitis [6].

Regarding intestinal inflammatory diseases, previous studies have reported probiotic strains with different mechanisms to modulate cell apoptosis. Angulo et al. (2011) [7] showed that *Lactobacillus brevis* and *Streptococcus thermophilus* sonicates induced more apoptosis in lamina propria mononuclear cells (LPMC) isolated from patients with Crohn's disease and ulcerative colitis than control LPMC. They also demonstrated that the pro-apoptotic effect of these probiotics was mediated by the neutral sphingomyelinase/ceramide pathway. Therefore, promoting apoptosis by these sonicates could stabilize the deficient cell death and decrease the inflammation response in IBD [7]. Moreover, Chiu et al. (2010) [4] described that heat-stable factor(s) (5–30 kDa fraction) produced by *Lactobacillus rhamnosus* promoted apoptosis in lymphocytes and monocytes isolated from healthy blood donors and human monocytic leukemia-derived cell lines (THP-1) by a mitochondrial pathway without affecting human colonic epithelial carcinoma cells (HT-29), suggesting its administration to prevent IBD. However, the effect on apoptosis in lamina propria mononuclear cells obtained from patients with intestinal pathologies was not determined. Interestingly, Yan et al. (2011) [6] reported an anti-apoptotic effect of a derived soluble protein (p40) produced by *L. rhamnosus* GG, which prevented cytokine-induced apoptosis in intestinal epithelial cells mediated through activation of the epidermal growth factor receptor (EGFR) phosphorylation in young adult mouse colon epithelial cells and HT-29 cells. In addition, p40 reduced intestinal epithelial apoptosis in dextran sulfate sodium-induced acute colitis and oxazolone-induced chronic colitis. This anti-apoptotic effect of *L. rhamnosus* GG was also observed previously [8]. This probiotic strain reduced staurosporine-induced apoptosis in rat intestinal epithelial cells (IEC-6) and using *ex vivo* models in mice, inhibiting caspase-3 activation and stimulating the up-regulation of anti-apoptotic genes.

With respect to models with tumoral cells, most studies reported the induction of apoptosis as an anti-carcinogenic effect. Altonsy et al. (2010) [1] reported that *L. rhamnosus* GG and *Bifidobacterium lactis* Bb12 could provide protection against colon cancer by inducing apoptosis, via the mitochondrial route, as indicated by the re-localization of Bax from the cytoplasm to the mitochondria, the cytochrome c release from the mitochondria into the cytoplasm, and the caspase-9 and -3 activation in colon cancer cell line Caco-2. Chen et al. (2012) [5] described that the oral administration of *Lactobacillus acidophilus* NCFM in mice increased apoptosis of CT-26 murine colon adenocarcinoma cells in the segmental orthotopic colon cancer, and the expression of the caspase-3 and -9, attenuating the tumor growth during CT-26 cell carcinogenesis. Wang et al. (2014) [9] demonstrated that the cell extract from three lactobacilli possessed the ability to induce HT-29 cells apoptosis through the breakdown of mitochondrial membrane potential. Recently, Song et al. (2015) [10] indicated that the membrane proteins (12 and 15 kDa fractions) from heat-inactivated *Lactobacillus plantarum* L67 had a pro-apoptotic effect in HT-29 cells by the induction of the mitochondrial (intrinsic) cell death pathway confirmed by caspase-8-mediated cleavage of Bid to the t-Bid protein, induction of the translocation of cytochrome c from mitochondria to cytosol, and stimulation of the caspase-8 and caspase-3 activities. Similar results were observed in colon cancer SW620 cells treated with the supernatant obtained from *Lactobacillus delbrueckii*, which efficiently induced apoptosis through the intrinsic caspase 3-dependent pathway, with a corresponding decreased expression of Bcl-2 [11]. Furthermore, Baldwin et al. (2010) [12] demonstrated a synergistic pro-apoptotic effect of the combination of a chemotherapeutic agent, 5-fluorouracil, and a mixture of viable *L. acidophilus* CL1285 and *Lactobacillus casei* LBC80R probiotic strains in a colorectal carcinoma cell line LS513, correlated with the activation of the caspase-3 and a faster reduction of p21 expression.

In veterinary medicine, there are few studies concerning the mechanisms of action of probiotics in chronic enteropathies, being these studies focused specifically on dogs [13-16]. However, none of them related to the apoptotic effect of probiotics on intestinal cells.

In conclusion, *Lactobacillus* spp. is the most reported genus with ability to modulate apoptosis in intestinal immune and/or epithelial cells. Moreover, the most common mechanism by which probiotics exert their pro-apoptotic effect in colon cancer seems to be through the mitochondrial (intrinsic) pathway. However, further studies on pro- and anti- apoptotic effects of probiotics in chronic intestinal diseases should be carried out in an attempt to explain the specific mechanisms by which probiotics reduce the bowel inflammation promoting immune cell apoptosis and also protect intestinal integrity reducing intestinal epithelial cell apoptosis.

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