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Commentary

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

Alberto Roy*

American Institute of Immunotherapy, Bethesda, Maryland, United States.

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 provides 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

Now days, 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 orAPO-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 a pop to some complex with the apoptotic protease-activatingfactor-1 (Apaf-1) and activates caspase-9, which subsequently triggerscaspase-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 EndoG (caspase-independent pathway) [1-3]. Pro- and anti-a pop to twice 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 mono cytes 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 a pop to sis. Angulo et al. (2011) showed that Lactobacillus brevis and Streptococcus thermophiles 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

Correspondence to: Alberto Roy, American Institute of Immunotherapy, Bethesda, Maryland, United States, E-mail: alberto_na@za.us

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probiotics was mediated by the neutral sphingomyelinase/ceramide pathway. Studies concerning the mechanisms of action of probiotics in chronic enteropathies, being these studies focused specifically on dogs. However, none of them related to the apoptotic effect of probiotics on intestinal cells.

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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