

Novel Challenges in Disease Managements by Bacterial-Free Extracts with Benefits to the Host but without the Risk of Side Effects

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Paraprobiotics and postbiotics are derivatives of probiotic cultures and have been used in humans with beneficial effects that sometimes are linked to secreted probiotic-derived factors (viz postbiotic mediators). Supernatants harvested from *Lactobacillus rhamnosus* GG (LGG) cultures (ATCC53103 strain) was shown by a numerous group of authors [see references under reported] protect colonic human smooth muscle cells (HSMCs) from lipopolysaccharide (LPS)-induced myogenic damage.

Lactobacillus is a genus of Gram-positive facultative anaerobic bacteria belonging to the phylum of *Firmicutes* that has been shown to modulate gut innate immunity and to promote intestinal epithelial cell survival and barrier function. The effect of probiotics on gastrointestinal motility has been reported from different studies carried out in different animal models highlighting the gut motor-neural apparatus as a primary target for probiotics in gut post-infective disorders.

Lactobacillus species specifically regulate jejunal motility and colonic neuron excitability and alleviate visceral hypersensitivity. On human smooth muscle, LGG is able to counteract the inflammatory burst induced by LPS through the activation of membrane Toll-like receptor 2. On both mouse cardiac cells and rabbit colonic smooth muscle, Toll-like receptor 2 activation hampers the inflammatory the nuclear factor kappa-light-chain-enhancer of activated B cells pathway, through anti-inflammatory phosphatidylinositol-3'-kinase/protein kinase B signaling. This latter signaling pathway is responsible for the antiapoptotic effects reported for LGG culture supernatants.

The inhibition of LPS-induced IL-6 secretion from HSMCs by LGG supernatants suggests that LGG bioproducts exert an anti-inflammatory effect on human smooth muscle as well. downregulation by *Lactobacilli* of proinflammatory cytokine release has been previously reported in human intestinal dendritic cells challenged with *Salmonella* and in human peripheral blood monocyte-derived macrophages primed by LPS. Similar downregulation of inflammatory response has been observed with *Lactobacilli* metabolic products.

Purification of LGG supernatants has highlighted mostly the presence of 2 proteins, the first with a molecular mass of 40 kDa about and the second of 75 kDa (namely, p40 and p75, respectively) whose effects have been tested on both murine and human cell lines and cultured colon explants. These two proteins prevent tumor necrosis factor-induced intestinal epithelial cells and organ culture damage, inhibit apoptosis, and stimulate proliferative epithelial cell responses. The first has relevant immunoregulatory functions, acting on macrophages and lymphocytes to directly downregulate proinflammatory cytokine production and modulate intestinal epithelial homeostasis.

Interesting is the observation of the different effects of LGG supernatants on cell contraction depending on the time of collection from the broth of the culture. Supernatants collected in the middle exponential phase of growth induced a significant contraction of HSMCs and possessed only a slight protective effect on LPS-induced impairment of contractile response; whereas supernatants collected in the overnight phase of growth were able to restore contraction after LPS exposure and had by themselves only light contractile activity. These

results, only apparently unadequate suggest that the presence/absence or loss of activity of different postbiotic mediators in the collected samples may exert contradictory effects on human cells.

Finally, results obtained by different authors [1-4 see references under reported] fortify the therapeutic value of the probiotic strain LGG in contrasting LPS tissue damages and emphasize the role of LGG probiotic mediators. Given that there is an urgent need to seek and develop innovative treatments to successfully interact with the microbiota and the human immune system in the coronavirus crisis, further research will be necessary to investigate the postbiotic mediators involved. Such studies will emphasize novel potentials in probiotic use, allowing the avoidance of existing issues linked to the use of live cells of probiotic bacterial strains such as bacterial viability, bacterial load, and vitality maintained in the gastrointestinal tract, and the problematic linked to the antibiotic resistance spread.

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