Lactobacillus casei strain Shirota – Research Update

IMPROVEMENT IN INTESTINAL HEALTH

1. Effect of fermented milk containing Lactobacillus casei strain Shirota on constipation-related symptoms and haemorrhoids in women during puerperium.

Summary

Constipation and haemorrhoids are common complaints after childbirth. The objective of this pilot study was to evaluate the impact of fermented milk containing Lactobacillus casei strain Shirota (LcS) on stool consistency and frequency, constipation-related symptoms and quality of life and incidence of haemorrhoids in women during puerperium.

Forty women who had natural childbirth were randomised into two groups consuming either one bottle/day of fermented milk containing at least $6.5\times10^9$ cfu of LcS or placebo for 6 weeks after childbirth. Subjects filled in a diary on their bowel habits including number of bowel movement, stool consistency and incidence of haemorrhoids and answered questionnaires on constipation-related symptoms (PAC-SYM) and quality of life (PAC-QOL) during the study period.

The probiotic group showed better scores on overall PAC-SYM ($P=0.013$), PAC-SYM subscales of abdominal symptoms ($P=0.043$) and rectal symptoms ($P=0.031$) and PAC-QOL satisfaction subscale ($P=0.037$) in comparison with the placebo group. Two to four subjects experienced haemorrhoids during the first 3 weeks of treatment in the probiotic group. The number decreased in week 4 and none of the subjects experienced haemorrhoids in week 5-6. In the placebo group, on an average four subjects had haemorrhoids from the beginning and no obvious change was observed until week 6. No statistically significant effect was observed on stool consistency and frequency. The study products did not cause any adverse event in the subjects.
Results of this study indicate that continuous consumption of fermented milk containing LcS might alleviate constipation-related symptoms, provide satisfactory bowel habit and result in earlier recovery from haemorrhoids in women during puerperium.

2. Human Gut Dendritic Cells Drive Aberrant Gut-specific T-cell Responses in Ulcerative Colitis, Characterized by Increased IL-4 Production and Loss of IL-22 and IFNγ.

The pathogenesis of Inflammatory Bowel Disease is incompletely understood but results from a dysregulated intestinal immune response to the luminal microbiota. CD4 T cells mediate tissue injury in the inflammatory bowel disease-associated immune response. Dendritic cells (DC) generate primary T-cell responses and mediate intestinal immune tolerance to prevent overt inflammation in response to the gut microbiota. However, most information regarding function of intestinal DC has come from mouse models, and information in humans is scarce.

The intestinal DC subsets are skewed in ulcerative colitis (UC) in humans, with a loss of CD103 lymph-node homing DC; this intestinal DC subset preferentially generates regulatory T cells in mice. The study show infiltrates of DC negative for myeloid marker CD11c, with enhanced expression of Toll-like receptors for bacterial recognition. After mixed leukocyte reaction, DC from the inflamed UC colon had an enhanced ability to generate gut-specific CD4 T cells with enhanced production of interleukin-4 but a loss of interferon γ and interleukin-22 production. Conditioning intestinal DC with probiotic strain *Lactobacillus casei* Shirota in UC partially restored their normal function indicated by reduced Toll-like receptor 2/4 expression and restoration of their ability to imprint homing molecules on T cells and to generate interleukin-22 production by stimulated T cells.

This study suggests that T-cell dysfunction in UC is driven by DC. T-cell responses can be manipulated indirectly through effects of bacterial conditioning on gut DC with implications for immunomodulatory effects of the commensal microbiota in vivo. Manipulation of DC to allow generation of DC-specific therapy may be beneficial in inflammatory bowel disease.
1. **Heat-killed probiotic bacteria differentially regulate colonic epithelial cell production of human β-defensin-2: dependence on inflammatory cytokines.**  

**Summary**

The aim of this investigation was to determine the effect of selected probiotic strains on hBD-2 production by epithelial cells induced by pathologically relevant pro-inflammatory cytokines and the role of cytokine modulators in controlling hBD-2. Caco-2 colonic intestinal epithelial cells were pre-incubated with heat-killed probiotics, i.e. *Lactobacillus casei* strain Shirota (LcS) or *Lactobacillus fermentum* strain MS15 (LF), followed by stimulation of hBD-2 by interleukin (IL)-1β and tumour necrosis factor alpha (TNF-α) in the absence or presence of exogenous IL-10 or anti-IL-10 neutralising antibody. Cytokines and hBD-2 mRNA and protein was analysed by real-time quantitative polymerase chain reaction and enzyme-linked immunosorbent assay.

LcS augmented IL-1β-induced hBD-2 whereas LF enhanced TNF-α- and suppressed IL-1β-induced hBD-2. LF enhanced TNF-α-induced TNF-α and suppressed IL-10, whereas augmented IL-1β-induced IL-10. LcS upregulated IL-1β-induced TNF-α mRNA and suppressed IL-10. Endogenous IL-10 differentially regulated hBD-2; neutralisation of IL-10 augmented TNF-α- and suppressed IL-1β-induced hBD-2. Exogenous IL-10, however, suppressed both TNF-α- and IL-1β-induced hBD-2; LcS partially rescued suppression in TNF-α- and IL-1β-stimulation, whereas LF further suppressed IL-1β-induced hBD-2.

This study concludes that probiotic strains differentially regulate hBD-2 mRNA expression and protein secretion, modulation being dictated by inflammatory stimulus and resulting cytokine environment.

2. **Immune system stimulation by probiotic microorganisms.**  

**Summary**

Probiotic organisms are claimed to offer several functional properties including stimulation of immune system. This review is presented to provide detailed informations about how probiotics stimulate our immune system. *Lactobacillus rhamnosus* GG, *Lactobacillus casei* Shirota,
Bifidobacterium animalis Bb-12, Lactobacillus johnsonii La1, Bifidobacterium lactis DR10, and Saccharomyces cerevisiae boulardii are the most investigated probiotic cultures for their immunomodulation properties.

Probiotics can enhance nonspecific cellular immune response characterized by activation of macrophages, natural killer (NK) cells, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in strain-specific and dose-dependent manner. Mixture and type (gram-positive and gram-negative) of probiotic organisms may induce different cytokine responses. Supplementation of probiotic organisms in infancy help prevent immune-mediated diseases in childhood, whereas the intervention in pregnancy affect fetal immune parameters, such as cord blood interferon (IFN)-γ levels, transforming growth factor (TGF)-β1 levels, and breast milk immunoglobulin (Ig)A.

Probiotics that can be delivered via fermented milk or yogurt improves the gut mucosal immune system by increasing the number of IgA(+) cells and cytokine-producing cells in the effector site of the intestine.