

## *Lactobacillus rhamnosus* GG: Experimental Evidence for a Clinical Utilization in Inflammatory Bowel Disease

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The last decades have seen a dramatic increase in the research of the intestinal microbiota, and, as a consequence, of the possible manipulation of the gut flora for therapeutic purposes by means of probiotic bacteria supplements. Accordingly, probiotic bacteria have been proposed for a plethora of pathologic situations, but real evidence for their application is limited to few diseases. In particular, probiotic utilization have been proposed in inflammatory bowel disease (IBD), that are two pathologic conditions (ulcerative colitis and Crohn's disease) of unknown etiology and immunologic pathogenesis, characterized by a chronic inflammation of the gut leading to a condition characterized by the alternation of flares and remission of disease. Despite studies on probiotic utilization in IBD have increased in the last years, to date the most solid evidence regards the use of probiotic in remission maintenance of pouchitis, while recent clinical data suggest a possible use in mild-moderate ulcerative colitis too [1]. Indeed, IBD represent a not homogenous condition that may present consistent differences in term of disease activity, location, course and behavior even inside the two distinct clinical entities, so that clinical studies, designed without appropriate selection of patients with specific disease features, may have led to disappointing results for the efficacy of probiotics. Moreover, probiotic studies examined many different formulations including mono- and multi-species compounds, each one with bacterial species with peculiar characteristics, with heterogeneous doses and treatment duration, so that results are not easily synthesizable [2,3].

Bearing in mind the aforementioned limits of the clinical studies, the most of the published studies about probiotics involves *in vitro* systems and experimental models of IBD [4]. Even though data from such studies are not directly reproducible in human condition, they may provide further insights into possible mechanism of action of probiotics and useful suggestion for specific clinical utilization of the bacteria in IBD patients. Among probiotic bacteria, *Lactobacillus rhamnosus* GG (LGG) represents one of the more largely studied and it has demonstrated *in vitro* and in experimental model peculiar features suggesting a possible therapeutic utilization in IBD. In fact, considering together the recent advances in the field of microbiota research and in IBD pathogenesis, an ideal probiotic candidate for an efficacious usage in this setting should present three peculiar characteristics among the others: the capacity to adhere and persist at the intestinal mucosal level, to stimulate local innate immune response (i.e. epithelial functions), and to exert anti-inflammatory activity.

Although *in vivo* studies on mucosal adhesion of probiotic are scanty, *in vitro* experiments have shown that LGG presents an elevated binding capacity to the mucosal surface [5]. Genetic studies have recently shown the presence of pili that enhance the adhesive capacity of the bacteria [6]. Moreover, LGG can produce specific mucus binding proteins that further explain the high colonization capacity of this bacteria at mucosal level [7,8]. Further studies investigating the pattern of adhesion of LGG in the different segments of the colon might identify a subset of IBD patients with a localization of inflammatory disease that may be particularly eligible for therapeutic administration of LGG supplement. Similarly to other Lactobacilli, LGG electively interact with the intestinal epithelium with the result of a decrease of the intestinal

permeability, stimulation of barrier effect through production of anti-bacterial molecules (i.e. mucins, defensins) and mucus, competition with pathogenic bacteria and local microflora modulation [9-11]. Most of the positive effect of the LGG on the epithelial function appears to be mediated by nuclear factor  $\kappa$ B (NF- $\kappa$ B) modulation [12]. In addition, LGG may exert mucosal anti-inflammatory effect by a direct interaction with macrophages, dendritic cells and CD4+ lymphocytes, resulting in decreased production of pro-inflammatory cytokines, namely TNF, IL-2, IL-4 [13-15].

In conclusion, even though solid evidence for a clinical effectiveness of probiotic bacteria in IBD are lacking, data from *in vitro* and experimental models indicate that LGG may represent a probiotic bacteria of particular interest for a clinical utilization in such conditions. Well-designed clinical studies are eagerly needed to properly translate into clinical setting the suggestion coming from the basic research. It is desirable that further evidences about the beneficial effects of probiotics and increased understanding of their underlying biochemical and immunological mechanisms of action will improve the treatment options for gut inflammation disorders and lead to a more rational and focused utilization of bacterial supplements in specific clinical conditions.

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