*Review paper*

# Biological functions of exopolysaccharides from probiotic bacteria

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***Abstract***

*It is well established that probiotic bacteria have beneficial influence on health of the host. The probiotic effects ascribed to lactic acid bacteria, the major probiotics, result not only from the action of whole microorganisms and cell wall components, but also from the action of extracellular polysaccharides (exopolysaccharides – EPS). However, the mechanisms responsible for these effects are still poorly understood, especially the immunoregulatory properties of EPS are not well defined.*

*This review attempts to answer the question what is the role of EPS in bacteria physiology, biofilm formation, and whether EPS can contribute to immunomodulatory potential of probiotic lactic acid bacteria?*

***Key words****: exopolysaccharides, biofilm, probiotic bacteria, lactobacilli.*

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## Introduction

Probiotic bacteria have the ability to produce exocellular polymers called exopolysaccharides (EPS). It has been suggested that the health benefit of probiotic bacteria can be attributed to the production of EPS. However, the composition, structure and biological functions of EPS may vary depending on the type of microorganism and environmental conditions. Some data suggest that EPS production is under control of quorum sensing (QS) through regulation of gene expression for proteins involved in EPS biosynthesis [1].

EPS is the main substance involved in biofilm formation and may achieve 50-90% of the total organic substances such as proteins, lipids and nucleic acids [1]. Bacteria develop biofilms to protect the microbial community against environmental stress. It has been established that both pathogenic, as well as commensal bacteria, generate biofilms in human mucosas. Biofilm formation is associated with bacterial infection but it may also play a protective role. For example, biofilm-like communities of the gastrointestinal and female urogenital tracts contain beneficial lactic acid bacteria. It has been shown that the cell wall components of probiotic bacteria, such as peptidoglycans or teichoic acids play an important role in activation of immune cells. By contrast, the role of EPS in modulation of the immune system is still unclear.

## Probiotic bacteria

Probiotics are live microorganisms which exert a beneficial effects on the host. The Food and Agriculture Organization of the United Nations defines them as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [2, 3]. Members of genera *Lactobacillus* and *Bifidobacterium* are the most common probiotics used not only for human consumption [4] but also in pharmaceutical preparations or in biomedicine [5]. One of the main criteria for selection of oral administration of probiotics is their ability to adhere to the intestinal mucosa allowing a transitory colonization of the gastrointestinal tract [6]. Probiotics maintain the balance within such complex ecosystem as human intestine in many ways: inhibition of the proliferation of pathogens by competition between bacteria and pathogens for adhesion, suppression of production of virulent factors by pathogens secreting bacteriocins, or modulation of the host immune system via interaction between probiotic bacteria and intestinal epithelial cells [7-9]. However, the effectiveness of probiotics is strain-specific and each strain

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may affect the host health trough different mechanisms [10-13]. For instance, lactic acid bacteria (LAB) diminish symptoms of lactose intolerance, reduce serum cholesterol, prevent diarrhea, enhance immune responses and anti-carcinogenic activities, alleviate allergies [14-17]. Lactic acid bacteria can even prevent or inhibit growth of pathogenic bacteria [18]. All these effects depend on adhesion of bacteria and their survival in specific regions of the gastrointestinal tract, competition with pathogens, presence of harmful antigens in the environment and mucosal barrier function.

The idea of using LAB to cure diseases and to promote health has been existing for at least 100 years, but the mechanisms of these actions are still poorly understood. Nevertheless, recent studies show that the probiotic effects of LAB result not only from whole microorganisms and cell wall components but also from peptides, nucleic acids and extracellular polysaccharides produced during growth of these bacteria [19-21]. It is postulated that this effect is related to diversity of exopolysaccharide polymers produced by bacteria [22].

## Structure of lactic acid bacteria derived exopolysaccharides

Almost all LAB have ability to secrete polysaccharide polymers, which are called exopolysaccharides (EPS). *Lactobacillus*, *Streptococcus* and *Lactococcus* prevail mostly among these genera [21-23]. Some strains of *Bifidobacterium* are also able to produce EPS [24]. EPS is secreted in two forms: as a capsular exopolysaccharide which is associated with the cell surface or as slime exopolysaccharide secreted as free polymers to the environment [25, 26]. Chemical structure of EPS has been studied in details [27-30]. There are over 50 different EPSes derived from LAB described and they are mostly composed of repeated units of a certain number of diverse sugar residues or sugar derivatives [28, 30]. Two main groups of EPSes are described: homopolysaccharides and heteropolysaccharides (Fig. 1). Structure of EPS depends on chemical composition. Homopolysaccharides contain a single type of monosaccharide and it is usually glucose or fructose. Thus, they are called α-glucans (dextrans) or fructans. Repeated units consist often of three to eight monosaccharides. EPS of *Streptococcus thermophilus* was the first heteropolysaccharide studied and described in details [31]. Heteropolysaccharides are composed of at least two different sugars out of glucose, galactose and rhamnose at different ratios. The molecular mass of these polymers ranges between $4.0 \times 10^4$ and $6.0 \times 10^6$ Da [32]. The composition and nature of EPS is affected by environmental conditions, biosynthetic pathways or rate of microbial growth. Residues such as sn-glycerol-3-phosphate, *N*-acetyl-aminosugars, phosphate and acetyl groups can

**I**

a) →6)-α-D-Glc-(1→6)-α-D-Glc-(1→6)-α-D-Glc-(1→

b) →2)-β-D-Fru-(2→6)-β-D-Fru-(2→6)-β-D-Fru-(2→

c) →1)-β-D-Fru-(2→1)-β-D-Fru-(2→1)-β-D-Rru-(2→

**II**

a) →3)-α-D-Glc*p*-(1→2)-β-D-Gal*f*-(1→6)-α-D-Gal*p*-(1→6)-α-D-Galc*p*-(1→3)-β-D-Gal*f*-(1→

b) β-D-Gal*p*-(1→4)-β-D-Glc*p*
1
↓
4
→2)-α-L-Rha*p*-(1→2)-α-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→3)-α-D-Gal*p*-(1→3)-α-L-Rha*p*-(1→

c) β-D-Gal*p*
1
↓
6
→3)-α-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→3)-β-D-Gal*f*-(1→

**Fig. 1.** Examples of primary structure of EPS produced by LAB [28,33]. I: homopolysaccharides: a) dextran, b) levan, c) inulin; II: heteropolysaccharides: a) *Lactobacillus rhamnosus* KL37, b) *Lactococcus lactis* subsp. cremoris NIZO B39, c) *Streptococcus thermophilus* Sfi32

also be found [30, 33]. This and the molecular weight determines the functional properties of EPS [22, 34]. However, not only LAB can produce EPS; some pathogenic bacteria can synthesize these molecules as well [35, 36].

## Biosynthesis and genes of exopolysaccharides

All homopolysaccharides are synthesized by extracellular specific enzyme – glycosyl transferase and energy for this synthesis comes from hydrolysis of sucrose [33]. Heteropolysaccharides are polymers of sugar precursors in the cytoplasm and several enzymes or proteins are involved in their synthesis and secretion [37]. The genes for these enzymes and proteins have been revealed in several strains of LAB. Genes for EPS synthesis in *Lactococcus lactis* and *Lactobacillus casei* are located in the plasmids [38] in contrast to all thermophilic LAB, genes of which are located in a bacterial chromosome [33]. There have been described sequences of genes for *Streptococcus thermophilus* Sfi6 [39, 40], *S. thermophilus* NCFB 2393 [41] and *S. thermophilus* MR-1C [42]. Organization of these genes appears to be highly conserved [33]. There is no gene cluster found in *Lactobacillus delbrueckii* ssp. *bulgaricus* so far despite its importance for the production of fermented products such as yogurts [43].

## Biofilm formation – the role of exopolysaccharides

There is an increasing interest among researchers concerning EPS, but the physiological role of these molecules is still not clear [22, 44, 45]. Most of this research relate to biofilm formation and its role in bacterial ecology [46, 47]. The term 'biofilm' was used for the first time in 1978 by Costerton *et al*. [48]. Studies on the role of EPS in biofilm formation are generally focused on pathogenic bacteria which are mostly Gram-negative species [49, 50]. Less is known about EPS in Gram-positive species. EPS fills intracellular space between bacteria and together with proteins, nucleic acids and lipids composes the structure of the biofilm matrix. EPS in biofilm protects bacterial cells from desiccation, phage attack, antimicrobial compounds, osmotic stress and predatory attack from protozoa [46, 51-53]. It helps bacteria to survive in detrimental conditions such as too low or too high temperature or pH. Capsular polysaccharides can promote the adherence of bacteria to biological surfaces, thereby facilitating the colonization of various ecological niches [25, 30]. EPS also can enable probiotics to survive in gastric acid and bile salts [19]. Biofilm produced by pathogenic bacteria makes them less susceptible to antibiotics and attacks by innate host defense. It plays an important role in many chronic bacterial infections [54, 55]. Biofilm formation and EPS production is under control of regulatory pathway of QS. It has been suggested that QS allows bacteria to communicate and regulate the expression of genes which are required for synthesis of EPS in response to changes in bacteria density [1].

## LAB derived exopolysaccharides and the immune system

Immunomodulating mechanism of LAB is obscure. However, it has been shown that the cell wall components of these bacteria, such as peptidoglycan or teichoic acids may play an important role in activating immune system cells in the gut [56]. An extract (without peptidoglycan) of cell walls from *Lactobacillus rhamnosus KLC37* containing EPS was tested *in vitro* in our laboratory for immunomodulating capacity. It was compared with lipopolysaccharide (LPS) from *Escherichia coli*. It turned out that it stimulated production of proinflammatory cytokines by mice macrophages in a dose-dependent manner and this stimulation depended on p38 and ERK kinase activity. However, participation of this extract in immunological response of macrophages was slightly comparable to that of whole bacteria. Only LPS, but not the extract, could induce hyporesponsiveness to a subsequent stimulation with LPS. Interestingly, extract-primed macrophages increased their ability to bind LPS in studies with atomic force microscopy [our data, unpublished].

The health benefit of LAB have been attributed to the production of EPS [25]. LAB EPSes have been claimed to have immunostimulatory activity [57, 58], antitumor effects [59, 60] or blood pressure and cholesterol lowering activity [61, 62]. EPS reduces symptoms of lactose intolerance and prevents diarrhea [14]. There have been reports that sugar polymers have antimicrobial properties and help to heal wounds [63, 64]. It has been also shown that some EPSes induce cytokine production, act like lymphocytes B mitogens or change functions of splenocytes [65-67]. EPS can reduce the symptoms of collagen-induced arthritis or diminish arteriosclerosis in mice (our research, unpublished). Orally administrated EPS-producing LAB attenuate severity of colitis and may be a promising agent in therapy of inflammatory bowel disease [7, 68].

In our opinion, such wide diversity of EPS effects on the immune system results not only from strain specificity, but also from microenvironmental impact on the EPS metabolism of probiotic bacteria. However, it is still not clear whether EPS can be the ligand for pattern recognition receptors and how the immune system can differentiate pathogenic bacteria from commensal flora. It is possible that EPS plays a role of signaling molecule in the mucosal immune system.

## Conclusions

EPS is produced by many probiotic bacteria and it is a key molecule of the biofilm matrix. However, due to the extreme heterogeneity of EPS, strain specificity and

unpredictable enzymatic modifications, its immunomodulatory potential should be established individually for each isolated molecule separately. Moreover, the role of EPS in QS regulation remains to be explained.

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