The Protective Potency of Probiotic Bacteria and Their Microbial Products against Enteric Infections – Review

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ABSTRACT. The intestinal environment accommodates a wide range of contents ranging from harmless beneficial dietary and microbial flora to harmful pathogenic bacteria. This has resulted in the development of highly adapted epithelial cells lining the intestine. This adaptation involves the potential of crypt cells to proliferate and to constantly replace villous cells that are lost due to maturity or death. As a result, the normal intestinal epithelial integrity and functions are maintained. This phenomenon is eminent in intestinal defense whereby the intestinal epithelial cells serve as a physical barrier against luminal agents. The protection against agents in the gut lumen can only be effective if the epithelium is intact. Restitution of the damaged epithelium is therefore crucial in this type of defense.

Abbreviations
Hsp(s) heat-shock protein(s)
IL interleukin

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1 INTRODUCTION

The intestinal epithelium is exposed to an array of injurious agents ranging from pathogens like viruses or bacteria to their products, xenobiotics, chemicals, immune and inflammatory cytokines, and thermal and related stress stimuli. To some extent, it serves as a protective barrier between these agents and the sterile host environment. Exposure to such noxious stimuli may lead to a complex, but well coordinated, signal transduction process to maintain intestinal integrity and function. The well-coordinated mechanisms result in increased proliferation of crypt cells, secretion of enzymes, and synthesis and secretion of immune and inflammatory cytokines and heat shock proteins (Malago et al. 2002; Trebichavský and Šplíchal 2006). Recent studies by different scholars and our own work revealed that these protective mechanisms are influenced by normal intestinal microflora and its fermentation products. In fact, the findings that intestinal microflora and its fermentation products influence the immune response of the intestinal epithelium have been the basis for intervening intestinal conditions. The intervention has benefited patients with various intestinal disorders.

In this review we highlight the role of intestinal microflora, commonly taken as probiotics, and their fermentation products in the protection of intestinal epithelium. Specifically, we show recent by proposed mechanisms by which they interact with mediators of immunity especially the putative protective heat shock proteins under stress conditions.
2 CYTOPROTECTION OF INTESTINAL EPITHELIUM AGAINST STRESS

2.1 The role of immune mediators

Apart from being a physical barrier, intestinal epithelial cells produce immune mediators, such as inflammatory cytokines and Hsps, in response to pathogens, adverse conditions, and various forms of stress (Hobbie et al. 1997; Awane et al. 1999; Elewaut et al. 1999; Ovelgönne et al. 2000; Malago et al. 2002). These mediators are aimed at eliminating the pathogens and protecting the cells by rescuing the already synthesized proteins. However, persistent production of pro-inflammatory cytokines often causes chronic inflammation followed by damage to the intestinal epithelium. In most cases, therefore, their production is down-regulated after resolving the inflammation. This down-regulation is mediated, at least in part, by way of Hsp synthesis (Cahill et al. 1996; Chu et al. 1997; Yoo et al. 2000; Malago et al. 2005). The expression of Hsps by intestinal epithelial cells could then, be part of a protective mechanism against stress, infection or inflammation of the intestinal epithelium. Though their actual mechanisms are indistinct, Hsps interfere with trans-activational activities of activators of several genes including the nuclear factor κB (NF-κB) and mitogen-activated protein kinases (MAPK) that are involved in the production of inflammatory, growth and stress mediators (Hobbie et al. 1997; Yoo et al. 2000).

2.2 The role of intestinal microflora and its fermentation products

The common intestinal luminal contents like dietary products and intestinal microflora substantially influence the cytoprotection of the intestinal epithelial cells. The bacterial microflora, for instance, ferments dietary components to yield biologically active products. In particular, short-chain fatty acids (formate, acetate, propionate, and butyrate) which are the fermentation products of saccharides (Cummings and Branch 1990) are repeatedly found in the colon of animals at various concentrations (Cummings et al. 1987; Treem et al. 1994). Their presence in the human colon affects important biological processes, such as growth, metabolism and differentiation of the intestinal epithelial cells (Bernard and Warwick 1993; Frankel et al. 1994). These processes are vital in maintaining the intestinal barrier integrity that separates and thus protects the sterile host milieu from the luminal environment. For example, induction of differentiation is associated with an increased transepithelial resistance. Such resistance may account for the inhibition of the pathogenic invasion of differentiated as opposed to undifferentiated intestinal epithelial cells (Cocconnet et al. 1994).

2.3 Heat-shock proteins are central to the intestinal cytoprotection by fermentation products

While ample evidence is available to demonstrate the essential role of short-chain fatty acids to the intestinal immune system, it is unknown whether this effect involves Hsps. Several studies have linked short-chain fatty acids with the improvement of inflammatory bowel diseases, such as ulcerative colitis and Crohn’s disease in humans. Their deficiency exacerbates the development of these diseases whilst the restoration of the normal endogenous concentrations by intracolonic infusion improves the conditions (Musch et al. 1999; Liang and MacRae 1997). Though the exact mechanism is enigmatic, short-chain fatty acids, in particular butyrate, affect the intestinal epithelial cell production of inflammatory cytokines that are pivotal to inflammation (Bernard and Warwick 1993; Koyasu et al. 1986). In fact, it modulates the production of the chemoattractant IL-8, which is pivotal to many intestinal inflammations, in a special way in favor of intestinal epithelial cell protection (Malago et al. 2005). Butyrate also has the potential to induce the expression of Hsps in various mammalian cells including the intestinal epithelial cells (Frankel et al. 1994). Bearing in mind the anti-inflammatory role of Hsps, it is tempting to suggest that part of the anti-inflammatory role of butyrate is via production of Hsps.

At times of infection, Hsps may play a role in cellular inhibition of pathogenic invasion. This may be possible through stabilization of the cell cytoskeleton. In human intestinal epithelial cells, Hsps have been observed to protect the integrity of the actin cytoskeleton against oxidant-induced injury (Huang et al. 1997). In other systems Hsps play a role in the formation and function of the eukaryotic cell cytoskeleton (Andoh et al. 1999). Their mechanism involves stabilization of the actin filaments by cross-linking (Ren et al. 2001). In doing so, Hsps could prevent adherence and invasion of pathogens. Intestinal pathogens that distort the cell membranes by causing ruffles during invasion may induce the synthesis of Hsps as a response to stabilize the actin filaments and subsequently hamper further invasion.

2.4 Intestinal epithelial cytoprotection by probiotics

It is generally accepted that the colonization of the intestinal milieu by probiotic bacteria (Fig. 1) (life microbial food ingredients which are beneficial to health) is stable over time, implying that they mul-