Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mutation Research 591 (2005) 276–289
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

The potential mechanisms involved in the anti-carcinogenic action of probiotics

Daniel Commane [a,*], Roisin Hughes [a], Colette Shortt [b], Ian Rowland [a]

[a] *The University of Ulster, NICHE, Cromore Road, Coleraine, N. Ireland BT52 1SA, UK*
[b] *Yakult UK Ltd., Acton, London, UK*

Received 25 August 2004; received in revised form 10 February 2005; accepted 17 February 2005
Available online 10 August 2005

Abstract

Probiotic bacteria are live microbial food ingredients that provide a health benefit to the consumer. In the past it was suggested that they served to benefit the host primarily through the prevention of intestinal infections. More recent studies have implicated probiotic bacteria in a number of other beneficial effects within the host including:

- The suppression of allergies.
- Control of blood cholesterol levels.
- Modulation of immune function.
- And the prevention of cancers of the colon.

The reputed anti-carcinogenic effect of probiotics arises from in vivo studies in both animals and to a limited extent in man; this evidence is supported by in vitro studies with carcinoma cell lines and anti-mutagenicity assays. However, the mechanisms involved in any effect have thus far been difficult to elucidate; studies offer evidence for a variety of mechanisms; we have reviewed these and come to the opinion that, the anti-carcinogenic effect may not be attributable to a single mechanism but rather to a combination of events not yet fully elucidated or understood.

Keywords: Probiotics; Colon cancer; Prebiotics; Anti-cancer mechanisms

Abbreviations: LAB, lactic acid bacteria; GALT, gut associated lymphoid tissue; MNNG, *N*-methyl-*N*-nitro, *N*-nitrosoguanidine; DMH, 1,2 dimethyl hydrazine; AOM, azoxymethane; 4NQO, 4-nitroquinoline-*N*-oxide; DMAB, 3,2-dimethyl-4-aminobiphenyl; DMBA, 9,10 dimethyl-1,2-benz[α]anthracene; TrpP2, 3-amino-1-methyl 5 h pyrido[4,3-b]indole acetate; IQ, 2-amino-3-methylimidazo[4,5-f]quinoline; SCFA, Short chain fatty acids; L., *Lactobacillus*; B., *Bifidobacterium*

* Corresponding author.
E-mail address: danielcommane@yahoo.co.uk (D. Commane).

0027-5107/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrfmmm.2005.02.027

Contents

1. Introduction 277
2. Potential mechanisms of anti- cancer activity 277
3. Modulation of the intestinal microflora and its metabolism 279
4. The anti-genotoxic activity of probiotics 281
5. Effects of probiotics on the promotion phase of carcinogenesis 282
6. The role of the metabolites of probiotics 282
7. Immune system stimulation 284
8. Conclusions 285
References 285

1. Introduction

The EUROPREVAL project estimates a lifetime risk for colorectal cancer development at 2% for the European population [1]. Epidemiological studies show that colon cancer is of especially high incidence in the developed western world [2]. Whilst this may be, in part, related to a genetic susceptibility [3], the high fat low fibre diet typical of western culture is implicated in the aetiology of the disease. The broad variety of bacteria in the gut produces diverse, and often physiologically active, metabolites that influence the normal development and function of the host. Given the purported role of the intestinal microflora in colonic carcinogenesis [4], it may be postulated that factors that modulate composition and/or activity of the microflora may inhibit cancer development. Probiotic ingredients represent one such modulatory factor.

A probiotic, as originally defined by Fuller is "a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance" [5]. A definition more appropriate to human nutrition has been outlined by Salminen et al. [6], describing a probiotic as, "a live microbial food ingredient that is beneficial to health." Many probiotics are members of the genera Lactobacillus and Bifidobacteria [7].

To date, experimental evidence for anti-carcinogenic activity of probiotics comes primarily from in vitro studies of anti-genotoxic effects (reviewed by Burns and Rowland [8]) and in vivo work, showing the suppression pre-neoplastic lesions and chemically induced colon tumours in rodent models. A medline literature search (1996–2004), carried out for the purpose of this review, showed that, of 12 animal studies, only 2 reported no anti-carcinogenic effects of probiotics, against chemically induced tumours or pre-neoplastic lesions known as aberrant crypt foci (ACF) (Table 1). Typically, rodent models support anti-carcinogenic effects for probiotics. It has also been shown that the additional presence of prebiotics (such as non-digestible oligosaccharides) may result in amplification of this anti-carcinogenic effect. It must be noted that the rodent model of colon carcinogenesis is not ideal, especially in relation to the activities of the gut flora. The rat caecum and colon are anatomically distinct from that of the human [21]. Further, it may be argued that rodent based models are essentially offering evidence for a laboratory based phenomenon, given the high levels of dietary carcinogens and/or toxicants to which the animals are exposed and the relatively short time period for these studies. In their defence, the findings of the rodent studies are supported by data from in vitro and ex vivo studies. The ethical, technical and financial problems associated with conducting long-term human studies, using the ideal endpoint for anti-carcinogenic assessments (i.e the disease state itself), means that, we must continue to question the validity of our models and the appropriateness of the selected biomarkers. However, data thus far point to a role for probiotics in cancer prevention.

2. Potential mechanisms of anti- cancer activity

Colorectal cancers arise by a well-defined series of histological changes (the adenoma-carcinoma sequence), which is paralleled by mutations, activations, and deletions of oncogenes and tumour suppressor genes (Fig. 1). There is much debate in the literature