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Native κ-carrageenan induced-colitis is related to host intestinal microecology

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ABSTRACT

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, has gradually emerged as a public health challenge worldwide. Carrageenan is a popular food additive that has been in use for decades. However, controversy exists regarding to the safety of carrageenan due to its exacerbation of colitis in experimental models. In this study, we studied the effects of vehicle and host intestinal microflora on carrageenan inflammatory properties in C57BL/6 J mice. We found that in high-fat diet model, native carrageenan in drinking water increased the disease activity index (DAI), myeloperoxidase (MPO) activity and the mRNA expression of TLR4 in colon, whereas carrageenan-supplemented diet has no visible effects. However, no signs of colitis were observed under low-fat diet regardless of the mode of vehicle used. Moreover, we discovered that carrageenan-induced colitis in high-fat diet model was robustly correlated with changes in the composition of gut microbiota, specifically *Alistipes finegoldii* and *Bacteroides acidifaciens*. Hence, we propose that the inflammatory property of carrageenan is influenced greatly by its intake form via modification of host intestinal microecology.

1. Introduction

Carrageenan is a highly sulfated hydrophilic colloid extracted from red algae and is divided into various subtypes such as λ, κ, ι, ε, and μ [1–3], which are decided mainly on the number and location of sulfate groups, and the content of 3,6-*endo*-D-galactopyranoside [4]. Carrageenan has wide application in the food industry for its good gelation and thickening properties, often used as an emulsifier, thickener and stabilizer [5–7].

However, recent studies have suggested that carrageenan has biological toxicity, and is prone to causing damage to the intestinal mucosal immune function of the host, leading to inflammation of the intestine. Currently, most research on carrageenan focuses on tissue and cellular levels [8], involving different animal species, intake methods and doses. Those experimental studies have shown that the results about carrageenan-induced colitis were not consistent [5,9]. Shang et al. has determined that supplementing carrageenan in drinking water could cause colitis by reducing certain anti-inflammatory bacteria in the intestine of mice [10]. Moreover, exposure to carrageenan could activate pro-inflammatory genes *NF-κB* and *EGR-1* in epithelial cells, affecting *ZO-1* expression [11]. Some studies also showed that food-grade carrageenan is able to activate Bcl10 and *NF-κB* signal transduction pathways and *IL-8* synthesis in gastrointestinal epithelial cells, possibly mediated by *TLR4* signaling pathway on the surface of human intestinal epithelial cells [5,12]. In addition, it was found that κ-carrageenan can induce the secretion of *TNF-α* by monocytes in humans [13] besides enhancing inflammation-related genes in TNBS-induced mice [14].

Nevertheless, there are studies showing that κ-carrageenan from *Kappaphycus alvarezii* can be used as a functional food to prevent colon carcinogenesis [15]. Several studies on dietary κ-carrageenan have found no significant effects on colon [9,16]. In addition, reviews by major international agencies have determined carrageenan safety for human consumption [17,18]. For example, the United States Department of Agriculture (USDA) and Joint FAO Expert Committee on Food Additives (JECFA) expressly stated that food grade carrageenan can be used as a safe food additive [19].

In view of the large number of conflicting research results, further investigation into carrageenan consumption safety is warranted. Therefore, using native κ-carrageenan as our study material, we aimed to explore the possible role of intake methods and host physiology in determining the inflammatory property of carrageenan in C57BL/6J mice. Our results would provide further insights on the consumption safety conundrum of this important food additive.

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