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Invited Commentary

Commentary on 'Prebiotics, immune function, infection and inflammation: a review of the evidence'

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There is a growing awareness that the gut microbiota and an appropriately functioning immune system play an important role in maintaining human health. Recent population statistics have highlighted some worrying trends, specifically that there is a growing burden of immunological disease in Western populations, that Western populations are ageing, and that obesity, with its strong inflammatory component, is reaching epidemic proportions. For example, within the UK, 60 % of the male population and 25 % of children under 16 years of age are projected to be obese by 2050[1,2]. The interplay between our gastrointestinal microbiota and immune function throughout life is important in maintaining health and is becoming recognised as a therapeutic target with the potential of impacting on the adverse health consequences of these population trends. There are two main approaches with proven efficacy in modulating the composition and activities of the gut microbiota, namely antibiotics and functional foods (such as probiotics and prebiotics). Although antibiotics are effective in the short term and essential for treating bacterial infections, they have contributed to important medical problems such as the development of novel antibiotic-resistant pathogens, the increased incidence of antibiotic-associated diarrhoea and *Clostridium difficile*-associated diarrhoea. Functional foods, although widely researched for an array of health effects, are a very heterogeneous group of biologically active products and the gap between those likely to be of health benefit and those which have little impact on health above their basal nutritional value is likely to be great. However, within this group of foods, prebiotics, 'non-digestible (by the host) food ingredients that have a beneficial effect through their selective metabolism in the intestinal tract' are emerging as probably the most promising group of compounds with strong scientific support for their ability to modulate the gut microbiota, improve mineral absorption, protect against colon cancer, improve systemic metabolism (blood glucose, insulin and lipid levels) and impact of gastrointestinal and systemic immune function. Prebiotic interventions with inulin-derived fructans and galactooligosaccharides, usually in animal models of disease, but on some occasions in human trials, have shown positive effects in reducing the risk of colon cancer and inflammatory bowel disease, improving bone health, decreasing incidence, duration or recurrence of diarrhoea, relieving constipation and protecting against metabolic disease. As discussed by Lomax & Calder[3] in the current issue of the *British Journal of Nutrition*, prebiotics work through their selective stimulation of the beneficial moieties of the gut microbiota, stimulating colonic production of SCFA and leading to increased population levels of bifidobacteria in particular, which may then interact with colonic metabolic pathways and the human cells of the gut wall. However, the mechanisms underpinning these observed health effects *in vivo* are not as yet fully understood. One of the most direct mechanisms by which prebiotic-induced modulation of the gut microbiota may interact with host physiology is through the cross-talk between the gut microbiota and the host immune system, both at the level of the gut-associated lymphoid tissue and the systemic immune level. In terms of scientific reviews the impact of prebiotics on immune function is poorly served. Lomax & Calder[3] have written a comprehensive and critical review of the area, discussing experiments done in animal models and in human intervention studies. These authors have reviewed the current scientific understanding of how inulin-derived fructans, the best characterised prebiotics, through their impact on the gut microbiota, may help fight infection and beneficially impact on inflammatory processes and conditions.

Dividing the literature into innate and adaptive immune systems, and then into animal or human studies for both the gut-associated lymphoid tissue and systemic lymphatic tissue, Lomax and Calder made the point that although there is strong evidence linking inulin-derived fructan intake with improvements in several markers of immune function in the gut-associated lymphoid tissue and systemically, factors such as age (animal or human), anatomical region sampled, background diet (especially low-calcium animal diets) and fidelity of immune marker measured may all impact on the interpretation of results obtained upon prebiotic dietary intervention. Additionally, studies in humans in particular are further complicated because many are often carried out using prebiotics in combination with other biological agents such as probiotics, antioxidants, vitamins, minerals, other fibres and fats. This makes the data in relation to prebiotic immuno-modulatory efficacy difficult to interpret. The authors noted that there is a relative paucity of publically funded research in this area and that much of the research has been carried out with industrial support and therefore on specific food products or nutraceuticals already at or near market. They suggested, quite rightly, that there is a clear need for more independent research focusing on the mechanisms underlying prebiotic efficacy particularly in relation to the immune system.

In terms of the changing health of Western populations, research into the immuno-modulatory capabilities of prebiotics may impact on the three different segments of the population mentioned earlier. Lomax and Calder, focusing on the ability of inulin-derived fructans to reduce infections and limit inflammation, have presented the possible mechanisms by which prebiotics mediate immuno-modulation and reduce inflammatory disease burden throughout the life-span. Immunological diseases such as asthma, allergic diseases and inflammatory

bowel disease have increased dramatically over the past 50 years, affecting infants, children and young adults in particular. Humans derive their gut microbiota early in life and recently the ongoing EU-funded project EARNEST has shown that diet and microbiota programming early in infancy are closely linked to risk of disease in later life[4]. Diet plays an important role in the development of the gut microbiota, with breast-feeding selecting for an infant gut microbiota dominated by bifidobacteria. The successional development of the gut microbiota in turn educates the naïve immune system, establishing a commensal microbiota which by the age of 2 years is unique and characteristic to each individual and is seen as 'self' (i.e. tolerated) by the host's immune system, eliciting little or no adverse systemic immune response. Conversely, less than optimal cross-talk between gut microbiota and the host immune system seems to play an important aetiological role in the onset of allergic disease. Lomax and Calder have described how inulin-derived fructans may be employed to modulate these activities to reduce the risk of developing such diseases and facilitating the optimal development of host immune:microbiota cross-talk by stimulating bifidobacterial population levels in the gut upon prebiotic intervention. From the animal data it appears that inulin-derived fructan supplementation may protect against ulcerative colitis and necrotising enterocolitis, suggesting a prebiotic mode of immuno-modulation at the site of pathology. Human data again are sparse, but they do suggest that inulin-derived fructans may reduce inflammatory markers in ulcerative colitis patients.

There are currently 9.7 million people over the age of 65 in the UK comprising 16 % of the population. This is expected to increase to 22 % by the year 2031[1]. With ageing comes change both in immune function, with the onset of immune senescence, and in the composition of the gut microbiota, with reductions in relative population levels of bifidobacteria and changes in microbiota species richness often compounded by pharmaceutical intake (especially antibiotics). These changes coincide with increased disease burden in this population, particularly in winter infections (influenza, winter viral diarrhoea) and gastrointestinal infections including *C. difficile*. The elderly also have higher rates of heart disease and colon cancer, although the initiating stages of these diseases are likely to occur during earlier life stages. Lomax and Calder, upon reviewing the effect of inulin-derived fructan intervention on infections, concluded that prebiotics may reduce morbidity and increase survival upon pathogen challenge (intestinal parasites, *C. difficile*, *Listeria monocytogenes*, *Salmonella typhimurium*, *Escherichia coli* and rotavirus) in animal models of infection and that current human data are suggestive of a reduction in incidence or duration of some infections in children and to a lesser extent in adults where the number of studies is limited.

Obesity is characterised by low-grade inflammation that has been linked to insulin resistance, type 2 diabetes, some cancers and CVD. Importantly, this inflammation has also been linked to a number of putative diet-related aetiologies linked to the intestinal microbiota. Similarly, the gut microbiota has been shown to be directly linked to body weight with characteristic microbial ecologies being associated with the lean compared to obese states even within the same individuals on weight-loss dietary regimes. Because of the growing concern over the increased incidence of obesity, there is high-level interest, both from public authorities and the food industry, in designing foods which can impact on obesity itself or the diseases of obesity, many driven by inflammation. Although not covered by Lomax and Calder in their review, prebiotic–microbiota interactions with the immune system have been shown in an animal model of diet-induced obesity to reduce inflammatory markers linked to insulin resistance and metabolic disease[5]. However, Lomax and Calder did highlight the importance of fortifying the mucosal barrier as a possible mechanism of prebiotic effect, and one which constitutes the first line of defence against both invading pathogens and inflammatory compounds like lipopolysaccharides which may impact on systemic and metabolic health.

In conclusion, as humans have evolved alongside their intestinal microbiota over the millennia, so too has our immune system. A driving force in the development of an optimally functioning immune system is the need to accommodate a domestic commensal and diverse gut microbiota, which in turn allows the host to accommodate environmental (including food) antigens and possibly self-antigens. Modern living defined by advances such as the advent of antibiotics, changes in diet (the Western-style, high-fat, reduced fibre diet), more 'hygienic surroundings' and increased exposure to xenobiotic compounds, may all alter the gut microbiota in composition and activity, and also may be associated with defects in the development of immuno-regulatory pathways. Set against a background of genetic susceptibility, this alteration in the relationship between our immune system and our intestinal microbiota might explain the increased prevalence of inflammatory conditions and immunological disorders in industrialised countries over the past decades. In this perspective, prevention of the burden of immune-mediated disorders and infections, particularly in susceptible target populations, could be grounded in the rational use of prebiotics, probiotics and synbiotics to induce and maintain immune homeostasis.

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References

1. UK Statistics Authority (2007) Latest on ageing. www.statistics.gov.uk/cci/nugget.asp?ID=949
2. Foresight (2007) Tackling Obesities: Future Choices-Project Report Government Office for Science. http://www.foresight.gov.uk/Obesity/17.pdf
3. Lomax AR & Calder PC (2009) Prebiotics, immune function, infection and inflammation: a review of the evidence. *Br J Nutr* **101**, 633–658.
4. Fewtrell MS; EARNEST Consortium (2007) Session 6: Infant nutrition: future research developments in Europe EARNEST, the early nutrition programming project: EARly Nutrition programming-long-term Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research. *Proc Nutr Soc* **66**, 435–441.
5. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM & Burcelin R (2008) Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57**, 1470–1481.

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