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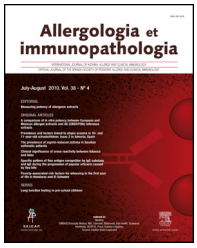

REVIEW

Modulation of gut microbiota downregulates the development of food allergy in infancy

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Abstract In humans, microbial colonisation of the intestine begins just after birth. However, development of the normal flora is a gradual process, which is initially determined by factors such as genetic aspects, the maternal–foetal interaction, place and mode of delivery, early feedings strategies, and the use of antibiotics. Current knowledge on the significance and impact of the gut microflora on the development of the gut immune system indicates that a close relationship between allergic sensitisation and the development of the intestinal microflora may occur in infancy. Intestinal micro-organisms could downregulate the allergic inflammation by counterbalancing type 2 T-helper cell responses and by enhancing allergen exclusion through an immunological response.

Introduction

As the prevalence rates of food allergy are increasing, hence there is an interest in understanding the reasons and in strategies to prevent or reduce the burden of the disease. The mechanisms leading to the incremented incidence of the allergic diseases are not fully understood. However, they are known to involve genetic factors as well as complex interactions between the host and the allergen exposure as well as other environmental stimuli on gut microbiota. Gut microbiota, which consists of microorganisms that live in the digestive tract, is the largest reservoir of human flora, having a continuous and dynamic effect on the host's gut and systemic immune system.[1]

Given the relative instability of the intestinal colonisation process during the first months of life, it is not surprising that any perturbation of this process may affect the microbiota, which may, in turn, have an impact on function and also potentially on the host's health. Delayed colonisation of the infant gut with commensal bacteria or alterations in the microbiota profile are suggested to be strong risk factors for the development of immune-mediated chronic disorders such as allergic diseases. Original research studies published in English between 1985 and 2012 were selected (Pubmed and Scopus). Computer searches used combinations of key words relating to ''food allergy'', ''microbiota'' and ''infancy''. In addition, the reference lists of the

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retrieved articles helped in the search for other relevant articles which were not found during the initial search procedure. Thus, 37 studies were selected and discussed here (15 randomised controlled trials, 10 cross-sectional, 4 case control, and 8 population based studies). The potential factors which may bias the findings of this review are the restriction to articles in English, together with database, and citation bias.

The aims of this review are to define potential factors which modify the intestinal microbiota of infants, to characterise the key mechanisms and their role in the development of food allergy.

The gastrointestinal microbiota: diversity and properties

Ninety per cent of the human body is composed of prokaryote cells, and this group of microorganisms is known as microbiota.[2] Microbiota is concentrated in the gut and plays a key role in the preservation of the host's health. The relationship between gut flora and humans is not merely commensal (a non-harmful coexistence), but rather a mutualistic relationship.[3] The gastrointestinal tract, the largest immunological organ in the body, is in constant interaction with a high load of enteric flora and food antigens, resulting in a sustained state of low level physiological intestinal inflammation, protecting the host against severe infections but which allows immunological tolerance to endogenous and foreign antigens.[4] The use of modern methods in molecular biology has provided further insight into the diversity of intestinal microbiota, which comprises hundreds of different species [5] that form a complex and highly interactive biomass (microbiome) of at least 1014 bacteria within the human gastrointestinal (GI) tract (Fig. 1). This microbiome contains more than 100-fold more genes than the human genome. The composition of the microbiota differs not only along with the length of the GI tract, but also cross-sectionally with different populations inhabiting the GI mucosa and lumen.[6] The most common anaerobic genera in terms of concentration within the GI tract are *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Fusobacterium*, *Clostridium* and *Lactobacillus*. Among the facultative anaerobes are the Gram-negative enteric bacteria (*Escherichia coli* and *Salmonella* spp.), the Gram-positive cocci (*Enterococcus*, *Staphylococcus* and *Streptococcus*) and fungal species (predominantly *Candida albicans*).[7]

Another parameter which seems to contribute to the gut diversity is atopy. Dysfunction at the gastrointestinal barrier might contribute to an aberrant or exaggerated inflammatory response. Animal studies have shown that increased intestinal permeability is associated with food allergy.[8,9] In addition, studies have also shown that early colonisation with potentially more pathogenic bacteria such as *Clostridium difficile* and *Staphylococcus aureus* is more likely to occur in children who go on to develop allergy. In contrast, lactic acid bacteria (Lab) and Bifidobacteria (Bfdba) are found more commonly in the composition of the intestinal flora of non-allergic children (Table 1). The enhanced presence of these probiotic bacteria in the intestinal microbiota seems to correlate with protection against atopy, by contributing to the production of T helper-1 immune responses,

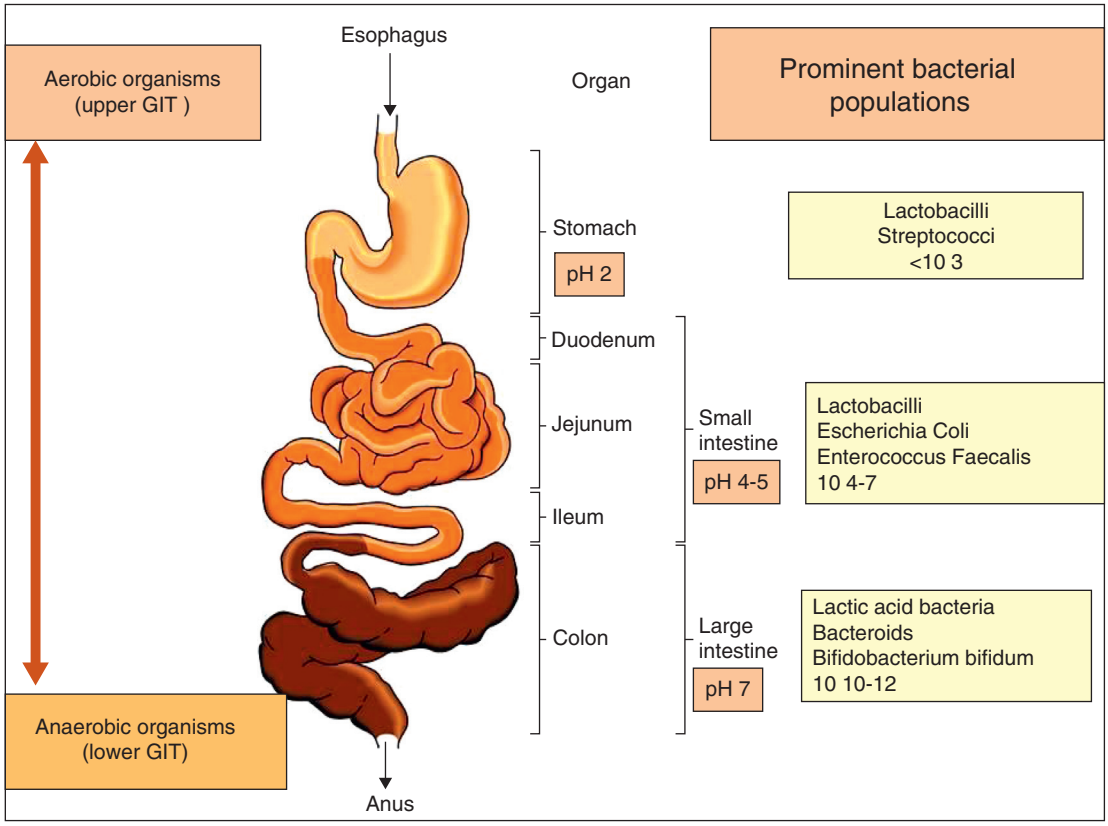

Figure 1 Gradient of intestinal microbiota along the gastrointestinal tract.