Beneficial bacteria as a treatment for allergic asthma

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The limitations of the current therapy for allergic asthma highlight the need for novel therapeutics with long-term benefits, greater disease control and increased efficacy. Interventions targeting the gut microbiota have gained a lot of attention as a treatment approach for a range of allergic disorders. In accord, there is a growing interest in the use of potentially beneficial bacteria as a therapy for allergic asthma. Animal models played a key role in the understanding of the immunomodulatory capacity of specific bacteria. These models revealed that the gut microbiota can influence the immune function beyond the gut. Therapeutic effects of beneficial bacteria alone or in combination with non-digestible oligosaccharides in animal models included reducing allergic airway responses and allergic symptoms. Beneficial bacteria-based therapeutic strategies proved also to be useful in patients, reducing the allergic response and preventing asthma-like symptoms. Studies conducted so far indicate clear bacterial strains-dependent treatment effects. A better understanding of the cross talk between the administered beneficial bacteria and the host mucosal immune system is required before clinically effective bacteria-based strategies can be developed. This brief review addresses current evidence for the potential of beneficial bacteria as a treatment approach for allergic asthma and discusses opportunities for beneficial bacteria interventions in allergic asthma.

Keywords: Bifidobacterium breve; Lactobacillus rhamnosus; allergic asthma; airway inflammation

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Allergic asthma is a chronic inflammatory disorder of the airways characterized by episodes of reversible airway narrowing, bronchial hyper-responsiveness and chronic pulmonary inflammation and airway remodeling [1]. The prevalence of this T helper type-2 (Th2) cell-mediated disease is increasing since the 1980’s, particularly in children [2]. More than 150 million people worldwide are diagnosed with asthma, with higher disease prevalence in developed and westernized countries [3-4]. It is believed that this increased prevalence of asthma is due to changes in western lifestyle and housing (i.e. exposure to house dust mite, decreased exposure to various microorganisms, increased prevalence of obesity and changes in the western diet) [5].

For many years, asthma was considered as a bronchoconstrictive disease and is predominantly treated with bronchodilators (i.e. β2 agonists) [6]. Currently, corticosteroids therapy alone or in combination with long-acting β2-agonists is aimed at targeting the chronic
inflammatory process observed in asthmatic subjects [6–7]. Although, corticosteroids are the most effective anti-inflammatory treatment for asthma, a high percentage of asthmatics are poorly controlled and often show poor compliance. There is still a major unmet need for effective asthma therapies as corticosteroids have long-term side effects [7]. The link between long-term use of long acting β2 and increased risk of mortality and desensitization of the β2 receptor is also of concern [8–9].

In the past years, the effect of changes in the gut microbiota on the (systemic) immune system has gained attention. Altered gut microbiota composition has been thought to contribute to or at least to be correlated with the development of various inflammatory diseases, including asthma [10–11]. Additionally, animal studies have demonstrated a substantial influence of the gut microbiota on immune function beyond the gut [11–12]. On the other hand, it is hypothesized that besides its effects on the airways and lungs, asthma can also affect the gastrointestinal tract [13]. Recently, beneficial bacterial strains with or without non-digestible oligosaccharides, as potential modulators of the intestinal microbiota and mucosal and systemic immune responses, have gained a lot of attention as a promising approach for the treatment of allergic diseases such as asthma [13–16].

Regarding the microbiome–immune system interaction, toll-like receptors (TLRs), especially TLR2 and TLR9, were reported to be involved in the induction of regulatory T cell (Tregs) responses by the intestinal microbiota and this might be responsible for the protective effects in allergy [15–16]. ‘Probiotics are live microorganisms with a health benefit for the host’ [17–18]. *Bifidobacterium* and *Lactobacillus*, which occur naturally as part of the gut microbiota, are the most frequently used bacterial genera [17, 19].

An international expert group from the International Life Sciences Institute (ILSI) proposed a beneficial role of these beneficial bacterial strains in the prevention and management of allergy upon evaluating the findings from clinical studies regarding the functionality of these bacterial strains in a wide range of disorders [19–20]. The composition of the gut microbiota was different in countries of high and low prevalence of allergy and between healthy and allergic infants [21–26]. In allergic rhinitis patients, symptom severity and medication use was reduced by specific bacterial strains [27]. In the context of allergic asthma, different species of *Lactobacillus* inhibited the allergic airway hyper-responsiveness, modulated T helper type 1 (Th1)/Th2 imunobalance and prevented asthma in mice [17, 27–30]. Administration of *Bifidobacterium* during lactation suppressed both allergic and autoimmune responses in the progeny [31], and these bacteria reduced allergic symptoms in ovalbumin (OVA)-sensitized mice [32]. Additionally, a TLR driven response can be potentiated by these Gram positive bacterial strains as they contain TLR ligands. Beneficial bacteria also exert their immunomodulatory effect by shifting the balance from a Th2 to a Th1 and/or Treg response [15]. Non-digestible oligosaccharides (ie galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS)) are oligosaccharides that resist digestion but are fermentable by the intestinal microbiota. GOS and FOS are beneficial for the host as they increase the survival of beneficial bacteria in the intestinal tract [14–15]. *Bifidobacterium breve* M-16V combined with short-chain GOS (sc-GOS) and long-chain FOS (lc-FOS) reduced allergic responses in mice [32–34]. In allergic asthmatic adults, allergen-specific Th2-response was reduced and peak expiratory flow was improved by this same combination [35]. In another study, the same mixture prevented asthma-like symptoms in infants with atopic dermatitis [36]. In mice, several parameters of allergic asthma were reduced by a specific mixture of oligosaccharides consisting of scGOS/lcFOS and scGOS/lcFOS/pectin-derived acidic oligosaccharides (pAOS) [36].

Recently, we demonstrated that *Bifidobacterium breve* M-16V in combination with a specific mixture of sc-FOS, lc-FOS and AOS suppressed airway inflammation and reduced airway remodeling in a murine ovalbumin-induced chronic asthma model [37]. Treatment of mice with this specific combination of beneficial bacteria and non-digestible oligosaccharides induced regulatory T cells responses by increasing *Il10* and *Foxp3* transcription in lung tissue and augmenting Foxp3 protein expression in blood Treg cells. In the same study we showed that this specific combination of beneficial bacteria and non-digestible oligosaccharides reduced T cell IL-2, IL-6 and TNF-α production and inhibited mast cell degranulation. In another study we compared the therapeutic effects of *Bifidobacterium breve* and *Lactobacillus rhamnosus* bacteria with those of glucocorticoids on the inflammatory response in a murine ovalbumin-induced chronic allergic asthma model [38]. *Bifidobacterium breve* M-16V and *Lactobacillus rhamnosus* NutRes1 have strong anti-inflammatory properties, which are comparable to budesonide. These beneficial bacterial strains were as effective as budesonide in suppressing pulmonary airway inflammation, airway remodeling and inhibiting mast cell degranulation. Additionally, *Lactobacillus rhamnosus* reduced lung resistance and T cells IFN-γ production in the thoracic lymph nodes. In this same study, *Bifidobacterium breve* increased *Il10* and *Foxp3* transcription in lung tissue and augmented the mean fluorescence intensity of Foxp3 in blood CD4+ T cells. mRNA expression of pattern recognition receptors, T helper-specific cytokines and transcription factors were differentially modulated by different treatments.
All together, these findings show that treatment with specific beneficial bacteria strains alone or combined with non-digestible oligosaccharides might be a promising approach for the management of chronic allergic asthma in a therapeutic way.

**Conflicting interests**

The authors have declared that no competing interests exist.

**References**


