

## EDITORIAL

# Galectin-9: a suppressor of food allergy?

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The prevalence of food-induced allergy, which affects approximately 5% of children and 3–4% of adults, is on the rise. It is manifested in a variety of symptoms and disorders involving the gastrointestinal and respiratory tracts as well as skin (1). The pathogenesis of allergic diseases, such as allergic asthma, allergic dermatitis or food allergy is characterized by an imbalance of T helper type 1 (Th1) and type 2 (Th2) function. There are different strategies to modulate immune responses in allergic diseases and many are aimed at decreasing the Th2 response and/or stimulate Th1 immunity (2). Selected probiotic strains, such as bifidobacteria or lactobacilli proved to be effective in preventing allergy by enhancement of the Th1 response (3). The modification of the fecal flora with growth of bifidobacteria could be achieved in infants by dietary supplementation with a special mixture of galacto- and fructo-oligosaccharides (4). In adults with asthma, synbiotics (90% short-chain galacto-oligosaccharides, 10% long-chain fructo-oligosaccharides and *Bifidobacterium breve* M-16V) were shown to decrease the influx of inflammatory cells into the lung and reduce allergen-induced Th2 response (5). In addition, synbiotics may prevent asthma-like symptoms in infants with atopic dermatitis (6). Moreover, probiotic bacteria reduced the incidence of eczema in high-risk children (7) and lactobacillus GG taken during pregnancy was shown to prevent eczema in a randomized controlled trial (8). The underlying mechanism of the protective effects of synbiotics on allergic inflammation is little known. Recently, a probiotic mixture was demonstrated to be effective in redirecting allergen-specific Th2-polarized immune responses towards Th1-T regulatory responses and in the protection against anaphylactic reactions induced in a murine model of food allergy (9). In the present issue of *Allergy*, de Kivit et al. (10) reported that treatment of whey sensitized mice with a mixture of galacto- and fructo-oligosaccharides and *Bifidobacterium breve* M-16 (GF/Bb) diminished allergen-induced inflammatory symptoms while significantly increasing the levels of galectin-9 in the intestinal epithelial cells and serum. The authors raised the possibility that galectin-9 is involved in the beneficial effects of GF/Bb in whey-induced food allergy.

### Galectin-9 as an immune regulator

Soluble pattern recognition molecules with carbohydrate binding capabilities, such as ficolins, pentraxins and the collagenous lectins (collectins) (11–13), have been implied in diverse host defense and immune regulatory activities. Galectins are beta-galactoside binding lectins containing a highly conserved sequence motif in their carbohydrate recognition domain (14). Although all galectins bind galactose, they have

different affinity to oligosaccharides (15). Galectins were shown to regulate various cellular functions mainly related to inflammatory processes, including cell growth, apoptosis, cell adhesion, migration and immune responses (16). Recently, increased levels of galectin-9, a member of tandem-repeat type galectins were reported in models of allergic airway (17, 18) and skin inflammation (19) as well as food allergy (20). The role of galectin-9 in immunoregulation appears to be complex. Originally galectin-9 was suggested to induce the death of Th1 lymphocytes *via* the T-cell-immunoglobulin-domain and mucin-domain (Tim)-3 (21). Recently, however, Su et al. (22) suggested that galectin-9 regulates T-cell function independently from Tim-3 and can elicit the production of pro-inflammatory cytokines in a dose-dependent manner. Dai et al. (23) found that galectin-9 can stimulate the maturation of dendritic cells and promote Th1 effector responses by triggering the production of IFN- $\gamma$  and IL-2. On the other hand, galectin-9 was shown to induce differentiation of naive T cells into Treg cells, suppress the differentiation of Th17 cells *in vitro* and to decrease the levels of IL-17 dose-dependently in experimental autoimmune arthritis *in vivo* (24). In the report by de Kivit et al. (10), these latter observations were well corroborated by showing that elevated galectin-9 expression was associated with increased Th1/Th2 and Treg/Th2 ratio in whey-sensitized mice fed GF/Bb. Galectin-9 directly increased the proportion of CD69/CXCR3 and CD25/FOXP3 positive CD4 positive T- cells as well as IFN- $\gamma$  and IL-10 production in a dose-dependent manner *in vitro*, indicating induction of Th1 and Treg immunity.

### Galectin-9 in food allergy

Given the increased expression of galectin-9 in basolateral epithelial cells and the above effects on T-cells, de Kivit et al. hypothesized that this molecule has a significant immunoregulatory function during food-induced allergic inflammation and that galectin-9 may mediate the effects of GF/Bb supplementation in murine model of cow's milk allergy (Fig. 1). This hypothesis is in contrast to an earlier proposal by Chen et al. (20) who suggested that enhanced expression of galectin-9 in the intestinal epithelial cells of patients with food allergy may contribute to the maintenance of the allergic status of the intestine. The work of de Kivit et al. (6) demonstrates however that elevated levels of galectin-9 in the serum and intestinal epithelial cells of whey-sensitized mice after GF/Bb treatment in fact negatively correlated with airway hyper-responsiveness and serum mast cell protease levels. Further, while GF/Bb administration diminished the IgE-mediated mast cell degranulation and therefore alleviated the severity of the disease, these protective effects of synbiotic

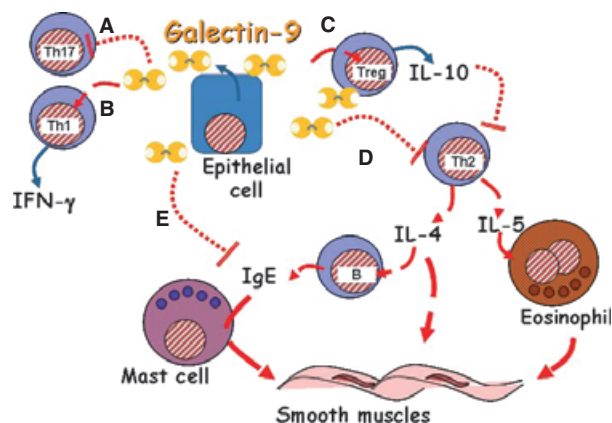


**Figure 1** Galectin-9 plays a protective role during the allergic immune response. Galectin-9 production and release is upregulated by epithelial cells in response to inflammatory stimuli. Released galectin-9 suppresses Th17 function (A) but enhances Th1 (B) as well as Treg (C) activation. Th2 immunity is suppressed by galectin-9 both indirectly through Treg cells and directly (D), diminishing IL-4 and IL-5 production and the ensuing activation of eosinophilic granulocytes and IgE-producing B-cells. Galectin-9 can additionally, directly bind IgE and prevent antigen-IgE complex formation and mast cell degranulation (E), thereby attenuating the physiological consequences (i.e. smooth muscle activation) of the allergic response.

treatment were partially abolished by the neutralization of serum galectin-9. The GF/Bb-induced suppression of allergic symptoms was also associated with increased galectin-9 levels in the serum of children suffering from IgE-mediated atopic dermatitis. In addition to the potential Th1 polarizing effects and stimulation of Treg differentiation, galectin-9 may have a beneficial role in interfering with IgE-mediated events. Indeed, Niki et al. (25) recently described that galectin-9 binds strongly to IgE, a heavily glycosylated immunoglobulin, preventing the antigen-IgE complex formation and thereby exerting anti-allergic effects.

In summary, galectin-9, an epithelial product is expressed in mucosal surfaces during inflammatory responses. It is particularly interesting that administration of synbiotics, such as galacto- and fructo-oligosaccharides and *Bifidobacterium breve* M-16 co-treatment, significantly enhances release of galectin-9 in the gastrointestinal tract. The results of de Kivit et al. (6) strongly suggest that the protective effects of synbiotic treatment are, at least partly, mediated by a dual anti-allergic action of galectin-9 *via* modulation of Th1 and Treg cell polarization and IgE sequestration resulting in attenuated mast cell degranulation. Based on these findings clinical verification of the therapeutic significance of galectin-9 is warranted.

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#### Author contribution

ES and ÁV have written and edited the manuscript. AH created Fig. 1, and has written and revised the manuscript.

#### Conflict of interest

The authors declare no conflicts of interest.

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