Inflammation and Regeneration Vol.35 No.3 May 2015

Special Issue: Interaction between gut microbiota and host immune cells

Mini Review

Regulation of allergy by probiotics

Satoshi Hachimura

Research Center for Food Safety, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

A considerable number of reports show that administration of probiotics may prevent or alleviate allergy. These may be direct effects of bacterial components on immune system, or through indirect effects through alteration of intestinal microbiota. Animal and cellular studies imply that direct effects may be through inhibition of Th2 responses by enhancement of Th1 response, induction of apoptosis, induction of regulatory T cells, and other mechanisms. One mechanism of the indirect effects may be regulatory T cell induction by metabolites of microbiota. Further studies are required to fully understand the mechanisms.

Rec.2/13/2015, Acc.4/14/2015, pp137-139

Correspondence should be addressed to:
Satoshi Hachimura, Research Center for Food Safety, Graduate School of Agricultural and Life Sciences, The University of Tokyo 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan. Phone: +81-3-5841-5230, Fax: +81-3-5841-5230, E-mail: ahachi@mail.ecc.u-tokyo.ac.jp

Key words allergy, *Bifidobacterium*, lactic acid bacteria, *Lactobacillus*, probiotics

Regulation of allergy by probiotics

Allergy is hypersensitivity to harmless antigens such as pollen and food. Probiotics are defined as living micro-organisms with beneficial effects when administered orally. At the start of the 21st century, it was reported that intestinal microbiota are different between allergic and non-allergic individuals[1, 2]. This lead to trials to inhibit allergy by administration of lactic acid bacteria (LAB). It was shown by Kalliomaki et al. that the administration of lactic acid bacteria to pregnant mothers and the new born babies could prevent the prevalence of atopic skin disease in the newborns[3]. Since then, many trials have been performed to prevent or alleviate allergy by oral administration of LAB or other probiotic bacteria. Concerning effects of probiotics on allergy, meta-analyses have been performed[4, 5]. One such analysis show the efficacy of probiotics in prevention rather than treatment of pediatric atopic dermatitis[4]. Another concludes that prenatal and/or early-life probiotic administration reduces risk of atopic sensitization and decreases IgE level in children[5]. In Japanese studies, besides the inhibition of atopic dermatitis[6], it has been shown that oral administration of a *Lactobacillus* strain[7] or a *Bifidobacterium* strain[8] could alleviate pollen allergy.

Mechanisms of inhibition of allergy by LAB and other probiotic bacteria

The inhibition of allergy may be either direct effects through bacterial components or indirect effects through intestinal

Table 1 Mechanisms of regulation of allergy by probiotics

Direct effects
Inhibition of Th2 responses by enhancement of Th1 responses mediated by IL-12
Inhibition of Th2 responses by apoptosis induction
Induction of regulatory T cells by enhancement of RALDH activity
Inhibition of Th2 chemokines
Indirect effects
Induction of regulatory T cells by commensal metabolites

microbiota (Table 1). One mechanism of direct effects is the inhibition of excess Th2 response, being one of the major causes of allergy. It has been shown in cellular and animal models that certain LAB could inhibit Th2 responses. One of the well documented mechanisms is the induction of Th1 and inhibition of Th2 response through the enhancement of IL-12 response[9-11]. However this does not seem to be the case for all LAB. Certain LAB are capable of inhibiting Th2 response without enhancing Th1 response[12]. We found that such strain of *Lactobacillus acidophilus* induced apoptosis of activated T cells mediated by dendritic cells[12]. In these cases in which Th1 responses are not enhanced, IL-10 may be produced, as shown in the case of a *Lactobacillus plantarum* strain[13]. A further mechanism to inhibit allergy is the induction of regulatory T cells[14]. Retinoic acid, a vitamin A metabolite has activity to induce Foxp3$^+$ regulatory T cells. The induction of RALDH2 activity, a key enzyme in the production of retinoic acid, is an interesting mechanism of regulatory T cell induction[15]. A strain of *L. plantarum* has been shown to induce ALDH activity in MLN dendritic cells and induce Foxp3$^+$ regulatory T cells in mice[14,15]. We have shown a yet another mechanism for *Bifidobacterium* to inhibit Th2 response, being the inhibition of Th2 chemokines[16]. A strain of *Bifidobacterium longum* inhibited the production of TARC induced by T cell and antigen-presenting cell interactions[16]. These direct effects of bacterial components could be observed in case of 'killed' bacteria, implying that at least part of the 'probiotic' effects do not necessarily require 'live' bacteria. It has been suggested that these bacterial components are recognized by immune competent cells through pattern recognition receptors such as TLRs. Some studies demonstrate the involvement of TLR2, which seem to mediate the induction of IL-10[17]. TLRs may not be involved in the induction of IL-12, and one study shows that the IL-12 enhancing effect is not altered in TLR2$^{-/-}$TLR4$^{-/-}$TLR9$^{-/-}$ mice[18]. Of interest is the recent report demonstrating that double-stranded RNA derived from LAB recognized through TLR3 inhibits inflammation by induction of type I interferon[19].

The indirect effects through intestinal microbiota are less documented. The alterations of intestinal microbiota after administration of a *Bifidobacterium* strain that has anti-allergic affects has been shown[20]. However, the mechanisms that alleviate allergy underlying are not clearly understood. The relation between certain commensal bacteria and immune response may give hints. *Clostridium* species induce regulatory T cells and in the mouse model, mediate IgE inhibition[21]. The induction of regulatory T cells may be due to the commensal metabolites such as butyrate[22].

Conclusion

Although there are considerable reports in humans showing regulation of allergy by probiotics (and non-viable bacteria)[3-8], other reports suggest they are ineffective[4, 5]. Various mechanisms have been demonstrated in animal and cellular models[9-22]. It is necessary to elucidate the difference of species and strains for a better understanding.

Acknowledgements

The author is grateful to all collaborators concerning this topic.

Source of funding

None

Conflict of interests

No conflicts of interest to be disclosed.

Abbreviations

LAB: lactic acid bacteria

References

1) Björkstén B, Sepp E, Julge K, Voor T, Mikelsaar M: Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol. 2001; 108: 516-520.
2) Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E: Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol. 2001; 107: 129-134.
3) Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E: Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial.

Lancet. 2001; 357: 1076-1079.
4) Lee J, Seto D, Bielory L: Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. J Allergy Clin Immunol. 2008; 121: 116-121.
5) Elazab N, Mendy A, Gasana J, Vieira ER, Quizon A, Forno E: Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials. Pediatrics. 2013; 132: e666-e676.
6) Torii S, Torii A, Itoh K, Urisu A, Terada A, Fujisawa T, et al: Effects of oral administration of Lactobacillus acidophilus L-92 on the symptoms and serum markers of atopic dermatitis in children. Int Arch Allergy Immunol. 2011; 154: 236-245.
7) Ishida Y, Nakamura F, Kanzato H, Sawada D, Yamamoto N, et al: Effect of milk fermented with Lactobacillus acidophilus strain L-92 on symptoms of Japanese cedar pollen allergy: a randomized placebo-controlled trial. Biosci Biotechnol Biochem. 2005; 69: 1652-1660.
8) Xiao JZ, Kondo S, Yanagisawa N, Takahashi N, Odamaki T, et al: Probiotics in the treatment of Japanese cedar pollinosis: a double-blind placebo-controlled trial. Clin Exp Allergy. 2006; 36: 1425-1435.
9) Shida K, Makino K, Morishita A, Takamizawa K, Hachimura S, Ametani A, et al: Lactobacillus casei inhibits antigen-induced IgE secretion through regulation of cytokine production in murine splenocyte cultures. Int Arch Allergy Immunol. 1998; 115: 278-287.
10) Murosaki S, Yamamoto Y, Ito K, Inokuchi T, Kusaka H, Ikeda H, Yoshikai Y: Heat-killed Lactobacillus plantarum L-137 suppresses naturally fed antigen-specific IgE production by stimulation of IL-12 production in mice. J Allergy Clin Immunol. 1998; 102: 57-64.
11) Fujiwara D, Inoue S, Wakabayashi H, Fujii T: The anti-allergic effects of lactic acid bacteria are strain dependent and mediated by effects on both Th1/Th2 cytokine expression and balance. Int Arch Allergy Immunol. 2004; 135: 205-215.
12) Kanzato H, Fujiwara S, Ise W, Kaminogawa S, Sato R, Hachimura S: Lactobacillus acidophilus strain L-92 induces apoptosis of antigen-stimulated T cells by modulating dendritic cell function. Immunobiology. 2008; 213: 399-408.
13) Noguchi S, Hattori M, Sugiyama H, Hanaoka A, Okada S, Yoshida T; Lactobacillus plantarum NRIC1832 enhances IL-10 production from $CD4^+$ T cells in vitro. Biosci Biotechnol Biochem. 2013; 77: 1826-1831.
14) Yoshida T, Fujiwara W, Enomoto M, Nakayama S, Matsuda H, Sugiyama H, et al: An increased number of CD4+CD25+ cells induced by an oral administration of Lactobacillus plantarum NRIC0380 are involved in antiallergic activity. Int Arch Allergy Immunol. 2013; 162: 283-289.
15) Yoshida T, Enomoto M, Nakayama S, Adachi Y, Fujiwara W, Sugiyama H, et al: Induction of ALDH activity in intestinal dendritic cells by Lactobacillus plantarum NRIC0380. Biosci Biotechnol Biochem. 2013; 77: 1826-1831.
16) Iwabuchi N, Takahashi N, Xiao JZ, Yonezawa S, Yaeshima T, Iwatsuki K, Hachimura S: Suppressive effects of Bifidobacterium longum on the production of Th2-attracting chemokines induced with T cell-antigen-presenting cell interactions. FEMS Immunol Med Microbiol. 2009; 55: 324-334.
17) Kaji R, Kiyoshima-Shibata J, Nagaoka M, Nanno M, Shida K: Bacterial teichoic acids reverse predominant IL-12 production induced by certain lactobacillus strains into predominant IL-10 production via TLR2-dependent ERK activation in macrophages. J Immunol. 2010; 184: 3505-3513.
18) Ichikawa S, Fujii R, Fujiwara D, Komiyama Y, Kaisho T, Sakaguchi M, Konishi Y: MyD88 but not TLR2, 4 or 9 is essential for IL-12 induction by lactic acid bacteria. Biosci Biotechnol Biochem. 2007; 71: 3026-3032.
19) Kawashima T, Kosaka A, Yan H, Guo Z, Uchiyama R, Fukui R, et al: Double-stranded RNA of intestinal commensal but not pathogenic bacteria triggers production of protective interferon-β. Immunity. 2013; 38: 1187-1197.
20) Odamaki T, Xiao JZ, Iwabuchi N, Sakamoto M, Takahashi N, Kondo S, et al: Influence of Bifidobacterium longum BB536 intake on faecal microbiota in individuals with Japanese cedar pollinosis during the pollen season. J Med Microbiol. 2007; 56: 1301-1308.
21) Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature. 2013; 500: 232-236.
22) Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al: Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013; 504: 446-450.