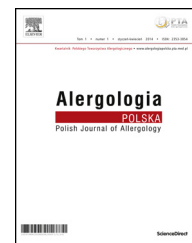


Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/alergo

Review/Praca pogładowa

The role of microbiota in allergy development



Monika Marko, Rafał Pawliczak*

Zakład Immunopatologii, Katedra Alergologii, Immunologii i Dermatologii Uniwersytetu Medycznego w Łodzi, Poland

ARTICLE INFO

Article history:

Received: 13.03.2017

Accepted: 21.03.2017

Available online: 31.03.2017

Keywords:

- Microbiota
- Allergy
- Probiotics
- Hygiene hypothesis

ABSTRACT

The increase of allergic diseases incidence has been noticed in industrialized countries. The reason for that is sought in increasing environment pollution and hygienisation of life. Diseases including asthma, hay fever, eczema and food allergies have dramatically increased over the last century. Microbiota (intestinal microflora) is a community of microorganisms, mainly bacteria that forms in the human digestive system a complex ecosystem. Recently more and more attention is paid to the connection of intestinal microflora with the occurrence of allergic diseases. Microbiota and the beneficial effects of probiotic bacteria on human health is becoming increasingly important in allergy development. However, the importance of probiotics in the prevention of these diseases has not been proven. It is a necessity to design and carry out thorough and detailed research to confirm significance of treatment with using probiotics strains.

© 2017 Published by Elsevier Sp. z o.o. on behalf of Polish Society of Allergology.

Human microbiota

The correct composition of the intestinal ecosystem, a group of physiologically bacteria inhabiting the human digestive tract – microbiota, is necessary to maintain the health and proper functioning of our body [26]. The impact of intestinal bacteria is not restricted strictly to the gastrointestinal tract, but it affects the proper functioning of virtually the entire organism. So versatile activity of described ecosystem is due to the multiplicity of functions performed by him. The most important tasks of intestinal bacteria should include protective, immune and digestive function [20].

The hygiene hypothesis of allergic diseases

The increase in the number of cases of allergy diseases, observed in recent years, has become an inspiration to explore new concepts to explain the development of this group of diseases. In the populations affected by this phenomenon the role of environmental factors was revealed. Especially interesting topic is the relationship between an increased incidence of allergic diseases and the increased hygienization of life [22]. Hygiene hypothesis was proposed by Strachan et al. and it says that increase in sterility of our surroundings, the widespread availability of antibiotics and simultaneous migration of population from rural to urban

* Corresponding author at: Zakład Immunopatologii, Katedra Alergologii, Immunologii i Dermatologii Uniwersytetu Medycznego w Łodzi, ul. Żeligowskiego 7/7, 90-752 Łódź, Poland.

E-mail address: rtp@csk.umed.lodz.pl (R. Pawliczak).

<http://dx.doi.org/10.1016/j.alergo.2017.03.002>

2353-3854/© 2017 Published by Elsevier Sp. z o.o. on behalf of Polish Society of Allergology.

areas significantly reduced human contact with the microbial world – bacteria, viruses or parasites [24]. These in turn are the main target of the immune system. As a result, our immune system, looking for new “enemies” began to actively respond to basically harmless particles of food or pollen. Because the normal intestinal ecosystem regulates the immune system, the risk of allergy or atopy is probably the higher, the stronger the dysbiosis of the gastrointestinal tract is. It is known that intestinal bacteria play a significant role in shaping the normal immune response. When the composition of the microbiota is correct, we observe generally balanced ratio of Th1/Th2 and tolerance of food intake. In patients with impaired intestinal ecosystem ratio of Th1/Th2 moves in a direction of decreasing in the activity of Th cells 1. Consequently, there is a mental process of capturing food allergens, so that they penetrate into the blood. Following are produced IgE antibody associated with type I food allergy, so-called immediate type reactions. The strong correlation between the composition of the intestinal ecosystem incidence of food or inhaled allergies has been shown in many scientific studies [22–24].

The intestinal microflora in allergic Estonian and Swedish 2-year-old children

Research conducted by a team of researchers from Estonia pointed to a relationship between the occurrence of allergic disease and the composition of the intestinal ecosystem [1]. In the study of Bjorksten, which the composition of the microbiota of children from the richer, more highly developed economically country (Sweden) with children in a developing country (Estonia). In Swedish children researchers found out strong disorders microflora, primarily lower number *Lactobacillus* sp. and higher numbers of aerobic bacteria especially *Enterobacteriaceae* and *staphylococci*, as well as lower counts of *Bacteroides* in the gastrointestinal tract, which was associated with a higher incidence of allergies [1].

Children who developed atopic dermatitis in their two first years of life were found out to be less often colonized with *enterococci* during the first month of life and *bifidobacteria* during the first year of life. In addition higher amount of *clostridia* at 3 months of age and lower counts of *Bacteroides* at 12 months were observed for allergic infants. Higher spread of colonization with *Staphylococcus aureus* in allergic children was established in comparison to reference group at 6 months old [2]. Differences of the gut microbiota composition between allergic and healthy subjects were confirmed in case-control studies and concerned various particular genera and species, especially *Bifidobacterium*, *Clostridium*, *Bacteroides*, *Lactobacillus* and *Enterobacteriaceae*. Higher concentration of isovaleric acid, due to presence of *Clostridium difficile* and higher *C. difficile* IgG antibody levels, was detected in fecal of allergic infants at one year than non-allergic infants [3, 4]. On the other hand the FISH analysis carried out in order to count bacteria indicated that colonization by *Clostridium* sp. was lower in allergic than reference subjects [5] and no significant difference in *Clostridium* counts were found between preschool controls and

children with allergy-associated atopic eczema/dermatitis syndrome (AAEDS) and non-allergic atopic eczema/dermatitis syndrome (NAAEDS) [6]. Colonization with *Bifidobacterium*, which is a dominant genus in infant fecal microbiota and may have beneficial effect, was proven to have quantitative differences by many studies [7]. Also, prevalence of *Bifidobacterium* has been found to be similar in healthy and allergic subjects, with no regard to allergic diseases, atopic dermatitis or wheezing [8–11]

Food allergy and the role of microbiota

The mucous membrane of the gastrointestinal tract is constantly exposed to a large amount of food and bacterial components. Healthy digestive immune system maintains a balance between immunological defense of mucous membranes and systemic tolerance [14, 27, 28]. In the case of food allergy this balance is disturbed and the body develops tolerance for input from food allergens or it is insufficient. Development of food allergy is caused by risk factors, immature gut barrier and type 2 T-helper (Th2) cell-skewed cytokine profile, which are present in early childhood. The antigen uptake is aberrant and Th2 cells further produce interleukin (IL)-4, a cytokine essential for B-cell differentiation into immunoglobulin (IgE)-producing cells, and IL-5, which is important for the activity of eosinophils which promotes the development of food allergy [14]. Bacteria colonization of mucous membranes of the digestive tract begins after birth, however, the development of normal microflora is gradual, initially depends, among the composition of the intestinal flora of the mother and the surrounding environment, as well as possible genetic factors [29, 30].

Bacterial flora of the gastrointestinal tract counterbalance the activity of Th2 cells and promotes the development of food tolerance [31, 32]. Studies on germ-free mice (sterile, devoid of microflora) indicate that normal flora of the digestive tract also affects many other parameters of the immune response [14, 33]. In these animals noticed reduced non-specific immune response and reducing the amount of Peyer's tufts, decreased concentration of sIgA and disturbances in the production of microvilli [34, 35]. Furthermore, colonization of mice germ-free mixture of three bacterial strains of the genus *Lactobacillus* significantly affected the increase in integrity of the small bowel mucosa and the induction of antibody production IgA12 [34]. Numerous studies indicate that the dysbiosis intestinal, or qualitative and quantitative abnormalities in the composition of the microflora may be one of the factors involved in the pathogenesis of a number of disorders such as necrotizing enterocolitis newborns (NEC), celiac disease, inflammatory bowel disease, irritable bowel syndrome, atopic dermatitis, allergic disorders, depression, cancer and other [1, 34, 35, 36].

The connection between prevalence of food allergy and abnormal intestinal microflora was suspected in the early 80s [37]. Russian scientists reported that the administration of a mixture containing *Propionibacteria* and *Lactobacillus acidophilus* bacteria hastened the disappearance of food

allergy manifestations [38]. Other studies have shown that volunteers taking yoghurt have lower concentrations of IgE levels and a lower incidence of allergies [39]. The effect of yoghurt on cellular, humoral and phagocytic function in adults with atopic allergy was observed in further studies [40].

IgG- and IgE-dependent food allergy

The disorder composition of the intestinal bacteria is also a predisposing factor for the development of food allergy IgG-dependent, which has delayed reaction mechanism. In contrast stands the IgE-dependent, where symptoms do not appear immediately after ingestion of food, but even several days delay. For example, food eaten on a Monday can trigger first signs of allergy appear only on Friday, which prevents self-identification of the allergen by the patient [14, 21].

The cause of delayed allergy is a damage to the continuity of the intestinal barrier. The role of this barrier is selective, selectively passing through the intestine wall of the essential nutrients, electrolytes and fluids and the simultaneous retention of toxins, bacterial antigens, and other substances harmful to the body [14].

When described barrier is working well, only properly distributed food particles, bacteria, and toxins are transported into the bloodstream, while other potentially harmful substances are retained on its surface. Damage of that specific filter leads to the development of the so-called Leaky Gut Syndrome, equivalent to the loss of control over the type of substance penetrating into the blood. In our bloodstream are present the molecules of food we eat, as well as there is larger risk of penetration by bacteria, viruses or toxins. The occurrence of any antigen, whether it be food or microbial in blood, enables the production of specific IgG antibodies and the development of inflammatory response. Immune response to food is similar as in the case of bacteria, toxins or virus, although the food particles cannot multiply in the blood and are potentially harmful. This condition is called delayed allergy, IgG-dependent. This allergy is characterized by a highly diverse symptoms ranging from gastro-intestinal, skin problems, headaches, depression and the considerable lag time of their occurrence [12, 13, 19].

Modern lifestyle, environmental pollution, the addition of preservatives and colorings to food are conducive to damage to the intestinal barrier [25]. An important element of this barrier are the intestinal bacteria. The balance of microbial ecosystem in the gut is an important factor in preventing the occurrence of delayed allergies. Patients undergoing multiple antibiotics therapies, particularly those with broad spectrum of action, often develops delayed food allergy. Gaining more and more evidence that the development of allergies is associated with impaired intestinal ecosystem composition, the researchers began the attempt to eliminate the bacterial dysbiosis in patients with allergies or predisposed to the development of allergic diseases. To restore intestinal balance, in addition to the elimination of allergenic foods, it seems to be a promising method of prevention of atopic diseases [15, 25].

Probiotics

So far, the treatment of food allergy was based mainly on the exclusion of allergenic foods from the diet [14]. However, recent studies clearly show that the antibacterial therapy with probiotics is important in the treatment of allergic inflammation associated with food allergy [14, 41].

Nowadays, change in the intestinal ecosystem can be achieved primarily through the use of probiotics. Probiotics are live strains of certain bacteria, which have a positive effect on human health and well-being, if given in the right amounts [26]. It should be realized that the bacteria present in the probiotic preparations are derived from strains colonizing the human digestive tract. These are the most common bacteria of the genus *Lactobacillus* and *Bifidobacterium* [20, 26]. It is those bacterial strains that have a highly desirable impact on human health. Studies have shown that the selected strains of probiotic bacteria modulate humoral and cellular response of the body, while also affecting the state of the entire system and immune-mediated gastrointestinal tract [20].

Consumption of yoghurt, fermented with *L. bulgaricus* and *Streptococcus thermophilus*, induced no significant changes in any of the immune parameters investigated [40]. Supply of an extensively hydrolyzed whey formula supplemented with the probiotic *L. rhamnosus* strain GG [ATCC 53103] has positive results in infants with atopic eczema and cow's milk allergy. In comparison to control subjects who received unsupplemented, extensively hydrolyzed whey formula, probiotic supplementation resulted in a significant improvement of clinical symptoms and alleviation of intestinal inflammation associated with food allergy [14, 40, 41].

The pathogenesis of allergic diseases has been described as an imbalance in Th1/Th2 response. Probiotics inhibit an allergic disease by suppressing Th2 cell responses. Interleukins (IL)-4, IL-5 and IL-13 are cytokines released by Th2 cells [42, 43]. In order to investigate the mechanism of action of probiotics many studies have been conducted, the results of which are different. Therefore, the role of cell Th1/Th2 in the development of allergic diseases is not fully understood. In result, the mechanism of action of probiotics still remains to be resolved [42, 44].

The mechanism was soon ousted after the discovery of a new theory on the development of allergic diseases. According to it, in a study conducted in a mouse model of asthma, Th17 cells induce allergic inflammation, and probiotics suppress the action [45]. Probiotics suppressed Th1 cytokines, IL-4, and CD4 Th17 cells of the spleen and increased expression of IL-10 and TGF- β in the mesenteric lymph nodes [46]. The influence of probiotics on the differentiation of T cells may suggest that dendritic cells (DCs) play an important role in the mechanism of action of probiotics in allergic diseases [44]. It is therefore to say that probiotics inhibit the differentiation of T cells into Th2 cells. Furthermore, probiotics inhibit the differentiation of mature dendritic cells in vitro. Further research is needed on human and animal models in order to identify additional mechanisms of action of probiotics in allergic diseases [44, 46].

Kalliomaki's studies

In Finnish study of Kalliomaki *Lactobacillus rhamnosus* GG (LGG) was administered prenatally to children whose mothers (or their partners) will have at least one first-degree relative suffering from atopic dermatitis, allergic rhinitis or asthma [16]. Then the strain was administered to infants 6 months after birth. As a result of a two-year supply of LGG strain, the occurrence of atopic dermatitis in the group receiving the probiotic was less than half of that of the control group [17]. Also, other studies have shown that prenatal supplements LGG strain contributed to the reduction of atopic eczema by half, as compared with the control group, but did not produce satisfactory results in prevention of this disease. As a result of a three-month supplementation of *Lactobacillus paracasei* and *B. lactis* in a group of 208 infants with atopic dermatitis aged 3–6 months, the incidence of atopic eczema severity significantly reduced [17, 18].

In another analysis done by Sjögren et al., it showed that reducing the biodiversity of intestinal microflora in the first 2 months of life was associated with a higher percentage of allergies in the first 5 years of life. In particular, it was correlated with a reduction in the number of bacteria of the genus *Lactobacillus* and *Bifidobacterium* in children who developed an allergy. What is interesting, genetic predisposition on the part of both parents early colonization of the neonatal chopsticks *Lactobacillus* acted protectively, and reduced the occurrence of allergies in offspring [47].

Conclusion

Intestinal barrier acts as the main filter between the outside environment and the interior of our body. Without the microbiota of the intestinal immune system no human could function properly. In the gastrointestinal tract is the largest collection of immunocompetent cells that is responsible for resistance throughout the body. Intestinal microorganisms are not only well tolerated, but even necessary for the proper functioning of the immune system of the gastrointestinal tract and keep it in constant activity. The change in the intestinal ecosystem can be achieved primarily through the use of probiotics. Probiotics are live strains of certain bacteria, which have a positive effect on human health and well-being, if given in the right amounts. Knowledge of the intestinal microflora and the beneficial effects of probiotic bacteria on human health is becoming increasingly important in the prevention of many diseases. Increasing allergy prevalence and the adoption of a modern, urbanized lifestyle were linked by many epidemiological studies. Many evidence indicates that improper colonization with particular commensal flora badly effects induction of the immunoregulatory network creating a predisposition to Th2-driven immune overreaction. In order to confirm the importance of microbiota in allergy development comprehensive and multidisciplinary well-designed clinical trials are necessary. This research may result in more effective allergy treatment and prevention strategies in near future.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES / PIŚMIENNICTWO

- [1] Bjorksten B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy* 1999;29:342–346.
- [2] Bjorksten 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.
- [3] Bottcher MF, Nordin EK, Sandin A, Midtvedt T, Bjorksten B. Microflora-associated characteristics in faeces from allergic and nonallergic infants. *Clin Exp Allergy* 2000;30:1590–1600.
- [4] Woodcock A, Moradi M, Smillie FI, Murray CS, Burnie JP, Custovic A. *Clostridium difficile*, atopy and wheeze during the first year of life. *Pediatr Allergy Immunol* 2002;13:357–360.
- [5] Mah KW, Bjorksten B, Lee BW, Van Bever HP, Shek LP, Tan TN, et al. Distinct pattern of commensal gut microbiota in toddlers with eczema. *Int Arch Allergy Immunol* 2006;140:157–163.
- [6] Kendler M, Uter W, Rueffer A, Shimshoni R, Jecht E. Comparison of fecal microflora in children with atopic eczema/dermatitis syndrome according to IgE sensitization to food. *Pediatr Allergy Immunol* 2006;17:141–147.
- [7] Ventura M, van SD, Fitzgerald GF, Zink R. Insights into the taxonomy, genetics and physiology of bifidobacteria. *Antonie Van Leeuwenhoek* 2004;86:205–223.
- [8] Stsepetova J, Sepp E, Julge K, Vaughan E, Mikelsaar M, De Vos WM. Molecularly assessed shifts of *Bifidobacterium* ssp. and less diverse microbial communities are characteristic of 5-year-old allergic children. *FEMS Immunol Med Microbiol* 2007;51:260–269.
- [9] Waligora-Dupriet AJ, Campeotto F, Romero K, Mangin I, Rouzaud G, Menard O, et al. Diversity of gut *Bifidobacterium* species is not altered between allergic and non-allergic French infants. *Anaerobe* 2011;17(3):91–96.
- [10] Gore C, Munro K, Lay C, Bibiloni R, Morris J, Woodcock A, et al. *Bifidobacterium pseudocatenulatum* is associated with atopic eczema: a nested case-control study

- investigating the fecal microbiota of infants. *J Allergy Clin Immunol* 2008;121:135-140.
- [11] Murray CS, Tannock GW, Simon MA, Harmsen HJ, Welling GW, Custovic A, et al. Fecal microbiota in sensitized wheezy and non-sensitized non-wheezy children: a nested case-control study. *Clin Exp Allergy* 2005;35:741-745.
 - [12] Wall R, Ross RP, Ryan CA, Hussey S, Murphy B, Fitzgerald GF, et al. Role of gut microbiota in early infant development. *Clin Pediatr Emerg Med* 2009;3:45-54.
 - [13] Haevy PM, Rowland IR. The gut microflora of the developing infant: microbiology and metabolism. *Microb Ecol Health Dis* 1999;11:75-83.
 - [14] Kirjavainen PV, Apostolou E, Salminen SJ, Isolauri E. New aspects of probiotics – a novel approach in the management of food allergy. *Allergy* 1999;54:909-915.
 - [15] Tlaskalova-Hogenova H, Stepankova R, Hudcovic T. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. *Immunol Lett* 2004;93:97-108.
 - [16] Kalliomäki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119:1019-1021.
 - [17] 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.
 - [18] Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361:1869-1871.
 - [19] 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(1):116-121.
 - [20] Hardy H, Harris J, Lyon E, Beal J, Foey AD. Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology. *Nutrients* 2013;5(6):1869-1912.
 - [21] Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004;53:1459-1464.
 - [22] Azad MB1, Konya T, Guttman DS, Field CJ, Sears MR, HayGlass KT, et al., Child Study Investigators. Infant gut microbiota and food sensitization: associations in the first year of life. *Clin Exp Allergy* 2015;45(3):632-643.
 - [23] Simms E. The intestinal microbiome in allergic disease. *UTMJ* 2015;92(3).
 - [24] Strachan P. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;55(Suppl. 1):S2-S10.
 - [25] Sekirov I, Russel S, Antunes CM, Brett B. Gut Microbiota in Health and Disease. *Physiol Rev* 2009;90:859-904.
 - [26] Özdemir Ö. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol* 2010;160:295-304.
 - [27] Isolauri E, Majamaa H, Arvola T, Rantala I, Virtanen E, Arvilommi H. *Lactobacillus casei* strain GG reverses increased intestinal permeability induced by cow milk in suckling rats. *Gastroenterology* 1993;105:1643-1650.
 - [28] Sanderson IR, Walker WA. Uptake and transport of macromolecules by the intestine: possible role in clinical disorders (an update). *Gastroenterology* 1993;104:622-639.
 - [29] Salminen S, Bouley C, Boutron-Ruault MC, Cummings JH, Frank A, Gibson GR, et al. Functional food science and gastrointestinal physiology and function. *Br J Nutr* 1998;80:147-171.
 - [30] van de Merwe JP, Stegeman JH, Hazenberg MP. The resident faecal flora is determined by genetic characteristics of the host. Implications for Crohn's disease? *Antonie Van Leeuwenhoek* 1983;49:119-124.
 - [31] Gaboriau-Routhiau V, Moreau MC. Gut flora allows recovery of oral tolerance to ovalbumin in mice after transient breakdown mediated by cholera toxin or *Escherichia coli* heat-labile enterotoxin. *Pediatr Res* 1996;39:625-629.
 - [32] Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997;159:1739-1745.
 - [33] Bauer H, Paronetto F, Burns WA, Einheber A. The enhancing effect of the microbial flora on macrophage function and the immune response. A study in germfree mice. *J Exp Med* 1966;123:1013-1024.
 - [34] Kozakova H, Schwarzer M, Tuckova L. Colonization of germ-free mice with a mixture of three *Lactobacillus* strains enhances the integrity of gut mucosa and ameliorates allergic sensitization. *Cell Mol Immunol* 2015 [Epub ahead of print].
 - [35] Hapfelmeier S, Lawson MA, Slack E. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. *Science* 2010;328:1705-1709.
 - [36] Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;474:307-317.
 - [37] Shaternikov VA, Kuvaeva ID, Ladodo KS, Orlova NG, Veselova OL. General and local humoral immunity and intestinal microflora in children with skin manifestations of food allergy. *Vopr Pitan* 1982;51-56.
 - [38] Loskutova IE. Effectiveness of using *Maliutka* and *Malysh* adapted propionic-acidophilus mixtures in the combined treatment of congenital hypotrophy. *Vopr Pitan* 1985;17-20.
 - [39] Trapp CL, Chang CC, Halpern GM, Keen CL, Gerschwin ME. The influence of chronic yoghurt consumption on population of young and elderly adults. *Int J Immunother* 1993;9:53-64.
 - [40] Wheeler JG, Bogle ML, Shema SJ. Impact of dietary yoghurt on immune function. *Am J Med Sci* 1997;313:120-123.
 - [41] Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997;99:179-185.
 - [42] Jang SO, Kim HJ, Kim YJ, Kang MJ, Kwon JW, Seo JH, et al. Asthma prevention by *Lactobacillus rhamnosus* in a mouse model is associated with CD4(+)CD25(+)Foxp3(+) T cells. *Allergy Asthma Immunol Res* 2012;4:150-156.
 - [43] Feleszko W, Jaworska J, Rha R-D, Steinhilber S, Avagyan A, Jaudszus A, et al. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. *Clin Exp Allergy* 2006;37:498-505.
 - [44] Kim H-J, Kim HY, Lee S-Y, Seo J-H, Lee E, Hong S-J. Clinical efficacy and mechanism of probiotics in allergic diseases. *Korean J Pediatr* 2013;56(9):369-376.
 - [45] Jan RL, Yeh KC, Hsieh MH, Lin YL, Kao HF, Li PH, et al. *Lactobacillus gasseri* suppresses Th17 pro-inflammatory response and attenuates allergen-induced airway inflammation in a mouse model of allergic asthma. *Br J Nutr* 2012;108:130-139.
 - [46] Kwon HK, Lee CG, So JS, Chae CS, Hwang JS, Sahoo A, et al. Generation of regulatory dendritic cells and CD4+Foxp3+ T cells by probiotics administration suppresses immune disorders. *Proc Natl Acad Sci USA* 2010 Feb;107:2159-2164.
 - [47] Sjögren YM, Jenmalm MC, Fagerås-Böttcher M. Altered early infant gut flora in children developing allergy up to five years of age. *Clin Exp Allergy* 2009;39:518-526.