Chapter 6

Probiotics and Allergic Diseases — Usefulness of Animal Models — From Strains Selection to Mechanistic Studies

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1. Introduction

The prevalence of allergies has dramatically and rapidly increased over the past decades in areas with a "westernized" or "industrialized" lifestyle. This increase and the dichotomy in the rate of allergic disease between industrialized and developing countries are two lines of evidence suggesting that environmental changes are a major factor in the development of allergies. There is mounting evidence that the microbiota is a key environmental factor that influences oral tolerance. Alterations in the sequential establishment of gut microbiota observed in western countries could therefore be responsible for a T-helper balance deviation toward a Th2 profile, a major factor in the rise of allergic diseases. Likewise treatment with broad spectrum antibiotics in infancy leading to microbiota alterations and dysbiosis, is associated with increased susceptibility to allergy [1]. Indeed recent epidemiological studies have linked factors influencing microbiota establishment and risk of allergy [2,3]. Hence, increasing evidences suggest that the composition of the microbiota influences intestinal barrier functions [4,5] and both local [6] and systemic immune responses [7]. A specific signature of the microbiota has been associated with allergy sensitivity [8-10]. This hypothesis has been confirmed by studies using mice models which have shown that the gut microbiota is likely to play a role in the development of oral tolerance. We and other have shown that the lack of gut microbiota in germ free mice is associated with the development of Th2 and IgE responses to dietary antigens [11,12]. The specific gut microbiota observed in mice with food allergy by Noval-Rivas *et al* was able of transmitting disease susceptibility to naive germ-free recipients [9]. In humans, several studies highlighted differences in the composition of bacterial communities in the feces of subject with or without allergic diseases; however, available epidemiological studies remain controversial [13]. Numerous studies support that a

low diversity of the gut microbiota in infancy is important, more than the prevalence of specific bacterial taxa but this low diversity can also be attributed to specific bacterial group, such as *Bacteroidetes* and *Proteobacteria* [14-17]. Interestingly, Ling *et al* described distinct alterations of the gut microbiota in IgE and non-IgE mediated food allergy [18]. Despite discrepancies between clinical studies, the likely relationship between the intestinal microbiota and allergy assess the usefulness of modulation of the gut microbiota that may help prevent and manage allergic diseases. This notion supports the use of probiotics, prebiotics and symbiotics.

If present results of clinical trials do not allow concluding unambiguously in favor of probiotics, studies have shown the benefits of this approach, justifying further research in this direction [13,19-21]. Recent reviews reported studies showing the beneficial effects in the prevention of atopic dermatitis [19-21]. Prevention of respiratory allergies also seems possible [21]. Differences between studies are most likely due to differences in the populations studied - in terms of type of allergy, evolutionary stage of the disease, environment, genetic background - but also to the various probiotic used in terms of strain, dose, duration and time of administration in relation to the development of allergy, and finally the follow-up period [13, 19]. The combined prenatal and postnatal administration of probiotics appears more effective [21]. However, the conflicting results reported today do not allow the recommendation of the use of probiotics in prevention of allergy by expert committees. Despite the promising results on prevention and treatment of allergic diseases by various strains, EFSA did not delivered favorable opinions on requests. Progress in our basic knowledge of probiotic strains, in strain selection, and in understanding their mechanisms of action is needed to give credibility to the health claims made for probiotics and especially for the design of efficacious therapeutic agents. For these reasons, animal models constitute unavoidable tools for biomedical research. They are used for their potential to mimic the human disease process, and allow better understanding of key events of allergic disease development.

2. Animal models of food allergy, asthma and atopic dermatitis

In this chapter, only animal models that have been used to characterize the impact of probiotics on allergy will be described.

The impact of probiotics on allergy – including food allergy, asthma and atopic dermatitis – was mainly studied on small laboratory animals (mice and rats), but domestic animals, as dogs and piglets, were also used. It is important to carefully choose animal model because it can deeply affect the study. Indeed, genetic predispositions condition IgE responsiveness [22].

2.1. Rodent models

2.1.1. Mice model

Mice are the first model organism because of its easy reproduction and its low cost of maintenance. This model does not completely mirror the human but it shares with him similar mechanisms of immune regulation, notably in T cell polarization [23]. These animals have the

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capacity to produce IgE and IgG1 antibodies, and, depending on their genetic background, strains can be divided into high or low IgE responders [22]. There are also differences in their ability to produce Th1 and Th2 cytokines.

Murine models of food allergy and asthma have been investigated in several strains, including BALB/c, C57BL/6 and C3H/HeJ. BALB/c strain is the most commonly used in models of experimental induced allergy. Indeed, BALB/c mice develop a strong Th2 response following sensitization and challenge with an allergen, with higher levels of allergen-specific IgE. It can be explained by a genetic predisposition towards the development of Th2 cells, implicate in allergy process [24]. This bias is caused by the loss of functional IL-12 receptor which leads to promote the generation of IL-4-producing cells. Indeed, IL-12 favors the generation of Th1 effector cells which antagonize the effects of IL-4 [25]. Many authors have succeeded to sensitize BALB/c mice with different allergens, such as ovalbumin (OVA) [26,27], ovomucoid [27] and β-lactoglobulin [28]. However, according to protocols, teams have obtained conflicting results. For instance, Morafo *et al* have demonstrated that BALB/c mice failed to produce cow's milk-specific IgE and did not reproduce symptoms after cow's milk challenge [29].

C57BL/6 mice are intermediate IgE responders [22] and have been used successfully in allergen challenge studies [30-32]. C57BL/6 strain has the advantage of being stable and having its genome entirely sequenced. Moreover, the most available knock-out strains mice are created on C57BL/6 genetic background.

C3H/HeJ strain is also used [33-35]. It has a mutation in the gene *tlr4* which recognize LPS. This loss of function leads to a higher susceptibility to allergy, with a skewing of the cytokine response to a Th2 phenotype and an aggravated anaphylactic reaction [36,37]. C3H/HeN strain, which don't have this mutation, is also used to obtain an anaphylactic response [11].

One study has compared these three mice strains in a model of asthma [38]. After immunizations to OVA/alum, BALB/c strain develops an α-actin smooth muscle hyperplasia and an airway responsiveness which was more important than in C57BL/6 and C3H/HeJ. These results have been confirmed by Van Hove *et al.* [39]. The choice of the murine strain is therefore of great importance, and must be determined in accordance with objectives. Hence, in food allergy, BALB/c and C3H/HeJ strains are more relevant to study sensitization with a high IgE response and anaphylaxis, respectively [29].

Strain NC/Nga, firstly developed by Matsuda *et al* in 1997, is widely used in models of atopic dermatitis (AD) [40]. Inbred NC/Nga can develop skin lesion similar clinically (on face, neck, ears, nose and dorsal skin) and histologically (with an increase of the number of mast cells and $CD4^+$T cells, and infiltration of numerous eosinophils) to human. IgE levels increase in association with clinical severity. These symptoms and signs appear when the mice are raised under conventional conditions, and not under specific pathogen-free conditions, environmental factors provoking AD-like signs [41]. BALB/c strain has also been used for this application [42].

2.1.2. Rat model

The rat is another small animal model to examine food allergy, but it is few implemented [43-45]. Due to the size of this species, it is possible to monitor within individual animals the kinetics of specific serum antibody responses. They have the capacity to produce IgE and IgG2a antibodies [46]. The Brown Norway strain is a suitable model with a high-IgE response after oral sensitization [47,48]. However, Dearman *et al* [49] have showed that the ability of this strain to mount IgE responses is somewhat variable and subject to a number of influences including environmental conditions and/or sub-clinical infection. Sprague-Dawley strain has also been used to test the impact of probiotic supplementation [44].

2.2. Large animal models

Swine and dogs are an example of large animal models that have been investigated for allergy. They are less commonly used because they are most expensive than rodents and their housing is uneasy. However, in many aspects, closer similarities exist between these large animal species and humans. First, dog's gut anatomy and physiology and nutritional requirements are similar to humans [50]. Second, atopic dogs share many allergies with human. Indeed, it develops spontaneously allergic reaction to dust mites and foods for example, with an incidence of 10% [51]. In this way, dogs present frequently IgE-mediated food hypersensitivity, with clinical symptoms comparable to those of human including gastrointestinal and dermatologic reactions. Of this fact, this model can be utilized for mimicking and characterizing mechanisms involved in the development of food allergies in children. To the best of our knowledge, up to now, the impact of probiotics has been only study on atopic dermatitis [52,53].

Only two teams used swine model within the framework of food allergy [54] and asthma [55]. Swine presents a number of important advantages for study allergy. Indeed, they have a similarity with young children in terms of size, organ development, intestinal physiology, whether anatomically or histologically, mucosal immunity and disease progression [56]. They are able to produce IgG and IgE [51].

3. Protocols of allergic sensitization

Multiple methods are used to induce allergy in animal models. Differences between protocols consist of the nature and dose of the allergen, and the strategy used to sensitize the animal prior to challenge (route of exposure and use or not of an adjuvant). The number of sensitizations is also extremely variable from one study to another, between 1 and 4 per week, during 1 from 8 weeks, according to the model, the use or not of an adjuvant, and the route of exposure (Tables 1 to 3).

3.1. Allergens

Many allergens are used to sensitize the different animal species. Ovalbumin (OVA), the main protein found in egg white, is used in more than 50% of publications on probiotic and allergy.

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Other major allergens are peanut extract in food allergy [30,35,43,57], birch pollen from *Betula verrucosa* (Bet v 1) [58-60] and house dust mite *Dermatophagoides pteronyssinus* (Der p) [32,61,62] in asthma. The capacity to induce the immune system to produce IgE antibodies, elicit allergic symptoms, and bind to allergen-specific IgE depend of allergen [63]. For example, by oral route, the allergenic potential of peanut extract is far higher than the one of cow's milk [63], and egg, Brazil nut and spinach [64]. The different allergens induce different types of antibody isotype patterns, whether it be IgG1, IgG2a, IgE and IgA. The allergenic potential of these molecules depends on the size and physicochemical properties of the protein, the glycosylation status, the biologic and enzymatic activities and the way in which the protein is processed and presented to the immune system [64]. Moreover, all mice strains are not susceptible to the same allergens. For example, BALB/c genetic background is completely resistant to peanut-induced anaphylaxis unlike C3H strain [37]. Experimental and clinical data indicate a difference in gender susceptibility to allergic inflammation [65,66]. These differences appear to vary with the route of administration used (see 3.2).

The dose of allergen and its frequency of administration are also important parameters in the magnitude of the immune response. Kroghsbo *et al* [27] have orally immunized BALB/c mice with a low (0.5 mg) or a high (5 mg) dose of OVA. Results revealed that the OVA dose had no impact on the production of IgG1 and IgA, but had an impact on production of IgG2a and IgE, with a higher level obtained with the higher dose of allergen. Nevertheless, the allergen dose administered should not be too high. Indeed, a high-dose of allergen can be associated with an induction of tolerance, while low-dose is known to induce sensitization [51,67]. In addition to the dose, the frequency of antigen exposure plays also a role. Nelde *et al* have showed that, after intraperitoneal (IP) sensitization of BALB/c mice, IgE synthesis was best induced by increasing the frequency of OVA application with low-dose than with few exposures with high doses [68]. The magnitude of the sensitization therefore depends on the type and the dose of the used allergen, but also on the route of administration (see below).

3.2. Route of exposure

The route by which antigen is administered has its advantages and disadvantages, and affects both the magnitude and the type of response obtained. It must be chosen depending on the purpose of the study. The route of delivery to animals should closely look like about the projected route of administration to humans. The most common routes for allergen administration are oral, IP and epicutaneous (EC) routes. Intra-nasal (IN) - for administration of pneumallergen in model of asthma [69], intra-tracheal (IT) [55], and subcutaneous routes (SC) [55,59,60,62,70,71] are more rarely employed.

3.2.1. Oral route

To model food allergy, antigen administration via the gastrointestinal tract – in other words, by gavage (IG) – provides clear ties to the human condition, and it is thus very relevant for exposure to food antigens. Additionally, it has the advantage of being economical, convenient, and relatively safe. Oral route also allows testing different allergens to evaluate their allergenic potential [64]. Oral immunization does not discriminate between males versus females, with

no differences in their level of Th1 (i.e. IgG2a) or Th2 -associated (i.e. IgE and IgG1) antibodies [65]. This route can be used for sensitization studies [30,33-35,43-45,72-75] but also for tolerance studies [76-78]. Consequently, this route is principally used to study the impact of probiotics on food allergy.

3.2.2. Intraperitoneal route

The intraperitoneal administration is a common technique in laboratory rodents. It can be used to administer large volumes of fluid safely, unlike oral route which only tolerate low volumes [79]. The pharmacokinetic of substances administered by this route is closed to those seen after oral administration, with a passage by the liver. Special care must be taken regarding the injected substances which should be sterile, isotonic and nonirritating. There are differences in sensitization according to the gender when this route is applied. Bonnegarde-Bernard *et al* have therefore showed that female mice C57BL/6 sensitized by intraperitoneal route develop higher level of allergen-specific IgE, IgG2a and IgA than males [65]. This route is used in experimental murine models of food allergy and asthma, in sensitization or tolerance induction studies [80-83].

3.2.3. Epicutaneous route

Some substances can also be administered directly to the skin surface (epicutaneous administration) for a topical affect. The allergen is captured by skin dendritic cells that migrate to the afferent lymph nodes and activate immune responses and allergen-specific cytokine production [84]. Several studies have demonstrated that this route allows to sensitize to various antigens, in the absence of adjuvant [85], with a strong Th2 response [86,87]. For that, they utilized occlusive dressings and/or prolonged exposure to the antigen. The extent of absorption of substances through the skin and into the systemic circulation depends on many parameters, as for example the surface area of application, the integrity of the skin and the contact time [79]. Contrary to the oral route, the epicutaneous administration is inadequate to discriminate the allergenic potential of proteins [64]. This route is very employed in atopic dermatitis model [52,53,66,88-95].

3.2.4. Comparison of routes of exposure

Several publications have compared the impact of these different routes of administration on sensitization. Animals can be sensitized to many allergens, but in an adjuvant-dependent manner, whatever the route practiced (IP, SC, IG, EC, and IN), with a significant production of allergen-specific IgE, IgG1 and IgG2a [49,64,85]. The maximal level of these immunologic markers is attained via the cutaneous route [85]. A mucosal administration (i.e. IG, SC or IN administrations) was shown to develop a robust allergen-specific IgA response by contrast with a cutaneous exposure [85]. The intraperitoneal route allowed a stronger IgE and IgG response compared with that obtained by oral route [49], but this response was weaker than the one observed with intranasal and epicutaneous allergen application [68]. Contrary to the oral route, intraperitoneal and epicutaneous administrations did not allow the induction of oral tolerance [87].

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3.3. The use of adjuvant

Most proteins are poorly immunogenic or non-immunogenic when administered on their own. To increase the immune response and thus sensitize animals, the majority of experimental studies utilize an adjuvant. The latter leads to a Th2 skewing, and abrogates the establishment of oral tolerance [96, 97]. There are exogenous Th2 adjuvants as glycans, endogenous adjuvants as thymic stromal lymphopoietin (TSLP) and experimental adjuvants as cholera toxin, aluminum hydroxide and enterotoxin B from *Staphylococcus aureus*.

3.3.1. Cholera toxin

Cholera toxin (CT) is secreted by the bacterium *Vibrio cholerae*, which is responsible for aqueous diarrhea. The major effect of CT is to promote the uptake of antigen by antigen-presenting cells and to facilitate the presentation of antigen to T cells by favoring the intestinal permeability. Indeed, it induces *in vivo* the maturation and the migration of gastrointestinal dendritic cells (DCs) from the *lamina propria* to the mesenteric lymph nodes where they present antigen to naive T cells. CT also enhances the migration from the subepithelial dome region of Peyer's patches to the interfollicular T-cell areas. This maturation of DCs also includes the up-regulation of the co-stimulatory molecules OX40L and TIM-4, known to facilitate differentiation of responder T cells into Th2 cells. The neutralization of these two molecules has been shown to abrogate Th2 skewing in the gastrointestinal tract [96, 98].

3.3.2. Aluminum hydroxide

Aluminum hydroxide (alum) rarely induces cellular immune responses. However, it slows down the rate of release of the antigen and in this way increases the duration of antigen interaction with the immune system. It also promotes macrophage uptake. Therefore, it enhances the immune response against the antigen [97,99].

3.3.3. Enterotoxin B from Staphylococcus aureus

The enterotoxin B (SEB) is produced by *Staphylococcus aureus* in a variety of environments, including food substrates [97]. It causes severe diarrhea, nausea and intestinal cramping often starting within a few hours of ingestion. In the same way as the cholera toxin, the SEB induces the up-regulation of co-stimulatory molecules TIM-4, but also CD80 and CD86, which promotes the Th2 skewing.

3.3.4. Impact of dose of adjuvant

Few studies have focused on the impact of dose adjuvant on sensitization. Kroghsbo *et al* have tested three different CT doses (0.1, 1 or 10 μg) on BALB/c mice, sensitized to ovomucoid or ovalbumin [27]. They have observed a clear dose-dependent response on antibody induction, with the strongest response at the highest CT dose for any of the tested antibody isotypes (IgG1, IgG2a, IgE, and IgA). They were able to determine a threshold value (between 0.1 and 1 μg) for the lowest CT dose needed for sensitization. A weak dose of CT (0.1 μg) leads to initiation of IgG1 production. To observe an IgE production, a higher dose of CT (10 μg) is necessary.

4. Probiotic administration

Animal models can be used to select probiotic strains which can prevent or manage allergy, and to study their mechanism of action. Indeed, these animal models can be discriminant. For instance, if number of studies showed a positive impact of probiotic supplementation in their models of allergy (Tables 4 to 6), Meijerink *et* al showed a strain specific effect in a peanut allergy model [57]. Lee *et al* studied the protective impact on OVA sensitization of four strains of *Lactobacillus* [100]. None of them induced a change in IgE levels. Moreover, one of them led to an increase in allergic response. Likewise, de Jonge *et al* have found similar levels of IgG1 and IgG2a in Brown Norway rats sensitized to peanut extract, receiving or not a strain of *L. casei* Shirota by gavage [43]. A lack of benefit of supplementation was also observed in three models of asthma [62,70,71,101]. Sometimes, an improvement of symptoms, with a decrease of clinical signs after oral challenge, but without correlation with a decrease in markers of sensitization can be also observed [54,58,59].

4.1. Evaluation of beneficial effect of probiotic

The beneficial effect of probiotic supplementation is evaluated according to the model used.

4.1.1. Models of anaphylaxis

In models of anaphylaxis, clinical markers are analyzed after challenge by allergen, according to a scale score based on observed clinical symptoms (number of itches, mobility during the experiment, swelling of eyes and/or noise, aspect of hair, and body temperature). Thang *et al* and Schouten *et al* have scored symptoms of systemic anaphylaxis as follows: 0=no symptoms; 1=pilar erecti, scratching and rubbing around the nose and head; 2=pilar erecti, reduced activity; 3=activity after prodding and lowered body temperature; 4=no activity after prodding, labored respiration, and lowered body temperature; 5=death [28,74]. There are other models of anaphylaxis, in particular murine models of intestinal anaphylaxis induced by OVA. Food allergy symptoms are then scored by the criteria of diarrhea and rectal temperature [102,103]. However, this model has not been used yet to evaluate the impact of probiotic.

4.1.2. Models of asthma

In models of asthma, there is no scale of scores. The impact of probiotic is estimated by the determination of the cellular composition of bronchoalveolar fluid (total cell count and proportion of each cell type – lymphocytes, neutrophils, eosinophils and monocytes), the evaluation of number of infiltrated inflammatory cells in lung, and by the measurement of bronchial hyperresponsiveness [70,81,104].

4.1.3. Models of atopic dermatitis

As in models of food allergy, a scale of scores can be used in models of atopic dermatitis. Matsuda *et al* have estimated clinical skin condition after sensitizations as follows: 0=none, 1=mild, 2=moderate, 3=severe, for each of these symptoms: itch, erythema/hemorrhage,

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edema, excoriation/erosion and scaling/dryness [105]. The frequency and the duration of scratching, the numbers of infiltrated cells and the epidermal/auricular thickening can be also measured [88,90,105].

The limit of all these evaluations lies in its subjectivity despite a blind evaluation system. This subjectivity results in a problem of reproducibility of the method. An analysis of biological markers of allergic reaction, i.e. the dosage in plasma of mast cell protease-1 (MCP-1) and/or histamine release during mast cell degranulation, provides less subjective data than clinical score [30,34,35]. These models also allow evaluating sensitization through dosage of allergen-specific and total IgE, IgG1 and IgG2a [60,92,100].

4.2. Route and dose of probiotic supplementation

The dose of probiotic is often comprised between 10^6 and 10^9 CFU. When the dose of probiotic is tested, the highest dose shows, most of the time, better results [35,62,89,94,106]. Jan *et al* have tested three increasing doses of *Lactobacillus gasseri* (1, 2 and 4.10^6 CFU) in BALB/c mice, in a model of asthma. Only the highest dose (4.10^6 CFU) caused a significant decrease in the number of monocytes, lymphocytes and neutrophils in bronchoalveolar lavage fluid [62].

In oral administration, we distinguish the intra-gastric (IG) administration, in other words the gavage (with a needle), from oral administration (PO) (probiotic mixed in water or food). These two routes of exposure are principally used for the probiotic supplementation and whatever the types of allergy study. Gavage allows giving a precise dose of bacteria, but it is constraining because each animal must be handled individually leading to an additional stress in animals. Administration of the probiotic strains in drinking water or food avoids these problems of stress, but it raises the problem of their stability. Moreover, it does not allow knowing precisely the amount of bacteria received per day per animal. Probiotic can also be given by intranasal administration in models of asthma, or by epicutaneous exposure in models of atopic dermatitis. Intranasal administration allows a contact more extended with the probiotic, and therefore a longer action. However, according to the protocols, an anesthesia is necessary [107,108]. It could affect the lung antigen deposition by changing the breathing pattern and airway reflexes in animal [109]. Pellaton *et al* have demonstrated that intranasal exposure is more effective than gavage, with a lesser infiltration of eosinophils, in a model of asthma [106].

4.3. Window and frequency of probiotic administration

In the window of administration, we will consider the number of weeks of supplementation as well as the number of administration per week. According to studies, the probiotic is administered between 1 to 15 weeks, during 3 to 7 days per week.

The term "prevention" refers to an administration of the probiotic that starts prior to sensitizations and continues throughout the experiment. On the contrary, the term "management/treatment" refers to an administration of the probiotic that starts after sensitizations until the end of protocol.

In studies, probiotic is mainly tested for prevention and therefore administrated until two weeks before the start of sensitizations. Meijerink *et al* began administration of probiotic by

gavage 14 days prior to sensitizations [57]. Each of the three strains of *Lactobacillus* had a different impact on allergy. The strain of *L. plantarum* WCFS1 have promoted allergic response (increase of IgE, IgG1 and MCP-1), the strain of *L. casei* Shirota had no impact on allergy, while the strain of *L. salivarius* HMI001 allowed the decrease of peanut-specific IgE and MCP-1. Yu *et al*, in a model of asthma, have given a strain of *L. rhamnosus* Lcr35 in BALB/c mice, 7 days before sensitizations. They observed a decrease in both bronchial hyperresponsiveness and number of cells in bronchoalveolar fluid [110]. Some studies have administered the probiotic in treatment, i.e. after the last sensitization, in models of food allergy and asthma, with a positive impact of supplementation. Schiavi *et al* have demonstrated, in a model of shrimp tropomyosin allergy, that the administration of VSL#3 during 20 days after the fourth sensitization allowed a decrease of clinical scoring and specific IgE, together with an induction of IgA on C3H/HeJ mice [34]. Similar results have been found in studies of Zhang *et al* [35], and Forsythe *et al* [111], with the administration of ImmuBalance™ in a model of food allergy, and with the gavage of strain *L. reuteri* ATCC 23272 in a model of asthma, respectively.

This high heterogeneity in the different protocols of probiotic administration make difficult, even impossible, comparisons between studies, and prevents establishment of an optimal administration scheme of probiotic. Comparison between prevention and management protocols shows that the window of administration plays a key role in the efficiency of probiotic, with a better effect in prevention. Indeed, in a model of food allergy, Kim *et al* [33] have showed, on C3H/HeJ mice sensitized to OVA, an improvement of allergic symptoms on the tail associated with a decrease of specific IgE in prevention, more important than those observed in treatment. Tanaka *et al* [42] in a model of atopic dermatitis and Yu *et al* [110] in a model of asthma have obtained comparable results. On the contrary, Bickert *et al* revealed a positive impact of probiotic, with an IP administration of *Escherichia coli* Nissle 1917 mixed with OVA, at the same time of sensitizations [31]. In study of Huang *et al*, similar effects of probiotics in prevention and treatment have been observed, suggesting that a long-term supplementation was not necessary [45]. Zuercher *et al* have obtained more contrasted results. They have observed that an oral administration of *Lactococcus lactis* NCC 2287 was effective in the management of food allergy symptoms in sensitized BALB/c mice, with a decrease in symptoms upon OVA challenge. However, this administration had no effect on the prevention of sensitization, with similar levels of OVA-specific IgE and IgG1, and MCP-1 [75].

4.4. Age and sanitary status of animals

The age and the sanitary status of animals have also an influence. In study of Lyons *et al*, the strain of *Bifidobacterium* AH1205 led to an increase of the percentage of CD4/CD25$^+$cells in spleen and Peyer's patches in pups but not in adult mice. The strain of *Bifidobacterium* AH1206 had the same impact, but in both pups and adult mice. These two strains were then tested in models of asthma and food allergy. Only the strain AH1206, which had an impact on pups and adult mice, showed a positive impact on allergy, with a decrease in bronchoalveolar cell number and OVA-specific IgE [112]. Similarly, depending on whether mice are germ-free or conventional, the induction of CD4/CD25/Foxp3$^+$cells in spleen was not the same, with a lower induction in germ free, whatever the strain studied [112].

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5. Concluding remarks

At a time when probiotics seem promising products for the prevention and treatment of allergy, fundamental and clinical studies failed the issuance of health claims and the implementation of recommendations by expert committees. The use of animal models is an essential step in the selection of strains of interest. However, such a use must be part of a rationalization process taking into account the 3Rs (Reduce, Reuse and Recycle) and ethical rules. *In vitro* models can bring the prior information on the behavior of the strains with respect to immunostimulary capacities. For instance, Foligne *et al* have discriminated pro- and anti-inflammatory strains in a model of human peripheral blood mononuclear cells according to their cytokine profile [113]. Dendritic cells model can also allow selecting probiotic strains able to prime monocyte-derived DCs to drive the development of Treg cells [114]. Based on this first strain selection, animal models allow analyzing their mechanism of action. Indeed, probiotics can act on various actors of immunity. They can improve the barrier integrity [115], induce IgA secretion [28], and/or modulate T-helper balance, switching from Th2 to Th1 response [116] or enhancing Treg activity [34]. However, one should consider carefully the choice of the model and the design of probiotic administration to provide results which could be considered predictive for benefits in human and support the design of clinical studies.

Strain	Age	Allergen	Route	Adjuvant	Window	References
BALB/c	6 wks	BLG	IP	alum	1/wk, x1 wk	[80]
BALB/c male	3 wks	BLG	IP	alum	1/wk, x3 wks	[28]
BALB/c female	6 wks	OVA	IP	alum	1/2wks, x2	[100]
OVA-TCR female	8 wks	OVA	IG	/	4/wk, x2 wks	[73]
C3H/HeOuJ female	6 wks	peanut extract	IG	CT	3/wk then 1/wk, x3 wks	[57]
BALB/c	6 wks	OVA	IG	CT	4/wk then 1/wk	[75]
Swiss Albino	6-8 wks	OVA	IP	alum	1/wk, x2 wks	[116]
C3H/HeJ female	8 wks	shrimp tropomyosin	IG	CT	1/wk, x4 wks	[34]
BALB/c female	18-22g	OVA	IP	SEB	3/wk, x1 wk	[115]
C3H/HeJ female	5 wks	peanut extract	IG	CT	1/wk, x8 wks	[35]
BALB/c male	7 wks	OVA	IP	alum	1/wk, x2 wks	[83]
C3H/HeJ	5 wks	OVA	IG	CT	3/wk then 1/2wks, x2	[72]

Strain	Age	Allergen	Route	Adjuvant	Window	References
female						
C3H/HeOuJ female	3 wks	whey protein	IG	CT	1/wk, x6 wks	[74]
BALB/c	8 wks	OVA	IP	CT	1/wk, x3 wks	[112]
C57BL/6 female	8 wks	peanut extract	IG	CT	1/wk, x4 wks	[30]
C3H/HeJ female	3 wks	OVA	IG	CT	3/wk then 1/2wks, x2	[33]
Sprague-Dawley male	150-180g	OVA	IG and IP	Freund	4/wk then 1/wk	[44]
Brown-Norway female	3 wks	OVA	IG	/	7/wk, x6 wks	[45]
Brown-Norway female	3-4 wks	peanut extract	IG	/	7/wk, x6 wks	[43]
Yorkshire	birth	ovomucoid	IP	CT	1/wk, x3 wks	[54]

Table 1. Protocols of sensitizations in food allergy

Strain	Age	Allergen	Route	Adjuvant	Window	References
GF BALB/c female	8 wks	Bet v 1	SC	alum	1/2wks, x3	[60]
BALB/c female	5 wks	cedar pollen	SC	/	5/2wks	[70]
GF BALB/c	birth	Bet v 1	SC	alum	1/2wks, x3	[59]
BALB/c female	6 wks	OVA	IP	alum	1/wk, x2 wks	[91]
BALB/c male	20-25g	OVA	IP	alum	1/wk, x2 wks	[104]
BALB/c female	6-8 wks	Der p	SC	Freund	1/wk, x2 wks	[62]
BALB/c female	6-10 wks	Bet v 1 + *Phleum pretense* 1 and 5	IP	alum	1/2wks, x3	[58]
BALB/c male	5 wks	OVA	IP and IN	alum	1/2wks (IP) then 3/wk, x4 wks (IN)	[69]
BALB/c female	3 wks	cedar pollen	SC	/	4/wk then 1/wk	[71]
BALB/c female	6-8 wks	OVA	IP	alum	1/2wks, x4	[82]
BALB/c male	5-8 wks	OVA	IP	alum	1/wk, x2 wks	[81]
C57BL/6 female	6-8 wks	OVA	IP	alum	1/2wks, x2	[31]
BALB/c	20-25g	OVA	IP	alum	2/wk, x1 wk	[111,117]

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Strain	Age	Allergen	Route	Adjuvant	Window	References
male						
C57BL/6 female	3-4 wks	Der p2	EC	/	1/2wks, x3	[32]
BALB/c	20-25g	OVA	IP	CT	2/wk, x1 wk	[112]
BALB/c	-	Der p1	IP	alum	1/wk, x3 wks	[61]
BALB/c female	6 wks	OVA	IP	alum	1/wk, x2 wks	[110]
BALB/c female	4 wks	OVA	IP	alum	1/2wks, x2	[106]
BALB/c female	8 wks	OVA	IP	/	3/wk, x2 wks	[118]
BALB/c female	6-8 wks	OVA	IP	alum	1/2wks, x2	[119]
BALB/c female	8 wks	Par j 1	IP	alum	1/3wks, x2	[101]
Duroc x Landrace	3 wks	*Ascaris suum*	SC et IT	alum	1/2wks, x3 (SC) then 1/2wks, x2 (IT)	[55]

Table 2. Protocols of sensitizations in asthma

Strain	Age	Allergen	Route	Adjuvant	Window	References
NC/Nga	-	FITC	EC	dibutyl phtalate	1/wk, x3 wks	[92]
NC/Nga male	6 wks	DNCB	EC	/	2/wk, x2 wks	[120]
NC/NgaTnd	8 wks	/	/	/	/	[105]
SKH-1/fr female	4 wks	OVA	EC	/	1/3wks, x3	[90]
NC/Nga	6 wks	Df	EC	SDS	1/wk, x5 wks	[95]
NC/NgaTndCrlj female	10 wks	Df	EC	SDS	2/wk, x4 wks	[88]
BALB/c female	8-10 wks	OVA	IP and EC	alum	1/2wks, x2 then 7/2wk, x3	[94]
NC/NgaTnd	5 wks	/	/	/	/	[42]
NC/Nga male	4 wks	DF	IP	/	1/wk, x14 wks	[121]
NC/Nga female	6 wks	DNCB	EC	/	2/wk, x3 wks	[89]
NC/Nga female	birth	/	/	/	/	[122]
NC/Nga	6 wks	Df	EC	/	3/wk, x5 wks	[66]
NC/Nga male	6 wks	PCl	EC	/	1x	[93]
Beagle	birth	Df	EC	/	3/wk, x1 wk	[53]
Beagle	birth	Df	EC	/	2/wk, x12 wks	[52]

Table 3. Protocols of sensitizations in atopic dermatitis

Probiotic	Route	Window	Dose	Impact		References
L. plantarum NRIC0380	IG	3/wk, x4 wks	200μg or 2mg	sensitization	↘	[80]
VSL#3	IG	7/wk, x5 wks	15.10^9 CFU	clinic sensitization	↘ ↘	[28]
L. casei YIT9029 (L1) *L. casei* HY7201 (L2) *L. brevis* HY7401 (L3) *L. plantarum* HY20301 (L4)	IG	7/wk, x3 wks	2mg	sensitization	L1, L3, L4, ↗ L2	[100]
L. brevis HY7401 (LB) *L. casei* Shirota YIT9029 (LC) *L. longum* HY8001 (BL)	IG	4/wk, x2 wks	2mg	clinic sensitization	↘ LB, LC, BL ↘ LB, LC, BL	[73]
L. plantarum WCFS1 (LP) *L. salivarius* HMI001 (LS) *L. casei* Shirota (LC)	IG	3/wk, x6 wks	10^9 CFU	sensitization	↗ LP, ↘ LS, LC	[57]
L. lactis NCC2287	PO	7/wk, x1 (M) or 8 (P) wks	5.10^8 CFU/mL	clinic sensitization	P, ↘ M P, M	[75]
Dahi	PO	7/wk, x1,2 or 3 wk(s)	-	sensitization	↘	[116]
VSL#3	IG	7/wk, x3 wks	$7,5.10^8$ CFU	clinic sensitization	↘ ↘	[34]
Bifidobacterium	IG	7/wk, x1 wk	10^8 CFU/mL	sensitization	↘	[115]
ImmuBalance™	PO	7/wk, x4 wks	0,5 or 1%	clinic sensitization	↘ ↘	[35]
L. pentosus S-PT84	PO	7/wk, x5 wks	0,075%	sensitization	↘	[83]
B. bifidum BGN4	PO	7/wk, x7 wks (P) or 7/wk, x2 wks (M)	0,2%	clinic sensitization	↘ P, M ↘ P, M P > M	[72]
Immunofortis (IF) *B. breve* M-16V (BB) symbiotic (SY)	PO	7/wk, x10 wks	2%	clinic sensitization	↘ IF, BB, SY ↘ SY, IF, BB	[74]
B. breve AH1205 (BB). *B. longum* AH1206 (BL) *L. salivarius* AH102 (LS)	IG	7/wk, x5 wks	2.10^9 CFU	sensitization	↘ BL, BB, LS	[112]
VSL#3	IG	7/wk, x3 wks	$7,5.10^8$ CFU	clinic	↘	[30]
B. bifidum BGN4 (BB) *L. casei* 911 (LC) *E. coli* MC4100 (EC)	PO	7/wk, x7 wks	0,2%	sensitization	↘ BB, LC, EC BB, LC > EC	[33]
LGG *B. animalis* MB5	IG	7/wk, x4 wks	10^9 CFU	-		[44]

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Probiotic	Route	Window	Dose	Impact		References
LGG + *B. longum* BB536	IG	7/wk, x2, 3 or 10 wks	0,5.10^9 CFU	sensitization	↘	[45]
L. casei Shirota	IG	7/wk, x8 wks	10^9 CFU	sensitization		[43]
L. lactis MG1363	IG	7/wk, then 3/wk then 1/wk, x3 wks	10^9 CFU	clinic sensitization	↘	[54]

Table 4. Protocols of probiotic administration in models of food allergy

Probiotic	Route	Window	Dose	Impact		References
B. longum ssp. *longum* CCM7952	IG	1x (parents before coupling)	2.10^8 CFU	sensitization	↘	[60]
E. faecalis FK-23	IG	7/wk, x3 wks	60mg	infiltration sensitization		[70]
L. paracasei NCC2461	PO	7/wk, x4 wks	2.10^9 CFU/mL	clinic sensitization	↘	[59]
L. rhamnosus Lcr35	IG	7/wk, x3 wks	10^9 CFU/ 600µL	infiltration	↘	[91]
E. faecalis FK-23	IG	7/wk, x4 wks	60mg	infiltration	↘	[104]
L. gasseri A5	IG	7/wk, x4 wks	1,2 or 4.10^6 CFU	sensitization		[62]
L. paracasei NCC2461 *B. longum* NCC3001	IN	day of sensitization (M) or 3/wk, x2 wks (P)	5.10^8 CFU	sensitization	↘ M, P NCC3010 > NCC2461	[58]
L. crispatus KT-11 (LC) LGG (LG)	PO	7/wk, x8 wks	5.10^7 CFU/g	clinic sensitization	↘ LC, LG ↘ LC, LG	[69]
E. faecalis FK-23	IG	7/wk, x3 wks	30mg	sensitization		[71]
L. salivarius PM-A0006	IG	7/wk, x8 wks	2,6 or 5,5.10^6 CFU, or 3,6.10^7 CFU	infiltration sensitization	↘ ↘	[82]
B. breve M16V	IG	7/wk, x2 wks	10^9 CFU	infiltration sensitization	↘ ↘	[81]
E. coli Nissle 1917	IG	day of sensitization (M) or 7/wk, x4 wks (P)	10^8 CFU	infiltration sensitization	↘ M, P ↘ M, P	[31]
L. reuteri ATCC23272	IG	7/wk, x1 wk	10^9 CFU	infiltration sensitization	↘ ↘	[111,117]
L. casei Shirota	IG	3/wk, x4 wks	10^9 CFU	sensitization	↘	[32]
B. breve AH1205 (BB) *B. longum* AH1206 (BL)	IG	7/wk, x2 wks	2.10^9 CFU	infiltration	↘ BL, BB, LS	[112]

Probiotic	Route	Window	Dose	Impact		References
L. salivarius AH102 (LS)						
E. coli Nissle 1917	IN	3/wk, x2 wks	10^9 CFU	sensitization	↘	[61]
L. rhamnosus Lcr35	IG	7/wk, x3 wks (P) or 1 wk (M)	10^9 CFU	infiltration sensitization	↘ P, M ↘ P, M	[110]
L. paracasei NCC2461 (A) *L. plantarum* NCC1107 (B)	IN or IG	7/wk, x1 wk	10^9 CFU	infiltration	↘ A, B IN > IG	[106]
LGG (LG) *B. lactis* Bb-12 (BB)	IG	4/wk, x8 wks	10^9 CFU	infiltration sensitization	↘ LG, BB ↘ LG, BB	[118]
L. rhamnosus HN001	PO	7/wk, x7 wks	10.10^{10} CFU	clinic	↘	[55]

Table 5. Protocols of probiotic administration in models of asthma

Probiotic	Route	Window	Dose	Impact		References
Vitreoscilla filiformis	CUT	1/wk, x4 wks	20% v/v	clinic sensitization	↘	[92]
L. sakei probio 65	IG	7/wk, x2 wks	5.10^9 CFU/mL	clinic sensitization	↘ ↘	[120]
ImmuBalance™	PO	7/wk, x2 wks	$1,8.10^8$/g	clinic infiltration sensitization	↘ ↘ ↘	[105]
L. rhamnosus Lcr35	IG	7/wk, x8 wks	10^9 CFU/ 600µL	clinic infiltration sensitization	↘ ↘ ↘	[90]
L. plantarum CJLP55 (A) *L. plantarum* CJLP133 (B) *L. plantarum* CJLP136 (C)	PO	7/wk, x8 wks	10^{10} CFU	clinic infiltration sensitization	↘ A, B, C ↘ A, B, C ↘ A, B, C	[95]
B. subtilis JCM20036	IG	6/wk, x4 wks	$1,2.10^{17}$ CFU	clinic infiltration	↘ ↘	[88]
E. coli Nissle 1917	PO	7/wk, x4 wks	10^7 or 10^8 CFU	clinic infiltration sensitization	↘ ↘	[94]
L. rhamnosus CGMCC1.3724	PO	7/wk, x12 wks (P) or 7/wk, x7 wks (M)	5.10^8 CFU/mL	clinic sensitization	↘ P, M ↘ P, M	[42]
L. crispatus KT-11 (A) *L. crispatus* KT-23 (B) *L. crispatus* KT-25 (C)	PO	7/wk, x15 wks	1mg	clinic sensitization	↘ A, B, C ↘ A, B, C	[121]
B. subtilis KCTC1666 + *L. acidophilus* KCTC3155	PO	7/wk, x3 wks	1 or 2%	clinic sensitization	↘ 2% > 1%	[89]

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Probiotic	Route	Window	Dose	Impact		References
LGG	PO	7/wk, x10 wks	4.10^4 CFU/g	clinic infiltration sensitization	↘ ↘	[122]
L. johnsonii NCC533	IG	2 days	$1,5.10^{11}$ CFU/mL	clinic sensitization	↘	[66]
L. paracasei KW3110 + LGG	PO	7/wk, x11 wks	0,03% or 0,3%	clinic sensitization	↘ 0,3% > 0,03%	[93]
LGG Culturelle®	IG	7/wk, x6 months	20.10^9 CFU	-		[53]
LGG	IG	7/wk, x6 months		clinic	↘	[52]

Impact of probiotic by comparison with control mice, in term of clinical score (clinic); markers of sensitization, i.e. allergen-specific and total IgE and IgG1 (sensitization); and infiltration of inflammatory cells, i.e. lymphocytes, neutrophils, eosinophils and monocytes, in lung and/or bronchoalveolar fluid (infiltration).

↗ increase in symptoms or negative effect; ↘ decrease in symptoms or positive effect;→ no change in symptoms or no effect

Table 6. Protocols of probiotic administration in models of atopic dermatitis

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