# EDITORIAL: Probiotics, Gut Microbiota and Immunomodulation: Is this the Key to Counteract the Allergy Epidemics?

Allergic diseases have been described since the antiquities [1], but major advancements on understanding of their pathogenic mechanisms and clinical implications date to the end of the 19$^{th}$ and the first half of the 20$^{th}$ century [2, 3]. In the meantime, during the last decades, the prevalence of allergic diseases remarkably increased, paving the way to the definition of "allergy epidemics" [4].

But what happened in the second half of the 19$^{th}$ century that gave rise to this phenomenon? As far as we know, at least two major changes took place, which led to an increase of allergic diseases. The first one was a major change in life and social conditions, with decrease of family size, people progressively moving from the countryside to the cities, and consistent improvements in public hygiene, with widespread availability of clean water and use of antibiotics, just to name two [4]. The second one was the increasing concentration of airborne pollens, due to the diffusion of new grasses, such as *Lolium perenne* in England in the late 19$^{th}$ century, and to the increasing presence of infesting grasses due to changes in farming techniques and increase in arable farming. By the mid-forties, hay fever became such a severe health problem in the New York city area that a ragweed eradication campaign was initiated by the city council [5].

If the link between the increase of airborne pollens in the air and allergic diseases caused by the pollens themselves is clear, this is not the same for the first explanation.

In 1989, David P. Strachan published on *The Lancet* the results of his epidemiologic investigation on 17414 British children who were followed-up until the age of 23 [6]. He aimed to investigate the relationship between the increase of hay fever and sixteen different perinatal, social and environmental factors. What he found was a striking association of hay fever with family size and position in the household during childhood [6]. In his evaluation, the single most influential variable was the number of older children in the household, and he hypothesized that allergies could be prevented – during childhood – by cross-infections among family members, facilitated by unhygienic contact with other siblings. This was the birth of the "hygiene hypothesis", which is still today a milestone to explain the rise of allergic diseases [6, 7].

In the last decades of the 20th century, new information came from *in vitro* studies about CD4+ T-lymphocyte subpopulations [8]. T Helper-1 (Th1) cells were characterized as T lymphocytes capable of prevalent production, in response to microbial stimuli, of interleukin-2 (IL-2), interferon γ (IFN-γ), and transforming growth factor β (TGF-β), subsequently referred to as "Th1-cytokines"; these cytokines were recognized a prominent role in defense against most infectious agents [8]. Th2 cells, on the contrary, were characterized by the prevalent production of IL-4, IL-5, IL-9, and IL-13 (Th2-cytokines) who gave rise to an eosinophilic-rich immune response, primarily implicated in immunity against parasites and multicellular organisms but less crucial for immune responses in modern westernized countries [8].

It became later clear that Th1 and Th2 cells develop from the same naive Th cell under the influence of both environmental and genetic factors and therefore they are not two distinct CD4+ T-cell subsets, but are the expression of two differently polarized forms of the highly heterogeneous T cell–mediated immune response [8]. We now know that the regulation of the immune response is even much more complex than this, with other T-cell subsets besides the Th1 and the Th2 [9]. We also know that a Th2-skewed immune response favors the rise of allergic diseases.

In this context, gut microbiota – which consists of a complex community of microorganism species that live in the digestive tract – has been increasingly recognized as an important part of the balance, being able to favor – depending on their composition in the specific subject and period – a different polarization of the immune response.

Gut microbiota is an integral part of the gastrointestinal system, with an estimated population of more than $10^{13}$ bacteria and more than 400 phylia, accounting for a genomic diversity of more than 3 million of genes [10]. It plays a determinant role in the development of immune system, driving both local immune maturation and systemic immune programming [11].

Nobel Prize-winner Ilya Ilyich Metchnikoff, in 1908, was the first to postulate a beneficial effect of microorganism on human health, and on immune system regulation [12].

It is now known that a well-balanced gut microbiota is crucial for the development of healthy regulation of immune responses, therefore resulting in appropriate activation against pathogens and systemic hyporesponsiveness to harmless antigens (including allergens) [13]. Changes to the gut microbiota, on the other hand, could be part of the pathogenic mechanism implied in the shift toward Th2-driven immune-responses.

In this regard, a consistent body of evidence suggests that a decreased microbial exposure, especially in the early life period, can be associated with the rising prevalence of allergic diseases [13]. Epidemiologic data show that environmental changes resulting in reduced microbial contact early in childhood, especially in the industrialized world, have paralleled the increase of allergic diseases such as atopic eczema, allergic rhinoconjunctivitis and bronchial asthma, food allergy, but also non-allergic disorders such as inflammatory bowel disease and diabetes [13-15]. These observations indirectly support Dr. Strachan's observations and his already mentioned hygiene hypothesis [6].

At the beginning of this century, some Authors proposed that specific microbes in the commensal gut microflora can be even more crucial than sporadic infections in atopic disease prevention [16]. These cells can promote potentially antiallergenic processes, comprehending a) stimulation of Th1-skewed immune responses [17] by increased production of Th1-cytokines and b) inhibition of Th2-dominated responses, by increased production of TGF-β, which has a pivotal role in suppression of the allergic inflammation [18, 19] and in oral-tolerance induction [20]. Microbial cells have also been found to modulate specific and nonspecific immune responses to allergens by affecting phagocytosis and production of proinflammatory cytokines and IgA [21, 22].

Moreover, microorganisms belonging to the intestinal microflora could stabilize intestinal permeability and contribute to the mucosal barrier function, which is a crucial issue in atopic diseases such as atopic dermatitis (AD). Disruption of the intestinal barrier function may represent a primary abnormality of the gut, but may also reflect a mucosal damage by local inflammatory reactions. Furthermore, studies have shown that patients with AD presented some modifications in the intestinal microbiota composition; indeed, the counts of *Bifidobacteria* were significantly lower in patients with AD than in healthy subjects, whereas the number of *Staphylococci* was significantly increased [23].

The important role of gut bacteria has suggested the possibility of preventing or treating AD by manipulating the intestinal microflora with a probiotic supplementation. Probiotics, defined by WHO as living microorganisms which, when ingested in adequate amounts, may have a healthy effect on the host, have been shown to reduce intestinal permeability, limiting the absorption of noxious molecules from the gut lumen. They also influence the innate inflammatory response of epithelial cells, reducing mucosal inflammation.

Probiotics, in this regard, could be functional to restore a well-balanced microbiota, thus influencing immune system functions and potentially representing – at least in part – a solution for the allergy epidemics.

Many studies have addressed the role of probiotics in the prevention of atopic eczema and most of them found a positive effect; a minority, however, even if the same probiotic strains and similar protocols were used, failed to confirm the same results [24].

In 1997, Isolauri *et al.* showed that addition of probiotics in an extensively hydrolyzed whey formula in infants with atopic eczema and cow's milk allergy resulted in a reduced clinical score of atopic dermatitis after 1 month [25].

In 2001, Kalliomaki *et al.* demonstrated that supplementation of *Lactobacillus Rhamnosus* given for 2-4 weeks prenatally and 6 months postnatally resulted in a halved probability of developing atopic eczema by age 2 [16]. These results were confirmed in two subsequent follow-up studies in which a minor incidence of atopic disease was confirmed after 4 and after 7 years, respectively [26, 27].

In 2008 Winkens *et al.* showed in a DBPC study that a supplementation with *Lactobacillus Rhamnosus* and *Bifidobacterium animalis* sbp *lactis* given at 35 weeks of gestation and for 6 months postnatally resulted in a lower probability of developing atopic eczema and improvement of SCORAD by age 2 [28]. Two subsequent follow up

studies up to 4 and 6 years, confirmed the long-lasting effect and also showed a statistically significant increase of IFN-γproduction in the treated group vs placebo group [29, 30].

The studies by Kalliomaki and Winkens thus demonstrated that a preventive probiotic supplementation with *L. Rhamnosus* in a high risk population during the last quarter of pregnancy and 6 months postnatally has a protective long term effect against the development of atopic eczema.

Several studies in the following years explored the role of probiotics in prevention and treatment of allergic diseases (atopic eczema, asthma/wheezing, rhinitis, atopy). In 2010, a milestone meta-analysis summed up these results, confirming that probiotics can have a beneficial role in prevention of atopic eczema, given that their administration is started prenatally and stressing out the role of *Lactobacilli* [31]. Another meta-analysis published in 2014 confirmed these data and showed that in 25 different DBPC randomized trials cumulatively including more than 1600 patients, SCORAD values of probiotic-treated group were significantly lower respect to those of the placebo group at the end of the observational period [32].

Recently, a novel meta-analysis confirmed and extended these findings, analyzing the results from 21 randomized-controlled trials on a total of 4755 children who were administered probiotics prenatally and/or during early life [33].

Upon this increasing body of evidence, the World Allergy Organization (WAO) in 2015 released guidelines for allergic disease prevention (GLAD-P) focusing on probiotics. In this document, the panel of experts – despite a quality of evidence defined as “low” – suggest that probiotics should be used in pregnant women, during breast-feeding and in the first months of life if the newborn has an increased risk of developing allergies [34]. In this case, children were considered at increased risk for allergies if they had a “biological parent or sibling with existing or history of allergic rhinitis, asthma, eczema, or food allergy” [34].

Very recently the WAO released a second position statement focusing on prebiotics (a substance, typically a non-digerible fiber compound, that induces the growth or activity of microorganisms) for prevention and treatment of allergic diseases [35]. In this document, the WAO experts panel suggests to use prebiotic supplementation in not-exclusively breastfed infants, both at high and at low risk for developing allergy but not in exclusively breastfed infants (conditional recommendation, very low certainty of the evidence). No recommendation was provided for pregnant and breastfeeding women owing to lack of experimental and observational studies in these categories.

Summed up, the results from interventional studies with probiotics in allergic diseases, support the existence of a “window of opportunity”, a period very early in life and even in the last part of pregnancy, in which microbiome manipulation could significantly modulate of the immune responses later in life, thus resulting in a different risk of developing allergies.

The gut colonization of the baby takes place through vertical transmission from mother to child during pregnancy; this process starts and finishes at the time of childbirth. A secondary route to the vertical transmission of microorganisms is breastfeeding, as the DNA of bacteria belonging to the gut microbiome has been detected in human milk [36].

However, according to some studies, a first, initial contact with the microbiota would already happen during fetal life: traces of bacterial DNA have been identified in the placenta, umbilical cord, in the amnion fluid and in the meconium of infants delivered at term by cesarean section and in the meconium of pre-term newborns birthed after 23-32 weeks of gestation [36].

The most accredited hypothesis suggests that dendritic cells would be able to penetrate maternal intestinal epithelium, "take" microorganisms and transport them to the placenta, presenting them to the fetus and thus contributing to the development of his immune system.

This concept is very intriguing and could explain the important role of probiotics supplementation during the last term of pregnancy, in order to achieve an immunomodulating effect in the fetus.

Since different probiotic strains have different characteristics, it is unlikely that a single organism has the capacity to accomplish more than a few effects [37], while different strains could have synergistic or antagonistic functions. For

this reason, the concept that probiotic effects are species-specific and strain-specific is emerging, thus leading the way to the development of single products (single strain probiotics but also multi-strain formulations [38] and symbiotics) specifically devoted to be used in a precise clinical condition or to exploit a specific immunomodulating effect [39-41].

Currently, given the large diffusion of probiotics-containing products, it is also of crucial importance that an adequate safety profile is guaranteed. For this reason, the Qualified Presumption of Safety (QPS) certificate issued by the European Food Safety Authority (EFSA) or the Generally Recognized as Safe (GRAS) certificate issued by the Food and Drug Administration (FDA) distinguish those products which contain probiotics with ascertaining of taxonomic position, thus allowing the recognition of the bacterial species with a long history of safe consumption. The identification of the species makes use of sequencing of DNA coding for 16S rRNA and nucleic acid hybridization. The typing of the bacterial strain can be made by pulse field gel electrophoresis (PFGE). The safety assessment requires that potential transmission of antibiotic resistance from the probiotic to other microorganisms is ruled out.

Finally, another major challenge for probiotics use is their survival and persistence to gut extreme conditions, during their transit. To enhance the rate of colonization, strain phenotyping modulation and alternative technologies such as encapsulation should be taken into account in order to ensure higher probiotics' survival, protecting them from acidity, bile salts, molecular oxygen concentration, bacteriophages, chemical and antimicrobial molecules [42].

Given the epidemic proportions of the allergic burden worldwide and its direct and indirect costs, probiotics could represent an interesting approach to counteract the allergy epidemics. More studies, however, are necessary to investigate the most suitable strains and dosing schedules for this purpose.

This thematic issue about "Probiotics in Allergic Diseases" of the Journal of Pharmacology and Nutritional Sciences contains interesting reviews as well as original studies on this topic. The original works by Dominguez-Ortega, [43] Rial-Prado [44] and Rossi [45] shed light about their application in respiratory allergies, atopic eczema and as adjuvants in allergen-specific immunotherapy, respectively.

## CONFLICT OF INTEREST DECLARATION

Filippo Fassio received consultancy fees from Allergy Therapeutics Italia. Fabio Guagnini is an employee of Allergy Therapeutics Italia.

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