Arch Clin Biomed Res 2020; 4 (3): 169-183 *DOI: 10.26502/acbr.50170096*

Review Article

Role of Microbiota in Atopic Dermatitis and Bronchial Asthma - Triangular Cross-Talk among Skin, Airway and Gut

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Received: 18 January 2020; **Accepted:** 23 January 2020; **Published:** 29 May 2020

Citation: Yukihiko Kato, Yasuhiro Matsumura. Role of Microbiota in Atopic Dermatitis and Bronchial Asthma - Triangular Cross-Talk among Skin, Airway and Gut. Archives of Clinical and Biomedical Research 4 (2020): 169-183.

Abstract

The development of allergy is partly dependent on changes in individual's microbiota which were interacted with the environment. Microbiota can be modulated by early-life microbial exposures, diet, antibiotics. Lower microbial diversity is pivotal factor in developing diseases.

Certain types of microorganisms are involved in a disease activity. Early life exposure to non-pathogenic *Proteobacteria* has a protective effects in developing allergies. Later, bacterias, involving *Staphylococcus aureus* (S.aureus) in the skin or pathogenic *Proteobacteria* in the airway, affects patients with atopic dermatitis (AD) and bronchial asthma (BA) respectively. Similarly *Acinetobacteria* in early exposure protectively effect BA. The pathogenic role of *Proteobacteria* phylum might differ between bronchial and skin inflammation. The microbiota at local sites is also involved in the development and activity of diseases in remote organs via'triangular cross talk'. Cross talk among skin, air way, and gut is not surprising, because they are the superficial organs.

Lactobacilus in the *Firmicutis* phylum always protectively work for allergic diseases of skin and bronchus. Therefore probiotics, which mature the gut barrier and prime the immune function, are currently being used to prevent and treat AD and BA. The accumulated data, however, have failed to substantiate fully the effects of probiotics against allergic disorders.

Keywords: Atopic dermatitis; Bronchial asthma; Microbiome; Probiotics; Proteobacteria phylum

Introduction

Not surprisingly, the collective genomes of the microbiota, or the microbiome, in the human body influence the prevention and development of diseases, since the genetic repertoire of the healthy microbiome is approximately 100 times that of the human genome [1]. Reviews in the past were often discussed from the point of the development of the microbiomes and diseases, based on the hygene hypothesis. In this review the relationship between microbiomes (Table 1) and allergic diseases was discussed clinically, especially the association among remote organs.

Phylum	Family	Genus	Species
Proteobacteria		*Haemophilus*	*H. parainfluenzae*
		Klebsiella	
		Moraxella	*M. catarrhalis*
		Helicobacter	*H. pylori*
		Acinetobacter	*A. lwoffii*
	Comamonadaceae		
	Oxalobacteraceae		
Firmicutis	*Lactobacillaceae*	*Lactobacilus*	*L. rhamnosus*
			L. paracasei
			L. fermentum
			L. salivarius
			L. reuteri
			L. gasseri
	Staphylococcaceae		*Staphylococcus aureus*
	Bifidobacteriaceae		
	Ruminococcaeae	*Ruminococcus*	
Bacteroidetes		*Prevotella*	*P. melaninogenica*
Actinobacteria	*Bifidobacteriaceae*	*Bifidobacterium*	*B. lactis*
			B. longum

Table 1: Taxonomy of microbiomes implicated in skin and lung allergies.

The taxonomy shows the phyla, families, genera, and species according to the International Conference on Genomics (ICG).

Environmental exposure to microorganism and allergic diseases

Early environmental exposure to microorganisms [2], antibiotic therapy [3] [4] [5] [6] [7], and diet [8] [9] [10], influence the composition of this microbiota. The gut microbiota is crucial to the development and maturation of the host immune system [11]. A lack of early microbial stimulation provokes an aberrant immune response to antigens leading to the development of allergies [12] (Figure 1).

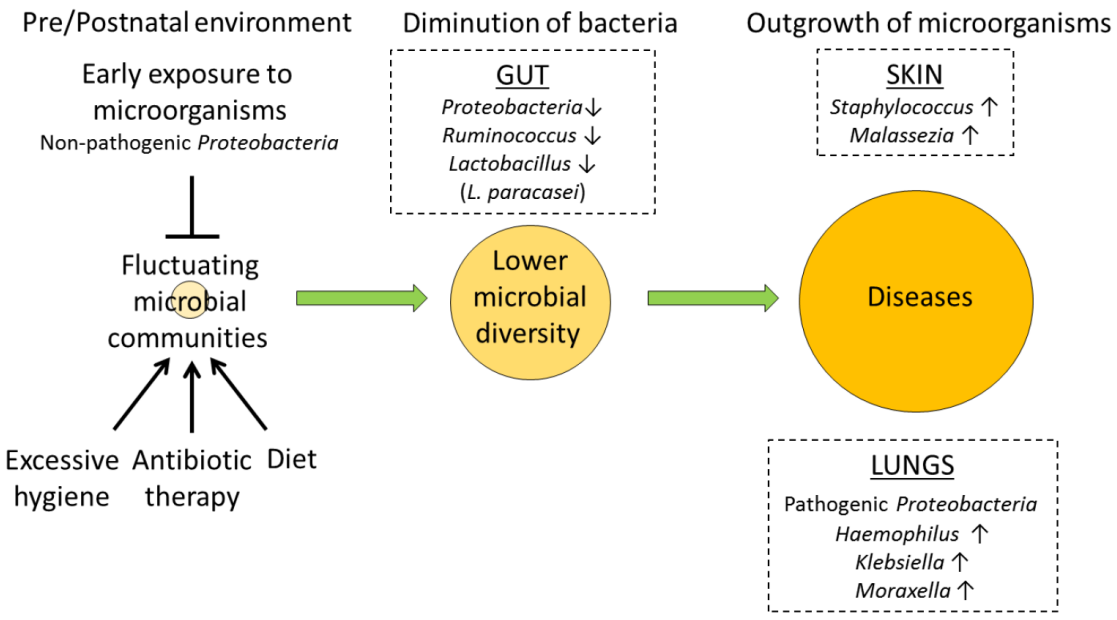

Figure 1: Microbiota and its implication in allergy development

Immunological changes occur at mucosal surfaces of gut due to extensive microbial colonization in early lifetime. Microbiota can be modulated by early-life microbial exposures, diet, antibiotics. Reduced diversity of gut microbial is associated with risks of allergic diseases. Certain types of microorganisms are involved in a disease activity.

Early exposure to a rural or agricultural environment influences the development of allergic symptoms later in life via microbial exposure, which elicits long-lasting effects on invariant natural killer T (iNKT) cells [13]. Acinetobacter lwoffii F78 and Lactococcus lactis G121, isolated in cowsheds of farms, were able to induce a T-helper 1 (Th1)-polarizing program in dendritic cells in mice [14] [15]. It has also been shown that *Acinetobacter lwoffii* F78 confers a protective effect against allergy via Toll-like receptor (TLR) signaling [16]. A recent study indicated that a lower prevalence of allergies was associated with a greater abundance and diversity of bacteria of the genus *Acinetobacter* at the skin and nasal mucosa in children [17].

Neonatal gut with less *Bifidobacteriaceae* and *Lactobacillaceae*, and higher *Candida* and *Rhodotorula*, is a risk of allergic diseases [18]. A particular microbiota in gut shift immune development toward Th17 responses, resulting in allergy later in childhood [19].

Skin microbiota influences AD

The skin acts not only as a physical, but also as an immunological barrier to the external environment. Human skin houses on average one million bacteria per square centimeter, which may play a role in modulating allergic disorders of the skin [20] by priming resident T lymphocyte function [21] [22] and the homeostasis between Th1 and Th2 cells, resulting in anti-inflammatory responses to environmental allergens. Although a preceding Th2-skewed immune response has not been clearly demonstrated, the absence of microbiota enhances thymic stromal lymphopoietin (TSLP) expression in mice with a defective skin barrier [23].

Microbes are thought to communicate with the cells of the surrounding skin or subcutaneous tissue. A recent study demonstrated that bacteria exist not only on the surface of the epidermis but normally also in the various layers of the dermis and subcutaneous tissue. This astonishing study suggested that bacteria could penetrate the skin barrier and interact with a wide variety of cells of the epidermis, dermis, and adipose tissue [24]. Adipocytes respond to invasive *S. aureus* by producing the antimicrobial peptide, cathelicidin, suggesting that subcutaneous adipocytes produce an important host defense response against skin infections [25].

Normal skin microbial flora mainly consist of the bacterial phyla, *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* [26][27]. The microbial community at disease sites of AD patients was dramatically different from that of controls. Although infants with AD were not colonized with *Staphylococcus aureus* (*S. aureus*) before the development of AD [28], colonization of AD skin by *S. aureus* has been correlated to an increase in disease severity [29] [30] [31] (Figure1). However, a causal association has not been established since the elimination of *S. aureus* does not constitute a cure for AD. On the other hand, *Acinetobacter Iwoffii*. induced Th1 and anti-inflammatory responses in immune and skin cells and protected against allergic sensitization and lung inflammation by way of the skin [32]. The recovery of bacterial diversity is apparently related to the achievement of remission via treatment, suggesting that the loss of microbial diversity may contribute to the pathogenesis of AD [26] [33]. Early gut microflora precede the later development of atopic sensitization [56]. Studies focusing oncorrelations between reduced early-life gut microbial diversity and elevated risks of eczema have been reported [57] [58]. A relatively diminished population of bacteria including *Ruminococcus* and *Proteobacteria* was associated with development of IgE-associated eczema [59] (Figure1). The colonization by *L. paracasei* decreased the risk of AD development [60].

Fungi are also part of the commensal flora in all body sites. Yeasts of the genus *Malassezia* in particular are associated with AD. Unlike healthy individuals, a high proportion of AD patients are sensitized to *Malassezia* spp. [34] (Figure1).

Airway microbiota influences bronchial asthma

The formation of the airway microbiota plays an important role in regulatory cells induction early in life [35]. During infancy an excessively "hygienic" environment decreases bacterial diversity in the airway, leading to increased susceptibility to allergic diseases [36].

The microbiota of asthmatic airways is often disturbed or altered [37] [38] and may modulate inflammatory processes in patients with severe BA and related phenotypes. A greater prevalence of *Proteobacteria* in the bacterial composition of the airway has been reported among patients with asthma. *Haemophilus* species were much more frequent in the bronchi of adult asthmatics [39], who also showed an increasing enrichment in *Klebsiella* spp. with increasing severity of the disease [40]. An altered upper airway microbiota characterized by lower microbial diversity and a preponderance of genus *Moraxella* was associated with asthma [41]. The presence of the *Comamonadaceae*, *Sphingomonadaceae*, and *Oxalobacteraceae*, in patients with BA correlated with bronchial hyper-responsiveness [42]. As well, the abundance of *Moraxella catarrhalis* or *Haemophilus* spp. correlated with severer pulmonary dysfunction and a higher sputum IL-8 concentration and neutrophil count [43].

Glucocorticoid (GC)-resistance is a major barrier in managing bronchial asthma [44] and requires a novel therapeutic strategy. GC responsiveness has been linked to the airway bacterial microbiome in the following manner [45]: altered airway microbiome composition stimulates airway cells, resulting in a reduced cellular response to GC. *Haemophilus parainfluenzae* and *Prevotella melaninogenica* inhibit GR-mediated mitogen-activated kinase phosphatase 1 (MKP-1) production, which dephosphorylates activated p38 mitogen-activated protein kinase via activation of transforming growth factor-β–associated kinase-1 (TAK1) and suppresses GR inhibition of NF-κB–induced IL-8 production in monocytes/macrophages [46]. Furthermore, pulmonary exposure to *Escherichia coli*, resulted in a protective effect against Th2-associated allergic responses [47].

Link between gut microbiota with AD and BA

The host' s disease is reflected by the composition of microorganisms inhabiting local sites, skin and lung. Disturbances in the microbiota result in an imbalanced immune system with consequent susceptibility to AD and BA (Figure 2). Signals from microbes can influence the cell-mediated immune system and allergies through phenotypic changes in Dendric cells (DCs), promoting regulatory T (Tregs), Th1, and natural killer (NK) cells, which inhibit Th2 inflammation [48]. Commensal-derived signals were found to influence basophil development by limiting proliferation of bone marrow-resident precursor populations, indicating that basophils are an important link between the gut microbiota and Th2 cytokine-dependent inflammation and allergic disease [49].

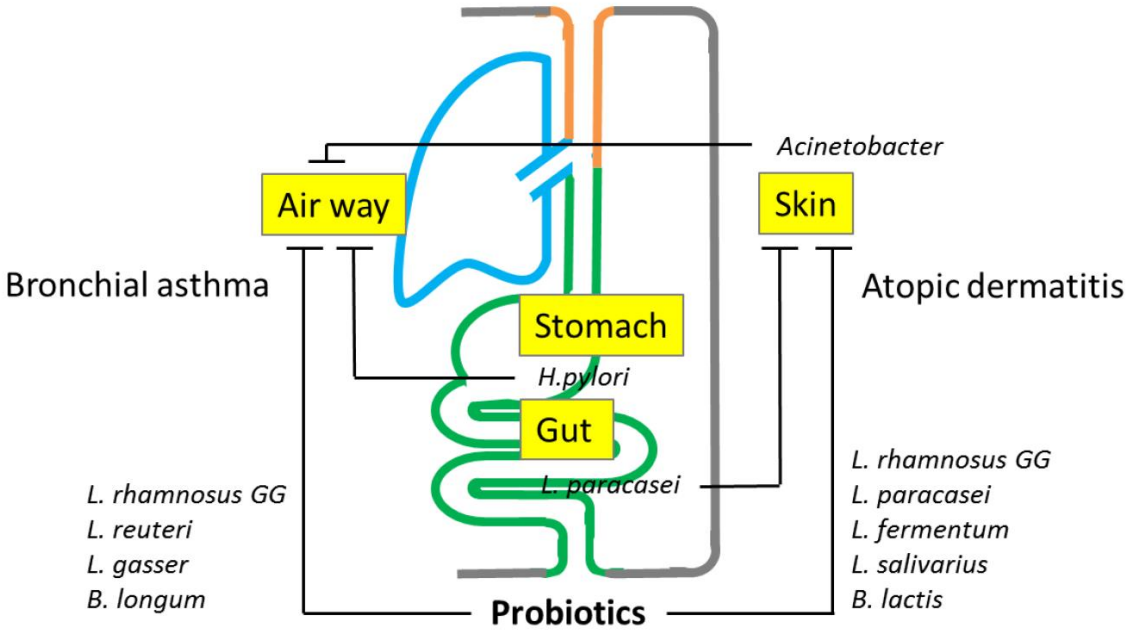

Figure 2 : 'Triangular Cross Talk' and disease suppression via organ microbiota interations

The host' s disease is reflected by the composition of microorganisms inhabiting local sites. Disturbances in the microbiota result in an imbalanced immune system with consequent susceptibility to AD and BA. The microbiota at local sites is also involved in the development and activity of diseases in remote organs via 'triangular cross talk'. Microbiota in the gut, skin and lungs can influence each other in the inception and progress of diseases.

Lactobacillus plantarum (L. plantarum) crosstalks to intestine DCs via its encypted pepide, which expands the production of regulatory IL-10 [50]. *Bacteroides fragilis* [51] and *Clostridium* strains [52] [53] can promote Treg activity to induce mucosal tolerance in the intestine. Responses to microbial components and products are key to protect indivisuals from developing allergic diseases. Bacterial polysaccharides activate CD4(+)Foxp3(-) T cells upon exposure in the gut and facilitate resistance to unnecessary inflammatory responses via the production of IL-10 [54]. Capsular polysaccharide A, produced on the surface of *Bacteroides fragilis*, promotes production of Th1 cytokines [55].

While direct airway microbiome manipulation influences airway immune responses, the gut microbiome has a demonstrable effect on the pathogenesis of BA similar to that seen in AD. Several studies using animal models have identified an association between alterations in the composition of gut bacterial communities and the development of BA. Germ-free mice exhibited an increase in airway eosinophils, Th2 cytokine production, IgE, and altered

numbers and phenotypes of DCs after sensitization with ovalbumin (OVA). Recolonization with complex commensal flora abolished the phenotype, suggesting that the presence of commensal bacteria was critical for allergic airway inflammation [61]. Mice infected neonatally with *Helicobacter pylori* demonstrated greater protection against asthma [62], supporting the "disappearing microbiota" hypothesis [63], which postulates that the loss or disappearance of our ancestral indigenous microflora, rather than a general decline in arbitrary childhood infections, is associated with asthma epidemics. Helminths promote remote, protective, antiviral effects in the lung through induction of a microbiota-dependent type I IFN response [65]. Fermentable dietary fiber and short-chain fatty acids (SCFAs), its metabolites, can shape the immunological environment in the lungs, suggesting that the metabolic product of intestinal microbiota may dampen allergic responses in the lungs [66].

Fungal and bacterial microbiota during the first 100 days of life is important in the development of atopic wheeze [67]. Gut fungi are involved in promoting allergic inflammations [68]. Colonization of mice by *Candida albicans* following broad-spectrum antibiotic therapy promoted the development of allergic airway disease [69] [70]. Recent high dietary intake of sugar and carbohydrates and frequent use of antibiotics may be associated with *Candida* overgrowth in the gut. Gut fungal overgrowth promotes allergic airway inflammation.by elevated plasma PGE2 that promoted M2 macrophage polarization [71]. The microbiota at local sites is also involved in the development and activity of diseases in remote organs via triangular cross talk.' Microbiota in the gut, skin and lungs can influence each other in the inception and progress of diseases (Figure 2). Further studies should be expected about the association between the function and microbiomes.

The effect of probiotics on allergic disorders

Bacteria-host interactions may bring about beneficial changes in immune responses. Probiotics, defined as live micro-organisms introduced into the body, promote the enrichment of regulatory dendritic cells (rDCs) and Tregs in areas of inflammation. An increase in $CD4^{+}Foxp3^{+}$ Tregs in the mesenteric lymph node (MLN) after administration of probiotics was observed in a murine model [72]. Probiotics also enhanced the secretion of interleukin (IL)-10 and Foxp3 expression in the peripheral blood of humans [73].

In mice, heat-treated *Lactobacillus rhamnosus* GG (L. GG) may be able to delay the onset and suppress the development of atopic dermatitis, probably through strong induction of IL-10 systemically, and in the intestinal lymphoid organs, in mice [74], and was effective in preventing early atopic disease in children with a high risk of AD development [75]. Administration of L. GG to infants with a high risk of atopy and/or their mothers appeared effective in preventing AD development [76].

A combination of *L. rhamnosus* and *Bifidobacteria lactis* improved AD in food-sensitized children [77]. Clinical improvement was reported in children with AD after they were given a mixture of *L. paracasei* and *L. fermentum* [78]. Probiotic *L fermentum* VRI-003 PCC is beneficial for improving the extent and severity of AD in young children with a moderate or severe form of the disease [79]. *L. salivarius* LS01 (DSM 22775) improved the quality of life of children affected by AD [80], and

its potential usefulness in treating adult patients with AD [81] has also been reported. A meta-analysis examined randomized (placebo) controlled trials (RCTs) investigating the efficacy of probiotics in the management and prevention of AD in comparison with a placebo [82] [83] [84] [85]. Currently available evidence does not indicate that probiotic supplementation reduces the risk of allergies developing in children. However, the WAO guideline panel has suggested conditional recommendations supported by very low quality evidence [86].

Probiotics have been proposed as a therapeutic agent for BA because it is known that the generation of Treg cells is one of the mechanisms by which probiotics suppress inflammation in asthma [87] [88].

In BALB/c mice pretreated with L.GG [87] [88] [89] [90], *Lactobacillus reuteri* (*L. reuteri*) [91] [92], *L. gasseri* [93], and *Bifidobacterium longum* [94] [95], attenuated asthmatic responses induced by allergen challenges have been reported, suggesting a preventative effect. However, the results of randomized controlled trials investigating the therapeutic effectiveness of probiotics in patients with BA are not yet available.

Conclusions

The skin, as the outer surface of the body, and the lungs and the gastrointestinal tract, which comprise the inner surfaces, are the predominant sites of microbial contact. Diversity of the commensal bacteria protects against AD and BA, and alterations in the microbiota of affected tissues and intestine influence the disease state. The influence of bacteria on diseases is age-sensitive, and their role varies among species and affected sites. Modulating the gut microbiota composition is a promising strategy for treating AD and BA. Unfortunately, the findings accumulated thus far are too variable to allow hard and fast conclusions to be drawn as to the effect of probiotic use in AD and BA.

Author contributions

Yukihiko Kato wrote the AD part and Yasuhiro Matsumura did BA part mainly.

Disclosure

All authors reports no conflicts of interest in this work.

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