



Diversity of intestinal microbiota in infancy and the risk of allergic disease in childhood

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Purpose of review

Numerous studies have attempted to describe specific microbiota deviations that may precede atopic sensitization and atopic disease in childhood. This has given rise to a hypothesis suggesting that a reduced intestinal microbial diversity in infancy increases the risk of allergic manifestations. This review intends to sum up the main findings and discuss relevant exposures that regulate intestinal microbial diversity.

Recent findings

Taken together the three studies in this review lend support to the diversity hypothesis, but reported differences related to atopic sensitization and clinical expression are discussed. A summary on analytic methods and functional aspect of the microbiota in allergic disease is presented to ameliorate a presentation of recent articles on environmental and host-factors regulating microbiota composition and diversity.

Summary

The current evidence indicates that intestinal microbiota diversity can be associated with allergic diseases, but the exact mechanisms and interactions contributing to this effect are far from understood and need further investigation.

Keywords

childhood, diversity, environment, host-factors

INTRODUCTION

The intestinal microbiota contains as many as 10^{14} microbial cells spanning more than 1000 different species. High-throughput molecular technologies have enabled researchers to investigate the complexity of this environment and the cross-talk that occurs between the host's immune system and the intestinal microbial community [1[•],2^{••},3]. Insight in the properties of the commensal microbiota, has demonstrated that intestinal microbial exposure is a protective factor against autoimmunity and allergy [4,5,6^{••}].

The initial microbiota consist of aerobes and facultative anaerobic microbes derived mainly from the birth canal and the surrounding environment [7]. Subsequent microbiota development depends on the mode of delivery, dietary factors and a variety of environmental exposures in interplay with the infant's genetic disposition [8,9]. Aberrant colonization has been associated with immunologic deviation in the host, disturbed immunologic tolerance [10[•]], and the pathogenesis of immune-related conditions such as Inflammatory bowel disease (IBD), diabetes, obesity, atopy, and allergic diseases [11,12[•],13,14].

Numerous studies [15,16[•]] have attempted to describe specific microbiota deviations in infancy and early childhood that may precede atopic sensitization and subsequent manifestation of atopic disease. Inconclusive and conflicting results have confirmed that there is no single microbial specie or small group of microbes, which may be perceived as the 'allergy-promoting microbes' [17–19]. However, these studies [6^{••},13,20^{••}] have given rise to a hypothesis suggesting that a reduced intestinal microbial diversity in infancy increases the risk of allergic manifestations in childhood.

This review provides a summary of the analytic methods for investigating microbial diversity, and presents an update on the function and diversity of

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KEY POINTS

- Recent findings support the hypothesis that reduced intestinal microbial diversity is associated with increased risk of atopic sensitization or allergic disease.
- Intestinal microbiota diversity is associated with environmental diversity and regulated by host immunity and host genetics.
- The exact mechanisms for the cross-talk between intestinal immune responses and systemic immunity is not well understood.

the human intestinal microbiota in development of allergic sensitization and disease. Finally, there is a review of the evidence for environmental and host factors which have the potential to modify intestinal microbiota composition and diversity.

METAGENOMIC AND HIGH-THROUGHPUT METHODS IN STUDIES OF MICROBIAL DIVERSITY

Broadly defined, metagenomics refers to the assessment of complex microbial communities using 'bulk' genetic information, that is, the total DNA isolated directly from the total community [21]. Initial characterization of microbial communities, such as the intestinal microbiota, tends to focus on the identification of the microbial species or group of species (taxa), which are present. The taxonomical diversity can be considered from two perspectives. Alpha-diversity describes the community from the inside, without comparison to others. It provides information on how many unique constituents there are (richness) and how these are distributed (evenness) in the microbial community [22]. Beta-diversity describes the diversity between communities, or, more pertinently to the intestinal microbiota, the stability of a given community over time [22].

The technological approaches to investigate the gut microbiota composition and diversity can generally be separated in targeted hypothesis-driven and nontargeted explorative approaches. Currently, the most widely used targeted approaches include quantitative PCR and microarrays. Quantitative PCR involves the simultaneous amplification and quantification of a genetic target [23]. The benefit of this technology is the simple application and the large dynamic range, whereas the disadvantage is that only a few targets can be investigated simultaneously. On the contrary, microarray analysis allows investigation of, up to several thousand targets [24].

The explorative approaches were introduced in the early 2000s using massive parallel sequencing [25], and the next-generation sequencing have been revolutionized by the development of pyrosequencing [26]. This technology allows relatively long read-lengths of about 500 nucleotides. In parallel with pyrosequencing, sequencing with reversible chain terminators was developed [27]. The benefit of this technology is that it is cheaper than pyrosequencing. The disadvantage is reduced specificity due to the relative short read-length of less than 250 nucleotides.

FUNCTIONAL ASPECTS OF THE MICROBIOTA IN HEALTH AND DISEASE

Knowing the taxonomical diversity of the community does not imply knowledge of its functional capacity. However, to understand the cross-talk between the host and gut microbes, it is crucial to be able to describe what functions the microbial community has. Generally, the neonatal gut is first colonized by aerobic or facultative anaerobic bacteria, such as *Enterobacteria*, *Enterococci*, and *Staphylococci*. When they consume oxygen, it enables proliferation of anaerobic bacteria like *Bifidobacteria*, *Clostridia* and *Bacteroides*. After the first 2 years of life, anaerobic and facultative anaerobic bacteria dominate the microbiota, and the complexity and the α -diversity increase towards an adult pattern [5,9]. The Human Microbiome Project (HMP) and Metagenomics of the Human Intestinal Tract (MetaHIT) are among the most extensive international initiatives aiming to describe and understand the composition and functional characteristics of the intestinal microbiota from infancy to adulthood in health and disease [2nd,3]. The HMP research team found wide variation in the diversity and abundance of microbes among healthy patients with a strong microbial site specialization within the gastrointestinal tract. All the same, there was a remarkable functional stability, suggesting that there are many ways a microbial community may perform similar functions [28th]. The MetaHIT team, on the contrary, found that the human gut microbiota was separated in three main assemblages, or so-called enterotypes that represent stable networks of interacting microbes [29].

A healthy gut microbiota represents a rich microbiota with a high α -diversity. The diversity, stability and resilience of the intestinal microbiota are essential for the complex immunologic development and maturation of the host's immune system [1st,30]. Dysbiosis, defined as disturbances in the intestinal microbiota, are associated with immunologic deviations, demonstrated in intestinal diseases

as IBD and colorectal cancer, and in systemic disorders as diabetes, metabolic syndrome and atopy [31,32].

THE INTESTINAL MICROBIOTA IN ALLERGIC DISEASE

The association between intestinal microbiota composition and allergic disease is well documented and generally accepted [6^{''},33^{''}]. An example is a reduced microbial diversity in infancy, characterized by fewer *Lactobacilli* and *Bifidobacteria* and increased colonization with *Staphylococcus aureus* and *Clostridium difficile*, associated with sensitization and allergic diseases in childhood [18,34^{''}]. Specific microbial-associated molecular patterns (MAMPs) on the surface of a variety of commensal microbes binds with pattern recognition receptors (PRRs) on intestinal dendritic cells [35]. An important group of PRRs is the Toll-like receptors (TLR) that recognize specific MAMPs, such as lipoteichoic acid (TLR2) and lipopolysaccharide (TLR4) on the commensal bacteria cell membrane [36]. TLR signalling initiate regulatory and effector functions involving dendritic cells, immature T-cells differentiating to Th1, Th2, Th17 or Treg cells, inducing cytokines and chemokines with the capacity to either induce CD4⁺ Th2-type allergic responses or promote Treg cell-induced tolerance to prevent allergic sensitization [37]. The composition and development of the microbiota are vital for the immune response outcome, and the diverse intestinal bacterial community interacts to shape the composition and genetic diversity of the microbiota [38^{''}]. There is increasing evidence that the intestinal microbiota also promote immune differentiation beyond the intestinal mucosa [39], although the exact mechanisms involved in the intestinal-systemic immunity cross-talk is not well understood [40^{''}].

DIVERSITY OF INTESTINAL MICROBIOTA AND ALLERGIC DISEASE

It is clear that the unique composition of every individual's microbiota is essential in establishing an immunological homeostasis in the host intestinal mucosa [41]. This together with the similarities in microbiota composition and diversity among individuals with immune-related diseases [34^{''},42^{''}] has shed new light on observations underlying the 'hygiene hypothesis' and have helped to clarify earlier inconsistencies regarding immunologic development and allergic disease [19,41]. The conception that microbiota diversity is associated with allergic diseases emerged a number of years ago. In a prospective case-control study [43] on atopic eczema in

infancy, microbiota diversity increased between the ages of 1 and 4 months only in controls. Similarly, a reduced diversity in faecal flora at 1 week postpartum was found among children diagnosed with eczema at 18 months [44]. Recent studies with access to improved characterization of microbiome composition and better indices for diversity have investigated this to a further extent. In the Danish COPSAC-study, Bisgaard *et al.* [34^{''}] followed a birth cohort of 411 high-risk children for 6 years by clinical assessments of allergic disease, allergic sensitization and microbiota composition analyzed with 16S rRNA PCR technique and conventional culturing. It was found that reduced bacterial diversity of the infant's intestinal flora was associated with increased risk of allergic sensitization, allergic rhinitis, and peripheral blood eosinophilia, but not asthma or atopic eczema. In a prospective study from Sweden, Abrahamsson *et al.* [20^{''}] described intestinal microbial composition and diversity in children from families with high risk of allergy, using barcoded 16S rRNA pyrosequencing in faecal samples at 1 week, 1 month and 12 months in 20 sensitized infants with atopic dermatitis and 20 control infants who had no sensitization or allergic disease up to 2 years of age. Among infants with atopic eczema, there was a lower diversity of the total microbiota and reduced levels of *Bacteriodes* genus and the Bacteriodes and Proteobacteria phyla. Among healthy children *Proteobacteria* and gram-negative bacteria were more abundant. In contrast to Bisgaard *et al.* [34^{''}], the results support the hypothesis that low microbial diversity early in life is associated with increased risk for atopic eczema.

In a study to compare the very early diversity of day-7 fecal microbiota in high-risk infants regarding atopic eczema and sensitization status during the first year of life, Ismail *et al.* [42^{''}] also found that infants with atopic eczema at 12 months of age had a reduced early microbial diversity. The diversity of the intestinal microbiota was not related to infant sensitization status or the allergic status of the parents. The fact that this study failed to demonstrate an association between diversity and atopic sensitization may be because sensitization status was only assessed at 12 months, when some of the children may not yet have been sensitized.

These results should be interpreted with some caution and are not necessarily valid for a 'normal-risk' population or for populations in other parts of the world. All three studies were performed in high-risk populations, in which maternal atopy was present for a majority of the children, and it cannot be excluded that the colonization pattern for these children differs from the general population based on genetic traits among the mothers transmitted to their offspring, and inflicting microbiota composition in

both mother and child [45,46]. It is also necessary to consider whether faecal samples are representative for colonic mucosal microbial exposure. Recent articles indicate that host regulatory mechanisms actively contribute to a stable and resilient mucosal microbiota and protect against pathogens and other undesirable microbes left for faecal elimination [47]. Nevertheless, the results taken together support the hypothesis that microbiota diversity is associated with IgE-mediated allergic disease. It is also evident that further investigations in this field need to be done in larger, population-based, prospective designs with exploration of new sampling techniques from mucosal and luminal microbiota from different parts of the gastrointestinal tract to come closer to an understanding of the essentials in host-microbiota-diversity cross-talk.

ENVIRONMENTAL FACTORS INFLUENCING DIVERSITY

Accumulating evidence from studies [40²²,41,48] in gnotobiotic mice and human patients suggests that perturbations of the commensal intestinal microbiota, for example by exposure to broad spectrum antibiotics, can predispose to immune deviations and development of systemic allergic diseases. Dietary interventions with probiotics to modify the microbiota, and thereby to induce beneficiary microbial activation of immune responses, have shown promising but also conflicting results [33²,49]. Even though several probiotic studies have shown promising results when it comes to a clinical effect on atopic eczema, there has generally been no effect on sensitization status or permanent effect on intestinal microbial diversity [50²²]. Finally, recent

investigations on the interaction between environmental biodiversity, immune development and allergic disease have suggested a rationale for the so-called ‘Farm-effect’, showing that atopic sensitization and allergy in childhood were associated with a relatively reduced environmental biodiversity in the children’s surroundings [51²,52]. If, and how, this exposure may influence the generally anaerobic intestinal microbial community remains to be investigated, but it is tempting to suggest that the very early microbiota with more aerobic and facultative bacteria are particularly receptive to environmental microbial exposure.

HOST FACTORS INFLUENCING DIVERSITY

The mucus protecting the intestinal mucosa contains IgA that binds with epitopes that are shared by many gut bacteria and trigger bacterial agglutination and clearance, thereby shaping the microbiota, particularly in the small intestines. The host mucosa also produces antimicrobial compounds (defensins, cathelicidins and lectins), which have the potential to change the composition of the luminal microbiota [53].

Environment and genetic polymorphisms in the host have been shown to modulate the intestinal colonic microbiota in experimental mouse studies [46,54²]. The colonization and homeostasis of the microbiota are regulated by host genetic makeup and depend on interactions between innate and adaptive immune mechanisms particularly in relation to PRRs [55²²]. Host genetic factors, mainly related to immunity, have been shown to have a measurable contribution to the diversity of the microbiota [45]. This implies that genetic

Table 1. What we know and what we do not know	
What we do know	What we do not know
A reduced intestinal microbial diversity in infancy increases the risk of allergic manifestations among high risk children in childhood	How important are the intestinal microbial diversity for normal immunologic development and for prevention of allergic disease in a ‘normal’ or low-risk population?
The diversity, stability and resilience of the intestinal microbiota are essential for the complex immunologic development and maturation of the host’s immune system	How can an intestinal dysbiosis be restored to a beneficiary, stable and resilient microbiota?
Environmental microbial diversity is associated with intestinal microbiota development and diversity	Is the composition of the intestinal microbiota cause or consequence of the host’s immune condition?
Genetic polymorphisms help shape the intestinal microbiota of mammals. There is evidence that the microbiome to some extent is actively selected by the host	To what extent is a host-specific microbiota critical for a normal immune system development?
	What are the exact mechanisms involved in the cross-talk between intestinal and systemic immunity?
	How can we ensure that microbial samples from the gastrointestinal tract are representative of intestinal microbial colonization?

differences between hosts can contribute to observed differences in microbiota composition. Recent findings suggest that a host-specific microbiota is critical for a healthy immune system, and that only certain host-specific commensals give rise to a mature intestinal immune system in mice. Germ-free mice inoculated with commensal microbiota from humans, rats and mice only develop normal immune responses with a mice-specific microbiota [56[■], 57[■]], suggesting that the fitness of the host also can be an important contributing factor to diversity.

CONCLUSION

The current evidence indicates that intestinal microbiota diversity can be associated with allergic diseases, but the exact mechanisms and interactions contributing to this effect are far from understood. The task of revealing the complexity and diversity of the human microbiome and how environmental and host factors together modify immune system development and maturation in health and disease is immensely challenging (Table 1).

To revisit the Hygiene hypothesis, recent evidence on the impact of the human microbiota diversity and the interplay with environmental microbial exposure has shifted the attention from 'hygiene' to the diversity of the microbial world we live with and within us. A number of exposures are leading to a loss of microbial diversity, like diet, birth, and maternity routines, antibiotics and reduced environmental microbial diversity. Accumulating evidence indicate that we are genetically equipped to design, at least to some extent, a beneficiary intestinal microbiota to ensure a homeostatic and tolerogenic immune system functionality. Evolution over millennia has made us able to, and maybe even dependent on, a coexistence with a vast diversity of microbial life-forms to develop a healthy immune system to cope with life through health and disease. In westernized societies, a deprived microbial exposure throughout life may represent a pathogenic factor for immune and inflammatory conditions. Further research to reveal the enormous complexity of mechanisms and interactions regarding intestinal microbiota diversity and the interplay between humans and their microbial partners may provide future strategies to cope with the epidemic of immune disorders, including allergic disease.

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Conflicts of interest

There are no conflicts of interest.

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