Special Issue: Interaction between gut microbiota and host immune cells

Mini Review

Interaction between gut microbiota and host immune cells

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The intestine, skin, and respiratory tract harbor pools of commensal microbes, known as microbiota. Over the last few years, the field of mucosal immunology has revealed that the microbiota play important roles in the host immune system. Here, we have summarized recent studies regarding the interaction between microbiota and the mucosal immune systems in health and diseases. The application of 16S rRNA PCR and new sequencing technology have enabled us to understand the composition of intestinal microbiota. Here, we specifically assess their contribution to obesity and cancer (chronic inflammatory conditions) as well as to inflammatory autoimmune diseases (e.g., inflammatory bowel disease and type 1 diabetes) and allergic syndromes. Optimization of the microbiota composition has been attempted via the intake of probiotic bacteria in various fermented foods and via fecal microbiota transplantation (FMT) from healthy donors to patients with *Clostridium difficile*-induced colitis. The presence of certain microbiota species affects the development and function of various types of immune cells, such as regulatory T (Treg) cells and interleukin-17-producing helper T (Th17) cells. Furthermore, innate lymphoid cells (ILCs) have also been shown to be regulated by microbiota. These findings indicate that manipulation of the microbiota could improve health and chronic diseases via immune regulation.

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Development of microbiota

The surface of the human body, including the respiratory and gastrointestinal (GI) tracts, is populated with complex communities of microorganisms, termed microbiota, with the highest density of colonization (>10^{12} organisms/cm^2) found in the GI tract[1)]. The vast majority of these organisms have not been cultivated as they are anaerobic bacteria, which require complicated techniques for phenotypic profiling and

application[2, 3]. Recent advances in culturing techniques, however, have allowed the retrieval of hundreds of bacterial species from human stool samples[4].

Over the past few decades, researchers have attempted to determine the number and phylogeny of microbiota species by analyzing the well-conserved 16S rRNA genes[5, 6] using hybridizing probes[7]. A broad comparison of microbial communities has also been facilitated by the use of real-time PCR with primers specific to 16S rRNA sequences[8]. Although these findings may have underestimated the microbial diversity in the microbiome, they have also promoted investigation into the factors affecting microbiota composition[9]. 16s rRNA gene sequencing technology, especially the cloning method, has allowed the identification of organisms at strain level and has revealed significant differences in the microbiomes of lean and obese individuals[10] as well as a great deal of information about the evolution of the microbiome during development[11]. Recent advances in high throughput sequencing of genomic libraries made from mixed samples, termed metagenomics, have facilitated investigation of the complexity of microbiota communities and clarified the contribution of changes in this composition (dysbiosis) to many complex diseases, including obesity, cancer, autoimmune, and allergic diseases[12, 13]. In addition, the use of probiotics in preventive medicine and the use of fecal microbiota transplant (FMT) for pathogenic bacterial infections are well documented.

It has been shown that the main microbiota populations stabilize during the first year of life but continue to develop throughout life(1). The initial colonies comprise facultative anaerobes, which are soon overwhelmed by the establishment of anaerobic bacteria, including *Bacteroides* and *Clostridium* species[14]. By 3 years of age, the gut microbiota has attained a composition and diversity similar to that seen in adulthood, and from that point it remains stable throughout life[15], although diet and antibiotic medication can have strong effects on the microbiota[16, 17].

Relationship between microbiota and diseases (Fig. 1)

1)Obesity

Comparisons of gut microbiota from mice and humans have revealed an intriguing association between obesity and changes in the relative abundance of the two dominant bacterial divisions, viz., Bacteroidetes and Firmicutes. Obese humans and mice had a lower proportion of Bacteroidetes than of Firmicutes, which increased their energy harvest from fiber fermentation[18-20]. Although an imbalance between energy intake and output is critical in weight gain, alterations in the composition of the microbiota can also contribute to fat storage in the microenvironment. Obesity-associated diseases and their risk factors (metabolic syndrome) are closely linked to inflammation; accordingly, the term “meta-inflammation” has been proposed to refer to a chronic low-grade inflammatory response to obesity[21]. This inflammatory response may be triggered by the leakage of lipopolysaccharide (LPS) through the intestinal barrier into the body from gram-negative bacteria in the GI[22]. Dysbiosis-induced chronic inflammation has also been implicated in cancer (e.g., colorectal cancer), type 2 diabetes (T2D), and atherosclerosis[23, 24].

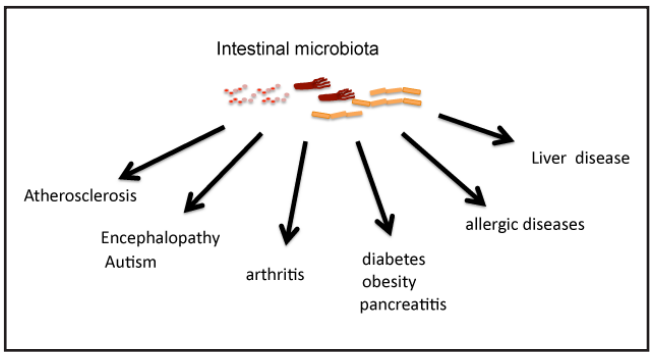

Fig. 1 Association of microbiota with diseases outside of the gastrointestinal tract

The intestinal microbiota may be lined to various diseases in remote organ systems. Increased intestinal Th1 and Th17 cells by microbiota may enhance the expansion of pathogenic autoantigen-specific T cells that promote autoimmune diseases including rheumatoid arthritis (RA), T1D and multiple sclerosis (MS). Development of Th1, Th17, ILC1 and ILC3 in the gut may de dependent on microbiota, and these are included in the suppression of Th2 type allergic diseases including food allergy. Balance in the microbial community also determines susceptibility to metabolic syndrome including T2D and obesity. Recent reports suggest a relationship between mental dieses and microbiota. By contrast, 'beneficial' commensal bacteria can attenuate CNS inflammation through the induction of Treg cells.

2)Autoimmune disease

Inflammatory bowel disease (IBD) is thought to involve aberrant host immune responses to the microbiota, since antibiotic treatment for IBD has met with some success in both humans and a mouse model, and since bacteria are known to be present in the inflammatory lesions of the IBD colon[25]. IBD is an example of an immune disorder, comprising impaired barrier function and innate immune

response, that could be understood as being bidirectionally related to dysbiosis[26].

Type 1 diabetes mellitus (T1D) is a consequence of selective destruction of pancreatic beta cells in the islets of Langerhans. Autoimmune reaction against beta cells may arise from immune activation due to environmental epitope mimicry. Recently, inadequately developed regulatory immune responses were proposed to play a role in T1D, as they do in other autoimmune diseases. In an experimental model, germ-free[27] mice exhibited a high incidence of T1D, while mice given antibiotic treatments exhibited a reduced incidence of T1D[28-30]. Because of the long lag period between the induction phase and the clinical onset of T1D, it is difficult to evaluate the role of microbiota throughout the disease course from pre-symptomatic to terminal status. Similarly, in rheumatoid arthritis models, GF mice and rats showed reduced clinical and autoimmune markers[31, 32].

3)Allergy

In recent years, the worldwide prevalence of allergic disease has increased, particularly in economically developed countries. The hygiene hypothesis posits that excessively hygienic conditions limit the number of natural infectious stimuli from the environment, disturbing the homeostasis of immune cells, particularly that of regulatory T cells[33, 34]. Several epidemiological studies have shown that exposure to not only pathogenic but also commensal stimuli is inversely correlated with the incidence of allergic disease[35, 36]. It is noteworthy that the most important differences between patients appear in the first month of life, indicating that early maturation of the immune system due to the presence of the appropriate microbiota might regulate the patient's subsequent susceptibility to allergy.

4)FMT

Transient treatment with antibiotics alters the microbiota composition, providing a niche for pathogenic bacteria. In the case of *Clostridium difficile* infection (CDI), additional treatment with antibiotics to correct the dysbiosis counter-intuitively results in further damage to the microbiota and exaggerates the dysbiosis[37, 38]. FMT is the most widely and effectively used therapy for CDI[39]. Unlike probiotics, FMT can introduce a complete, stable, and durable microbiota composition from a healthy donor to a patient[40, 41]. Therefore, it is to be expected that FMT would be useful in treating IBD patients; indeed, in IBD patients with CDI co-infection, colitis symptoms were improved successfully with this approach[42, 43].

To date, studies examining changes in the microbiota composition in connection with various inflammatory diseases have tended to assess the correlations between such changes and disease risk rather than disease status or progression. To facilitate disease prediction, the interactions between alterations in the microbiota and immune development will need to be elucidated.

Immune cell regulation by microbiota

1)Intestinal Th17 and Treg cells

Recent studies of gnotobiotic mice reconstituted with refined microbiota have allowed the identification of commensal species with specific immune functions. Treg and Th17 cells are required for immune suppression and for host defense against pathogenic microbes, respectively. These cells are severely reduced in GF animals, but are quickly restored by transplantation of *Clostridium* species, *Bacteroides fragilis*, and segmented filamentous bacteria (SFB)[44-48]. The mechanism by which SFB mediates protection through stimulating Th17 generation remains to be established; nevertheless, SFB are currently the only known commensal species.

2)Short chain fatty acids

Tregs expressing the transcription factor FoxP3 are maintained by microbiota-derived products via epigenomic modification. The main products of the fermentation of non-digestible dietary components in the gut are short chain fatty acids (SCFAs). SCFAs can be incorporated by intestinal epithelial cells or diffuse into the lamina propria[49, 50] and can regulate inflammation-related G-protein coupled receptors through dependent and independent pathways[51, 52]. The most abundant SCFAs in the intestinal lumen are butyrate, propionate, and acetate, which are decreased in the intestine of GF animals[53]. SCFAs strongly inhibit histone deacetylase (HDAC) *in vitro*, which means that studies of HDAC must be performed in intestinal immune cells[54, 55]. Tregs express Foxp3 stably or unstably depending on CD25 expression levels. Recent studies have revealed that histone H3 acetylation at specific loci of Foxp3 and acetylation of Foxp3 by butyrate are important for the stability of Foxp3 expression[56-58].

3)DNA methylation

GF mice colonized with *Clostridium* strains also up-regulate a DNA-methylation adaptor, ubiquitin-like with

PHD and ring finger domains 1 (Uhrf1), in intestinal Treg cells[59]. Uhrf1 regulates the proliferation of Treg cells, which is required for the spontaneous suppression of colitis, via epigenetic mechanisms. In contrast, invariant NKT cells accumulate in the large intestine via elevated expression of the chemokine ligand CXCL16 in the colon under GF conditions[60]. *Cxcl16* contains five potential CpG sites, which are hypermethylated in the gene in the colon under GF conditions; this regulates *Cxcl16* expression in response to environmental factors. Currently, the mechanism by which this epigenetic regulation occurs at certain loci or molecules is of great interest.

4)IL-10 and TGF-β

The probiotic *Clostridium* strain *CB* has been used to treat various human gastrointestinal diseases in clinical settings. *CB* has been used as a probiotic in clinical practice[61], and we have demonstrated that administration of *CB* prevents experimental colitis via an IL-10-dependent mechanism[62]. In a DSS-induced colitis model, IL-10 is mainly produced by F4/80$^+$CD11b$^+$CD11c^{int} intestinal macrophages, but not by CD4$^+$ Tregs. However, we have shown that depletion of Tregs by anti-CD25 antibody overrides the protective effect of *CB*, raising a possibility that *CB* affects not only macrophages but also Tregs[62]. We demonstrated that *CB* induces iTregs in the large intestine. This is consistent with recent reports showing a preferential induction of Tregs by murine and human *Clostridium* species[45, 63]. However, it is still unclear why particular *Clostridium* species specifically enhance iTregs. Atarashi et al. showed that *Clostridium* species induce TGF-β from epithelial cells[45, 63]. Although TGF-β is produced by a large variety of cells in the intestinal mucosa, including intestinal epithelial cells, lymphocytes, macrophages and dendritic cells (DCs), the source of the TGF-β that contributes to iTreg generation in the intestine has not been determined. Although it is not clear where iTregs are developed, CD103$^+$ DCs in the intestine are now widely believed to induce iTregs by providing the antigens RA and TGF-β. Recently, we demonstrated that the probiotic bacterial strain *CB* promotes iTreg generation by inducing large amounts of TGF-β from DCs both *in vivo* and *in vitro*. Induction of TGF-β is TLR2-dependent, and the ERK-AP1 pathway plays an important role in TGF-β promoter activation. We have also identified an autoinduction mechanism of TGF-β production in which the TGF-β-Smad3 pathway directly activates the *Tgfb1* promoter.

Role of ILC2 in allergic diseases and its regulation by microbiota

Intestinal microflora has been implicated in regulation of allergies evoked by type 2 immunity. Th2 cells have been characterized as producers of the cardinal cytokines IL-4, IL-5, and IL-13[64], although the recent discovery of innate lymphoid cells (ILCs) raises the possibility of their involvement as innate sources of type 2 cytokines. Group 2 ILC (ILC2)[65, 66] produces IL-5 and IL-13 in a process that is dependent on RORα and GATA3, but not on RORγt. ILC2 cells are negative for lineage markers, but express c-Kit (CD117), Sca-1, KLRG1, ST2 (IL-33 receptor), Thy-1 (CD90), and IL-7Rα (CD127). ILC2s produce cytokines in response to IL-25 and IL-33, and are involved in the induction of goblet cell hyperplasia and eosinophilia as well as protection against helminth infections[27, 65, 67, 68]. Lung-resident ILC2 has also been shown to contribute to airway hyper-reactivity induced by virus or allergen challenge[67, 69-73]. A recent study also demonstrated that ILC2 plays an important role in atopic dermatitis as a source of IL-5 and IL-13 in mice and humans[74]. Thus not only Th2 cells but also ILC2s play a role in food allergy, although the relationship between ILC2 and intestinal microbiota has not been established. Recently, we demonstrated that intestinal

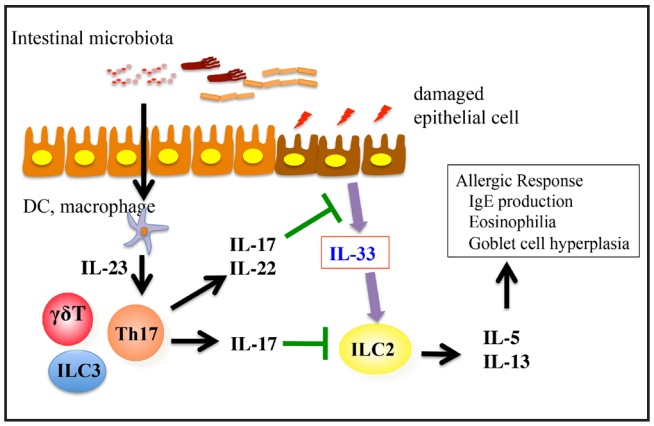

Fig. 2 How intestinal microbiota and its cytokine network regulate food allergic response

Lack of microbiota in intestinal mucosa resulted decrease of Il-17/IL-23 axis. In turn, IL-33 secretion from epithelial cell was augmented by damage such as, toxin or mechanical stress since IL-17 and IL-22 contribute to protection of epithelial cell. IL-33 upregulation enhance ILC2 accumulation and IL-5/IL-13 production together with GATA3 expression in mucosa. Finally, susceptibility to allergic response was augmented, however IL-17 could suppress IL-5/IL-13 production from ILC2 through inhibiting GATA3 expression.

microflora play a protective role in the food allergy model by inducing Th17-type cytokines, which suppress ILC2 activation. Both germ-free[27] and antibiotic-treated (Abx) mice were susceptible to food allergy, and lamina propria cells of these mice produced smaller amounts of IL-17 and IL-23 but larger amounts of IL-5 and IL-13 compared to mice with conventional microbiota. In the food allergy model, IL-5 and IL-13 are mostly produced by ILC2, which are dependent on IL-33. IL-17 and IL-22, which reduce food allergy, are produced by Th17 cells, which are stimulated by intestinal microbiota. IL-17 suppresses cytokine production from isolated ILC2, and IL-17 and IL-22 inhibit IL-33 release from epithelial cells. We propose that the presence of commensal bacteria down-regulates food allergy by suppressing IL-33 release as well as ILC2 activation through the development of intestinal Th17 cells (Fig. 2).

Conclusion

Taken together, the results of metagenomic studies and molecular-based evidence from experimental models will provide more detail about the relationships between the host and microbiota, which could improve our understanding of immune and metabolic homeostasis.

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None

Conflict of interests

None

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