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Alterations in Gut Microbiota and Immunity by Dietary Fat

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Gut microbiota play critical physiological roles in energy extraction from the intestine and in the control of systemic immunity, as well as local intestinal immunity. Disturbance of gut microbiota leads to the development of several diseases, such as colitis, inflammatory bowel diseases, metabolic disorders, cancer, etc. From a metabolic point of view, the gut is a large metabolic organ and one of the first to come into contact with dietary fats. Interestingly, excessive dietary fat has been incriminated as a primary culprit of metabolic syndrome and obesity. After intake of high-fat diet or Western diet, extensive changes in gut microbiota have been observed, which may be an underlying cause of alterations in whole body metabolism and nutrient homeostasis. Here, we summarize recent data on changes in the gut microbiota and immunity associated with dietary fat, as well as their relationships with the pathogenesis of metabolic syndrome. These findings may provide insight into the understanding of the complex pathophysiology related to the development of metabolic diseases and offer an opportunity to develop novel candidates for therapeutic agents.

Key Words: Gut microbiota, gut immunity, obesity, diabetes

INTRODUCTION

With greater industrialization, people have shown stronger preferences for Western-style diets of high fat content than traditional diets. This change in dietary preferences has contributed to a dramatic increase in metabolic diseases, such as obesity and type 2 diabetes, over the last decade, and these diseases now are a significant threat to the public health.[1] In obesity and type 2 diabetes, inflammatory cells infiltrate adipose tissues, the liver, and pancreatic islets leading to the production of proinflammatory cytokines and chemokines; these metabolic diseases are now considered as chronic low-grade inflammatory diseases. Metabolic inflammation consequently causes insulin resistance, contributing to the development of metabolic syndrome.[2] However, the underlying mechanisms of low-grade tissue inflammation inducing metabolic symptoms have still not been clearly elucidated. Recently, a modest increase in plasma contents of lipopolysaccharide (LPS) has been incriminated as an etiological event causing metabolic inflammation. The gut microbiota are a strong candidate as sources of the noted increases in plasma LPS.[3] In this regard, gut microbiota seem to influence systemic immunity and local intestinal immunity. Moreover, gut microbiota are changed by obesity, which is followed by the altered intestinal immunity, contributing substantially to the pathogenesis of metabolic diseases. In this review, we summarize recent findings on changes in gut microbiota and intestinal immunity in association with diet-induced obesity and insulin resistance.

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CHANGES IN GUT MICROBIOTA ASSOCIATED WITH METABOLIC SYNDROME

How does intestinal microbiota influence obesity and diabetes?

The gut microbiota in humans consist of 10–100 trillion microorganisms and outnumber all somatic and germ cells by 10,[4]

although it has recently been claimed that such number could be an overestimation. Further, the collective genomes of the gut microbiome contain 100-fold more genes than our own genome.[5] Gut microbiota have coevolved with humans, eliciting profound effects on various physiological processes, such as nutrient metabolism and immunity. For instance, dietary fibers that the human host cannot digest are metabolized by gut microbiota into short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate. SCFAs act through G protein-coupled receptors GPR41 and GPR43 expressed in enteroendocrine cells, enteric neurons, and enteric leukocytes.[6] Butyrate and propionate activate intestinal gluconeogenesis and exert beneficial effects on glucose and energy homeostasis: butyrate activates gluconeogenesis gene expression in a cAMP-dependent manner, whereas propionate does it through gut-brain neural circuits.[7] Intestinal gluconeogenesis elicits beneficial effects on systemic glucose profiles through portal vein glucose sensors transmitting the signal to the brain.[8] Butyrate also enhances gut barrier function and can protect enterocytes from injury or colitis,[9] which might be related to the role of butyrate as a histone deacetylator inhibitor.[10,11] On the immunological aspect, butyrate can promote Treg cell generation in the intestine.[12] Acetate has anti-inflammatory activity against colitis and arthritis.[13] Meanwhile, however, acetate may also increase glucose-stimulated insulin secretion and ghrelin secretion via parasympathetic activation, leading to increased food intake and obesity.[14] In addition to these effects, SCFAs can contribute to improvement of metabolic syndrome by promoting secretions of peptide hormones, such as peptide YY and glucagon-like peptide-1, that decrease appetite and increase insulin release, respectively (Fig. 1).[15]

Recently, many studies have shown that change in the gut microbiota is related to the development of obesity and diabetes: germ-free (GF) mice are resistant to high-fat diet (HFD)-induced obesity and glucose intolerance due to de-repressed expression of fasting-induced adipose factor (Fiaf) in the intestinal epithelium.[16,17] Fiaf, which prevents fat storage in adipocytes via inhibition of lipoprotein lipase and is also called angiopoietin-like protein 4 (Angptl4), is suppressed by gut microbiota. Interestingly, transfer of gut microbiota from obese mice to recipient GF mice significantly increased body fat content and insulin resistance, compared to the transfer of gut microbiota from lean mice.[18,19] These results suggest a crucial role of gut microbiota in nutrient homeostasis and also a possible etiological role of altered gut microbiota in the development of metabolic syndrome.

Phylum level changes and enterotype

To investigate the role of microbiota in nutrient uptake or in the development of metabolic syndrome, identification of individual microorganism is crucial. However, identification of gut microbiota has been extremely difficult since they are largely recalcitrant to *in vitro* culture. This technical obstacle can now be overcome with the advent of a revolutionary method of microorganism identification, sequencing of 16s rRNA genes that are ubiquitous and highly conserved among microorganisms.[20] Combined with next-generation sequencing technology, 16s rRNA gene sequencing allows the identification of enormous complexity of enteric bacteria.

In the intestines of mouse and humans, >90% of bacterial species are composed of *Bacteroidetes* and *Firmicutes* phyla, while *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* constitute relatively minor proportions. Compared with their lean counterparts, leptin-deficient *ob/ob* mice have a decreased abundance of *Bacteroidetes* and a correspondingly increased abundance of *Firmicutes*.[21] Further studies have confirmed similar changes in mice with diet-induced obesity, a more physiological model of obesity than *ob/ob* mice, while overall diversity among *Firmicutes* is different from that of *ob/ob* mice.[18] Similar changes in gut microbiota have also been observed in humans.[19] Furthermore, there seems to be a causality between changes in gut microbiota and obesity, since transfer of gut microbiota from obese mice to recipient GF mice promotes fat deposition.[18] The mechanism of increased *Firmicutes* abundance in obesity might be related to an enrichment of homoacetogens belonging to *Firmicutes* in obesity, which facilitates disposal of H2 produced by anaerobic bacteria during fermentation of nutrients.[22] Among *Bacteroidetes*, a role for *Bacteroides thetaiotaomicron*, a glutamate-fermenting bacteria, in obesity was addressed in a recent study. Administration of *Bacteroides thetaiotaomicron*, the abundance of which was reduced in mice fed HFD, lowered fat mass and metabolic inflammation, which was associated decreased serum concentrations of glutamate and branched-chain amino acids.[23]

Although it has been generally accepted that the abundance of *Bacteroidetes* is decreased and that of *Firmicutes* are increased in obesity, it does not necessarily mean that the abundances of all bacteria belonging to *Firmicutes* phylum increase and those of all bacteria belonging to *Bacteroidetes* phylum decrease. Instead, at the genus level, the abundance of Gram-positive *Lactobacillus* belonging to *Firmicutes* phylum decreases and the abundances of Gram-negative *Bacteroides* and *Prevotella* belonging to *Bacteroidetes* phylum increase.[24] Given that a major component of the outer membrane of Gram-negative bacteria is endotoxin or LPS, an increased abundance of Gram-negative *Bacteroides* and *Prevotella* may be linked to endotoxemia-induced metabolic inflammation.

It has also been reported that patients with diabetes have a reduced abundance of butyrate-producing *Clostridiales* belonging to *Firmicutes* (*Roseburia* and *Faecalibacterium prauznitzii*) and an increased abundance of non-butyrate-producing *Clostridiales*, suggesting differential regulation of the same *Clostridiales*, depending on the production of SCFAs.[25,26] *Faecalibacterium prauznitzii* produces not only butyrate but also microbial anti-inflammatory molecules that can affect gut inflammation.[27] Besides microbiota belonging to *Bacteroidetes*

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and *Firmicutes* phyla, abundance of *Proteobacteria* phylum has also been reported to be increased by HFD.[28] Since *Proteobacteria* are Gram-negative bacteria, their increase may be related to endotoxemia-induced metabolic inflammation.

Gut microbiota is also important in the digestion of dietary fiber, which can modulate diverse aspects of gut immunity and metabolism. Dietary fiber-induced improvement of glucose profiles has been shown to be associated with an increased abundance of *Prevotella* species, such as *P. copri*, a Gram-negative bacteria belonging to *Bacteroidetes* phylum.[29] Indeed, *Prevotella* has been reported to reflect long-term intake of carbohydrates, while *Bacteroides* reflects that of animal fat, among three bacteria characterizing enterotypes (*Prevotella*, *Bacteroides*, and *Ruminococcus*).[30]

These changes in microbiota composition in obesity may be able to work as early diagnostic markers in the clinic to better identify obese subjects who are prone to develop diabetes, and could be also novel therapeutic targets in the manage-

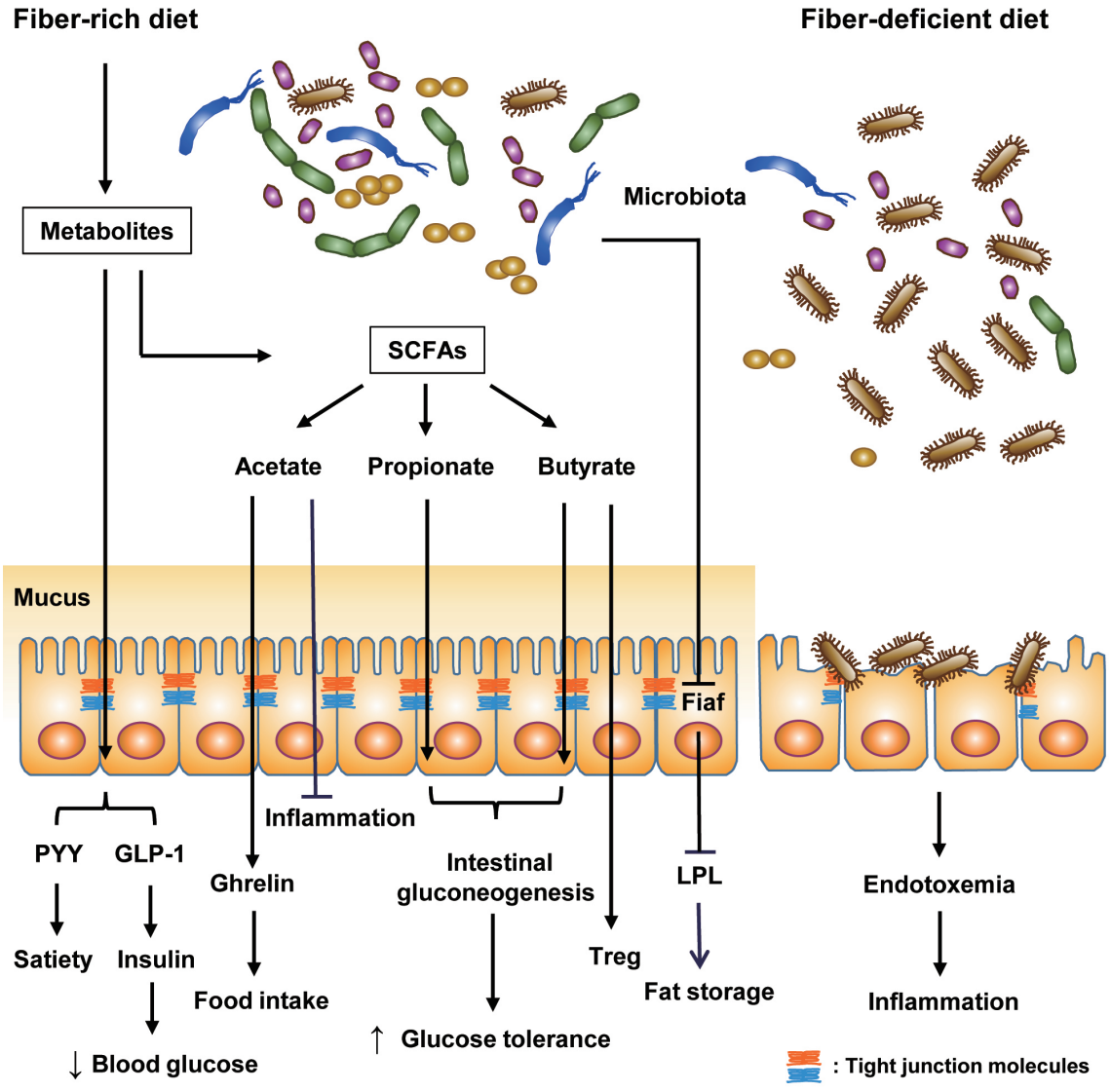

Fig. 1. Regulation of host metabolism and immunity by gut microbiota. Under a fiber-rich diet, gut microbiota metabolize undigested dietary fiber into SCFAs (acetate, propionate, and butyrate), affecting host metabolism and immunity. Microbial metabolites from this process improve host metabolism. In particular, the secretion of peptide hormones, such as PYY and GLP-1, is promoted by microbial metabolites: PYY decreases appetite and GLP-1 lowers blood glucose level via promotion of insulin secretion. Among SCFAs, butyrate and propionate activate intestinal gluconeogenesis and improve systemic glucose profiles. Meanwhile, acetate promotes secretion of ghrelin, a hunger hormone, and increases food intake, consequently causing hyperphagia and obesity. Nevertheless, acetate has anti-inflammatory function like butyrate. Butyrate enhances gut barrier function of intestinal epithelial cells and increases regulatory T (Treg) cells. In addition, gut microbiota suppress expression of fasting-induced adipose factor (Fiaf), an inhibitor of LPL, promoting fat storage in adipocytes. Under fiber-deficient diet, mucus-degrading bacteria expand and impair the integrity of the mucus layer. Thereby, endotoxemia-induced metabolic inflammation ensues. SCFAs, short-chain fatty acids; PYY, peptide YY; GLP-1, glucagon-like peptide-1; LPL, lipoprotein lipase.

ment of obesity or diabetes.

Changes in *Akkermansia* in metabolic syndrome

One of the prominent changes in gut microbiota associated with metabolic syndrome is that of *Akkermansia muciniphila*. *Akkermansia muciniphila* has recently been identified as a Gram-negative bacteria with mucolytic activity and the most abundant species of the *Verrucomicrobia* phylum. An abundance of *Akkermansia* muciniphila has been shown to be inversely correlated with body weight and reduced by HFD.[31,32] Fish oil consumption has been found to increase the abundance of *Akkermansia*, which is associated with metabolic improvement.[33] These results suggest that decreased abundance of *Akkermansia* may contribute to the metabolic deteriorations associated with HFD. Nevertheless, there is also a report that an abundance of *Akkermansia* increases in patients with diabetes,[26] which might be related to patient selection, such as inclusion of patients under treatment with antidiabetic medicines affecting gut microbiota. Changes in *Akkermansia* abundance associated with HFD are opposite those in *Bilophila wadsworthia*,[34] which is increased by milk-derived saturated fat and can aggravate colitis.[35] The abundance of *Akkermansia* is decreased in older adults, although the significance of this finding is unclear.[36]

The *in vivo* effect of *Akkermansia* on systemic metabolism was demonstrated by oral administration of *Akkermansia* to mice with diet-induced obesity. *Akkermansia* administration improves glucose profiles and insulin sensitivity.[37,38] Although the underlying mechanisms of the beneficial metabolic effects of *Akkermansia* are unclear, *Akkermansia* seems to decrease metabolic inflammation through Treg cell induction in adipose tissue.[34,38] In addition to the indirect effect of *Akkermansia* on systemic metabolism through regulation of the immune system, *Akkermansia* may directly affect metabolic processes. The abundance of *Akkermansia* is reduced after prolonged cold exposure. Furthermore, adaptive changes maximizing caloric uptake, such as increased intestinal villi length during cold exposure, are attenuated by *Akkermansia* transfer, suggesting negative energy balance by *Akkermansia*.[39] *Akkermansia* abundance is also correlated with the gene expression of fatty acid oxidation and fat browning.[34]

The beneficial metabolic effect of *Akkermansia* was also demonstrated in other experimental systems. For instance, the abundance of *Akkermansia* is increased in animals with gastric bypass showing reduced body weight, and is positively correlated with metabolic improvement after calorie restriction in experimental animals.[40,41] Additionally, *Akkermansia* has a protective effect against the development of atherosclerosis.[42]

The metabolic action of metformin, the first-line anti-diabetic therapy recommended by the American Diabetes Association and the European Association for the Study of Diabetes, also appears to be related to changes in gut microbiota. Metformin administration increases the abundance of *Akkermansia*, which is accompanied by an increase in mucin-producing goblet cells. Moreover, administration of metformin ameliorates metabolic inflammation and restores Treg cells in adipose tissue, similar to the effect of *Akkermansia* administration.[38,43] In a previous study, metformin action on gut microbiota of HFD-fed mice is analogous to the metformin action on gut microbiota of *Caenorhabditis elegans*, which results in alteration of folate and the methionine metabolism of *E. coli* in the intestine of the worm.[44] Intriguingly, metformin administration greatly increases the abundance of *Akkermansia* in patients with type 2 diabetes as well.[45,46]

While these results suggest potential therapeutic value of *Akkermansia* or its components as a drug candidate against metabolic syndrome, such prospects have been hampered by the sensitivity of *Akkermansia* to oxygen, the presence of animal-derived compounds in its growth medium, and the absence of metabolic effects of killed bacteria.[37,38] However, a recent paper showed that *Akkermansia* can be cultured successfully in a synthetic medium, which contains no compounds that are incompatible with human administration, and also that the pasteurized *Akkermansia* has stronger effects than live bacterium. Furthermore, Amun_1100, active component of *Akkermansia* that is resistant to pasteurization was identified, brightening the prospect for the development of novel therapeutics against metabolic syndrome and diabetes.[47]

CHANGES IN INNATE IMMUNITY OF THE INTESTINE IN METABOLIC SYNDROME

Role of gut innate immune receptors in metabolic syndrome

Several recent studies have suggested that disruption of the gut barrier function and the gut microbiota-derived LPS could contribute to the pathogenesis of metabolic syndrome and diabetes. HFD increases gut permeability and reduces the expression of tight junction proteins, such as occludin, in gut epithelium.[48] Gut barrier disruption in HFD-fed mice increases gut permeability, resulting in the passage of LPS into the systemic circulation and low-grade metabolic inflammation.[3,24] Consistent with these data, toll-like receptor 4 (TLR4)-knockout mice are resistant to diet-induced insulin resistance.[49] NACHT, LRR, and PYD domains-containing protein 3 (NLRP3), a member of the Nod-like receptor (NLR) family, plays a crucial role in inflammasome activation and metabolic inflammation associated with metabolic syndrome and diabetes.[50,51] Increased systemic LPS due to disrupted gut barrier function can activate not only TLR4 but also NLRP3, together with palmitic acid or other inflammasome activators that can be increased in obesity or metabolic syndrome.[51] However, it is not clear whether such metabolic inflammation is associated with changes of innate immune system in the intestine. Since several TLRs and NLRs are expressed in diverse cells of the intestine,[52,53] it is likely that

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these innate immune receptors in the intestine contribute to the development of metabolic syndrome. A direct role of intestinal TLR in metabolic syndrome has been demonstrated using mice with targeted disruption of *MyD88*, specifically in gut epithelial cells that are partially protected from diet-induced obesity and metabolic inflammation.[54] In contrast, *MyD88* deletion in myeloid cells does not improve the metabolic profile of mice fed HFD, indicating a more important role of innate immune receptors in intestinal epithelial cells than in myeloid cells in the development of metabolic syndrome.

An intriguing model of metabolic syndrome associated with the activation of innate immune receptors in the intestine is the occurrence of metabolic syndrome in TLR5-knockout mice. The development of metabolic syndrome in TLR5-knockout mice appears to be due to changes in gut microbiota associated with the absence of TLR5 in the intestine, since fecal microbial transplantation confers transfer of metabolic phenotype to wild-type mice.[55] Following studies showed a crucial role of the absence of TLR5 in intestinal epithelial cells, but not that in dendritic cells (DCs), in the development of metabolic syndrome.[56] Altered gut microbiota in TLR5-knockout mice can increase hepatic lipogenesis mediated by stearoyl CoA desaturase through production of cecal SCFAs.[57]

Changes in innate immune cells in the gut of metabolic syndrome

At the cell level, several changes were noted in obese subjects or HFD-fed mice. Recent investigations revealed a critical role of innate lymphoid cells (ILCs) that are derived from common lymphoid progenitors, but devoid of antigen receptors, in the development of metabolic syndrome. In adipose tissue, group 2 ILCs (ILC2s) producing Th2 cytokines, such as interleukin (IL)-4 and IL-13, play important roles in beige fat biogenesis, thermogenesis, and polarization of alternatively activated (M2) macrophages, and the proportion of ILC2s is reduced by HFD.[58,59] In the intestine, NKp46+ group 3 ILCs (ILC3s) mainly producing IL-22 are decreased by HFD,[60] which could be due to reduced expression of IL-23, an upstream regulator of IL-22. Since it has been reported that IL-22 improves insulin sensitivity, preserves intestinal barrier function, decreases chronic inflammation, and regulates lipid metabolism in liver and adipose tissues,[61] NKp46+ ILC3s seem to alleviate metabolic syndrome via IL-22 production.

Macrophages and DCs are crucial members of innate immune cells belonging to antigen-presenting cells (APCs). In particular, macrophages and DCs in the intestine can be divided into several types with distinct functions.[62] However, owing to the difficulty in preparing immune cells from the intestine of HFD-fed mice, there are only few reports studying the changes of APCs in the intestine of experimental animals with metabolic syndrome. One study showed that expressions of ICAM1, CD86 costimulatory molecule and certain cytokines (IL-6 and IL-12p40) in intestinal APCs are downregulated by HFD, which consequently affects intestinal adaptive immunity.[63] Another study showed that intestinal CX3CR1^{+} macrophages can be divided into two subsets with different functions, and the frequencies of these two subsets are significantly affected by HFD: the proportion of a CD103^{-}CX3CR1^{+}CD11c^{high} subset increases, whereas that of a CD103^{-}CX3CR1^{+}CD11c^{low} subset decreases (Fig. 2).[64] In contrast, the proportion of CD103^{+} DCs is not affected by HFD. Given that CD103^{-}CX3CR1^{+}CD11c^{high} macrophages preferentially induce Th1 cells and CD103^{-}CX3CR1^{+}CD11c^{low} macrophages preferentially induce Th17 cells, changes in their abundances may be linked to alternations of intestinal adaptive immunity (see below section regarding adaptive immunity of the gut).

CHANGES IN THE ADAPTIVE IMMUNITY OF THE GUT IN METABOLIC SYNDROME

Recent investigations have shown a significant change in the adaptive immunity of the intestine in association with metabolic syndrome: Th1 cell increases and Treg cell decreases in the intestinal lamina propria of HFD-fed mice.[60] In humans, CD8αβ^{+} intraepithelial lymphocytes (IELs) are increased by obesity, and these IELs impair insulin sensitivity of epithelial cells.[65] In addition to cells traditionally associated with metabolic abnormalities, Th17 cells in the intestine may also play a role in the control of metabolic inflammation. According to two recent studies, although Th17 cells are well-known potent effector cells in autoimmune diseases, their reduction in the small intestine has been found to contribute to onset of HFD-induced metabolic changes.[63] Supporting this contention, several studies have shown that Th17 cells do not always induce immune/inflammatory disorders and can be divided into pathogenic and non-pathogenic cells.[66,67] In this regard, intestinal Th17 cells decreased by HFD seem to be non-pathogenic Th17 cells, rather than pathogen Th17 cells. The loss of Th17 cells in the small intestine of HFD-fed mice can be explained by the diminished ability of intestinal CX3CR1^{+} macrophages to induce Th17 cells and a significant reduction of CD103^{-}CX3CR1^{+}CD11c^{low} macrophages, the most efficient Th17-inducing APC subset[64] (Fig. 2). Transfer of Th17 cells, unlike that of Th1 cells, was shown to alleviate weight gain, increased fat mass, and glucose intolerance of HFD-fed *Rag1*-knockout mice. However, Th17 cells from integrin *β7*-knockout mice had no such metabolic effects, suggesting that gut homing of Th17 cells is crucial in the metabolic improvement by Th17 cells. LPAM-1 (α4β7) is a critical receptor for gut homing of T cells.[68,69] In addition, IL-17 *per se* plays an important role in the improvement of metabolic profiles, since Th17 cells from IL-17-knockout mice have significantly less metabolic effects.[64] Given that Th17 cells produce IL-22, as well as IL-17, Th17 cells may also improve metabolic syndrome via IL-22 production.[61] Moreover, since Th17 cell transfer leads to expansion of microbiota associated with lean

phenotype, such as *Bacteriodetes* or *Akkermansia*,[64] the role of gut microbiota cannot be overlooked in regards to the metabolic improvement by Th17 cells. Alteration of gut microbiota by Th17 cells may be due to changes in antimicrobial peptides, such as *Reg3γ* produced by Paneth cells (Fig. 2). In support of this notion, reduced Paneth cell granules and *Reg3γ* expression in HFD-fed mice are reversed by IL-17 produced by Th17 cells.[64] IL-17 can also enhance gut barrier function through upregulation of tight junction molecules, such as claudin, in intestinal epithelial cells.[70] These data show an intriguing role of Th17 in metabolic regulation and the potential of gut-trophic Th17 cell transfer as a new therapy for metabolic syndrome or diabetes.

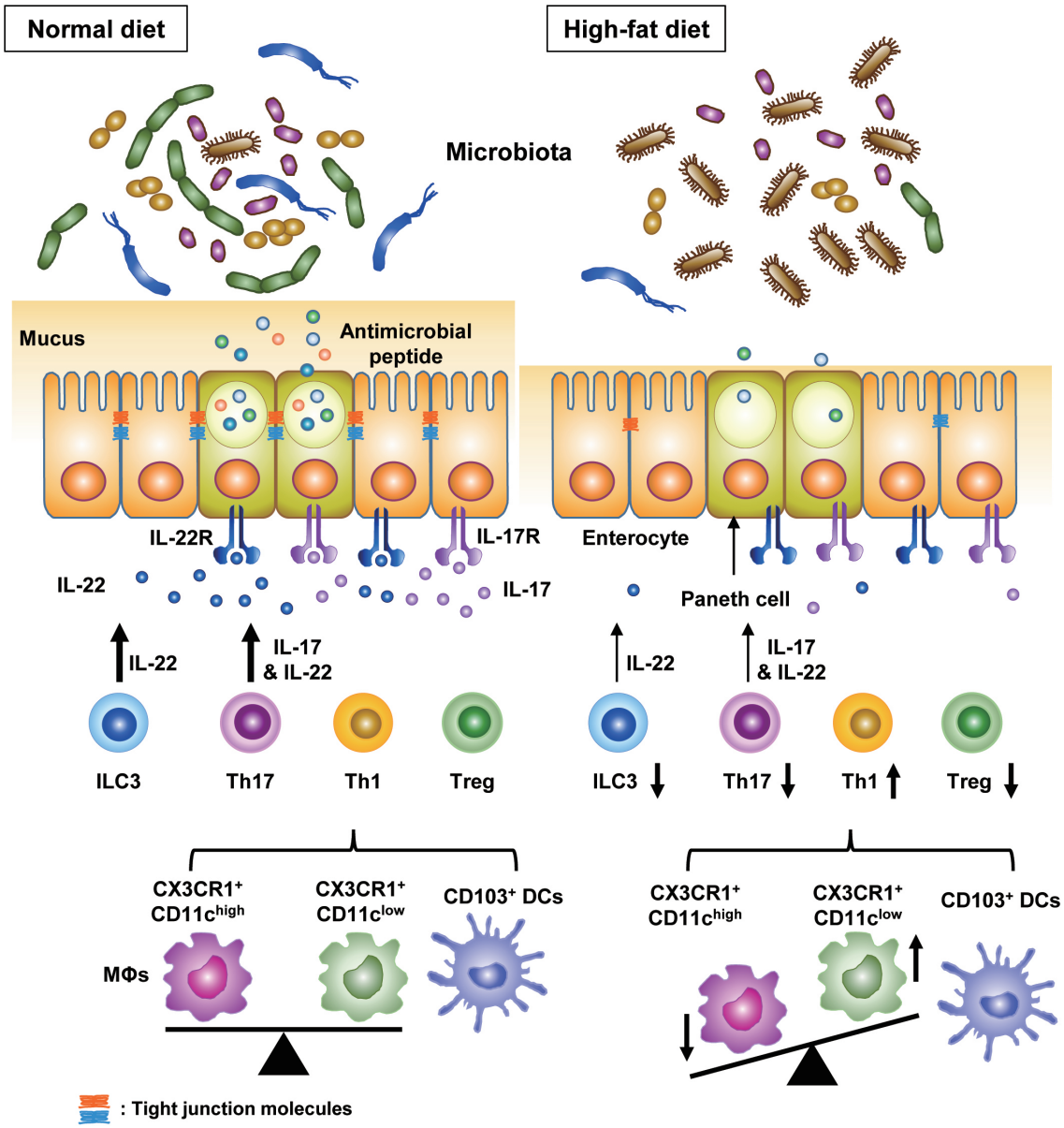

Fig. 2. Changes in the intestinal immunity by HFD. HFD changes intestinal immunity, as well as gut microbiota composition. HFD, in particular, increases the frequency of Th1 cells among the CD4 T cells and decreases those of Th17 and Treg cells. HFD increases the frequency of a $CX3CR1^{+}CD11c^{high}$ macrophage (MΦ) subset, preferentially inducing Th1 cells, and decreases that of a $CX3CR1^{+}CD11c^{low}$ MΦ subset, preferentially inducing Th17 cells without affecting that of $CD103^{+}$ DCs. Changes in the proportions of two MΦ subsets lead to the changes in Th1 and Th17 cells after HFD feeding. Intriguingly, intestinal Th17 cells play an important role in improving metabolic diseases through IL-17 and IL-22. IL-22 is produced also by ILC3 and functions to improve metabolic profiles. Proportions of ILC3 are decreased by HFD. IL-17, mainly produced by Th17 cells, reverses decreased granules and antimicrobial peptide production of Paneth cells, leading to expansion of microbiota associated with lean phenotype. In addition, IL-17 enhances barrier function of intestinal epithelial cell by increasing expression of tight junction molecules. HFD, high-fat diet; DCs, dendritic cells; IL, interleukin, ILC3, group 3 innate lymphoid cells.

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MODULATION OF GUT MICROBIOTA OR IMMUNITY AS A NOVEL THERAPEUTIC STRATEGY AGAINST METABOLIC SYNBDROME AND DIABETES

Gut microbiota and immunity can be modulated by prebiotics or probiotics. Prebiotics are food components that induce expansion of beneficial microbiota. For example, oligofructose promotes the growth of *Bifidobacterium* that reduces endotoxin levels and enhances intestinal barrier function, improving metabolic parameters.[71] In contrast to lard, fish oil rich in polyunsaturated fat promotes growth of beneficial bacteria, such as *Akkermansia*, *Bifidobacterium*, or *Lactobacillus*, and prevents metabolic inflammation in adipose tissue.[33] In addition, a fiber-rich diet may contribute to amelioration of metabolic syndrome by inhibiting expansion and activity of mucus-degrading bacteria that are harmful to the intestinal barrier function (Fig. 1).[72] Food enriched with inulin may have protective effects against gut injury associated with HFD and diet-induced obesity, since deficiency of inulin in HFD has been reported to a vital element in the loss of cecal and colonic mass due to HFD.[73]

Probiotics are live microorganisms that confer a beneficial effect on the host when administered properly. Some probiotic strains, especially those of the genera *Lactobacillus* and *Bifiodobacterium*, have been reported to ameliorate obesity and improve metabolic parameters. The suggested mechanisms thereof include inhibition of pathogen adherence to gut epithelium, stabilization of gut microbial community, and protection of mucosal integrity or barrier function.[71,74] Enhanced gut barrier function may be due to SCFA production by bacterial fermentation. A recent study reported direct beneficial activity of *Lactobacilli* on intestinal epithelial cells and on the enteric nervous system regulating gut motility.[75]

In addition to prebiotics and probiotics, drugs can also be employed to modulate gut microbiota or immunity. As discussed above, the anti-diabetic drug metformin can exert beneficial metabolic effects through modulation of gut microbiota in mice and human patients.[38,43,46] The action of metformin as an anti-aging or pro-longevity agent[38,43] may also be related to its effect on gut microbiota.[44] Anti-inflammatory agent 5-aminosalicylic acid can improve metabolic syndrome through suppression of inflammation as well.[60] Active components of *Akkermansia*, such as Amuc_1100, and delivery of gut-tropic Th17 cells or agents that can boost non-pathogenic Th17 cells, specifically in the intestine, may also be able to open a new horizon in the development of next-generation therapies against metabolic syndrome or diabetes.

CONCLUSION

Changes in the gut microbiota and immunity are being accepted as important elements in the development of metabolic syndrome and diabetes. However, still numerous questions need to be elucidated to clearly understand the interaction between microbiota and gut immunity or disturbance therein associated with the diseases. Future studies addressing the complex interplay between gut microbiota, immunity, and host metabolism in a physiological and pathological context will pave the way for the development of innovative therapeutic agents against metabolic syndrome and diabetes.

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