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High-fat diet aggravates food allergy via the microbiota-intestinal epithelium interactions: a review

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ABSTRACT: The rising incidence of food allergy attracts researchers to advocate that a high-fat diet (HFD) is an attention-grabbing trigger. However, the mechanism by which HFD aggravates food allergy remains largely unknown. In this context, intestinal epithelium dysfunction as a characteristic of food allergy is summarized. Specifically, we focus our attention on the microbiota-intestinal epithelium interactions and call attention to the underlying mechanism by which HFD promotes food allergy along the interactions. Escaped fat and excessed bile acids in the colon induced by HFD can disrupt gut microbiota, directly regulating intestinal epithelium function. Additionally, HFD contributes to indirectly destroying the intestinal epithelium and enhancing its permeability by altering the level of microbial metabolites. Consequently, these ways promote the influx of food allergens. Substantial quantities of food allergens traverse the intestinal epithelium, prompting heightened secretion of pro-inflammatory cytokines, thus favoring a Th2 immune response. In this situation, impaired differentiation of Treg and Th1 cells can aggravate food allergy. Clarifying the intricate relationship between HFD and food allergy from the microbiota-intestinal epithelium interactions may offer prevention strategies for food allergy.

Keywords: Food allergy; High-fat diet; Gut microbiota; Intestinal epithelium; Microbial metabolites

1. Introduction

Food allergy is characterized as an allergic disease involving adverse immune responses to food, resulting in a spectrum of clinical manifestations affecting the skin, respiratory system, and gastrointestinal tract[1]. Recently, the Food and Agriculture Organization (FAO), and the World Health Organization Committee (WHO) recommended that priority allergenic foods include eggs, milk, sesame, cereals containing gluten, peanuts and some nuts[2]. Immune-mediated food allergy affects individuals of various races, ages and genders, with a rising prevalence over the past two decades[3,4]. The diet hypothesis has been proposed to be one of the potential hypotheses for the drastically increased prevalence of food allergy[5]. Most notably, a dietary pattern characterized by a high intake of saturated fatty acids, known as a high-fat diet (HFD), is believed to elevate the prevalence of allergic disease[5]. However, how HFD aggravates food allergy remains

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largely unknown. Therefore, identifying the potential mechanisms that HFD connects to food allergy is an upcoming research area with implications for informing prevention and treatment strategies.

The gastrointestinal tract is well-established as the primary site for the development of oral tolerance and the manifestation of food allergy. Dysfunction in the intestinal epithelium, coupled with increased permeability, can facilitate the infiltration of food allergens, thereby contributing to the onset of severe food allergy[6]. Deviations in gut microbial diversity and composition, when observed in comparison to normal individuals, are acknowledged indicators of compromised intestinal epithelium. Notably, HFD is implicated in inducing changes in disease-associated microbiota, exerting a significant influence on the integrity of the intestinal epithelium[7,8]. However, whether alterations in gut microbiota induced by HFD mirror the reason for intestinal epithelium dysfunction associated with food allergy by promoting the penetration of food allergens, discussed is lacking in the literature. We focus here on a potential cause-and-effect connection between HFD and food allergy. The discussion is initiated by exploring the role of intestinal epithelium dysfunction in severe food allergy. Additionally, we underscore how HFD heightens susceptibility to food allergy through the intricate interplay between microbiota and the intestinal epithelium.

2. Intestinal epithelium dysfunction is a characteristic of food allergy

Food allergy is an immune-mediated abnormal response to allergens, mainly involving digestion in the gastrointestinal tract and uptake by the intestinal epithelium. The integrity of intestinal epithelium can separate food allergens by promoting the formation of Treg cells[8]. However, intestinal epithelium dysfunction plays an important role in facilitating the passage of food allergens and eliciting an immune response from immune cells in the lamina propria[9].

2.1 A brief description of the intestinal epithelium

The mammalian intestinal tract is an organ with immune properties that resides together with trillions of commensal microbiota and is responsible for regulating nutrient uptake, establishing a connection between adaptive and innate immune responses, and forming a large barrier to manage food allergen sensitization[10]. Unlike inhaled allergens, most food allergens involve the digestive process of the mammalian intestinal tract and they are resistant to hydrolysis by digestive enzyme[s][11]. The intestine tube with digestion and absorption function consists of the large intestine and small intestine (characterized by finger-like villi), and the intestinal wall comprises mucosa, the underlying submucosa and muscle layer[12]. As the majority of immunological sites for protecting the host and defending against antigens, the mucosa is subdivided into intestinal epithelium, lamina propria and muscularis mucosae[13]. The intestinal epithelium formed by specialized cells-a single cell layer-is connected by tight junctions and covered by a mucus layer rich in antibacterial peptides, mucins, secretory IgA (sIgA), and commensal microbial communities[14,15]. In general, a complete intestinal epithelium contributes to preventing the entry of harmful signals and fostering the production of anti-inflammatory cytokines, thereby orchestrating the regulation of oral tolerance. However, internal or external factors inducing the dysfunction of the intestinal epithelium, play a pivotal role in the influx of food allergens[6].

2.2 The involvement of intestinal epithelial cells and their secretions in the occurrence of food allergy

The susceptibility to food allergy is highly implicated in genetic factors. A study has shown that *SERPINB10* gene is involved in regulating the homeostasis of the intestinal epithelium to mediate susceptibility to food allergy[16]. However, the increased prevalence of food allergy cannot take into account genetic factors alone, and there seems to be a dietary influence. The epithelium of the gastrointestinal tract acts as a selective filter that allows nutrient absorption and restricts the entry of dietary antigens. To achieve the responses to luminal components, seven major specialized cell types that make up the intestinal epithelium-goblet cells, Paneth cells, microfold cells (M cells), tuft cells, enteroendocrine cells, enterocytes and cup cells-are developed from common stem cells located near the bottom of the crypts to fulfill specific niches[14]. Several intestinal epithelial cells mentioned above are involved in facilitating the transportation of dietary antigen from the lumen across intestinal epithelium to underlying lamina propria immune cells (Figure 1): (1) Goblet cells form goblet-associated antigen passages (GAPs) to transfer dietary antigen, (2) M cells transport dietary antigen via endocytic and pinocytic mechanisms, (3) enterocytes participate in transporting dietary antigen via low-affinity IgE receptor, FcεRII (CD23)-dependent processes, and (4) Paneth cells are also involved in the uptake of allergens[17,18]. In addition, these secretory intestinal epithelial cells also participate in the immune response. However, dysfunction of intestinal epithelial cells and their secreted products is observed in food allergy.

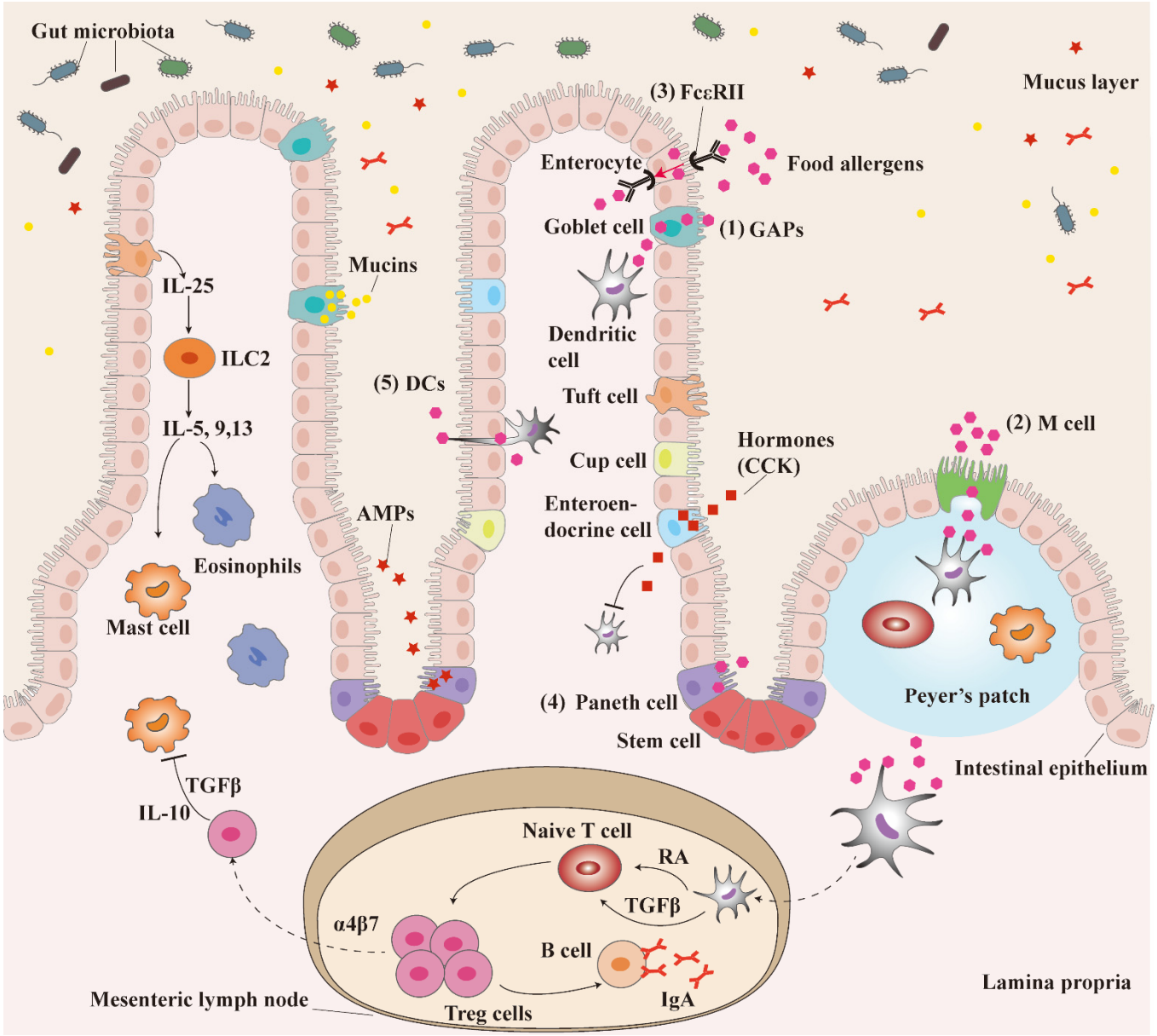

Fig. 1. Structure and specialized intestinal cells of intestinal epithelium and function in food allergen uptake and oral tolerance. The intestinal epithelium consists of the mucus layer, intestinal epithelium and lamina propria. The specialized intestinal cells include goblet cells, Paneth cells, M cells, tuft cells, enteroendocrine cells, enterocytes and cup cells. Food allergens transport from the lumen across intestinal epithelium to lamina propria via (1) goblet-associated antigen passages, (2) endocytic and pinocytic mechanisms mediated by M cells, (3) enterocytes associated FcεRII (CD23)-dependent processes, (4) Paneth cells and (5) dendritic cells sampling directly. In oral tolerance, food allergens are presented to naive T cells, and this interaction induces naive T cells differentiation into Treg cells. TGF-β and IL-10 secreted by Treg cells suppress mast cells and encourage B cell to produce IgA.

GAPs, goblet-associated antigen passages; ILC2, type 2 innate lymphoid cells; AMPs, antimicrobial peptides; CCK, cholecystokinin; TGF-β, transforming growth factor-β; RA, retinoic acid; DCs, dendritic cells.

Goblet cells, which approximately account for 15% of large intestinal epithelial cells and are the most common in the short villi of the distal small intestinal epithelium, are secretory[19]. The main function of goblet cells is synthesizing and further secreting mucin-2 (MUC2) to form the basic skeleton of mucus[20]. Of special characteristic is that goblet cells transcend protecting the epithelium from isolating harmful bacteria through hyperglycosylated mucin proteins by delivering antigens to dendritic cells in the lamina propria[21]. Goblet cells also contribute to producing anti-microbial angiogenin 4 (Ang4), trefoil factor 3 (TFF3), regenerating

islet-derived protein 3 beta (Reg3β), resistin-like molecule-β (RELMβ) and regenerating islet-derived protein 3 gamma (Reg3γ) to regulate the mucus layer[22]. In general, goblet cell hyperplasia is fundamental to allergic asthma[23]. T helper type 2 (Th2) cytokines, especially the overexpressed IL-13, can induce goblet cell hyperplasia through STAT6 signaling[24]. Lack of goblet cells in mice can impair oral tolerance to dietary antigens[25]. Interestingly, recent research has suggested that IL-33 exacerbates ovalbumin-induced food allergy in mice models by inducing goblet cell differentiation[26]. Certain food ingredients, such as β-carotene, have been shown to inhibit the excessive secretion of MUC2 by goblet cells, thereby reducing the severity of food allergy.[27]. Antibiotic-induced increased levels of jejunal goblet cells in mice can aggravate food allergy, further indicating that goblet cells are involved in food allergy and immunomodulation[28].

Paneth cells, also secretory cells, found only in the small intestine (especially in the ileum) with a life span of 1-2 months are the only specialized epithelial cell lines that migrate downwards to the base of the crypt of Lieberkühn after differentiation from stem cells[12]. Paneth cells produce antimicrobial peptides (AMPs) such as defensins (cryptdins in mice), lysozyme C, C-type lectins (islet-derived protein 3γ: REG3γ) and cathelicidins to regulate microbiota[29]. In addition to antibacterial function, these AMPs also play a crucial role in innate immunity. The role of Paneth cells in food allergy has to our knowledge been studied. A recent study has shown that Paneth cells are involved in the uptake of allergens in food-allergic mice[18]. The level of β-defensins and IL-22 in ovalbumin-allergic mice was decreased, however, olive oil intake increased their production in the mice[30]. The secretion of IL-22 promotes the production of AMPs, and insufficient IL-22 increases the risk of allergen sensitization[31]. Despite this key role in food allergen uptake and production of AMPs, a role for Paneth cells in relation to the signal pathway of food allergy remains almost unknown. A finding has indicated that OVA-sensitized BALB/c mice alter the Paneth cells, and OVA sampling is mediated by the IL-13/CD38/cADPR pathway[32].

Together with goblet cells and Paneth cells, the intestinal epithelium contains specialized antigen-sampling cells called M cells, which overlay gut-associated lymphoid follicles named Peyer's patches. M cells function as a bridge between sampled antigens and the underlying dendritic cells. Cross-linking of β-lactoglobulin increases the uptake of M cells and triggers serious allergic sensitization in mice, suggesting that M cells also act in the genesis of food allergy[33].

Tuft cells found in many animal tissues are described as apical microvillous cells that derive from LGR5+ stem cells or DLL1+ progenitors[34]. In the past, the research on tuft cells mainly focused on their important role in antiparasitic infection. Later, a study showed that tuft cells use succinate to monitor intestinal content and release cytokine IL-25 to regulate type 2 immune responses[35]. A study have shown that IL-25 secreted by tuft cells activates group 2 innate lymphocyte cells (ILC2s) and promotes them to release IL-5, -9, -13[36]. These produced cytokines promote the expansion of tuft cells and orchestrate IL-5-mediated and IL-13-mediated type 2 inflammation. An example of tuft cells in food allergy revealed by Leyva-Castillo et al[37] suggested that the release of IL-33 caused by tape-stripping skin mice synergizing with IL-25 derived from intestinal tuft cells stimulate ILC2s to produce IL-13, thereby increasing gut permeability and promoting

food allergy in sensitized mice. The excessive levels of succinate caused by microbiota dysbiosis also play an important role in severe food allergy via the activation of tuft cells[38].

Enteroendocrine cells are distributed throughout the gastrointestinal tract and represent about 1% of the intestinal epithelium with a continuous cell turnover of approximately 3-5 days[39]. Functionally, enteroendocrine cells respond to luminal contents such as food, microbiota and microbial metabolites by secreting more than 20 hormones such as serotonin (5-HT), cholecystokinin (CCK), glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide 1 (GLP-1), GLP-2, peptide YY (PYY) and neurotensin (NTS), including assisting in nutrient absorption, maintaining mucosal immunity, regulating inflammatory disease[40,41]. GLP-2 expressed by enteroendocrine cells has been shown to affect intestinal permeability by regulating tight junctions. CCK is associated with the inhibition of dendritic cells[41]. For all that, there is still a lack of research on the relationship between enteroendocrine cells and IgE-mediated food allergy. Enterocytes, as concentrated sites for digestive enzymes, are the dominant cell types in the intestinal epithelium and are involved in digesting dietary components. Cup cells, accounting for 6% of the ileal epithelial cells, are wine glass-shaped cells, and their role in food allergy is little known[42].

2.3 Abnormal tight junctions and intestinal hyperpermeability affect food allergy

The molecular composition of tight junctions belongs mainly to three families of transmembrane proteins, which are the claudin family, the Marvel domain-containing proteins (occludins, tricellulin, MarvelD2 and MarvelD3), and immunoglobulin superfamily (junctional adhesion molecules (JAMs), adenovirus receptor proteins (CARs) and Coxsackie). Claudins and occludins attach to zonula occludens protein-1, -2 (ZO-1, ZO-2) that are regarded as cytosolic scaffold proteins, and JAMs furthermore regulate the interaction of tight junctions[43]. Tight junctions are responsible for connecting adjacent epithelial cells and regulating intestinal permeability. Tight junctions not only regulate the transport of ions, macromolecules and metabolites to maintain the integrity of the epithelial barrier but also allow dendritic cells to sample external antigens. GTPases and phosphatase 2A are involved in the maturation of tight junctions. However, abnormal phosphorylation of claudin increases paracellular permeability[44]. Moreover, mast cell protease-1 degrading occludin, IL-13 triggering claudin-2 overexpression under pathological conditions, and tumor necrosis factor α inducing occludin endocytosis, are inducements to increase intestinal permeability[45]. Several studies have demonstrated that various factors, including HFD, dietary components such as gliadin, food allergens, microbial changes, and microbial products such as cholera toxin, can disrupt the structure of tight junctions and affect intestinal permeability[6, 46]. In addition, the interaction between ZO and actin cytoskeleton is crucial for maintaining the barrier integrity and regulating intestinal permeability.

Proper intestinal permeability is essential for nutrient absorption and oral tolerance development. However, increased intestinal permeability has connections with the occurrence of multiple diseases[46]. As discussed above, damage to tight junctions contributes to intestinal hyperpermeability. Interestingly, increased intestinal permeability was observed in individuals with food allergy, as increased intestinal permeability promotes the uptake of allergens. A study involving 19 patients with an allergy to lipid transfer

proteins revealed that impaired intestinal permeability was discovered in 12 patients[47]. LPS-binding protein, a marker of intestinal epithelial barrier permeability, is discovered in elevated levels in peanut-allergic individuals[48]. Järvinen et al[49] found that in a study involving 131 children, almost one-third of them with cow's milk and egg allergies had increased intestinal permeability, indicating that increased intestinal permeability may be an intrinsic characteristic of food allergy. Therefore, abnormal expression of tight junctions such as occludins and claudins can promote increased intestinal permeability, which plays an important role in food allergy.

2.4 Role of mucus layer thinning in food allergy

Mucus is a protective fluid that covers the intestinal epithelium, and inducers such as histamine, cholecystokinin octapeptide, prostaglandin E2 and carbachol can promote its secretion. In addition to the inducers mentioned above, luminal microbial metabolites can also affect mucus formation[50]. The structure of the mucus layer varies in different parts of the digestive tract, and single-layered mucus is formed in the small intestine while double-layered mucus is found in the stomach and colon. In a healthy state, microbiota is penetrable in the single mucus layer of the small intestine and the outer mucus layer of the colon, while is impermeable in the inner mucus layer of the colon. In addition to mucins (with a concentration of 1-5%) that form the skeleton of the mucus layer, mucus also includes kallikrein 1, anterior gradient protein 2 homologue, and calcium-activated chloride channel regulator 1, whose immunological function is little known[20]. As highly O-glycosylated glycoproteins, mucins consist of key mucin elements called mucin domains, which are rich in proline (Pro), threonine (Thr) and serine (Ser). The mucus barrier plays an important role in maintaining intestinal epithelium homeostasis and oral tolerance. MUC2 attenuates dendritic cells to produce proinflammatory cytokine IL-12 and IFN-γ in response to antigens, thereby eliciting its anti-inflammatory effect. Garaging *MUC2*$^{-/-}$ mice with MUC2 mitigate bacteria-induced gut inflammation not only by increasing ALDH1A1 and TGF-β secretion in dendritic cells in the lamina propria of the small intestine but also by augmenting Treg cells and reducing Th1 and Th17 cell counts[25]. The restoration of tolerance to oral soluble antigen OVA occurred in *MUC2*$^{-/-}$ mice by generating a signal-transducing Dectin-1-FcγRIIB complex on dendritic cells in the presence of galectin-3 when supplemented with MUC2[25].

The mucus layer can be disrupted when mucin synthesis fails to follow the degradation of mucin. Dysbiosis of gut microbiota caused by overconsumption of saturated fatty acid results in thinning of the mucus barrier. Such destruction of the mucus barrier may have an impact on food allergy. The Western diet fed in mice increases Proteobacteria and decreases Bifidobacterium spp, resulting in the degradation of the mucus layer[51]. However, supplementing HFD mice with dietary fiber can weaken the negative effects on the mucus layer by restoring gut microbiota. Western diet increases the penetrability of dietary antigens to the inner colonic mucus layer and stimulates immune responses[52]. Such a thin mucus layer may reveal a new mechanism of allergic sensitization, and future research needs to consider the impact of mucus destruction induced by HFD on food allergy. In sum, a systematic review of these studies found that intestinal epithelium

dysfunction is a characteristic of food allergy by affecting antigen uptake, the levels of inflammatory cytokines, etc.

3. Mechanism of HFD aggravating food allergy

3.1 Epidemiological evidence on HFD increasing the risk of food allergy

HFD generally refers to a dietary pattern where the fat content exceeds 40% based on animal fats, characterized by high levels of saturated fatty acids and ω-6/ω-unsaturated fatty acids, and low levels of dietary fiber. Food allergy incidence has been increasing in the past decades, allowing researchers to address that modern lifestyles are triggers to promote diseases in genetically susceptible individuals[53]. Many hypotheses have been used to explain the sudden rise in the incidence of food allergy, among which the diet hypothesis is the most concerned[54]. Although a modern diet is able to ensure the demand for nutrient supplementation, some observational studies provide evidence that a potential correlation exists between HFD and an increased risk of allergic diseases. In a study involving 3040 participants, it was found that allergic rhinitis is significantly associated with HFD in children[55]. A retrospective case of 2090 individuals showed that obese adults are prone to the development of atopic dermatitis[56]. In a retrospective study involving 246 adults, Fitzpatrick et al[57] found that obesity may be an exacerbating factor for atopic asthma in adults, with a higher IgE level in serum. Although there is limited epidemiological research on the relationship between HFD and food allergy, allergic diseases increase in tandem with HFD, indicating that HFD may also increase the risk of food allergy. Indeed, many studies have also provided a foundation for this theory.

A huge review of working patterns such as that conducted by Julia et al[58] showed that consumption of palm kernel oil rich in medium-chain fatty acids contributes to increasing allergic diseases such as food allergy, by promoting IL-25/IL-33 production and leading to Th2 cell responses. Like other allergic diseases, the inflammatory mechanisms of eosinophilic esophagitis are characterized by a deregulated T helper 2 immune response[59]. A study on the effect of obesity on eosinophilic esophagitis related to Th2 immune response showed that IL-10 and FoxP3 were higher in obese-allergic mice compared with lean-allergic mice. Maternal obesity decreases occludin and increases the levels of inflammatory factors in female offspring BALB/c mice after β-lactoglobulin sensitization[60]. In line, high sugar-butter diet induced obesity increases gut permeability and decreases Treg cells in mice, which promoted the occurrence of food allergy. Moreover, the administration of obese mice with ovalbumin disrupts oral tolerance and increases the occurrence of severe food allergy[61]. These studies have a commonality-HFD aggravates food allergy by promoting Th2 immune response, but the mechanism behind this is unknown. Therefore, elucidating the mechanisms underlying HFD elevates the risk of developing food allergy may contribute to offering prevention strategies.

3.2 Microbiota dysbiosis induced by HFD driving intestinal epithelium dysfunction and further aggravating food allergy

3.2.1 Gut microbiota dysbiosis and its interaction with intestinal epithelium

The human gastrointestinal tract harbors a complex and dynamic microbial community, which predominantly aids in homeostasis maintenance and disease protection. It is increasingly indicated that human

microbiota consists of more than 35 thousand bacterial species and is composed of 10^4~10^8 microbial cells per gram in the intestine[62]. Clone library analysis from the 16S rRNA gene reveals that the resident microbiota in mammals at the phylum level is mainly composed of Bacteroidetes (such as *Bacteroides*) and Firmicutes (such as *Lactobacillus* and *Clostridium*), which make up over 90% of gut microbiota. Also, other members of phylum such as Proteobacteria and Actinobacteria (*Bifidobacterium*) are involved[63]. The composition of microbial phylum varies with regions of the gastrointestinal tract and age as well: major phylum found in the stomach include Firmicutes, Bacteroidetes, Fusobacteria, Actinobacteria and Proteobacteria, whereas the dominant phylum of microbiota in jejunum is represented by Firmicutes, but also including a great abundance of Proteobacteria, Actinobacteria and Bacteroidetes; The phylum in a newborn are dominated by Proteobacteria and Actinobacteria, and replaced by Firmicutes and Bacteroidetes when they mature into the adults[64]. The microbiota composition is obviously different in the lumen, mucosa and feces. For example, *Lachnospiraceae* and *Ruminococcaceae* are enriched in feces compared with biopsies of the colonic mucosa[65].

Microbiome-wide studies have shown that gut microbiota transmits signals to intestinal epithelial cells, maintaining homeostasis by regulating the integrity of the intestinal epithelium and relaying signals to the lamina propria. *Lactobacillus rhamnosus* GG, a representative Gram-positive bacterium in the intestine of healthy individuals, can produce soluble protein p40 to prevent TNF-induced intestinal epithelial damage by activating the growth factor receptor and antiapoptotic PI3K/Akt pathway[66]. However, there is considerable evidence linking gut microbiota dysbiosis and intestinal epithelium dysfunction. Insulin receptor antagonist mediated dysbiosis characterized by an expansion of pro-inflammatory bacteria is tightly associated with impaired intestinal epithelium function[67]. In a study by Clark et al[68], disturbance of gut microbiota, such as the rise of *Gammaproteobacteria* follows intestinal epithelium dysfunction. Data indicated that the composition of the aged microbiota alters intestinal permeability but the composition of the microbiota interacting with other age-related changes in the host can enhance systemic inflammation[69].

Meanwhile, emerging evidence indicates that HFD affects the composition of gut microbiota and its interaction with intestinal epithelium. Dietary fat intake induces proportional changes in *Clostridia* and Ruminococcaceae in C57BL/6 J mice, which are related to the stimulation of tight junction proteins[69]. HFD feeding leads to an increase in the abundance of *Oscillibacter* in mice and a decrease in the ZO-1 mRNA expression[70]. In line, known mucus-degrading bacteria such as Actinobacteria, are discovered to impair the gut barrier[7]. Koshiro et al suggested that HFD can cause an increase in *Akkermansia muciniphila* and damage to the intestinal mucus layer, which is beneficial for promoting the IL-17 response in the spleen[71]. Therefore, we speculate that microbial dysbiosis induced by HFD is associated with intestinal epithelium dysfunction.–

3.2.2 Is microbiota dysbiosis caused by HFD driving intestinal epithelium dysfunction and further aggravating food allergy?

3.2.1 Mechanism of gut microbiota dysbiosis triggered by HFD

HFD can contribute significantly to the exacerbation of food allergy by inducing abnormalities in the gut microbiota or mitochondrial dysfunction. Mitochondria are key sites for oxidative phosphorylation, but excessive intake of saturated fatty acids generates a large amount of reactive oxygen species, which actively promote the intensification of inflammatory responses. Also, Alterations in microbial diversity and composition compared to normal individuals are thought to be a mark of subjects suffering from food allergy[72-74] (Table 1). In this review, we focus on the role of gut microbiota dysbiosis induced by HFD in food allergy. Abdel-Gadir et al[75] examined the capacity of six Clostridiales species and five Bacteroidales species to suppress food allergy using *Il4raF*^{709} mice (mice genetically prone to food allergy), following sensitization with chicken egg ovalbumin/staphylococcal enterotoxin B and challenge with chicken egg ovalbumin. Both Clostridiales and Bacteroidales consortium suppress jejunal mast cell expansion and IgE responses and further increase sIgA response and the numbers of ROR-γt+ Treg cells to protect against chicken egg ovalbumin allergy. Wang et al[76] showed that a high relative abundance of *Clostridium*, *Bifidobacterium*, *Akkermansia* and butyrate-producing bacteria in breastmilk is in connection with protecting against food allergy in infants by promoting Treg cell accumulation. Conversely, *Staphylococcus aureus*, *Ruminococcaceae*, *Lachnospiraceae*, *Oscillospira*, *Acinetobacter*, and *Pseudomonas* are potential microbiota for the development of food allergy[76-79]. These results further reveal that altering the composition of gut microbiota may change susceptibility to food allergy. Recent advances have clearly revealed that the dysbiosis of gut microbiota induced by HFD is related to food allergy[5]. Increased abundance of *Dorea*, *Erysipelotrichales*, *Bacilli*, *Ruminococcus*, *Clostridiales*, *Actinobacteria* and *Proteobacteria* is associated with HFD [80, 81].

Table 1 High fat diet aggravates food allergy via the microbiota-intestinal epithelium interactions

Model	Allergen	Gut microbiota dysbiosis	Epithelial barrier dysfunction	References
Palm kernel oil	Th2 cell responses to peanut protein	/	Delivery of allergens into Peyer's patches ↑	58
HFD-fed male BALB/c mice (60% calories from fat)	Eosinophilic esophagitis related to Th2 immune response when sensitized and orally-challenged with OVA	/	Mast cell and eosinophil accumulation in the gut ↑	59
HFD-fed rats (45 kcal% fat)	Inflammatory response	Ruminococcaceae/ Erysipelotrichaceae ↑	Occludin, ZO-1 and Claudin-1 ↓	95
Mice fed an HFD (45 kcal% fat)	Ovalbumin-induced allergy	Ruminococcaceae/ Desulfovibrionacea/ Rikenellaceae ↑ Muribaculaceae/ Prevotellaceae ↓	Intestinal permeability ↑ Occludin and tight junction protein 1 ↑	5
Maternal obesity	Exacerbates the responsiveness of offspring BALB/c mice to cow's milk protein-induced food allergy	/	Occludin mRNA ↓ IL-4, GATA-3, IgE and mMCP-1 ↑	60
High sugar-butter diet	Administration mice with ovalbumin increase food allergy	/	Gut permeability ↑ ZO-1 and claudin-2 ↓	61
High saturated fat diet	Inflammation	*Oscillibacter* ↑	ZO-1 ↓	108
HFD feeding	food allergies	/	atrophy of the small intestine	94

			and colon	
HFD-fed C57BL/6 male mice	Enhanced IL-17 response	*Akkermansia muciniphila* ↑	Mucin ↓	71
HFD-fed mice	Intestinal inflammation	SCFA-producing bacteria ↓ LPS-producing bacteria ↑	Claudin-1, Occludin and ZO-1 ↓	102
10% (w/w) of cocoa butter	Intestinal inflammation	Bacteroidetes ↑	Goblet cell mucin production ↑	109

So, what is the mechanism of gut microbiota dysbiosis induced by HFD. As we know, following the ingestion of dietary fats, gallbladder-secreted bile acids emulsify and decompose the hydrophobic fats into small droplets, which are further hydrolyzed by lipase into monoglycerides and free fatty acids. Then, monoglycerides and free fatty acids diffuse into small intestinal epithelial cells, where they reassemble into triglycerides within the endoplasmic reticulum. The reassembled triglycerides then combine with proteins to form water-soluble chylomicrons, which enter the liver through lymphatic and blood circulation for further decomposition. Excessive fat intake surpasses the digestive and absorptive capacity of the small intestine, leading to its excretion into the large intestine, which cannot directly absorb excess fats[82]. In general, 90-95% of bile acids are reabsorbed and recirculated to the liver, but excessive fat intake increases the secretion of bile acids, thereby increasing the amount of bile acids in the colon[82]. Consequently, the large amount of fat and primary bile acids that reach the colon are utilized by the gut microbiota.

Unabsorbed fat in the colon exerts its antibacterial effects and further alters the richness and diversity of the gut microbiota through two mechanisms: (1) solubilization, in which the cell membrane of gut microbiota is solubilized by fat; (2) substrate, in which fat is used as a metabolic substrate by gut microbiota. For instance, a greater influx of fat into the colon may favor Firmicutes rather than Bacteroidetes[82]. The primary bile acids entering the colon also provide substrates for microbial metabolism. Certain gut microbiota, showing bile salt hydrolase activity, deconjugate bile acids such as taurochenodeoxycholic acid (TCDCA) or glycochenodeoxycholic acid (GCDCA) into chenodeoxycholic acid (CDCA), and taurocholic acid (TCA) or glycocholic acid (GCA) into cholic acid (CA). Furthermore, gut microbiota harboring bile acid inducible (bai) genes can dehydroxylate unconjugated bile acids to form the secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA)[83]. In such cases, bile acid-tolerance microbiota such as Ruminococcaceae and Lachnospiraceae are enriched[83]. Therefore, the escape of digestive fats and the secretion of additional bile acids induced by HFD is an important factor in gut microbiota dysbiosis.

3.2.2 HFD aggravates food allergy via the microbiota-intestinal barrier interactions

After determining that intestinal epithelium dysfunction is a key feature of food allergy, that gut microbiota dysbiosis can cause intestinal epithelium dysfunction, and that HFD can destroy gut microbiota through the escape of digestive fats and the secretion of additional bile acids, we analyzed the possible mechanisms by which HFD aggravate food allergy and proposed that gut microbiota dysbiosis induced by HFD further damage the intestinal epithelium, which is the reason for aggravating food allergy. An in-vivo study using female BALB/c mice to study food allergy induced by ovalbumin confirmed that gut microbiota dysbiosis affects the decreased expression of claudin-1 and ZO-1, thus increasing the entry of ovalbumin into

tissues[28]. In a peanut allergy study, a high abundance of butyrate-producing bacteria such as *Clostridium cluster XIVa* has been proven to be increased after treating with the butyrate-releasing micelles, and mice are protected from an anaphylactic response by restoring barrier integrity[84]. The weight of evidence indicates that mucosa-associated *Clostridium clusters XIVa*, *XIVb*, and *IV* can protect against peanut allergy by activating *Reg3b* in intestinal epithelial cells which is responsible for encoding an antimicrobial peptide named REG3β. Furthermore, the proportions of Foxp3+Tregs in the intestinal lamina propria and the levels of IgA are also elevated[85]. Ovalbumin-sensitized *Il4raF*^{709} mice exhibit a low abundance of *Erysipelotrichaceae*/*Erysipelotrichales*/*Erysipelotrichi* belonging to Firmicutes and a high abundance of the *Enterobacteriaceae*/*Gammaproteobacteria*/*Enterobacteriales* of Proteobacteria family, and accompanied by small intestine tissue edema[86]. Interestingly, a recent study showed that mucin-degrading bacteria may play a potential role in food allergy by thinning the mucus layer[87]. Through summarizing these literatures, it was found that the microbiota-intestinal epithelium interactions plays an important role in the occurrence of food allergy.

In addition, an increase in Ruminococcaceae, Desulfovibrionacea along with Rikenellaceae, and a reduction in Muribaculaceae and Prevotellaceae induced by HFD correlate with food allergy[5]. The changed composition of maternal microbiota caused by HFD increases the susceptibility of offspring to allergens[88]. A long-term HFD significantly reduces the expression of tight junction proteins such as claudin-5, zonal occludens and occludin, and increases gut permeability in C57BL/6 mice[89]. After treatment of 45 juvenile grass carp with HFD for 10 weeks, it was found that the expressed tight junctions decreased, and inflammatory factors, as well as intestinal permeability, increased[90]. A study on rat mothers' long-term exposure to HFD revealed that a reduction of the expression of MUC1/MUC2 and genes such as *Ocln* and *Cldn4* is found in the male rats of their offspring[91]. The level of IL-1β, TNF-α and IL-6 is increased in the hippocampus when exposed to HFD, and a high level of TNF-α can increase the activity of myosin light chain kinase, resulting in endocytosis of occluding[45,92]. The LPS-containing bacteria proliferation caused by HFD is related to an increase in the concentration of LPS in the bloodstream, which activates specific signaling pathways to cause the destruction of tight junctions and the increase of intestinal permeability[48]. Guo et al[93] found that obesity can lead to an increase in pro-inflammatory cytokine levels in adipose tissue, causing damage to the intestinal epithelium and further increasing the risk of food allergy. Shohei et al found that a 3-week HFD feeding induced atrophy of the small intestine, which might be the reason for intestinal diseases such as food allergy[94]. Through an extensive literature review, we found that there is limited and insufficient research on the mechanisms by which HFD aggravates food allergy. We suggest that HFD can alter the composition of the gut microbiota, stimulate the release of inflammatory mediators from intestinal epithelial cells and increase intestinal permeability, thereby in favor of the susceptibility to food allergy (Figure 3). Work from Yu et al[95] revealed that HFD promotes inflammatory response via an imbalanced gut microbiota and enhanced gut permeability. In agreement with these findings, Lam et al[70] indicated that high saturated fat diet-increased *Oscillibacter* is directly relevant to depressed mRNA expression of ZO-1 in the proximal colon. Besides, the

Firmicutes/Bacteroidetes ratio is altered in mice fed with HFD, which contributes to increasing intestinal permeability by diminishing occludin expression[96]. In another study, A high-fat intake increases intestinal permeability and potentiates ovalbumin-induced allergic responses by changing the relative abundance and phylogenetic diversity of the gut microbiota[5].

Through reviewing these studies, we found that research has mostly focused on how HFD aggravate food allergy from the perspective of gut microbiota or the intestinal barrier. However, it is limited known how HFD specifically affects food allergy from the microbiota-intestinal epithelium interactions, and there is still a lack of research on which pathway is included behind the exacerbation of food allergy through HFD. More exploration is continuously focusing on the field and hopefully, we will see microbial dysbiosis-targeted or hyperpermeability-targeted therapeutics for eliminating the negative impact of unhealthy dietary patterns while relieving symptoms of food allergy.

3.2.3 HFD aggravates food allergy via the metabolites-intestinal barrier interactions

The gut microbiota can also play its role in maintaining the intestinal epithelium system and immune regulation through its metabolites (Figure 2). Escaping from digestive and absorbed dietary fiber become nutritional sources for the gut microbiota, resulting in the production of bacterial metabolites, such as short-chain fatty acids (SCFAs), which are involved in immune regulation. CD103+ DCs promote naive T cells to differentiate into Treg cells to regulate immune tolerance, and the weight of evidence indicates that SCFAs protect mammals from food allergy by promoting CD103+ DCs expression and activation of retinal dehydrogenase[97]. However, the characteristic of HFD is a decrease in dietary fiber intake and an increase in fat content, which affects the structure of the gut microbiota and thus influences the production of SCFAs, thereby affecting the intestinal barrier and ultimately affecting the occurrence of food allergy. The concentrations of butyrate and propionate can prevent food allergy by enhancing goblet cell differentiation and stimulating MUC2 expression to maintain their interaction with the intestinal epithelium[98, 99]. Wang et al[100] has uncovered that administration of sodium butyrate to piglets (weaned at (28 ± 1) d ag) for 2 weeks inhibits mast cell activation and reduces the level of its inflammatory mediators such as TNF-a, histamine and IL-6 to play its protective role on intestinal integrity. SCFAs can also act as ligands to activate G protein-coupled receptors (GPRs) such as GPR43 and GPR109A which are expressed on intestinal epithelial cells to aim to protect from food allergy[97, 101]. However, Wang et al[102] suggested that HFD can reduce SCFAs-producing bacteria, leading to dysbiosis of the microbiota. Simultaneously, the expression of Claudin-1, Occludin, and ZO-1 related to the intestinal epithelium is reduced, which promotes the development of inflammation. Therefore, we speculate that HFD can reduce the production of SCFAs, thereby affecting the health of the intestinal epithelium and increasing susceptibility to food allergy.

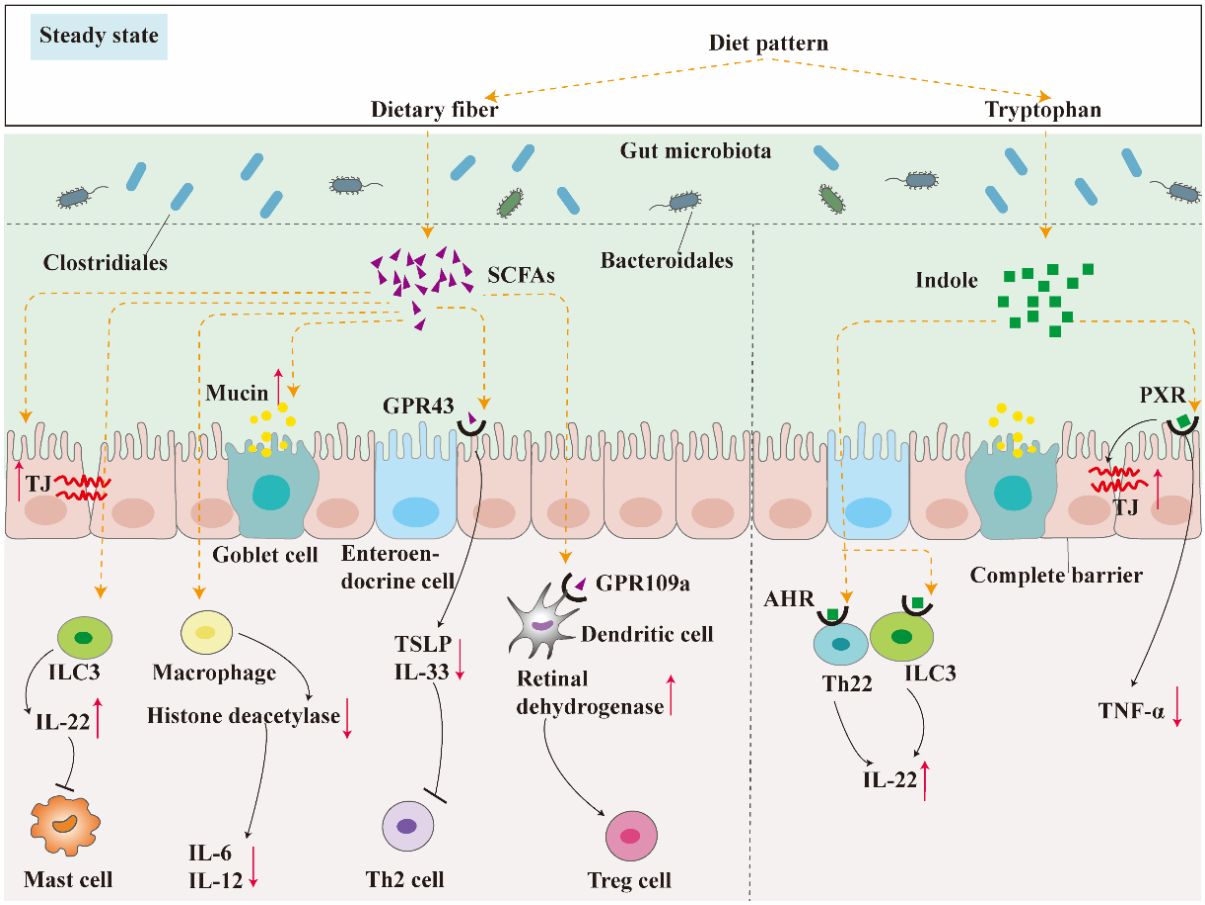

Fig. 2. Gut microbiota and its interaction with intestinal epithelium in steady state. Microbial metabolites, such as SCFAs, derived from microbial fermentation of dietary fiber, maintain the integrity of intestinal epithelium system by (1) increasing TJ expression, (2) promoting goblet to secret mucins, (3) stimulating ILC3 to secret IL-22, (4) inhibiting histone deacetylase activity of macrophage, (5) acting as ligands to activate GPR43 and (6) promoting $CD103^+$ DCs expression and activation of retinal dehydrogenase. Producing indole by microbial metabolism of tryptophan maintain the integrity of intestinal epithelium system by (1) acting as the ligands of AhR to induce Th22/ILC3 secreting IL-22 and (2) the ligands of PXR to promote the expression of TJ and downregulate TNF-α.

SCFAs, short-chain fatty acids; ILC3, type 3 innate lymphoid cells; GPR43, G protein-coupled receptor 43; AhR, aryl hydrocarbon receptor; PXR, pregnane X receptor; TJ, tight junction.

It was shown that *Lactobacillus spp*. and *Streptococcus spp.*, via the metabolism of tryptophan from dietary protein to produce aryl hydrocarbon receptor (AHR) ligands such as 3-indolepropionic acid and indole, balance mucosal response by tryptophan-derived metabolites engaging with AhR to induce immune cell secreting IL-22[103]. In a study assessing the ability of ligand-loaded β-lactoglobulin to confer resilience against allergy, results showed that the level of β-lactoglobulin-specific immunoglobulin classes and Th2 cell-associated cytokines significantly decreased in the mice treated with β-lactoglobulin that transport of FeQ2 ligands[104]. In addition, indole 3-propionic acid activation pregnane X receptor (PXR) can promote the expression of tight junction-associated molecules and downregulate TNF-α[105] (Figure 2). Furthermore, ligand quercetin provided an anti-inflammatory stimulus by facilitating AhR activation in cells. However, the characteristics of HFD are a decrease in the intake of high-quality protein and an increase in fat content, which can affect the structure of the gut microbiota, thereby affecting the production of AHR ligands and the intestinal epithelium, ultimately increasing the occurrence of food allergy.

The enrichment of monohydroxy fatty acids 12,13-diHOME in fecal samples is related to the increase of inflammation and reduction of Treg cells (Figure 3). Levan et al[106] indicated that those infants with asthma were enrichment with 12,13-diHOME in their feces, and 12,13-diHOME exhibited an increased risk of lung inflammation and a decrease in the number of Treg cells in allergen-challenged mice. Apart from the fact that gut commensal bacteria produce 12,13-diHOME, there is evidence that histamine-producing bacteria such as *Lactobacillus saerimneri* secrete high doses of histamine resulting in immune responses and deterioration of health[107]. Also, high levels of succinate induced by microbiota dysbiosis aggravate food allergy[38]. A study showed that hydrogen sulfide secreted by *Bilophila wadsworthia* inhibits butyrate oxidation to achieve the aim of hyperpermeability[108]. So we speculate that HFD may produce harmful metabolites by destroying the balance of gut microbiota, thereby disrupting the intestinal epithelium. This will facilitate the passage of allergens and aggravate food allergy.

In summary, we suggest that HFD can damage the intestinal epithelium by directly altering the structure of the gut microbiota or indirectly affecting the levels of microbial metabolites, thereby aggravating food allergy.

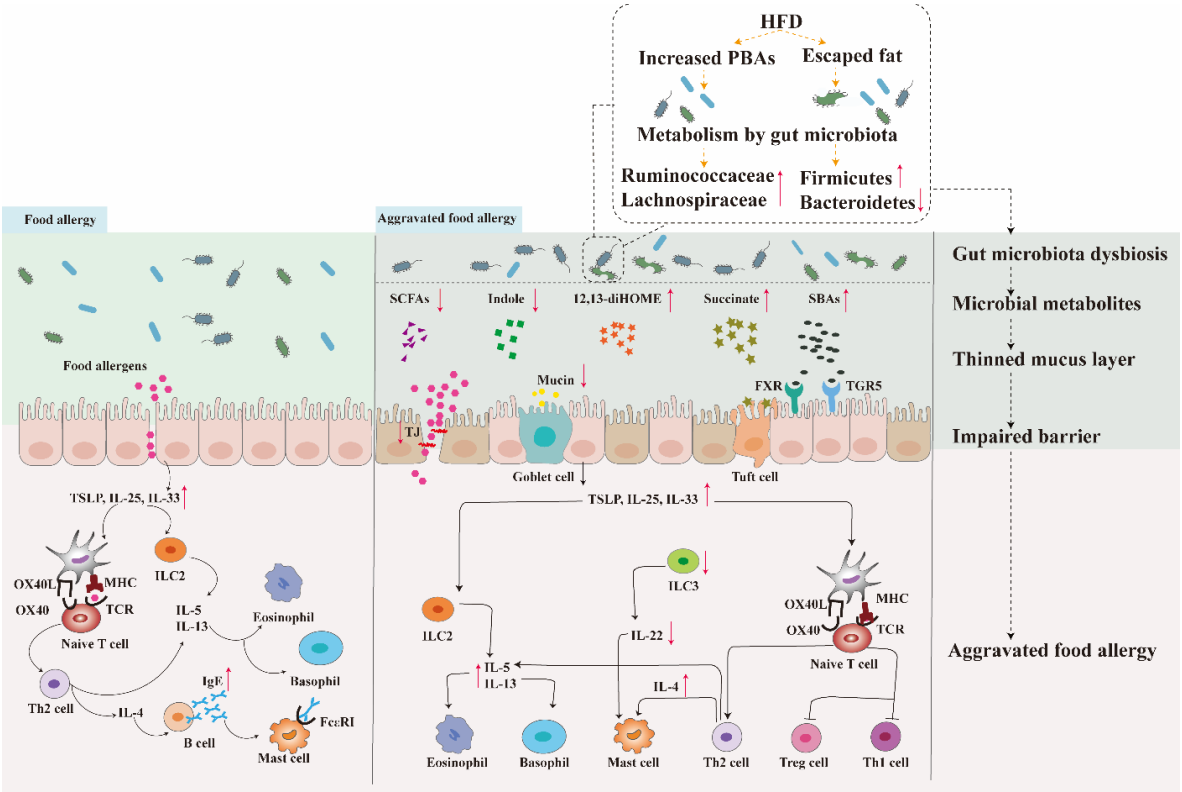

Fig. 3. HFD aggravates food allergy via the microbiota-intestinal epithelium interactions. Shown on the left, under food allergy, intestinal epithelium allows food allergens to penetrate and stimulate the secretion of TSLP, IL-25 and IL-33. The released cytokines promote ILC2 expansion and Th2 immune response. Th2 cells generate increased IL-4 to trigger IgE release. Shown on the right, escaped fat and excessed bile acids in the colon induced by HFD promote gut microbiota dysbiosis, increase metabolites SBAs, 12,13-diHOME and succinate production, decrease SCFAs and indole production, and destroy the mucus layer, aggravating food allergy. Low SCFAs/indole and high SBAs/12,13-diHOME/succinate lead to destruction of TJ and increased intestinal permeability, thus increasing food allergens access. The intestinal epithelium secretes increased TSLP, IL-25 and IL-33 to aggravate Th2 immune response and the production of IL-5 and IL-13 by ILC2. Furthermore, ILC3 produce a decreased level of IL-22. In this situation, impairs the differentiation of Treg cells and Th1 cells aggravate food allergy.

HFD, high-fat diet; TSLP, thymic stromal lymphopoietin; PBAs, primary bile acids; SBAs, Secondary bile acids; FXP, farnesoid X receptor; TGR5, G protein-coupled bile acid receptor; MHC, major histocompatibility complex.

4. Conclusions and perspectives

Generally, irrelevant aspects from various studies to underscore the potential role of HFD in exacerbating food allergy through microbiota-intestinal epithelium interactions have been pieced together in this review. Clearly, although HFD has been revealed by many epidemiological studies to be the reason for the rapidly increased incidence of allergic disease, less is known about the mechanisms by which HFD aggravates food allergy. In this context, the microbiota-intestinal epithelium interactions may form the missing piece in this puzzle. We have outlined not just the involvement of the intestinal epithelium in food allergy, but also synthesized the interplay between gut microbiota and the intestinal epithelium concerning food allergy. HFD-induced microbiota dysbiosis can directly or indirectly regulate intestinal epithelium function, so we consider that the microbiota-intestinal epithelium interactions are understudied factors that need to be taken into account when studying the mechanisms of HFD exacerbating food allergy. When HFD-induced microbiota dysbiosis or microbial metabolites disrupt the intestinal epithelium and increase intestinal permeability, the contact between the host immune system and food allergens increases, resulting in severe food allergy. Overall, studying the influence of HFD on food allergy from the microbiota-intestinal epithelium interactions is an imminent area of research. Further studies, especially in the context of the impact of HFD-induced gut microbiota metabolites, will be essential to identify whether accompanies and mediates these beneficial and detrimental effects in maintaining intestinal homeostasis and driving allergic sensitization. Also, further research is needed to ascertain whether the elevated levels of inflammatory cytokines in the bodies of individuals with food allergy will exacerbate the damage of HFD to the microbiota-intestinal epithelium interactions, and whether the relationship between the two should be prioritized or conducted simultaneously.

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