SOCIETY FOR MUCOSAL IMMUNOLOGY

REVIEW ARTICLE

Regulation of intestinal immunity by dietary fatty acids

Jinxin Qiu[1], Yanhui Ma[2]✉ and Ju Qiu[1]✉

Dietary fatty acids are absorbed through the intestine and are fundamental for cellular energy provision and structural formation. Dietary fatty acids profoundly affect intestinal immunity and influence the development and progression of inflammatory bowel disease, intestinal infections and tumors. Although different types of fatty acids exert differential roles in intestinal immunity, a western diet, rich in saturated fatty acids with abundant carbohydrates and studied as high-fat diet (HFD) in animal experiments, disturbs intestinal homeostasis and plays a pathogenic role in intestinal inflammatory diseases. Here, we review recent findings on the regulation of intestinal immunity by dietary fatty acids, focusing on HFD. We summarize HFD-altered immune responses leading to susceptibility to intestinal pathology and dissect the mechanisms involving the impact of HFD on immune cells, intestinal epithelial cells and the microbiota. Understanding the perturbation of intestinal immunity by HFD will provide new strategies for prevention and treatment of intestinal inflammatory diseases.

Mucosal Immunology (2022) 15:846–856; https://doi.org/10.1038/s41385-022-00547-2

INTRODUCTION

Fatty acids from various types of food are absorbed through the intestine and provide energy and structural components for mammalian cells. The intestine is in charge of primary digestion then absorption of fatty acids and their biological functions are intensively affected by dietary fat[1–3]. This includes the alteration of the intestinal immune system, the dysregulation of which is associated with inflammatory diseases including intestinal bowel disease (IBD), tumor, infections and allergies[1–3]. Systemic change of metabolism occurs upon uptake of a fat-containing meal[4–6]. Dietary fatty acids present in the food in the form of triacylglycerol acid (TG) are incorporated with cholesterol, hydrophobic vitamins into micelles, which are further emulsified by bile salts and digested by pancreatic lipases into free fatty acids (FFAs) and 2-monoglycerides for them to be absorbed by enterocytes[4–6]. In enterocytes, fatty acids and monoglycerides are reassembled into TG, which are converted to lipoproteins to form chylomicrons. The chylomicrons are transported through the lymphatic system into the thoracic duct and drained into circulation. During this process, partial FFAs are dissociated from chylomicrons through the interaction with apolipoprotein ApoC-2 present on the arteriolar endothelial cells[4–6]. The remaining chylomicron remnants are transported to the liver, where the liver TGs, cholesterol and other fats are packed together with ApoB-100 into very low density lipoprotein (VLDL)[4–6]. VLDLs sequentially become intermediate-density lipoproteins (IDLs) and low-density proteins (LDLs) as TGs and apolipoproteins are gradually removed from the capillaries of muscle and adipose tissues (Fig. 1)[4–6]. As a note, medium-chain and short-chain fatty acids do not enter the lymphatic system but directly enter the circulation through portal vein[4–6]. Taken together, fatty acids could be present in the circulation in the form of chylomicrons, LDL and FFA. Over-consumption of dietary fat will increase the serum levels of LDL and FFA. Uptake of lipids is mediated through LDL receptor (LDLR), scavenger receptors such as CD36 and Scavenger Receptor-B1 (SR-B1) expressed on the cell surface[7]. Notably, these receptors are also expressed on immune cells[8–11]. SR-B1 expressed by B cells has been shown to negatively regulate downstream signaling of TLR9 in B cells[9]. LDLR is induced to be expressed by T and B cells upon stimulation[12]. CD36 has been shown to mediate uptake of oxidized low-density lipoproteins by $CD8^+$ T cells in the tumor microenvironment, leading to lipid peroxidation and cell ferroptosis[10,11]. Therefore, the functions of intestinal immune cells could be modulated by directly sensing fatty acids and their cell-permeable metabolites. It remains to be demonstrated whether these receptors work redundantly or cooperatively to regulate fatty acids uptake by immune cells and affect the function of immune cells.

Major types of dietary fatty acids could be categorized into saturated long-chain fatty acids (LCFAs, e.g., C16:0 palmitic acid, C18:0 stearic acid), long-chain monounsaturated fatty acids (LC-MUFAs, e.g., C18:1 oleic acid), long-chain polyunsaturated fatty acids (LC-PUFAs, e.g., C18:2 linoleic acid, and C18:3 α-linolenic acid), medium-chain fatty acids (MCFAs, e.g., C8:0 caprylic acid, C10:0 capric acid, and C12:0 lauric acid)[13]. Short-chain fatty acids (SCFAs) including acetate, propionate and butyrate are not derived from food, but are generated by intestinal microbiota through fermentation of dietary fibers[13,14]. From the metabolic perspective, LCFAs but not MCFAs or SCFAs require carnitine shuttle to enter the mitochondria for oxidation[13,15]. Furthermore, SCFAs have been shown to bind to and agonize G-protein-coupled receptors (GPCRs)[14]. These differential characteristics in metabolic and signaling pathways of fatty acids may lead to distinct effects on intestinal immunity. HFD used in research contains mixed types of fatty acids and is rich in saturated LCFAs.

[1]CAS Key Laboratory of Tissue Microenvironment and Tumor, Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200031, China. [2]Department of Laboratory Medicine, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China.
✉email: mayanhui@xinhuamed.com.cn; qiuju@sibs.ac.cn

Received: 7 May 2022 Revised: 28 June 2022 Accepted: 28 June 2022
Published online: 12 July 2022

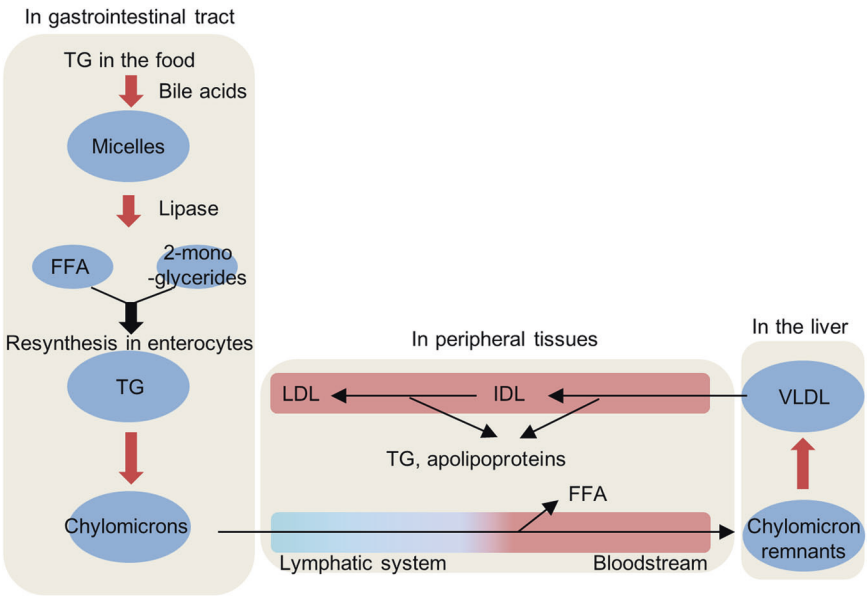

Fig. 1 Absorption and digestion of dietary fatty acids. Dietary fatty acids are packaged into micelles and digested by bile acids and lipase into FFAs and 2-monoglycerides, which are resynthesized into TGs in the enterocytes. TGs are converted to chylomicrons, which become chylomicron remnants with dissociation of FFAs. Chylomicron remnants are synthesized into VLDLs in the liver and delivered to the circulation, and gradually become IDLs and LDLs as TGs are removed from the capillaries of muscle and adipose tissues.

One of the broadly used HFD contains 35% fat by weight (60% by calories), 25% carbohydrate and 26% protein[16–19]. Lard is supplied as a source of fat composed of 38.7% saturated LCFA (mainly palmitic aid, stearic acid), 44.5% MUFA (mainly oleic acid) and 16.9% PUFA (mainly linoleic acid)[20]. Systemic metabolism of HFD also changes serum levels of cholesterol, fasting glucose and bile acids (BAs)[21–23]. These components in addition to fatty acids may be sensed by intestinal epithelial cells (IECs) and immune cells directly or indirectly to regulate intestinal immunity.

A central mechanism of how HFD regulates intestinal immunity is through the modulation of the intestinal microbiota[23]. It occurs even with a short-term HFD feeding (e.g., less than a week or temporarily during infancy) and could imprint a long term impact on intestinal immunity[19,24]. HFD has been found to alter the abundance of bacteria species responsible for induction of specific types of effector cells, which partially explains the HFD-skewed pro-inflammatory profile[25]. HFD-shaped microbiota also acts through pattern recognition receptors (PRRs) on IECs and antigen presenting cells (such as dendritic cells and macrophages), which may crosstalk with innate lymphoid cells and T cells and expand the inflammation[26]. The microbiota mediates the generation of secondary BAs, and different BAs act as agonists or antagonists on their receptors expressed by the IECs and further regulate liver BA synthesis[27]. BAs could in turn alter the microbiota profile by serving as nutrients to specific bacteria species and promoting their growth[28]. BAs could also directly act on intestinal immune cells to regulate their properties[29–31]. Therefore, the maintenance of intestinal homeostasis requires the intricate network coordinated by microbiota, IECs and immune cells.

In this review, we outline effects of dietary fatty acids, focusing on the HFD, on intestinal immunity under steady state and pathological conditions. We dissect the mechanisms of how HFD affects intestinal immunity into direct effect of fatty acids on intestinal immune cells and indirect regulation of intestinal immune responses by microbiota and IECs especially under the context of colitis, intestinal infections and tumor. Understanding these mechanisms may facilitate the development of potential strategies to treat intestinal inflammatory diseases.

Maintenance of immune homeostasis by intestinal immune cells

Intestinal immune cells localize in the epithelial layer, lamina propria and gut-associated lymphoid tissues (GALT), where they undergo efficient activation to eliminate pathogens and exhibit immune regulatory roles for timely immune resolution to prevent tissue damage. This includes the innate immune cell branch, including innate lymphoid cells (ILCs), macrophages, dendritic cells (DCs) and granulocytes, and the adaptive immune cell branch consisting of T and B cells[32].

Effects of T cells and innate lymphoid cells on intestinal immunity. The lymphoid lineage of intestinal immune cells encompasses the ILCs, T cells and B cells. T cells are one of the most abundantly present types of immune cells in the intestine[33]. Due to frequent communication with trillions of microbiota, intestinal T cells are highly activated[34]. $CD4^+$ T helper cells are classified into Th1, Th2, Th17, follicular helper T (Tfh) and regulatory T (Treg) cells based on their transcription factor expression and cytokine production[35,36]. Helper-like ILCs, lacking antigen specific receptors, mirror the characters of Th subsets[37–40]. ILC1s and Th1 cells express transcription factor T-bet, produce IFN-γ and facilitate the clearance of intracellular pathogens[41–43]. ILC2s and Th2 cells, expressing GATA3 and mainly secreting IL-5 and IL-13, are important for the expulsion of parasites and mediating allergic responses[43,44]. ILC3s share the expression of RORγt with Th17 cells, and both of them could produce IL-17 and IL-22[43,45]. ILC3s contain heterogeneous subsets including $CCR6^+NKp46^-$ILC3, $CCR6^-NKp46^-$ILC3 and $NKp46^+$ILC3[46–48]. The $NKp46^-$ILC3s are stronger producers for IL-17 and IL-22, whereas the T-bet-expressing $NKp46^+$ILC3s also secrete IFN-γ and TNF-α [46]. Studies indicate that $NKp46^+$ILC3s could be converted from $CCR6^-NKp46^-$ILC3s, and $NKp46^+$ILC3s may lose RORγt expression and become ILC1s[38,46,49]. This process is driven by pro-inflammatory cytokines such as IL-12, IL-15 and IL-18, and is considered to be implicated in the pathogenesis of Crohn's disease[38,50,51]. NK cells are cytotoxic ILCs. They are similar to the $CD8^+$ T cells and possess cytotoxic functions mediated by Perforin

and Granzyme B[52–54]. Notably, intestinal γδT cells are capable of secreting effector cytokines including IFN-γ, IL-17, and IL-22[55,56]. Intestinal Tregs are essential for controlling overt inflammation by suppressing the activity of $CD4^+$ effector T cells and myeloid cells[57–59]. Based on the origin and route of induction, intestinal Tregs could be divided into $Nrp1^+RORγt^-$ thymic-derived Tregs, $Nrp1^-RORγt^-$ food antigen-induced Tregs and $Nrp1^-RORγt^+$ microbiota-induced Tregs[60–62]. In the large intestine, $RORγt^+$ Tregs are major source of IL-10, an immunoregulatory cytokine that suppresses pathogenic T cells and supports the function of Tregs themselves[63,64].

Pro-inflammatory cytokines produced by lymphocytes exhibit immuno-defensive function to clear pathogens through recruiting and activating myeloid cells, including macrophages, neutrophils and eosinophils. IFN-γ activates macrophages by enhancing their chemokine secretion and microbial killing activity[65]. IL-5 promotes the differentiation and maturation of eosinophils[66]. IL-22 could act in synergy with IL-17 to stimulate chemokine expression such as CXCL1, which accumulates neutrophils to the inflammatory loci[67,68]. Macrophages and neutrophils are able to eliminate pathogens by phagocytosis and oxidative burst. However, this process also causes cell necrosis and tissue damage[69,70]. Importantly, IL-17 and IL-22 are critical for maintenance of intestinal homeostasis under steady state. The receptors of IL-17 and IL-22 are expressed on IECs[71,72]. IL-17 stimulates the IECs to express tight junction proteins[73], and IL-22 has been shown to promote epithelial cell regeneration by increasing the proliferation of intestinal stem cells[71,74]. Lacking IL-17 or IL-22 exacerbates experimental colitis[73,75,76].

Role of major histocompatibility complex class II (MHCII)-expressing cells in intestinal immunity. The intestinal macrophages and DCs expressing MHCII present antigens to $CD4^+$ Th cells for their activation[77]. Macrophages grouped into M1 and M2 macrophages are correlated with the activation of Th1 and Th2 cells respectively[78]. M1 macrophages are considered to be pro-inflammatory, whereas M2 macrophages have been indicated to play a protective role in IBD[79]. Recently, studies have uncovered complex features of tissue-resident macrophages outside of the M1/M2 macrophage realm[80,81]. Functional subsets of intestinal macrophages and DCs have been characterized based on surface markers into $MHCII^+CD11c^+CD103^-CD11b^+CX3CR1^+F4/80^+CD64^+$ macrophages and $MHCII^+CD11c^+CX3CR1^{int/-}F4/80^-CD64^-$ DCs[82]. The DCs could be further divided into subsets based on the expression of CD11b and CD103 to $CD103^+CD11b^-$ DCs, $CD103^+CD11b^+$DCs and $CD103^-CD11b^+$ DCs[82]. $CD11b^+CX3CR1^+$ macrophages have been shown to play a regulatory role in intestinal inflammation through producing IL-10 and maintaining Tregs[83]. They also respond to microbiota to produce IL-1β under steady state to support ILC3s to produce GM-CSF, which also supports intestinal Treg maintenance by sustaining TGF-β and retinoic acid (RA)-generating DCs[82]. Notably, among the DC subsets, the $CD103^+CD11b^+$DCs are the most potent generator of RA and contribute to both Tregs and Th17 cells generation[82,84,85].

Aside from the professional antigen presenting cells (DCs, macrophages and B cells) that express MHCII, intestinal MHCII has also been found to be expressed by ILC2s, ILC3s and IECs[86–89]. ILC3-derived MHCII has been shown to present antigens derived from intestinal microbiota to $CD4^+$ T cells to suppress their expansion and activation[86,87]. On the contrary, ILC2-derived MHCII enhances intestinal Th2 responses and accelerates the elimination of parasites[88]. IEC-derived MHCII communicates with intraepithelial $CD4^+$ T cells for them to maintain immunoregulatory functions[17,89]. Intestinal B cells and plasma cells are in charge of producing immunoglobulins essential for neutralization of pathogens and prevention of dysbiosis. B cells are particularly accumulated in Peyer's patches and isolated lymphoid follicles (ILFs) where they interact with T cells and DCs to mediate humoral responses[90,91]. Plasma cells are mainly located in the lamina propria[90]. Majority of bacteria-coated immunoglobulins are IgAs[92]. A larger proportion of intestinal IgAs are T cell independent, but both T cell dependent and independent IgA participate in regulating microbiota homeostasis[92–95]. Next, we will summarize how dietary fatty acids, focusing on the HFD, affect the functions of intestinal immune cells to modulate intestinal immunity.

Disrupted T and ILC3 responses by HFD associate with dysbiosis and colitis

Two forms of IBD in clinics are defined as the Crohn's disease (CD) and ulcerative colitis (UC). Different types of dietary fatty acids exhibit differential effects on IBD. It has been reported that intake of animal protein and n-6 PUFAs with less n-3 PUFAs increases the risk of CD, and increased intake of n-3 PUFAs reduces the risk of UC, highlighting a possible beneficial role of n-3 PUFAs in IBD[96,97]. It has been broadly demonstrated with animal experiments that increased uptake of saturated LCFAs (such as HFD feeding) induces obesity accompanied with exacerbated intestinal inflammation. However, a causal link for human obesity and IBD is not explicit[98]. Epidemiology studies have revealed a correlation between obesity and IBD, but this correlation differs in terms of age of patients, forms of IBD and requirement for surgery[99]. Research on pediatric cohorts has revealed that obesity is more likely to occur in UC than CD and is positively correlated with surgery requirements in UC, suggesting obesity a risk factor for UC[100–102].

Major changes of T and ILC3 responses by HFD. A concept acknowledged by the field is that HFD feeding or obesity is associated with an intestinal low-grade inflammation (LGI) that contributes to metabolic disorders and the susceptibility to colitis[103]. The LGI is accompanied with disrupted epithelial integrity and dysbiosis, which exacerbates the situation of each other and promotes the progression of LGI.

The LGI is reflected by aberrant T and ILC3 responses, and is present in both the lamina propria and among IECs. It has been reported that feeding of a HFD (60 kcal% fat) for 12–16 weeks leads to increased Th1, IFN-γ-producing $CD8^+$ T cells, IL-17-producing γδT cells and decreased Tregs in both the small intestine and colon lamina propria[103]. Ileum upregulation of Th1 cells and down-regulation of Tregs have also been reported by a study using 30-day HFD feeding (72 kcal% fat)[25]. The effect of HFD on Th17 cells has not been consistently observed. The same case exists for IL-6, a master inducer for Th17 differentiation in vitro and a cytokine increased with obesity. Some research has found that both IL-6 and Th17 cells are increased in fat-enriched diet (72 kcal% fat, 10 weeks; 30.9% crude fat, 4 weeks)-fed mice under steady state or in pathological conditions[104–107]. This may explain HFD-worsened 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis or autoimmunity experimental encephalomyelitis (EAE), where Th17 cells play pathogenic roles[104,106,107]. Intriguingly, other studies show contradictory phenotypes with unchanged or reduced IL-6 and Th17 cells in mice fed with HFD (72 kcal% fat, 30 days; 60 kcal% fat, 6 weeks or 10 weeks)[25,103,108]. It has been observed that HFD (60 kcal % fat, 12–14 weeks) suppresses the maintenance of $CX3CR1^+$ macrophages and $CD11b^+CD103^+$ DCs, which may contribute to the reduction of Tregs and Th17 cells[83,84,109]. Notably, ILC3s with overlapping functions with Th17 cells, have reduced IL-22 production after HFD feeding (60 kcal% fat, 4 weeks or 8 weeks)[16,110]. Another study found that mRNA expression of IL-22 was reduced in the colon of HFD-fed mice (60% fat, starting at the age of 4–8 weeks old for at least 8 weeks) upon *Citrobacter rodentium* infection[111]. Serum IL-22 level was found to be decreased in HFD-fed mice after flagellin injection[111]. Furthermore, the percentage of $CD4^+IL\text{-}22^+$ cells, which could be the IL-22-producing Th cells and/or the IL-22-producing $CD4^+$ ILC3s[43], was decreased in the draining lymph nodes of HFD-fed mice upon ovalbumin/complete Freund's adjuvant immunization[111]. Interestingly, increased $T\text{-}bet^+NKp46^+$ILC3s and ILC1s are found in high-fat and high-sucrose diet (40% fat, 12 weeks) fed mice[110],

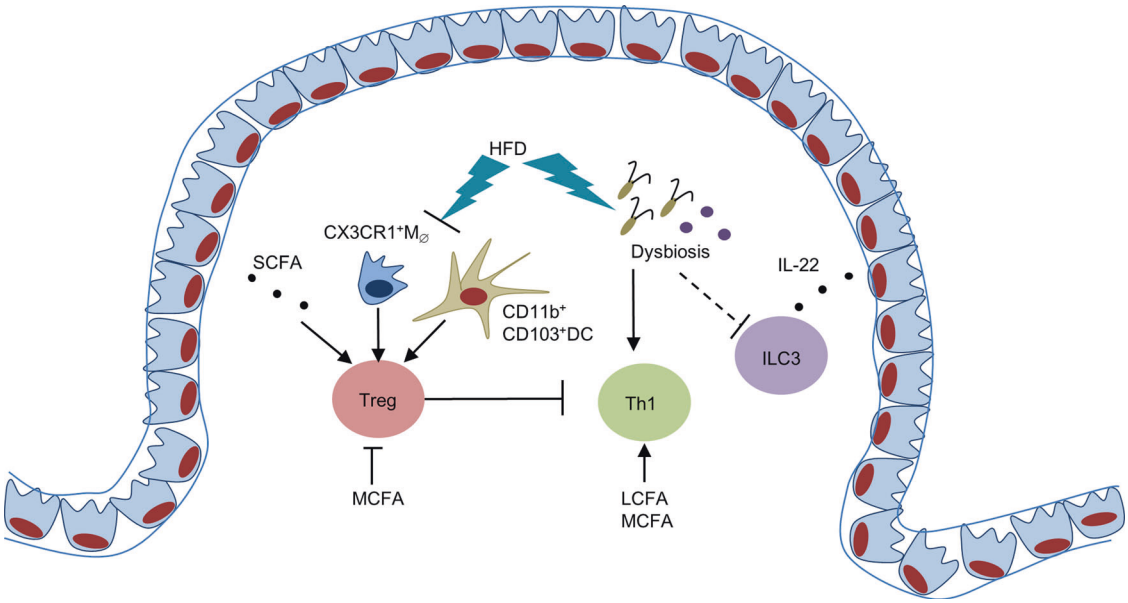

Fig. 2 HFD disturbs T and ILC3 responses in the intestinal lamina propria. HFD induces a pro-inflammatory profile manifested by reduced Tregs and IL-22-producing ILC3s, as well as increased Th1 cells in the intestinal lamina propria. The decrease of Tregs may be attributed to the ablated maintenance of Treg-promoting CX3CR1^{+} macrophages and CD11b^{+}CD103^{+} DCs. Moreover, HFD suppresses the SCFAs that have been shown to cell-intrinsically promote intestinal Treg induction. The decrease of Tregs may contribute to uncontrolled pro-inflammatory Th1 responses. In addition, HFD-induced dysbiosis may cause increased Th1 response while inhibiting IL-22 production by ILC3s. Fatty acids could directly act on Th cells. Both LCFAs and MCFAs increase Th1 differentiation, whereas MCFAs suppress Treg differentiation demonstrated by in vitro experiments.

implying the likely conversion of IL-22 competent NKp46^{-}ILC3 to NKp46^{+}ILC3 and ILC1, a process implicated in the development of IBD[50,51]. Mucosal-associated invariant T (MAIT) cells, expressing one invariant TCR α-chain and a limited number of β-chains, recognize antigens in the major histocompatibility complex-related molecule 1 (MR1)-restricted manner and play a critical role in mucosal immunity[112]. It has been shown that ileum MAIT cells are reduced but produce higher IL-17 in HFD-fed mice (60 kcal% fat, 12 weeks)[113]. Moreover, MAIT cells exacerbate intestinal inflammation by promoting M1 macrophage differentiation and inhibiting Tregs[113]. As discussed above, IL-17 acts as a double-edge sword in intestinal immunity. It is possible that IL-17 originated from different types of cells exhibits distinct roles by communicating with surrounding cells and initiates distinct downstream cascades. The inconsistency in HFD-induced Th17 responses may be due to variations in microbiota, time points of observation and disease situations. These precise mechanisms remain to be further investigated. Intraepithelial lymphocytes (IELs) contain heterogeneous subtypes, including the immunoregulatory T cells that secrete TGF-β and IL-10[114–117]. HFD depletes both intraepithelial CD4^{+} and CD4^{+}CD8^{+} αβ T cells probably by down-regulating the gut-homing molecules including CD103 and CCR9 expressed by IELs (60 kcal% fat, 7–46 weeks)[118]. Switching HFD to normal diet restores the αβ T cells of the IELs and resolves intestinal inflammation[118]. Taken together, disrupted immune homeostasis reflected by decreased immunoregulatory Tregs, IELs and IL-22^{+}ILC3s, in addition to increased pathogenic Th1 and IL-17^{+} MAIT cells, may cooperatively contribute to LGI and susceptibility to colitis (Fig. 2).

Direct effects of fatty acids on T cells. One mechanism explaining the immunological perturbation by HFD is through direct action of fatty acids on T cells. Different types of fatty acids have been found to play distinct roles in intestinal immune responses. Long-chain and medium-chain saturated fatty acids could promote the differentiation of Th1 and Th17 cells, and lauric acid as one type of the medium-chain saturated fatty acids also suppresses the differentiation of Tregs in vitro[106]. In vivo, feeding mice with lauric acid-enriched diet (30.9% crude fat rich in the lauric acid, 4 weeks) increased small intestinal Th1 and Th17 responses. A study showed that lauric acid-enriched diet resulted in decreased level of SCFAs possibly due to decreased *Bacteroidetes* facilitating fermentation of fiber-rich nutrition into SCFAs[106]. SCFAs have been consistently demonstrated to promote Tregs through directly activating FFAR2 expressed by Tregs and inhibiting JNK/p38 pathway[106,119,120]. These findings support a role of lauric acid in suppressing Tregs in vivo, although further data are needed to validate this hypothesis. PUFAs inhibit Th17 cells ex vivo and ameliorate experimental colitis in vivo[121,122]. Oleic acid is found to be one of the highest represented LCFA in human serum and promotes the induction and suppressive function of Tregs in vitro[123]. Mechanistically, it has been indicated that LCFAs support the proliferation and function of Tregs possibly through increasing fatty acid oxidation (FAO) and mitochondria oxidative phosphorylation[124]. But this concept has been challenged by the evidence that the rate-limiting enzyme carnitine palmitoyltransferase 1 (Cpt1a) for LCFA FAO may be dispensable for the induction or maintenance of Tregs both in vitro and in vivo[125,126]. It is interesting to observe that some types of fatty acids exhibit consistent functions on T cell responses in vitro and in vivo, suggesting that in vitro experiments can be an efficient system for screening fatty acids candidates to achieve specific regulation of intestinal immunity. However, it remains to be demonstrated if Th cells increase their fatty acids uptake and undergo metabolic change in vivo following dietary fatty acids or HFD feeding.

HFD shapes microbiota to modulate T and ILC3 responses. The microbiota plays a central role in regulating intestinal immunity in the context of HFD feeding. Revisiting different cohorts of studies indicate that HFD reproducibly alters the microbiota pattern by decreasing the ratio of *Bacteroidetes* over *Firmicutes*[13,16,127]. Many reports also consistently observe increased *Proteobacteria* and reduced *Bifidobacterium*[13,16,128]. Notably, *Lactococcus* species have been consistently found to be increased in HFD-fed animals[127]. However, this has been demonstrated to be due to nonviable

Lactococcus contamination from the irradiated HFD. Such a bias needs to be considered when performing bacteria sequencing analysis. Furthermore, *Lactococcus* has been indicated to have proinflammatory properties, which may affect the interpretation of altered intestinal immunity affected by live bacteria upon HFD feeding[127]. Intestinal Th cell and ILC3 responses are closely related to microbiota profile shaped by dietary fatty acids or HFD. Increased intestinal Th1 and Th17 responses in mice fed with lauric acid-enriched diet could be recapitulated in germ free mice fed with normal diet by fecal transplantation[106]. This may be attributed to the change of specific bacteria species being able to induce distinct immune responses. For example, Th17-inducing bacteria including *Porphyromonadaceae*, *Segmented filamentous bacteria* (SFB), and *Bifidobacterium* are decreased by lauric acid[25]. Restoration of *Bifidobacterium lactis* recovers the lauric acid-suppressed Th17 cells[25]. Notably, it has been consistently observed that HFD reduces the level of SCFAs (60 kcal% fat, 4 weeks)[16], which plays a regulatory role in intestinal immunity through induction of Tregs and supporting IL-22 production by ILC3s[119,129]. One of the explanations for this decreased SCFAs is that the recipe of HFD used by research is lack of soluble fiber, which is critical source for SCFA generation through bacterial fermentation[16]. But in a study without specifying the content of fibers, feeding mice with lauric acid could actively downregulate fecal SCFAs level, suggesting the participation of fiber-independent mechanisms such as microbiota[106]. Consistently, the addition of soluble fiber could upregulate SCFAs and recover reduced IL-22-producig ILC3s caused by HFD feeding. Nevertheless, the recovery of IL-22 production of ILC3s by fiber supplementation is through microbiota-dependent but SCFA-independent mechanism[16]. Although it has been well-acknowledged that the change of microbiota by HFD feeding affects intestinal T and ILC responses, a clear mechanistic link between microbiota and specific immune responses haven't been established. Antigens, virulence factors, or metabolites derived from different microbiota that contribute to skewed T/ILC3 responses upon HFD feeding remain to be determined.

HFD curtails intestinal IgA production

IgA is the major type of immunoglobulin generated in the intestine and is essential for defense against pathogenic bacteria and prevention of dysbiosis[93,95]. Studies indicate that IgA generation is reduced by HFD (60% kcal diet, 12–16 weeks), which possibly contributes to the disorganized microbiota and intestinal inflammation[109]. Reduction of intestinal IgA, IgG and IgM upon HFD (34.6% fat, 2 months) feeding has been revealed by proteomics analysis[130]. It has been shown that the colonic, rather than small intestinal or Peyer's patches, plasma cells have decreased IgA production in HFD-fed mice[109]. A potential mechanism is that HFD leads to decreased frequencies of colonic $CD11b^+CD11c^+CD103^+$ DCs, capable of converting vitamin A to RA to facilitate IgA generation[109]. Previous research has also demonstrated that dietary cholesterol could raise the level of 25-hydroxycholesterol, which inhibits Peyer's patches B cell activation and the generation of IgA through regulating SREBP2 expression in B cells[131]. This lack of IgA results in exacerbated *Salmonella* infection. As HFD increases serum level of cholesterol, there is a chance that metabolites of cholesterol such as 25-hydroxycholesterol is also increased and suppresses IgA production[21]. Interestingly, when supplied at a low ratio in contrast to the HFD recipe, palm oil (enriched in palmitic acid, 4%) but not soybean oil or coconut oil has been found to increase the intestinal IgA. Palm oil also boosts IgA against orally immunized antigens, proposing it being an adjuvant for oral vaccination[132]. This indicates that low dose of LCFA may have a beneficial role in intestinal immunity by promoting IgA production. It will be interesting to investigate how different types and doses of fatty acids affect the generation of T cell dependent or independent IgA production, which may affect intestinal microbiota distribution and intestinal immunity.

HFD disrupts IEC homeostasis and promotes colitis and tumor

IECs contain specialized and heterogeneous populations, including enterocytes, Paneth cells, goblet cells, enterochromaffin cells and tuft cells, in charge of nutrient absorption, mucin secretion, mucosal defense, transmission of lumen antigens and neuroendocrine functions[133]. We have summarized HFD-perturbed T cell and ILC responses that are closely related to dysbiosis and damaged epithelial integrity, leading to intestinal inflammation. Importantly, IECs could directly sense fatty acids and microbiota, act as an initiator of downstream inflammation cascades, and communicate with macrophages and T cells to affect intestinal immunity under the context of HFD feeding. HFD-disturbed IEC homeostasis exacerbates colitis and even leads to carcinogenesis.

Disruption of the mucin layer by HFD. Damage of the intestinal mucus layer by HFD is closely linked to dysbiosis. Transmembrane or gel-forming mucins secreted by intestinal enterocytes or goblet cells establish a barrier to prevent the intrusion of pathogens[134]. HFD (40% fat, 4 weeks) has been shown to cause decreased mucin production[128,135]. This could partly be due to the increased abundance of mucin-degrading bacteria[128]. Notably, one of the specialized mucin-degrading bacteria *Akkermansia muciniphila* has been observed to be decreased in HFD-fed mice (60% fat, 4 weeks) or obese people[136]. We speculate that while pathological amount of *A. muciniphila* disturbs intestinal mucus layer and is harmful to intestinal homeostasis, *A. muciniphila* at the physiological level utilizes the mucin glycan for their maintenance without causing damage to the mucus layer. Rather, *A. muciniphila* is required for intestinal homeostasis possibly by generating SCFAs and detoxifying hydrogen sulfide (H_2S)[137]. Another report has shown that *A. muciniphila*-derived extracellular vesicles increase occluding expression by human epithelial cell line[138], thereby improving the epithelial tight junction function. Restoration of *A. Muciniphila* significantly improves the epithelial barrier function, and *A. muciniphila* has been shown to play a protective role in preventing dextran sulfate sodium (DSS)-induced colitis[136,139]. Interestingly, it has been shown that peroxisome proliferator-activated receptor-γ (PPARγ) agonist ameliorates whereas PPARγ specific deletion in IECs exacerbates dysbiosis and mucin loss under HFD feeding[128]. Therefore, it is likely that IECs may directly sense fatty acids through PPARγ to interplay with intestinal microbiota and maintain a beneficially mutualistic environment.

Activation of microbiota-IEC-macrophage axis. Disruption of the mucin layer expands the interface for pathogen intrusion. The IECs express a series of PRRs sensing pathogens and MyD88 has been indicated as a common adaptor downstream of a group of Toll-like receptors (TLRs)[140]. MyD88 expression by IECs has been shown to play a pathogenic role in HFD-induced obesity and inflammation[141]. Deletion of MyD88 in IECs restores Tregs and improves dysbiosis. This may further lead to uncontrolled activation of pro-inflammatory T cells and exacerbate dysbiosis in a feed-forward loop. In addition to MyD88-dependent signaling, a study using zebra fish has revealed that acute HFD or high-cholesterol diet (HCD) feeding induces an IL-1β-dependent accumulation of myeloid cells in the intestine[142]. Further analysis has revealed that dietary fat facilitates HCD-induced inflammasome activation in IECs, which is responsible for recruitment of $CD11b^+$ and $CD11c^+$ myeloid cells. This process is dependent on the microbiota suggesting that the activation of inflammasomes may be attributed to upstream activation of PRRs such as the NOD-like receptor (NLR) family members by intruded pathogenic bacteria derivatives due to disrupted epithelial barrier[143]. Similar observations have also been reported in mouse studies. It has been shown that HFD (60% of fat, 24 weeks)-induced CCL2

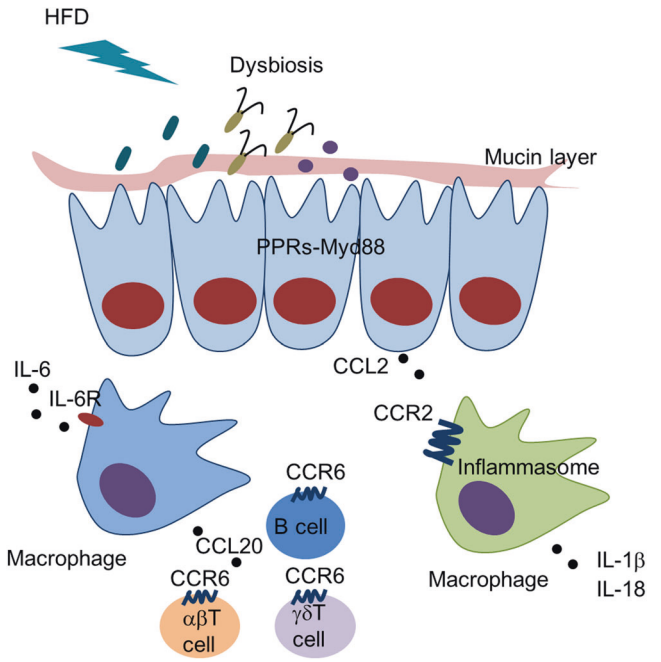

Fig. 3 HFD induces intestinal inflammation through the IEC-macrophage axis. HFD leads to decreased mucin production by intestinal goblet cells. Dysbiosis caused by HFD may exacerbate the destruction of mucin layer. This leads to intrusion of the intestinal pathogenic bacteria which activates IECs and macrophages through PRRs. HFD enhances CCL2 expression by IECs, accumulating $CCR2^+$ macrophages to the intestine. Inflammasome activation of the $CCR2^+$ macrophages mediates production of IL-1β and IL-18, which may increase intestinal inflammation. Moreover, increased IL-6 in the colon has been shown to induce CCL20 production by macrophages, which recruits the CCR6-expressing T and B cells to worsen CAC.

expression by IECs is required for the recruitment of $CCR2^+$ macrophages to the intestine. Inflammasome activation was found in colonic macrophages dependent on the CCL2-CCR2 axis[144]. This further led to overt production of IL-1β and IL-18, which may increase the susceptibility to colitis[145,146]. The recruited macrophages could also respond to increased IL-6 in the colon and enhance their production of CCL20[147]. The latter accumulates CCR6-expressing B cells, αβ T and IL-17-producing γδ T cells to the inflammatory site, which contributes to the pathogenesis of colitis-associated colorectal cancer (CAC)[147]. The above observations propose a model that epithelial integrity damaged by HFD promotes aberrant activation of IECs and macrophages to further expand the inflammatory circuit by aggravating dysbiosis and triggering the activities of proinflammatory lymphocytes (Fig. 3).

HFD suppresses MHCII expression by IECs. In addition to the bacteria-IEC-macrophage axis, IECs including the $Lgr5^+$ intestinal stem cells (ISCs) have been indicated to directly communicate with the T cells (IELs) through MHCII[17,18,89]. The MHCII expression by ISCs could be upregulated by activation of TLR2/NOD2 and IFN-γ[18]. Moreover, the expression of MHCII on IECs is diurnally regulated by dietary contents and microbiota[17]. Both HFD and antibiotics treatment ablate MHCII expression by IECs, and restoration of germ-free mice with microbiota of HFD-fed mice shows deficiency of MHCII expression by IECs[17]. Bacterial mono-colonization studies have revealed *Akkermansia*, *Lachnospiraceae* and SFB as "inducers" and *Lactobacillus murinus* as "suppressor" of MHCII expression by IECs[17]. The correlated change of microbiota in HFD-fed mice may account for decreased expression of MHCII by IECs. ISCs, localizing at the base of the crypt and giving rise to heterogeneous subtypes of

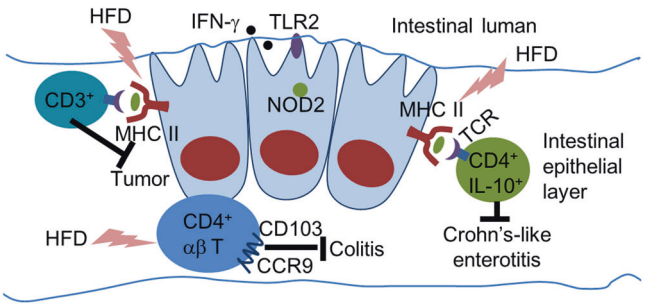

Fig. 4 HFD impairs the maintenance of IELs. Expression of MHCII by IECs could be induced by TLR2 and NOD2 signaling, as well as type 1 cytokine IFN-γ. IEC-derived MHCII sustains IELs including the immunoregulatory $CD4^+IL\text{-}10^+$ IELs and other tumor-suppressive $CD3^+$ T cells. HFD perturbs MHCII expression by IECs accompanied with decreased IELs. HFD has also been shown to reduce the expression of gut-homing molecules including CD103 and CCR9 by IELs. These mechanisms are considered to contribute to the HFD-increased susceptibility to Crohn-like enteritis, intestinal tumor and colitis.

IECs, are considered to be the origin of precancerous dysplasias and are key targets of the HFD-promoted carcinogenesis[148]. Genetic deletion of MHCII expression in ISCs specifically impairs the homeostasis of ISC-adjacent Th cells and the immunoregulatory $CD4^+IL\text{-}10^+$ IELs, therefore exacerbating Crohn-like enteritis[17]. This is likely to be a mechanism for HFD-sensitized colitis accompanied with depletion of IELs. HFD (60 kcal% fat, 9 to 14 months)-suppressed MHCII expression by ISCs also increases their tumor initiating capacity[18]. This is correlated with a loss of intraepithelial T cells possibly involved in anti-tumor immunity. These evidences support a notion that disruption of microbiota-MHCII-IEL axis by HFD contributes to the increased incidence of IBD and intestinal tumor (Fig. 4).

Single cell transcriptome sequencing will be helpful to identify phenotypes and functions of specific subsets of IECs, which may account for distinct immune responses affected by HFD feeding. This will facilitate the discovery of potential targets for treatment of IBD and colon cancer linked with western diet consumption or obesity. IECs also express sensors for different BAs altered by HFD to regulate intestinal immunity[149,150]. As increased studies have discovered the immunoregulatory role of BAs, we discuss these findings as a separate section below.

Emerging roles of BAs in HFD-caused intestinal pathogenesis

Primary BAs synthesized in the liver are present as chenodeoxycholic acid (CDCA, rapidly converted to muricholic acid (MCA) in rodents) and cholic acid (CA)[151]. The primary BAs stored in the gall bladder are conjugated with taurine (in mice) or taurine and glycin (in humans)[151]. Food ingestion stimulates the release of BAs to the duodenum to facilitate the digestion and absorption of fatty acids, cholesterol and fat-soluble vitamins. In the intestine, primary BAs undergo a series of bio-transformation procedures including deconjugation, 7α-dehydroxylation, oxidation and epimerization for generation of secondary BAs[27,151,152]. Intestinal microbiota plays a key role in BA metabolism[27,152]. Different types of bacteria are enriched in specific types of enzymes that catalyze distinct procedures of BA bio-transformation. As the HFD quickly and profoundly alters the microbiota profile, it also significantly changes the BA composition[22]. Different BAs act as agonists or antagonists for their receptors, categorized into several family members of proteins including farnesoid X receptor (FXR), the constitutive androstane receptor (CAR), the pregnane X receptor (PXR), the liver X receptor (LXR), and the vitamin D receptor (VDR), GPCRs, muscarinic receptors and sphingosine 1 (SP-1) receptor[152]. The above receptors could be expressed on IECs and intestinal immune cells, which serve as a base for the bioactivity of BAs on intestinal immunity.

Both primary and secondary BAs have been reported to be changed by HFD[22]. *Clostridioides difficile* infection, often caused by long-term antibiotics administration and one of the most common nosocomial infections, is reported to be accelerated by HFD (60 kcal% fat, 14–16 weeks)[153]. This has been found to be correlated with increased primary conjugated BAs that promote spore germination of *C. difficile*[153]. The composition of BA is differentially affected by different types of fatty acids. Milk fat (rich in saturated fatty acids, 37 kcal% fat, 5 weeks) but not safflower oil (rich in PUFAs) increases taurocholic acid, which could serve as sulfur source for sulfite-reducing bacteria *Bilophila wadsworthia*[154]. *B. wadsworthia* has been shown to promote Th1 responses and exacerbate the colitis of *Il10*$^{-/-}$ mice[154]. Notably, IECs directly sense HFD -induced BAs through receptors such as FXR and TGR-5 to affect their homeostasis. HFD increases the generation of tauro-β-muricholic acid (T-β-MCA) and deoxycholic acid (DCA) acting as FXR antagonist to relieve the proliferation of cancer stem cells (60 kcal% fat, 6 weeks)[149]. Interestingly, activation of TGR-5 expressed on ISCs by secondary BAs including the lithocholic acid (LCA) and DCA facilitates the growth of intestinal organoids[150]. These observations may be served as supplementary mechanisms for cancer-promoting effect of HFD described in the previous section.

Recently, several kinds of secondary BAs have been found to regulate intestinal Th cells. Through functional screening and validation, 3-oxoLCA has been identified to inhibit intestinal Th17 cells[30], whereas isoalloLCA and isoDCA promote intestinal Tregs[30,31]. The induction of Tregs by secondary BAs is protective against intestinal inflammation[29]. Importantly, the generation of RORγt^{+}Treg-inducing secondary BAs is dependent on bacterial expression of bile salt hydrolase[29]. Mechanistically, secondary BAs could signal through VDR expressed by Tregs or by inhibiting FXR activity expressed on DCs to promote intestinal Tregs[29,31]. These findings open an exciting research area to establish specific relationships among different types of fatty acids, microbiota and BAs-induced immune responses, which are valuable for potential treatment of IBD by targeting BAs.

Maternal HFD imprints a long-term effect on intestinal immunity in offspring

Recent studies suggest that maternal HFD increases the susceptibility to colitis in offspring. Even when the young descendants are switched back to and maintained on normal diet after weaning, they are still susceptible to colitis when grown to adults[24,105]. Infancy is found to be a critical period of time when there is a fluctuation of microbiota profile and stimulated immune responses, discovered as the "weaning reaction"[155]. It occurs between 2–4 weeks old in mice and is featured by transient increase in proinflammatory cytokine production accompanied with the generation of RORγt^{+}Tregs[155]. RA and SCFAs have been found to play a critical role in the generation of RORγt^{+}Tregs during weaning reaction, the lack of which predispose the offspring to colitis, allergy and cancer in adult stage[105,155]. Maternal HFD (60 kcal% fat, 6 weeks before gestation till the end of lactation) has been found to ablate the weaning reaction by causing overproduction of pro-inflammatory cytokines including TNF-α and IFN-γ, responsible for increased childhood intestinal permeability and adult sensitivity to colitis[24]. Meanwhile, maternal HFD (60% fat, at least 5 weeks before gestation till the end of lactation) increases in IL-17 expression by ILC3s through a microbiota dependent and adaptive immune system independent manner, resulting in childhood necrotizing enterocolitis[156]. Infancy HFD feeding also increases harmful H_2S production by pathogenic bacteria, and pharmacological inhibition of bacterial H_2S production or antibiotics treatment corrects intestinal inflammation and adult susceptibility to colitis[24]. Importantly, it has been shown that co-house of HFD-nursed (60 kcal% fat, during gestation and lactation) pups with normal diet nursed-pups eliminates potential inflammation[105]. Supplementing SCFAs, fermentation product of bacteria, to young mice under maternal HFD ameliorates colitis in a RORγt^{+}Treg dependent manner[24]. Strategies of blocking bacterial H_2S production or antibiotics treatment were performed during maternal HFD feeding. The above evidence strongly indicates a critical role of microbiota, rather than increased calorie intake, in imprinting a susceptibility to colitis in maternal HFD-fed offspring. However, it remains to be determined whether fatty acids or microbiota from the breast milk contributes to the dysbiosis in maternal HFD-fed offspring.

Summary and concluding remarks

HFD-induced obesity has been found to be closely associated with high incidence of intestinal inflammation and tumor. This usually starts with an intestinal LGI featured by pro-inflammatory immune cell activation, damaged epithelial integrity and dysbiosis. We have summarized the direct effects of fatty acids on specific immune cell subsets, which may explain the changed intestinal immune responses by HFD, as well as indirect effects of HFD on intestinal immune subsets by affecting microbiota or intestinal epithelial cells (Table 1). As a central change in HFD feeding, the

Table 1. Direct and indirect effects of HFD on intestinal immune cells.

Direct effects	
Types of fat	Effect on immune cells
LCFA and MCFA	Promote Th1 and Th17 differentiation in vitro[106]
Oleic acid (LCFA)	Promote the induction and suppressive function of Tregs in vitro[123]
Lauric acid (MCFA)	Suppress differentiation of Tregs in vitro[106]
PUFAs (0.17% α-linolenic acid)	Inhibit TGF-β1 and increased IL-10 expression by DCs ex vivo[121]
SCFA	Promote Tregs differentiation in vitro and in vivo[106,119,120]
Indirect effects	
Type of fat and feeding protocol	Effect on immune cells
Lauric acid (MCFA)	Increase intestinal Th1 and Th17 responses through microbiota[106]
HFD (60% fat, 8 weeks)	Suppress Tregs through activation of MyD88 in IECs[141]
HFD (7.8% Oil, 10 days)	Increase CD11b^{+} and CD11c^{+} myeloid cell accumulation through regulating IEC in zebrafish[142]
HFD (62% fat, 24 weeks)	Increase CCR2^{+} macrophages accumulation through inducing CCL2 expression by IECs[144]
HFD (60% fat, 5 months)	Increase IL-17 expression by ILC3s through regulating microbiota[156]
Milk fat (24 weeks)	Promotes Th1 responses through increasing taurocholic acid, which supports the growth of *Bilophila wadsworthia*[154]

shift of microbiota profile breaks the epithelial mucin layer and causes pathogen intrusion. This activates IECs or macrophages through PRRs and may further expand the inflammatory circuits by recruitment and activation of inflammatory T cells. HFD also inhibits MHCII expression by IECs, which may contribute to depletion of IELs and increase the occurrence of colitis and tumor. Although mechanisms of how HFD affects intestinal inflammation have been investigated extensively, there are variations in phenotypes and conclusions in terms of the change of specific types of inflammatory responses and altered bacteria species. This may be due to different types of dietary fatty acids, variation in percentages of calories from dietary fatty acids in HFD recipes, as well as different microbiota distribution in research facilities. However, consistency or inconsistency in these findings may be helpful to interpret complex situations in human populations with strong diversities in microbiota and types of dietary fat consumption. It will be interesting to dissect how specific types of fatty acids affect intestinal immunity and delineate their corresponding targets involving bacteria species, bacterial metabolites and their downstream signaling pathways.

HFD-induced obesity is accompanied with metabolic disorders manifested by elevated level of cholesterol, increased blood glucose and insulin resistance. Sensors for cholesterol metabolites[157], glucose transporters[158,159] and insulin receptor (InsR)[160,161] have been reported to be expressed by immune cells and affect the function of immune cells. It will be interesting to examine whether cholesterol and glucose metabolism, as well as insulin signaling, altered by HFD affect the function of intestinal immune cells and regulate intestinal immunity. The understanding of these mechanisms will be helpful for developing potential strategies for the diagnosis, prevention and treatment of intestinal inflammatory diseases.

REFERENCES

1. Basson, A. R. et al. Regulation of intestinal inflammation by dietary fats. *Front Immunol.* **11**, 604989 (2020).
2. Siracusa, F., Schaltenberg, N., Villablanca, E. J., Huber, S. & Gagliani, N. Dietary habits and intestinal immunity: from food intake to CD4(+) T H cells. *Front Immunol.* **9**, 3177 (2018).
3. Veldhoen, M. & Brucklacher-Waldert, V. Dietary influences on intestinal immunity. *Nat. Rev. Immunol.* **12**, 696–708 (2012).
4. Cheng, H.M., Mah K.K., Seluakumaran K. Fat digestion: bile salt, emulsification, micelles, lipases, chylomicrons. *Defining Physiology: Principles, Themes, Concepts*. Springer, Cham, 2020.
5. Voet, D., Voet, J.G. Lipid metabolism. *Biochemistry, 4th Edition*, 2010.
6. Vučić, V., Cvetković, Z. Cholesterol: absorption, function and metabolism. *The Encyclopedia of Food and Health, Five Volume Set*, 2016.
7. Abumrad, N. A. et al. Endothelial cell receptors in tissue lipid uptake and metabolism. *Circ. Res* **128**, 433–450 (2021).
8. Linton, M. F., Babaev, V. R., Gleaves, L. A. & Fazio, S. A direct role for the macrophage low density lipoprotein receptor in atherosclerotic lesion formation. *J. Biol. Chem.* **274**, 19204–19210 (1999).
9. Zhu, P., Liu, X., Treml, L. S., Cancro, M. P. & Freedman, B. D. Mechanism and regulatory function of CpG signaling via scavenger receptor B1 in primary B cells. *J. Biol. Chem.* **284**, 22878–22887 (2009).
10. Ma, X. et al. CD36-mediated ferroptosis dampens intratumoral CD8(+) T cell effector function and impairs their antitumor ability. *Cell Metab.* **33**, 1001–1012 (2021). e1005.
11. Xu, S. et al. Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8(+) T cells in tumors. *Immunity* **54**, 1561–1577 (2021).
12. Amirache, F. et al. Mystery solved: VSV-G-LVs do not allow efficient gene transfer into unstimulated T cells, B cells, and HSCs because they lack the LDL receptor. *Blood* **123**, 1422–1424 (2014).
13. Machate, D. J. et al. Fatty acid diets: regulation of gut microbiota composition and obesity and its related metabolic dysbiosis. *Int. J. Mol. Sci.* **21**, 4093 (2020).
14. Dalile, B., Van Oudenhove, L., Vervliet, B. & Verbeke, K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 461–478 (2019).
15. Schonfeld, P. & Wojtczak, L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J. Lipid Res.* **57**, 943–954 (2016).
16. Zou, J. et al. Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. *Cell Host Microbe* **23**, 41–53 (2018).
17. Tuganbaev, T. et al. Diet diurnally regulates small intestinal microbiome-epithelial-immune homeostasis and enteritis. *Cell* **182**, 1441–1459 (2020). e1421.
18. Beyaz, S. et al. Dietary suppression of MHC class II expression in intestinal epithelial cells enhances intestinal tumorigenesis. *Cell Stem Cell* **28**, 1922–1935 (2021). e1925.
19. Foley, K. P. et al. Long term but not short term exposure to obesity related microbiota promotes host insulin resistance. *Nat. Commun.* **9**, 4681 (2018).
20. Silva, R. S. F. et al. Interesterification of lard and soybean oil blends catalyzed by immobilized lipase in a continuous packed bed reactor. *J. Am. Oil Chem. Soc.* **88**, 1925–1933 (2011).
21. Fernandez, M. L. & West, K. L. Mechanisms by which dietary fatty acids modulate plasma lipids. *J. Nutr.* **135**, 2075–2078 (2005).
22. Zeng, H., Umar, S., Rust, B., Lazarova, D. & Bordonaro, M. Secondary bile acids and short chain fatty acids in the colon: a focus on colonic microbiome, cell proliferation, inflammation, and cancer. *Int. J. Mol. Sci.* **20**, 1214 (2019).
23. Howard, E. J., Lam, T. K. T. & Duca, F. A. The gut microbiome: connecting diet, glucose homeostasis, and disease. *Annu Rev. Med*. **73**, 469–481 (2022).
24. Al Nabhani, Z. et al. Excess calorie intake early in life increases susceptibility to colitis in adulthood. *Nat. Metab.* **1**, 1101–1109 (2019).
25. Garidou, L. et al. The gut microbiota regulates intestinal CD4 T cells expressing RORgammat and controls metabolic disease. *Cell Metab.* **22**, 100–112 (2015).
26. Brandsma, E., Houben, T., Fu, J., Shiri-Sverdlov, R. & Hofker, M. H. The immunity-diet-microbiota axis in the development of metabolic syndrome. *Curr. Opin. Lipido.* **26**, 73–81 (2015).
27. Ridlon, J. M., Kang, D. J. & Hylemon, P. B. Bile salt biotransformations by human intestinal bacteria. *J. Lipid Res.* **47**, 241–259 (2006).
28. Wahlstrom, A., Sayin, S. I., Marschall, H. U. & Backhed, F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metab.* **24**, 41–50 (2016).
29. Song, X. et al. Microbial bile acid metabolites modulate gut RORgamma(+) regulatory T cell homeostasis. *Nature* **577**, 410–415 (2020).
30. Hang, S. et al. Bile acid metabolites control TH17 and Treg cell differentiation. *Nature* **576**, 143–148 (2019).
31. Campbell, C. et al. Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. *Nature* **581**, 475–479 (2020).
32. Mowat, A. M. & Agace, W. W. Regional specialization within the intestinal immune system. *Nat. Rev. Immunol.* **14**, 667–685 (2014).
33. Ma, H., Tao, W. & Zhu, S. T lymphocytes in the intestinal mucosa: defense and tolerance. *Cell. Mol. Immunol.* **16**, 216–224 (2019).
34. Visekruna, A. et al. Intestinal development and homeostasis require activation and apoptosis of diet-reactive T cells. *J. Clin. Invest* **129**, 1972–1983 (2019).
35. Zhu, X. & Zhu, J. CD4 T helper cell subsets and related human immunological disorders. *Int. J. Mol. Sci.* **21**, 8011 (2020).
36. Li, P., Spolski, R., Liao, W. & Leonard, W. J. Complex interactions of transcription factors in mediating cytokine biology in T cells. *Immunol. Rev.* **261**, 141–156 (2014).
37. Vivier, E. et al. Innate lymphoid. *Cells.: 10 Years . Cell* **174**, 1054–1066 (2018).
38. Klose, C. S. N. et al. Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell* **157**, 340–356 (2014).
39. Diefenbach, A., Colonna, M. & Koyasu, S. Development, differentiation, and diversity of innate lymphoid cells. *Immunity* **41**, 354–365 (2014).
40. Guia, S. & Narni-Mancinelli, E. Helper-like Innate lymphoid cells in humans and mice. *Trends Immunol.* **41**, 436–452 (2020).
41. Spits, H., Bernink, J. H. & Lanier, L. NK cells and type 1 innate lymphoid cells: partners in host defense. *Nat. Immunol.* **17**, 758–764 (2016).
42. Cortez, V. S. & Colonna, M. Diversity and function of group 1 innate lymphoid cells. *Immunol. Lett.* **179**, 19–24 (2016).
43. Annunziato, F., Romagnani, C. & Romagnani, S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J. Allergy Clin. Immunol.* **135**, 626–635 (2015).
44. Gurram, R. K. & Zhu, J. Orchestration between ILC2s and Th2 cells in shaping type 2 immune responses. *Cell. Mol. Immunol.* **16**, 225–235 (2019).
45. Kumar, R., Theiss, A. L. & Venuprasad, K. RORgammat protein modifications and IL-17-mediated inflammation. *Trends Immunol.* **42**, 1037–1050 (2021).
46. Klose, C. S. et al. A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells. *Nature* **494**, 261–265 (2013).
47. Satoh-Takayama, N. et al. The chemokine receptor CXCR6 controls the functional topography of interleukin-22 producing intestinal innate lymphoid cells. *Immunity* **41**, 776–788 (2014).

48. Secca, C. et al. Spatial distribution of LTi-like cells in intestinal mucosa regulates type 3 innate immunity. *Proc. Natl. Acad. Sci. USA* **118**, e2101668118 (2021).
49. Rankin, L. C. et al. The transcription factor T-bet is essential for the development of NKp46+ innate lymphocytes via the Notch pathway. *Nat. Immunol.* **14**, 389–395 (2013).
50. Vonarbourg, C. et al. Regulated expression of nuclear receptor RORgammat confers distinct functional fates to NK cell receptor-expressing RORgammat(+) innate lymphocytes. *Immunity* **33**, 736–751 (2010).
51. Bernink, J. H. et al. Interleukin-12 and -23 control plasticity of CD127(+) Group 1 and Group 3 innate lymphoid cells in the intestinal lamina propria. *Immunity* **43**, 146–160 (2015).
52. Osinska, I., Popko, K. & Demkow, U. Perforin: an important player in immune response. *Cent. Eur. J. Immunol.* **39**, 109–115 (2014).
53. Rosenberg, J. & Huang, J. CD8(+) T cells and NK cells: parallel and complementary soldiers of immunotherapy. *Curr. Opin. Chem. Eng.* **19**, 9–20 (2018).
54. Shresta, S., Pham, C. T., Thomas, D. A., Graubert, T. A. & Ley, T. J. How do cytotoxic lymphocytes kill their targets? *Curr. Opin. Immunol.* **10**, 581–587 (1998).
55. Khairallah, C., Chu, T. H. & Sheridan, B. S. Tissue adaptations of memory and tissue-resident gamma delta T cells. *Front Immunol.* **9**, 2636 (2018).
56. Li, Y. et al. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **147**, 629–640 (2011).
57. Bauche, D. et al. LAG3(+) regulatory T cells restrain interleukin-23-Producing CX3CR1(+) gut-resident macrophages during Group 3 innate lymphoid cell-driven colitis. *Immunity* **49**, 342–352 e345. (2018).
58. Burzyn, D., Benoist, C. & Mathis, D. Regulatory T cells in nonlymphoid tissues. *Nat. Immunol.* **14**, 1007–1013 (2013).
59. Tanoue, T., Atarashi, K. & Honda, K. Development and maintenance of intestinal regulatory T cells. *Nat. Rev. Immunol.* **16**, 295–309 (2016).
60. Weiss, J. M. et al. Neuropilin 1 is expressed on thymus-derived natural regulatory T cells, but not mucosa-generated induced Foxp3+ T reg cells. *J. Exp. Med.* **209**, 1723–1742 (2012).
61. Ohnmacht, C. Tolerance to the intestinal microbiota mediated by ROR(gammat) (+) cells. *Trends Immunol.* **37**, 477–486 (2016).
62. Kim, K. S. et al. Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science* **351**, 858–863 (2016).
63. Chaudhry, A. et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. *Immunity* **34**, 566–578 (2011).
64. Atarashi, K. et al. Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* **331**, 337–341 (2011).
65. Hu, X. & Ivashkiv, L. B. Cross-regulation of signaling pathways by interferon-gamma: implications for immune responses and autoimmune diseases. *Immunity* **31**, 539–550 (2009).
66. Fulkerson, P. C. & Rothenberg, M. E. Eosinophil development, disease involvement, and therapeutic suppression. *Adv. Immunol.* **138**, 1–34 (2018).
67. Cox, J. H. et al. Opposing consequences of IL-23 signaling mediated by innate and adaptive cells in chemically induced colitis in mice. *Mucosal Immunol.* **5**, 99–109 (2012).
68. Sonnenberg, G. F. et al. Pathological versus protective functions of IL-22 in airway inflammation are regulated by IL-17A. *J. Exp. Med.* **207**, 1293–1305 (2010).
69. Wang, P. et al. Macrophage achieves self-protection against oxidative stress-induced ageing through the Mst-Nrf2 axis. *Nat. Commun.* **10**, 755 (2019).
70. Laforge, M. et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. *Nat. Rev. Immunol.* **20**, 515–516 (2020).
71. Dudakov, J. A., Hanash, A. M. & van den Brink, M. R. Interleukin-22: immunobiology and pathology. *Annu Rev. Immunol.* **33**, 747–785 (2015).
72. Wang, K. et al. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity* **41**, 1052–1063 (2014).
73. Lee, J. S. et al. Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. *Immunity* **43**, 727–738 (2015).
74. Lindemans, C. A. et al. Interleukin-22 promotes intestinal-stem-cell-mediated epithelial regeneration. *Nature* **528**, 560–564 (2015).
75. Yang, X. O. et al. Regulation of inflammatory responses by IL-17F. *J. Exp. Med.* **205**, 1063–1075 (2008).
76. Zenewicz, L. A. et al. Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease. *Immunity* **29**, 947–957 (2008).
77. Gaudino, S. J. & Kumar, P. Cross-talk between antigen presenting cells and T cells impacts intestinal homeostasis, bacterial infections, and tumorigenesis. *Front. Immunol.* **10**, 360 (2019).
78. Lawrence, T. & Natoli, G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. *Nat. Rev. Immunol.* **11**, 750–761 (2011).
79. Zhou, X. et al. YAP aggravates inflammatory bowel disease by regulating M1/M2 macrophage polarization and gut microbial homeostasis. *Cell Rep.* **27**, 1176–1189 (2019) .
80. Gautier, E. L. et al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. *Nat. Immunol.* **13**, 1118–1128 (2012).
81. Murray, P. J. et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity* **41**, 14–20 (2014).
82. Mortha, A. et al. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science* **343**, 1249288 (2014).
83. Denning, T. L., Wang, Y. C., Patel, S. R., Williams, I. R. & Pulendran, B. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nat. Immunol.* **8**, 1086–1094 (2007).
84. Coombes, J. L. et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J. Exp. Med.* **204**, 1757–1764 (2007).
85. Bain, C. C. et al. TGFbetaR signalling controls CD103(+)CD11b(+) dendritic cell development in the intestine. *Nat. Commun.* **8**, 620 (2017).
86. Hepworth, M. R. et al. Immune tolerance. Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4(+) T cells. *Science* **348**, 1031–1035 (2015).
87. Hepworth, M. R. et al. Innate lymphoid cells regulate CD4+ T-cell responses to intestinal commensal bacteria. *Nature* **498**, 113–117 (2013).
88. Oliphant, C. J. et al. MHCII-mediated dialog between group 2 innate lymphoid cells and CD4(+) T cells potentiates type 2 immunity and promotes parasitic helminth expulsion. *Immunity* **41**, 283–295 (2014).
89. Biton, M. et al. T helper cell cytokines modulate intestinal stem cell renewal and differentiation. *Cell* **175**, 1307–1320 e1322. (2018).
90. Fenton, T. M. et al. Immune profiling of human gut-associated lymphoid tissue identifies a role for isolated lymphoid follicles in priming of region-specific immunity. *Immunity* **52**, 557–570 (2020).
91. Bouskra, D. et al. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. *Nature* **456**, 507–510 (2008).
92. Bunker, J. J. et al. Innate and adaptive humoral responses coat distinct commensal bacteria with immunoglobulin A. *Immunity* **43**, 541–553 (2015).
93. Fadlallah, J. et al. Microbial ecology perturbation in human IgA deficiency. *Sci. Transl. Med.* **10**, eaan1217 (2018).
94. Takeuchi, T. et al. Acetate differentially regulates IgA reactivity to commensal bacteria. *Nature* **595**, 560–564 (2021).
95. Suzuki, K. et al. Aberrant expansion of segmented filamentous bacteria in IgA-deficient gut. *Proc. Natl Acad. Sci. USA* **101**, 1981–1986 (2004).
96. Shoda, R., Matsueda, K., Yamato, S. & Umeda, N. Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. *Am. J. Clin. Nutr.* **63**, 741–745 (1996).
97. Ananthakrishnan, A. N. et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. *Gut* **63**, 776–784 (2014).
98. Losurdo, G. et al. Prevalence and associated factors of obesity in inflammatory bowel disease: A case-control study. *World J. Gastroenterol.* **26**, 7528–7537 (2020).
99. Boutros, M. & Maron, D. Inflammatory bowel disease in the obese patient. *Clin. Colon Rectal Surg.* **24**, 244–252 (2011).
100. Pituch-Zdanowska, A. et al. Overweight and obesity in children with newly diagnosed inflammatory bowel disease. *Adv. Med Sci.* **61**, 28–31 (2016).
101. Chandrakumar, A., Wang, A., Grover, K. & El-Matary, W. Obesity is more common in children newly diagnosed with ulcerative colitis as compared to those with crohn disease. *J. Pediatr. Gastroenterol. Nutr.* **70**, 593–597 (2020).
102. Long, M. D. et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm. Bowel Dis.* **17**, 2162–2168 (2011).
103. Luck, H. et al. Regulation of obesity-related insulin resistance with gut anti-inflammatory agents. *Cell Metab.* **21**, 527–542 (2015).
104. Winer, S. et al. Obesity predisposes to Th17 bias. *Eur. J. Immunol.* **39**, 2629–2635 (2009).
105. Myles, I. A. et al. Parental dietary fat intake alters offspring microbiome and immunity. *J. Immunol.* **191**, 3200–3209 (2013).
106. Haghikia, A. et al. Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. *Immunity* **43**, 817–829 (2015).
107. Haase, S. et al. Propionic acid rescues high-fat diet enhanced immunopathology in autoimmunity via effects on Th17 responses. *Front. Immunol.* **12**, 701626 (2021).
108. Hong, C. P. et al. Gut-specific delivery of T-helper 17 cells reduces obesity and insulin resistance in mice. *Gastroenterology* **152**, 1998–2010 (2017).
109. Luck, H. et al. Gut-associated IgA(+) immune cells regulate obesity-related insulin resistance. *Nat. Commun.* **10**, 3650 (2019).
110. Okamura, T. et al. Trans fatty acid intake induces intestinal inflammation and impaired glucose tolerance. *Front. Immunol.* **12**, 669672 (2021).

111. Wang, X. et al. Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes. *Nature* **514**, 237–241 (2014).
112. Nel, I., Bertrand, L., Toubal, A. & Lehuen, A. MAIT cells, guardians of skin and mucosa? *Mucosal Immunol.* **14**, 803–814 (2021).
113. Toubal, A. et al. Mucosal-associated invariant T cells promote inflammation and intestinal dysbiosis leading to metabolic dysfunction during obesity. *Nat. Commun.* **11**, 3755 (2020).
114. Denning, T. L. et al. Mouse TCRalphabeta+CD8alphaalpha intraepithelial lymphocytes express genes that down-regulate their antigen reactivity and suppress immune responses. *J. Immunol.* **178**, 4230–4239 (2007).
115. Kamanaka, M. et al. Expression of interleukin-10 in intestinal lymphocytes detected by an interleukin-10 reporter knockin tiger mouse. *Immunity* **25**, 941–952 (2006).
116. Das, G. et al. An important regulatory role for CD4+CD8 alpha alpha T cells in the intestinal epithelial layer in the prevention of inflammatory bowel disease. *Proc. Natl Acad. Sci. USA* **100**, 5324–5329 (2003).
117. Chen, Y., Chou, K., Fuchs, E., Havran, W. L. & Boismenu, R. Protection of the intestinal mucosa by intraepithelial gamma delta T cells. *Proc. Natl Acad. Sci. USA* **99**, 14338–14343 (2002).
118. Park, C. et al. Obesity modulates intestinal intraepithelial T cell persistence, CD103 and CCR9 expression, and outcome in dextran sulfate sodium-induced colitis. *J. Immunol.* **203**, 3427–3435 (2019).
119. Smith, P. M. et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* **341**, 569–573 (2013).
120. Furusawa, Y. et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
121. Monk, J. M. et al. Th17 cell accumulation is decreased during chronic experimental colitis by (n-3) PUFA in Fat-1 mice. *J. Nutr.* **142**, 117–124 (2012).
122. Monk, J. M., Hou, T. Y., Turk, H. F., McMurray, D. N. & Chapkin, R. S. n3 PUFAs reduce mouse CD4+ T-cell ex vivo polarization into Th17 cells. *J. Nutr.* **143**, 1501–1508 (2013).
123. Pompura, S. L. et al. Oleic acid restores suppressive defects in tissue-resident FOXP3 Tregs from patients with multiple sclerosis. *J. Clin. Invest.* **131**, e138519 (2021).
124. Michalek, R. D. et al. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. *J. Immunol.* **186**, 3299–3303 (2011).
125. Softic, S. et al. Dietary sugars alter hepatic fatty acid oxidation via transcriptional and post-translational modifications of mitochondrial proteins. *Cell Metab.* **30**, 735–753 (2019).
126. Saravia, J. et al. Homeostasis and transitional activation of regulatory T cells require c-Myc. *Sci. Adv.* **6**, eaaw6443 (2020).
127. Bisanz, J. E., Upadhyay, V., Turnbaugh, J. A., Ly, K. & Turnbaugh, P. J. Meta-analysis reveals reproducible gut microbiome alterations in response to a high-fat diet. *Cell Host Microbe* **26**, 265–272 (2019).
128. Tomas, J. et al. High-fat diet modifies the PPAR-gamma pathway leading to disruption of microbial and physiological ecosystem in murine small intestine. *Proc. Natl. Acad. Sci. USA* **113**, E5934–E5943 (2016).
129. Chun, E. et al. Metabolite-sensing receptor Ffar2 regulates colonic group 3 innate lymphoid cells and gut immunity. *Immunity* **51**, 871–884 (2019).
130. Wisniewski, J. R., Friedrich, A., Keller, T., Mann, M. & Koepsell, H. The impact of high-fat diet on metabolism and immune defense in small intestine mucosa. *J. Proteome Res.* **14**, 353–365 (2015).
131. Trindade, B. C. et al. The cholesterol metabolite 25-hydroxycholesterol restrains the transcriptional regulator SREBP2 and limits intestinal IgA plasma cell differentiation. *Immunity* **54**, 2273–2287 (2021).
132. Kunisawa, J. et al. Regulation of intestinal IgA responses by dietary palmitic acid and its metabolism. *J. Immunol.* **193**, 1666–1671 (2014).
133. van der Flier, L. G. & Clevers, H. Stem cells, self-renewal, and differentiation in the intestinal epithelium. *Annu Rev. Physiol.* **71**, 241–260 (2009).
134. Paone, P. & Cani, P. D. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut* **69**, 2232–2243 (2020).
135. Jensen, B. A. H. et al. Lysates of Methylococcus capsulatus Bath induce a lean-like microbiota, intestinal FoxP3(+)RORgammat(+)IL-17(+) Tregs and improve metabolism. *Nat. Commun.* **12**, 1093 (2021).
136. Everard, A. et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc. Natl Acad. Sci. USA* **110**, 9066–9071 (2013).
137. Ottman, N., Geerlings, S. Y., Aalvink, S., de Vos, W. M. & Belzer, C. Action and function of Akkermansia muciniphila in microbiome ecology, health and disease. *Best. Pr. Res Clin. Gastroenterol.* **31**, 637–642 (2017).
138. Chelakkot, C. et al. Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Exp. Mol. Med.* **50**, e450 (2018).
139. Bian, X. et al. Administration of akkermansia muciniphila ameliorates dextran sulfate sodium-induced ulcerative colitis in mice. *Front. Microbiol.* **10**, 2259 (2019).
140. Gay, N. J., Symmons, M. F., Gangloff, M. & Bryant, C. E. Assembly and localization of Toll-like receptor signalling complexes. *Nat. Rev. Immunol.* **14**, 546–558 (2014).
141. Everard, A. et al. Intestinal epithelial MyD88 is a sensor switching host metabolism towards obesity according to nutritional status. *Nat. Commun.* **5**, 5648 (2014).
142. Progatzky, F. et al. Dietary cholesterol directly induces acute inflammasome-dependent intestinal inflammation. *Nat. Commun.* **5**, 5864 (2014).
143. de Zoete, M. R., Palm, N. W., Zhu, S. & Flavell, R. A. Inflammasomes. *Cold Spring Harb. Perspect. Biol.* **6**, a016287 (2014).
144. Kawano, Y. et al. Colonic pro-inflammatory macrophages cause insulin resistance in an intestinal Ccl2/Ccr2-dependent manner. *Cell Metab.* **24**, 295–310 (2016).
145. Coccia, M. et al. IL-1beta mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4(+) Th17 cells. *J. Exp. Med.* **209**, 1595–1609 (2012).
146. Nowarski, R. et al. Epithelial IL-18 equilibrium controls barrier function in colitis. *Cell* **163**, 1444–1456 (2015).
147. Wunderlich, C. M. et al. Obesity exacerbates colitis-associated cancer via IL-6-regulated macrophage polarisation and CCL-20/CCR-6-mediated lymphocyte recruitment. *Nat. Commun.* **9**, 1646 (2018).
148. Vermeulen, L. & Snippert, H. J. Stem cell dynamics in homeostasis and cancer of the intestine. *Nat. Rev. Cancer* **14**, 468–480 (2014).
149. Fu, T. et al. FXR regulates intestinal cancer stem. *Cell Prolif. Cell* **176**, 1098–1112 (2019). e1018.
150. Sorrentino, G. et al. Bile acids signal via TGR5 to activate intestinal stem cells and epithelial regeneration. *Gastroenterology* **159**, 956–968 e958. (2020).
151. Perino, A. & Schoonjans, K. Metabolic messengers: bile acids. *Nat. Metab.* **4**, 416–423 (2022).
152. Fiorucci, S. & Distrutti, E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. *Trends Mol. Med.* **21**, 702–714 (2015).
153. Jose, S. et al. Obeticholic acid ameliorates severity of Clostridioides difficile infection in high fat diet-induced obese mice. *Mucosal Immunol.* **14**, 500–510 (2021).
154. Devkota, S. et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10-/- mice. *Nature* **487**, 104–108 (2012).
155. Al Nabhani, Z. et al. A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. *Immunity* **50**, 1276–1288 (2019). e1275.
156. Babu, S. T. et al. Maternal high-fat diet results in microbiota-dependent expansion of ILC3s in mice offspring. *JCI Insight* **3**, e99223 (2018).
157. Bietz, A., Zhu, H., Xue, M. & Xu, C. Cholesterol metabolism in T cells. *Front. Immunol.* **8**, 1664 (2017).
158. Hochrein, S. M. et al. The glucose transporter GLUT3 controls T helper 17 cell responses through glycolytic-epigenetic reprogramming. *Cell Metab.* **34**, 516–532 (2022).
159. Macintyre, A. N. et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metab.* **20**, 61–72 (2014).
160. Tsai, S. et al. Insulin receptor-mediated stimulation boosts T cell immunity during inflammation and infection. *Cell Metab.* **28**, 922–934 (2018). e924.
161. Li, Y. et al. Insulin signaling establishes a developmental trajectory of adipose regulatory T cells. *Nat. Immunol.* **22**, 1175–1185 (2021).

ACKNOWLEDGEMENTS

The authors would like to thank members of J.Q. laboratory for their suggestions on this manuscript.

AUTHOR CONTRIBUTIONS

J.Q., J.Q., and Y.M. drafted and edited the manuscript. J.Q. performed final proof reading of the manuscript.

FUNDING

This work was supported by grant 2019YFA0802502 and 2020YFA0509103 to J.Q. from the Ministry of Science and Technology of China, grant 32022027 and 31970860 to J.Q. from the National Natural Science Foundation of China, and grant 22ZR1481800 and 20ZR1466900 to J.Q. from Shanghai Science and Technology Committee (STCSM).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Yanhui Ma or Ju Qiu.