ANNUAL REVIEWS

Annual Review of Food Science and Technology

The Influence of the Western Diet on Microbiota and Gastrointestinal Immunity

Vanessa Las Heras,[1,2,*] Silvia Melgar,[1,*] John MacSharry,[1,2,3] and Cormac G.M. Gahan[1,2,4]

[1]APC Microbiome Ireland, University College Cork, Cork, Ireland; email: c.gahan@ucc.ie

[2]School of Microbiology, University College Cork, Cork, Ireland

[3]School of Medicine, University College Cork, Cork, Ireland

[4]School of Pharmacy, University College Cork, Cork, Ireland

Annu. Rev. Food Sci. Technol. 2022. 13:489–512

First published as a Review in Advance on January 6, 2022

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-052720-011032

*V.L.H. and S.M. contributed equally to this work.

Keywords

Western diet, microbiome, inflammation, emulsifiers, immunity

Abstract

Diet exerts a major influence upon host immune function and the gastrointestinal microbiota. Although components of the human diet (including carbohydrates, fats, and proteins) are essential sources of nutrition for the host, they also influence immune function directly through interaction with innate and cell-mediated immune regulatory mechanisms. Regulation of the microbiota community structure also provides a mechanism by which food components influence host immune regulatory processes. Here, we consider the complex interplay between components of the modern (Western) diet, the microbiota, and host immunity in the context of obesity and metabolic disease, inflammatory bowel disease, and infection.

1. INTRODUCTION

Humans have coevolved with a symbiotic gastrointestinal microbiota that performs essential functions in the host. The microbiota contributes directly to energy harvest from foods but also influences local and systemic immune processes and gastrointestinal barrier function. The components of our diet (proteins, carbohydrates, and fats as well as emulsifiers and sweeteners) have the capacity to both directly influence immune cells and alter gut microbial composition and function with attendant effects on host immunity. Our dietary habits have changed markedly over the past 100 years with the advent of modern agricultural and food processing methods and a significant shift in dietary preferences toward foods that are high in saturated fat, refined sugars, salt, and sweeteners and low in natural plant-based complex carbohydrates (fiber) (Gonzalez Olmo et al. 2021). Although definitions vary, the aforementioned food characteristics can be broadly characterized as hallmarks of a Western diet (reviewed in Gonzalez Olmo et al. 2021). This major shift in the relative proportion and type of macronutrients has precipitated an increase in levels of obesity and metabolic disease that are broadly inflammatory in nature. Here, we examine the molecular mechanisms by which macronutrients associated with a Western diet may influence inflammation and microbiome community structure in the context of metabolic and inflammatory diseases, including obesity, inflammatory bowel disease (IBD), and infectious disease.

2. THE GASTROINTESTINAL MUCOSA AND BARRIER FUNCTION

Gastrointestinal cell homeostasis, differentiation, and proliferation are directly affected by diet and driven by the luminal content rather than systemic nutrients (Winesett et al. 1995). Diet also influences host immune function and therefore the interplay between gut epithelial cells and immune cells in the mucosa, which helps maintain barrier function (Statovci et al. 2017). Dietary nonstarch polysaccharides and lignin, more specifically, oligofructose and long-chain inulin, have been linked with an increased villus height, deeper crypts, and a thicker mucous layer associated with an increased population of goblet cells (Kleessen et al. 2003). Increased glucose intake induces general physiological changes at the level of the intestinal epithelium, such as an increase in the proliferation of cells in the crypt (Zhou et al. 2018). Similarly, increased dietary protein content has been linked to profound alterations in epithelial cell transcriptional responses reflecting the potential for increased cell proliferation and downregulation of biological pathways linked to nuclear factor κB (NF-κB) signaling, cell adhesion, and DNA repair (Beaumont et al. 2017a). Models of high-fat-induced obesity reveal that an elevated ratio of omega-6 polyunsaturated fatty acids (PUFAs) to omega-3 PUFAs drives low-grade inflammation, mesenchymal stem cell commitment, and adipogenesis (Ilich et al. 2014). Others have demonstrated that a high-fat diet compromised the integrity of the intestinal barrier, with downregulation of tight-junction proteins such as claudin-1 (Gulhane et al. 2016).

The host diet has a significant impact on the nutrient pool available in the gut and can modulate gut microbial community structure with consequences for microbial signaling processes that influence barrier function and in turn further mold microbial communities in the gut. A good example of such bidirectional microbe–host interactions includes the regulation of the antimicrobial lectin, RegIII-γ, in Paneth cells. RegIII-γ is induced by the microbiota and is important for host barrier function and homeostasis through maintenance of a 50-μm thick zone of separation between the microbiota and the intestinal epithelial surface (Vaishnava et al. 2011). Another mechanism involves bile acid metabolism by the host microbiota. In a model of gut immune homeostasis, commensal microbes modify bile acids to induce expression from a host bile acid receptor [farnesoid X receptor (FXR)], which can regulate local antibacterial immune responses, including inducible nitric oxide synthase (iNOS), interleukin (IL)-18 (Inagaki et al. 2006), and, potentially, RegIII-γ

(Joyce et al. 2014), in turn inhibiting local bacterial overgrowth and protecting the mucosa from inflammatory damage. Such homeostatic mechanisms are influenced by a balanced diet. In contrast, a pro-inflammatory Western diet leads to an altered microbiota promoting a reduction in barrier function and entry of pro-inflammatory factors such as lipopolysaccharide (LPS) into the bloodstream, thereby promoting metabolic endotoxemia and low-grade systemic inflammation, which is central to the development of obesity and related metabolic syndromes, including type 2 diabetes (reviewed in Regnier et al. 2021).

3. THE HUMAN GUT MICROBIOTA

The gut microbiota comprises bacteria predominately of the phyla Firmicutes, Bacteroidetes, and Actinobacteria alongside specific Archaea and Fungi (Rinninella et al. 2019a). These microorganisms coexist with a community of viruses (the virome) that is likely to play an important role in shaping the community structure of the higher-order microbes in the gut (Draper et al. 2020). The human gut microbiota matures following weaning, remains relatively stable throughout adulthood, and becomes less diverse in the later years of life (Rinninella et al. 2019b).

Despite significant interindividual variation, detailed analysis of the human gut microbiota broadly clusters individuals into enterotypes that are defined by predominant bacterial populations: *Bacteroides* (enterotype I), *Prevotella* (enterotype II), or *Ruminococcus* (enterotype III) (Costea et al. 2018). Wu et al. (2011) demonstrated that the *Bacteroides* enterotype is prevalent in individuals consuming a Western-type diet, whereas individuals consuming a broader range of carbohydrates and fruits and vegetables are more likely to have a *Prevotella*-dominant enterotype. Furthermore, individuals with a *Bacteroides*-dominant enterotype are likely to display low microbial gene richness, most likely reflecting low microbial diversity in the gut (Le Chatelier et al. 2013). This potentially has significant consequences for the overall health status of the individual, as bacterial gene richness correlates with overall metabolic health, and low bacterial gene richness is associated with obesity and impaired glucose metabolism (Cotillard et al. 2013, Le Chatelier et al. 2013). In the elderly, elevated microbial diversity correlates with improved host fitness and is linked to consumption of a balanced diet, whereas individuals with a low-diversity gut microbiota are more likely to demonstrate increased frailty (Claesson et al. 2012).

3.1. The Influence of the Western Diet on Microbiota in Obesity

Dietary habits are a significant driver of long-term gut microbiota composition in individuals (Wu et al. 2011). However, even short-term changes in diet can result in considerable changes in microbial community structure. Consumption of either a plant-based or animal-based diet in humans each resulted in rapid alterations to the microbiota, with an animal-based diet promoting bile-tolerant species and a reduction in bacterial taxa that metabolize plant-based polysaccharides (David et al. 2014). At the overall level of phyla, an increase in the Firmicutes to Bacteroidetes ratio is associated with a shift to a Westernized diet in both humans and animal models, with the resultant microbiota demonstrating an increased capacity for energy harvest (Ley et al. 2006, Turnbaugh et al. 2006), although the relevance of this as a marker of human obesity requires further study (Magne et al. 2020). Transplant of the microbiota from obese humans from twin pairs discordant for obesity into germ-free mice results in transmission of the phenotype, demonstrating that the microbiota plays a functional role in mediating obesity (Ridaura et al. 2013). Furthermore, fecal microbiota transplantation (FMT) from healthy donors into individuals with obesity and metabolic syndrome can significantly improve markers of metabolic health in the recipients (Vrieze et al. 2012). A study in patients with steatohepatitis, a condition with higher prevalence

in those consuming a Western diet, demonstrated that allogenic microbiota transplantation from healthy subjects consuming a largely plant-based diet improved markers of liver disease (Witjes et al. 2020). Such studies demonstrate that FMT is successful in altering the microbiota of subjects with obesity or metabolic syndrome and clearly indicate the functional consequences of the microbiota in altering metabolic parameters in the recipient (Aron-Wisnewsky et al. 2019).

3.2. Specific Taxa and Links to Mechanisms

Pinpointing specific genera or species of bacteria that mediate either obesity or leanness will enhance our understanding of the mechanisms by which the microbiota mediates positive effects on homeostasis and potentially lead to rational dietary approaches, next-generation probiotics, and/or microbial-derived drugs to reduce the effects of obesity or metabolic syndrome. Studies in humans and animals have associated high levels of *Akkermansia muciniphila* with a lean phenotype (Zhou et al. 2021). Levels of *A. muciniphila* are reduced in mice fed a pro-inflammatory high-fat (animal fat) diet but are relatively high if animals consume fish oils (Caesar et al. 2015). Effects of this species on the host are clearly functional, as administration of *A. muciniphila* in animal models of obesity and insulin resistance reduced weight gain and improved metabolic indicators of diabetes (Depommier et al. 2019, Everard et al. 2013). In a recent proof-of-concept study, oral administration of pasteurized *A. muciniphila* in obese human volunteers resulted in improved markers of gut barrier function and metabolic outcomes, including improved insulin sensitivity, although the intervention did not directly result in weight loss (Depommier et al. 2019). Many of the effects of *A. muciniphila* can be recapitulated using pasteurized bacteria, indicating that molecular components associated with the bacterium are sufficient to mediate host responses (Depommier et al. 2019, Plovier et al. 2017). Fractionation experiments reveal that an outer-membrane protein (Amuc_1100) of *A. muciniphila* interacts with host Toll-like receptor (TLR) 2 to, at least partly, mediate beneficial responses in a mouse diet-induced obesity model (Plovier et al. 2017). The bacterium also secretes a glucagon-like-peptide 1–inducing protein (called P9) that interacts with host ICAM-2 to improve glucose metabolism and ameliorate metabolic disease in mice (Yoon et al. 2021) (see **Figure 1**).

Gut-associated *Lactobacillus* species occupy both the small and large intestine and influence inflammation and bile acid metabolism in the host (Heeney et al. 2018, Nistal et al. 2016). *Lactobacillus* species have been associated with weight gain and adiposity in animals, with the administration of some species linked to weight loss and others to weight gain (Heeney et al. 2018, Million et al. 2012). Meta-analysis of human probiotic trials suggests that *Lactobacillus* generally can improve weight management in individuals with obesity but acknowledges that further mechanistic insights would provide for rational selection of particular interventions (Saez-Lara et al. 2016). One such mechanism may involve the ability of strains to metabolize host bile acids. Gut-associated *Lactobacillus* species are potent producers of bile salt hydrolase (BSH) enzymes that convert bile acids from the conjugated to unconjugated form through hydrolysis of the amino acid taurine or glycine (see **Figure 1**) (Begley et al. 2005). Evidence from animal studies and longitudinal studies in humans receiving antibiotics has equated antibiotic use in early life with a reduction in BSH activity, which correlates with an increase in host adiposity (Guban et al. 2006, Korpela et al. 2016). In contrast, other studies indicate that the antioxidant tempol reduces *Lactobacillus*-associated BSH activity in mice with a concomitant reduction in weight gain in mice (Li et al. 2013). The diverse outcomes associated with either elevated or reduced BSH activity may reflect subtleties in the host response to bile acids dependent on whether microbe-generated bile acid signatures trigger host FXR [broadly associated with weight gain (Gonzalez et al. 2016)] or TGR5 [broadly associated with increased energy expenditure and weight loss (Watanabe et al. 2006)]. Several studies suggest

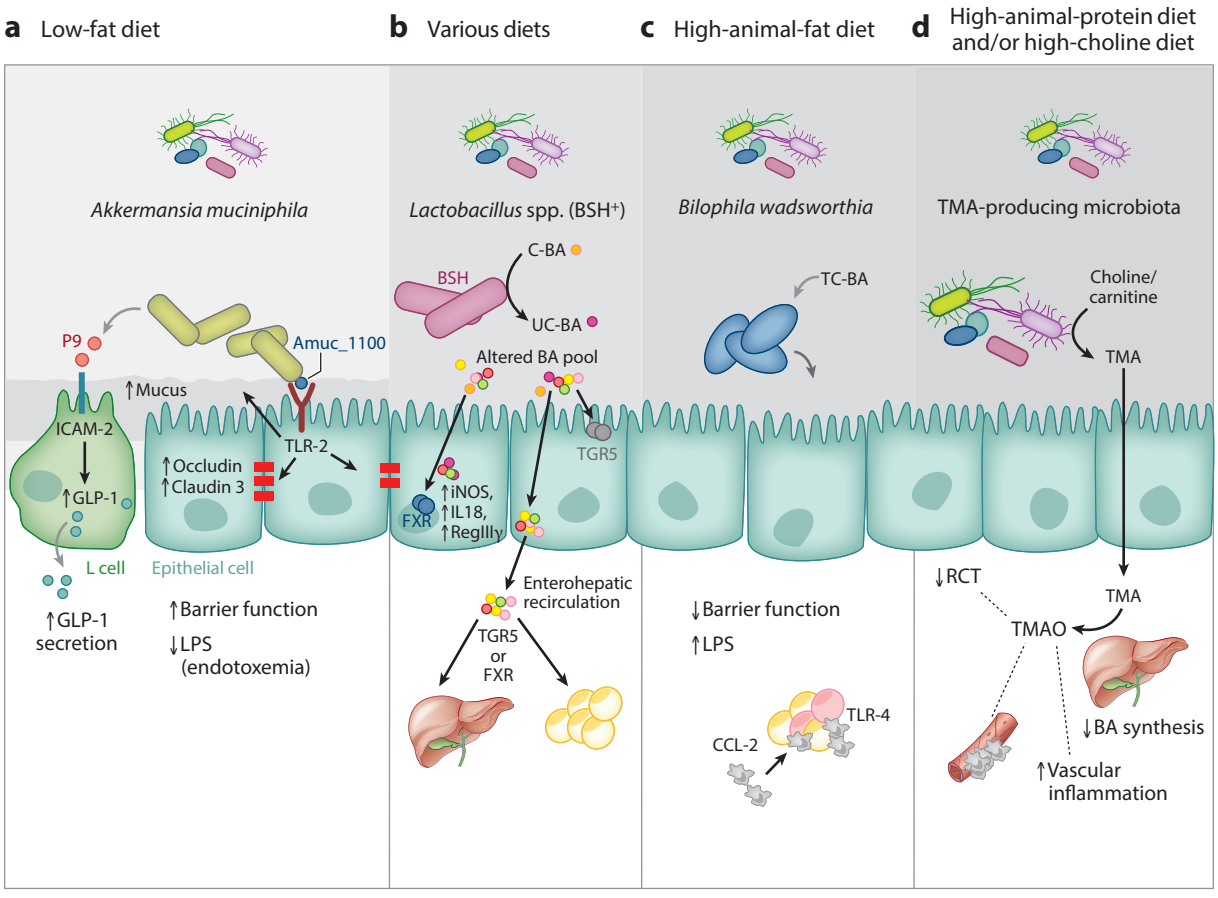

Figure 1

Proposed mechanisms by which the microbiota influences host physiology and inflammation. (*a*) A diverse low-fat diet promotes the outgrowth of *Akkermansia muciniphila*. *A. muciniphila* expresses the protein Amuc_1100, which improves gut barrier function through a mechanism that involves TLR2 (Toll-like receptor 2). Enhanced gut barrier function prevents the development of metabolic endotoxemia. *A. muciniphila* also produces a novel protein (P9) that stimulates GLP-1 (glucagon-like peptide 1) secretion by L cells (potentially in the gut or systemically) via a mechanism that involves ICAM-1 and also requires IL-6. (*b*) *Lactobacillus* species (and certain other members of the microbiota) produce the enzyme bile salt hydrolase (BSH), which converts conjugated bile acids (C-BAs) to unconjugated bile acids (UC-BAs), thereby altering the chemical nature of the bile acid (BA) pool. As yet, it is unclear how the chemical balance of this complex pool of BAs engages with BA receptors in the host. There is good evidence that engagement of BAs with the farnesoid X receptor (FXR) nuclear receptor in the gut influences local immunity and barrier function. Engagement with systemic, liver, or adipose FXR is thought to induce weight gain, whereas engagement with the TGR5 receptor induces weight loss. The ability of gut microbes to alter this signaling effect plays an important role in determining host adiposity. (*c*) Western diets rich in animal fats can promote the outgrowth of pathobionts such as *Bilophila wadsworthia*. Growth of *B. wadsworthia* is stimulated by elevated synthesis of tauro-conjugated BAs (TC-BAs) that are induced by the high-fat diet. Such pathobionts may cause local inflammation that damages the gut barrier, leading to further systemic inflammation and increased macrophage-mediated inflammation of adipose tissue that is both TLR-4 and CCL-2 dependent. (*d*) Consumption of diets high in carnitine or choline results in the production of the compound trimethylamine (TMA) by specific members of the microbiota. TMA is subsequently converted by liver enzymes to trimethylamine N-oxide (TMAO), which is known to elevate the risk of cardiovascular disease. Proposed mechanisms include decreased BA biosynthesis, elevated vascular inflammation, and reduced reverse cholesterol transport (RCT). Abbreviations: iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide.

that elevated BSH activity associated with probiotic administration in mice results in reduced engagement of intestinal FXR; however, further confirmation of these findings is necessary, and it is important to determine the impact of elevated BSH activity in humans (Degirolamo et al. 2014, Joyce et al. 2019).

It is clear that bile acid signatures influence microbial community structure in the gut (Islam et al. 2011) and are in turn influenced by the microbiota (Begley et al. 2005), thereby providing for a dynamic interplay between microbe and host via bile acid metabolism. High-fat diets have been shown to influence bile acid metabolism in the host and also promote inflammation, a process that is linked to microbiota changes in addition to the direct immune inflammatory properties of dietary components that are described below. The composition of dietary fats is known to influence microbiota composition, as saturated animal fats (milk fats), but not polyunsaturated plant-derived fats, promote the outgrowth of the pro-inflammatory pathobiont *Bilophila wadsworthia* by increasing tauro-conjugation of host bile acids (Devkota et al. 2012). In general, a high-fat (lard-based) diet has been shown to increase macrophage-mediated inflammation in white adipose tissue (WAT) through mechanisms that involve engagement of TLR4 and reflect alterations to gut microbiota and gut barrier function (Caesar et al. 2012, Cani et al. 2007). The chemical nature of the dietary fat is significant. In a murine model, an animal (lard)-based high-saturated-fat diet promoted TLR and CCL2-dependent macrophage accumulation in WAT that was commensurate with elevated levels of *Bilophila* and *Bacteroides* spp. in the gut microbiota. In contrast, feeding a fish-based high-polyunsaturated-fat diet promoted the outgrowth of *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* spp. in the gut microbiota and was protective against WAT inflammation (Caesar et al. 2015). Similar correlations between elevated serum endotoxin and elevated inflammatory tone in adipose tissue have also been demonstrated in humans with type 2 diabetes (Creely et al. 2007). Collectively, the data suggest a pattern of microbial changes in individuals consuming a diet rich in saturated fats that drives adipose tissue inflammation, with a polyunsaturated-fat diet having an anti-inflammatory impact on the host commensurate with elevated levels of *Akkermansia* and *Lactobacillus* species.

4. INFLUENCE OF DIETARY COMPONENTS ON HOST PHYSIOLOGY AND IMMUNE FUNCTION

The Acceptable Macronutrient Distribution Ratios (AMDR) were established by the former Institute of Medicine of the National Academies in North America to provide guidelines for the recommended distribution of dietary macronutrients. The guidelines suggest percentages of total energy from protein (10–35%), carbohydrate (45–65%), and fat (20–35%) (Dahl et al. 2020). The direct mechanistic impacts of these individual dietary components, as well as the potential impact of micronutrients, are beginning to be understood. Components of the diet have the potential to influence immune responses directly through TLRs, G protein–coupled receptors (GPCRs), the prostaglandin/cyclooxygenase pathway, cholesterol metabolism, and overall influences on M1/M2 macrophage responses and cell-mediated immunity (predominately influences Treg cell activity) (Statovci et al. 2017).

4.1. Fats and Dietary Fatty Acids

In this section, we outline recently reported mechanisms by which saturated and monounsaturated fatty acids and PUFAs influence host responses.

4.1.1. Saturated fatty acids. Saturated fatty acids (SFAs) contain predominately single C–C bonds, with shorter molecules (C8 to C12) found in vegetable oils and longer molecules (>12 C)

such as palmitic acid (C16:0) and stearic acid (C18:0) found in lard, butter, animal fats, eggs, and vegetable oils (Statovci et al. 2017). Studies have suggested that SFAs are generally pro-inflammatory, with some of the potential mechanisms outlined below. Engagement of the NLRP3 inflammasome by palmitic acid and potentially other dietary SFAs is considered to be a significant mechanistic contributor to increased adiposity. Expression of the NLRP3 inflammasome is elevated in macrophages in the adipose tissue of both mice and humans with obesity but is reduced upon calorie restriction or exercise-induced weight loss, and SFA-rich diets can also prime the NLRP3 inflammasome via TLR4 activation in dendritic cells in vitro (Vandanmagsar et al. 2011). Furthermore, the SFAs palmitate, myristate, and stearate, but not the unsaturated fatty acids palmitoleate and oleate, can induce inflammation by activation of TNFα and IL-1β and cell death in human monocytes. Palmitate activates the inflammatory caspase proteins caspase-1, caspase-4, and caspase-5, which are important for processing IL-1β and the induction of cell death via pyroptosis (Pillon et al. 2016). Previous studies have also reported that palmitic acid, stearate, and lauric acid regulate the inflammatory response via TLR4 and NF-κB signaling in immune cells (Lee et al. 2003, Statovci et al. 2017). TLRs signal via two cytosolic adaptor proteins, Myd88 and TIR domain–containing adaptor-inducing interferon-β (TRIF). Whereas Myd88 transduces the signal from all TLRs except TLR3, TRIF transduces the signal from the engagement of TLR3 and TLR4. A deficiency in TRIF resulted in worsening of diet-induced hepatic steatosis, which appeared independent of myeloid cell signaling but was dependent on the regulation of the rate-limiting enzyme for lipogenesis stearoyl–coenzyme A desaturase 1 (SCD1) in hepatocytes. This suggests a protective role for TRIF in metabolic disorders and potential caution when considering antagonizing TLR signaling in metabolic inflammatory conditions (Chen et al. 2017).

Individuals with obesity or type 2 diabetes are at increased risk of developing nonalcoholic fatty liver disease (NAFLD), which may involve significant inflammation of the liver [as nonalcoholic steatohepatitis (NASH)]. Palmitic acid or a high-fat diet can affect the development of NASH by targeting RIP1 kinase activity in liver macrophages, leading to an increased inflammatory response (IL-1β, TNFα, IL-6) and induction of cell death, both of which are typical features of NASH (Tao et al. 2021).

A hallmark of cellular homeostasis in the healthy liver is the process of autophagy, a mechanism used by cells to remove the accumulation of dangerous intracellular components. Significant alterations in autophagy are associated with several different conditions, including NAFLD/NASH and obesity. In hepatocytes, exposure to palmitic acid results in impaired autophagy and cellular accumulation of autophagosomes, which is dependent on MLKL but not RIPK3 (Wu et al. 2020). Similarly, $Mlkl^{-/-}$ mice fed a Westernized diet are protected from autophagy-related cellular impairments, resulting in a reduction in liver injury associated with reduced inflammation and a reduction in cell death (Wu et al. 2020). Palmitic acid can also impair autophagy in macrophages via the induction of hypoxia-inducible factor-1α, which results in inflammation regulated via the NF-κB pathway and production of pro-inflammatory cytokines such as TNF, IL-1β, and IL-6 (Wang et al. 2019). Similar results were observed in macrophages of mice fed a methionine- and choline-deficient (MCD) diet (used as a model for NASH) and in patients with NASH (Wang et al. 2019).

Protease-activated receptor 2 (PAR2) can modulate several physiological functions, including inflammation, metabolism, and anticancer responses. The metabolic consequences of PAR2 activation include increased insulin resistance and glucose intolerance, whereas in individuals with IBD, PAR2 can be both protective and pro-inflammatory (Badeanlou et al. 2011, Cenac et al. 2003, Hyun et al. 2008). An increase in PAR2 is observed in adipocyte tissues and macrophages of humans and rats consuming SFA-rich diets. In a model of dextran sodium sulfate (DSS)-induced

colitis, seven-day feeding of a high-fat diet to mice deficient in PAR2 resulted in exacerbation of colitis due to increased colonic pro-inflammatory cytokines (IL-1β, IL-6, IL-8) and, partly, inhibited autophagy (Her et al. 2021). Similar results, i.e., impaired autophagy, mitochondrial dysfunction, and cell death (cleaved caspase-3 and caspase-9 and PARP), are seen in epithelial cells treated with palmitic acid and a cytokine cocktail in the presence of a PAR2 antagonist (GB83) (Her et al. 2021). These data identify a new role for PAR2 as a regulator of autophagy in a metabolic-inflammatory environment, which is significant for inflammatory conditions such as IBD and is likely to have a role in obesity and metabolic comorbidities.

High-fat diet and SFAs can directly influence cellular processes in intestinal epithelial cells, including Paneth cells and stem cells (Beyaz et al. 2016, Mah et al. 2014). Paneth cells produce antimicrobial peptides and growth factors that sustain the stem cell niche, and as such these cells are important in maintaining homeostasis in the gut. Previous studies have shown dysfunction in these cells in models of IBD and obesity and in patients with IBD. Liu et al. (2021) determined a dysfunction in Paneth cells in patients with obesity. In mice fed a high-fat diet, the dysfunction of these cells was associated with the activation of type I interferons (IFNs) produced from myeloid cells and with FXR engagement (via alterations to the microbiota), further providing a link between the intestinal innate immune response and inflammation in association with the consumption of saturated fat (Liu et al. 2021).

Palmitic acid can be metabolized to palmitoleic acid, oleic acid, stearic acid, and sphingolipids. Such metabolites (in particular sphingolipids) can affect cellular apoptosis, proliferation, and migration (Statovci et al. 2017). Sphingolipids can also be produced by bacteria, e.g., from the phylum Bacteroidetes, and a glycosphingolipid produced from *B. fragilis* was shown to reduce the proliferation of colonic invariant natural killer T (iNKT) cells and ameliorate the development of colitis, thereby contributing to host defense (An et al. 2014). Other studies indicate that palmitic acid can directly and indirectly act via sphingolipids to affect IgA production and mount an IgA response, which could be relevant for the development of diet-derived mucosal adjuvants (Kunisawa et al. 2014). Palmitic treatment of hepatocytes leads to the release of lipotoxic extracellular vesicles containing sphingosine 1-phosphate (S1P), which stimulates the migration of macrophages, potentially promoting macrophage infiltration during hepatic lipotoxicity associated with NASH (Liao et al. 2018).

Recent work has investigated the epigenetic effects of a high-fat diet during gestation on susceptibility to disease in the offspring. In particular, the effect of a high-fat diet or obesity in pregnant dams confers a susceptibility of the offspring to colitis and obesity. Maternal high-fat-diet feeding (with either a high-fat diet or coconut oil) influenced impaired barrier function, increased production of pro-inflammatory cytokines, and increased production of hydrogen sulfide by the microbiota in the offspring during weaning, leading to worsening of DSS-induced colitis in adulthood. Neutralization of IFNγ and TNF pathways (by monoclonal antibodies) or using a myosin light-chain kinase (MLCK; regulates tight junctions in the gut) inhibitor during weaning leads to improved barrier function and reduced susceptibility to DSS-induced colitis in adulthood (Al Nabhani et al. 2019). A summary of identified mechanisms regulated by SFAs is presented in **Figure 2**.

4.1.2. Monounsaturated fatty acids. Monounsaturated fatty acids (MUFAs) are fatty acids containing a single C=C double bond and include palmitoleic acid (C16:1) and oleic acid (C18:1), which are found in olive oil, lard, macadamia nuts, and avocado (Statovci et al. 2017). A diet rich in MUFAs is associated with improved insulin sensitivity and reduced risk of atherosclerosis and cardiovascular disease (CVD) (Statovci et al. 2017). Among MUFAs, the lipokine palmitoleic acid has been shown to be anti-inflammatory by reducing the systemic expression of the

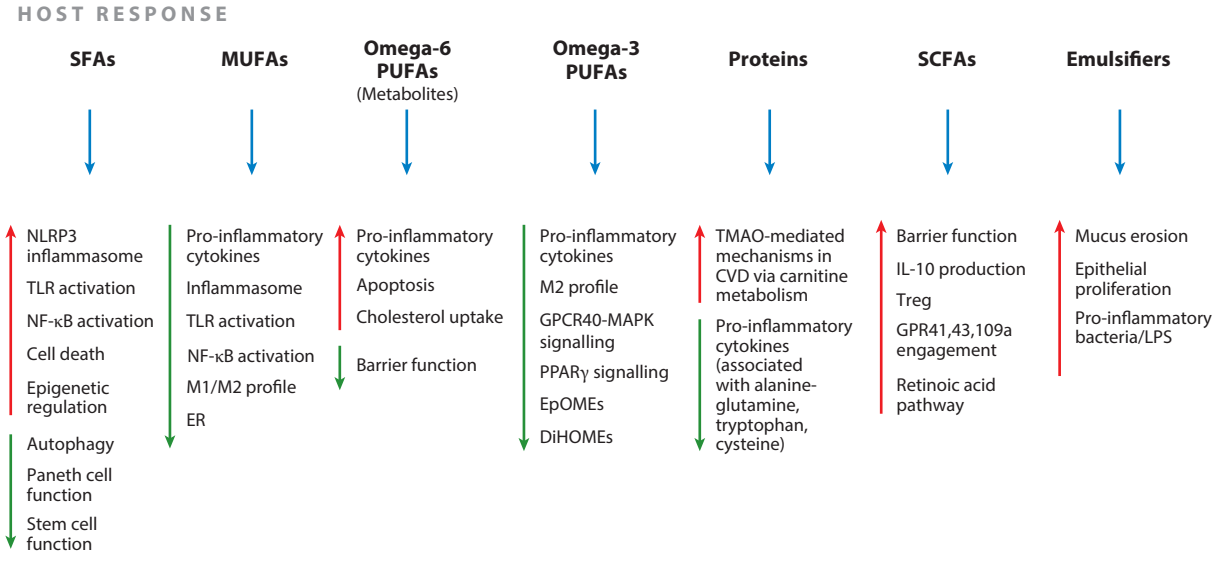

Figure 2

A summary of the proposed impacts of individual dietary macromolecules on host physiology and inflammation. Pathways activated by the specific dietary macromolecule are depicted by a red arrow and reduction of the pathway is depicted by a green arrow. Abbreviations: CVD, cardiovascular disease; DiHOMEs, dihydroxy-octadecenoic acids; EpOMEs, epoxyoctadecenoic acids; ER, endoplasmic reticulum; GPCR40, G protein–coupled receptor 40; LPS, lipopolysaccharide; M1, classical activated macrophages with pro-inflammatory properties; M2, alternative activated macrophages, with anti-inflammatory, wound-healing, and tissue-repair properties; MAPK, mitogen-activated protein kinase; MUFAs, monounsaturated fatty acids; PPARγ, peroxisome proliferator–activated receptor gamma; PUFAs, polyunsaturated fatty acids; NF-κB, nuclear factor κB; TLR, Toll-like receptor; SCFAs, short-chain fatty acids; SFAs, saturated fatty acids; TMAO, trimethylamine N-oxide.

pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 via remodeling of the endoplasmic reticulum membranes and reducing lipid-induced inflammasome in macrophages, thereby protecting mice against atherosclerosis (Cimen et al. 2016). In vitro studies showed that palmitoleic acid reduced LPS-induced inflammation in macrophages via the inflammasome and NF-κB and alteration to the M1/M2 profile. Although palmitoleic acid induced the expression of the anti-inflammatory transcription factor peroxisome proliferator–activated receptor (PPAR)α, which is a major regulator of energy homeostasis and a factor binding to the response element of NF-κB, the reduced inflammatory response was PPARα-independent (Souza et al. 2017). Contrary effects of palmitoleic acid were reported on lymphocytes, whereby high concentrations (over 50 mM) were toxic and lower concentrations reduced human peripheral blood lymphocyte proliferation and T helper (Th1) and Th17 responses (Passos et al. 2016). No effect on lymphocyte-associated cytokines (IFNγ, IL-17, IL-22) was reported in human peripheral blood mononuclear cells (PBMNCs) (Schirmer et al. 2016). The discrepancy between these findings may potentially be due to the use of different cell populations (isolated lymphocytes versus PBMNCs) (Passos et al. 2016, Schirmer et al. 2016). Thus, the effect of this MUFA on lymphocyte responses remains to be deciphered. A summary of identified mechanisms regulated by MUFAs is presented in **Figure 2**.

4.1.3. Polyunsaturated fatty acids. PUFAs contain more than one double C=C bond. The PUFAs omega-3 and omega-6 are not produced in the body and thus need to be supplemented in the diet. Generally, omega-3 fatty acids are considered to be anti-inflammatory and omega-6 fatty acids are considered to be pro-inflammatory. A balance between these is therefore

considered important for the maintenance of homeostasis, and an imbalance is associated with the development of several inflammatory conditions. Peroxidase lipids are products of the derived oxidation of PUFAs. Oxidation of the omega-6 fatty acid linoleic acid (LA) results in the formation of 13-hydroperoxy octadecadienoic acid (13-HPODE), which induces a pro-inflammatory cytokine (TNF-α, MCP-1, IL-6) response and apoptosis, reduced barrier function, and alterations in tight-junction proteins (occludin and claudin-1) in intestinal epithelial cells. Mice fed 13-HPODE demonstrated an increased inflammatory response upon short-term feeding (4 h) and reduced barrier function and increased cytokine response and CD36 (cholesterol uptake) in peritoneal macrophages upon chronic feeding (28 days), which is suggestive of enhanced intestinal inflammation (Keewan et al. 2020).

Among the omega-6 fatty acids, LA is one of the most abundant PUFAs found in human diets. PUFAs are metabolized by several different enzymes, including cyclooxygenase, lipoxygenase, and cytochrome P450 (CYP-450), all of which are important for the generation of essential metabolites, including eicosanoids and lipoxygenases. Among the CYP-450 generated metabolites from LA, the linoleic epoxides 9,10-epoxyoctadecenoic acid (9,10-EpOME or leukotoxin) and 12,13-epoxyoctadecenoic acid (12,13-EpOME or isoleukotoxin) appear to have immunomodulatory properties depending on the concentration and environment. In mice, supplementation of a high-fat diet (butter-based diet) with α-linolenic acid (ALA) led to reduced EpOMEs and dihydroxy-octadecenoic acids (DiHOMEs) in the liver and plasma, a reduction in the omega-6:omega-3 ratio, attenuation of inflammation due to reduced NF-κB activation, M1 macrophage polarization, and insulin resistance (Fan et al. 2020). Another study correlated the presence of 12,13-DiHOME with the microbiome of children that develop asthma by four years of age (Fujimura et al. 2016). The metabolite 12,13-DiHOME was reported to change the T cell profile to a Th2 phenotype and potentiate the risk of developing asthma. The microbiome of this high-risk group had a lower relative abundance of *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium* spp. and a higher relative abundance of certain fungi, including *Candida* and *Rhodotorula* spp. In line with this, treatment of mice with 12,13-DiHOME in a cockroach antigen model resulted in an exaggerated allergic response, with higher inflammatory infiltration and cytokine response (Fujimura et al. 2016).

ALA is considered a contributor to the differentiation of M2 macrophages, which display an anti-inflammatory phenotype. However, the mechanisms by which ALA contributes to M2 differentiation have been poorly characterized. A recent study showed that ALA and related metabolites generated from ALA by lactic acid bacteria [13-hydroxy9(Z),15(Z)-octadecadienoic acid (13-OH), and 13-oxo-9(Z),15(Z)-octadecadienoic acid (13-oxo)] regulated M2 polarization in the presence of Th2 cytokines (IL-4 and IL-13) partly via GPCR40-MAPK signaling and PPARγ signaling. Interestingly, feeding of mice with ALA, 13-OH, or 13-oxo for three days resulted in the differentiation of M2 macrophages in the small intestinal lamina propria without induction in adipose tissue, mesenteric lymph nodes, or gut-associated lymphoid tissues (Ohue-Kitano et al. 2018). Mechanisms by which PUFAs and associated metabolites regulate host responses are presented in **Figure 2**.

4.2. Proteins and Protein Derivatives

Protein is required in the diet to supply essential amino acids that cannot be synthesized de novo in humans (Wolfe et al. 2017). Recommendations under the AMDR suggest that proteins should account for 10–35% of energy from the diet, which equates to 1.05–3.67 g/(kg·day). This represents an increase from earlier established RDA guidelines [of 0.8 g(kg·day)] for protein intake and reflects suggested health benefits from an elevated protein diet, particularly in the elderly (Wolfe et al. 2017). Epidemiological studies suggest that relatively low protein intake in persons over 65 is associated with loss of lean mass, reduced bone density, and increased risk of mortality

(McCarty & DiNicolantonio 2015). It has been proposed that increased dietary cysteine intake (either from whole protein or supplementation with N-acetylcysteine) compensates for the reduced intracellular glutathione synthesis that occurs with aging, leading to a reduction of damage due to reactive oxygen species (McCarty & DiNicolantonio 2015). Dietary supplementation with N-acetylcysteine has been shown to benefit vascular health, bone density, cell-mediated immunity, systemic inflammation, and resistance to influenza infection (McCarty & DiNicolantonio 2015). Similarly, dietary supplementation with the dipeptide alanine–glutamine led to enhanced control of inflammation and enhanced barrier function and mucosal recovery in a DSS-induced colitis model in mice (Hou et al. 2013). Similar effects were seen with tryptophan supplementation in a porcine DSS-induced colitis model, with an overall reduction in inflammatory score linked to a reduction in Th1 responses (Kim et al. 2010).

Proteins represent key dietary antigens that influence local immune tolerance and are particularly relevant in the education of the small intestinal immune system in early life. Milk has been suggested to exhibit limited antigenic complexity, so food tolerance is primarily induced at weaning upon the introduction of a more complex protein-containing diet (Kim et al. 2016). Germ-free mice are depleted in Treg cells in the colon but not the small intestine, suggesting a role for microbiota-independent mechanisms in the generation of small intestinal (peripheral) pTreg responses. In a seminal study, Kim et al. (2016) raised germ-free mice on a protein-restricted diet and showed that subsequent exposure to dietary protein induced a small intestinal population of RORγt$^-$ pTreg cells. Subsequent experiments with conventionally raised mice treated with antibiotics at weaning showed that although small intestinal RORγt$^+$ pTreg cells are dependent on microbiota–host interactions, RORγt$^-$ pTreg cells are largely microbiota-independent and driven by dietary protein antigens. The findings have implications for understanding the development of food allergy and how complex proteins in the diet may influence local inflammation (Kim et al. 2016). Similarly, dietary proteins increase production of the anti-inflammatory cytokine IL-10 in resident macrophages in the small intestine in a manner that is independent of microbiota–host interactions and appears to be dependent on activation of mTOR (Ochi et al. 2016).

Although a balanced diet consisting of proteins from various sources is recommended, potentially adverse health effects have been described for diets rich in animal proteins. A large, unbiased prospective cohort study analyzing the diet of 67,581 participants associated high dietary protein intake from meat or fish (but not dairy or eggs) with an increased risk of IBD (Jantchou et al. 2010). A similar prospective study associated increased dietary intake of cured meats with a worsening of asthma symptoms (Li et al. 2017). Animal meat and fish are dietary sources of carnitine, an amino acid derivative that can be synthesized in eukaryotic cells, primarily in the liver and kidneys, from lysine and methionine (Statovci et al. 2017). Carnitine (along with choline and phosphatidylcholine) is a precursor of the systemic metabolite TMAO, elevated levels of which are a marker of increased risk of CVD (Wang et al. 2011). Furthermore, murine studies established a causal link between elevated TMAO and atherosclerosis (Wang et al. 2011). Precursors of TMAO are metabolized by the gut microbiota through the activity of specific TMA lyases to release TMA, which is transported to the liver via the portal vein (Witkowski et al. 2020). Bacterial TMA lyases, including the choline utilization (*cutCD*) gene cluster, have been described and functionally analyzed (Craciun & Balskus 2012). In the liver, TMA is metabolized to TMAO through the activity of host flavin monooxygenases (Witkowski et al. 2020). In an interesting recent study, cloning and expression of the *cutC* gene in commensal *Clostridium sporogenes* bacteria was able to restore TMA (and subsequent TMAO) levels in host gnotobiotic mice colonized with a defined polymicrobial community, thereby providing definitive proof of the importance of this microbial gene activity in the ultimate generation of the metaorganismal metabolite TMAO (Skye et al. 2018). Although

consumption of L-carnitine is associated with increased risk of CVD and related major cardiac events, the elevated risk is most pronounced in individuals with commensurately elevated TMAO, highlighting the potential for bacterial TMA lyases as future microbiota markers of CVD risk or as targets for reducing risk (Koeth et al. 2013). The potential mechanisms underlying the pathogenesis of TMAO-related CVD have been investigated in detail and include alterations to bile acid metabolism and signaling, reduction in reverse cholesterol transport, and increased vascular inflammation (**Figures 1** and **2**) (Koeth et al. 2013; this area is reviewed in detail in Witkowski et al. 2020).

Although the evidence of a role for TMAO in CVD risk is compelling, it should be noted that TMAO is thought to perform essential functions in the host, including a role in protecting kidney cells from stress mediated by urea (Ufnal et al. 2015). In addition, a large meta-analysis of CVD incidents failed to show an association between consumption of choline or betaine and CVD endpoints, although effects of dietary carnitine were not examined (Meyer & Shea 2017). It is likely that CVD risk can also be attributed to an independent role for the microbiota in the regulation of host bile acid metabolism (Ryan et al. 2017). In addition, given the complex chemical nature of foods, the effects of combinations of macronutrients should be considered when considering effects on disease risk. For instance, although oily fish are a source of carnitine they are also a source of anti-inflammatory omega-3 PUFAs, which have been shown to reduce TMAO levels and reduce atherosclerosis in $ApoE^{-/-}$ mice (He et al. 2019).

The impact of a high-protein diet on gut microbiome community structure in humans has been analyzed in a limited number of studies. In overweight volunteers who received a diet elevated in either soy protein or casein, there was no significant alteration to gut microbial community structure, although microbial metabolism was altered to reflect amino acid degradation with differences in metabolite profiles dependent on a dietary protein source (Beaumont et al. 2017b). Another study also examined how protein source (red meat, white meat, nonmeat) affected the gut microbiome, in this case in volunteers across a range of BMIs. The study determined that interindividual variation in microbiome community structure was the most important factor differentiating individuals, with a relatively minimal influence from dietary protein on microbiota changes (Lang et al. 2018). Overall, individuals with the highest microbial diversity at baseline were most resistant to dietary influences on the microbiota (Lang et al. 2018). A summary of identified mechanisms regulated by proteins is presented in **Figure 2**.

4.3. Carbohydrates

Carbohydrates comprise monosaccharides, disaccharides, oligosaccharides (typically comprising 3–10 units), and polysaccharides. Monosaccharides and disaccharides are described as sugars that are typically soluble and can be ingested as refined sugar/carbohydrates (sucrose, starch, fructose) in high-energy foods that are energy-dense but nutrient poor. When such foods represent a significant portion of the diet (such as in the Western diet), it is a risk factor for obesity, type 2 diabetes, and CVD (Statovci et al. 2017). Although there are several significant studies examining the effects of complex polysaccharides (fiber) on systemic metabolism, the microbiome, and immune function (Armet et al. 2020), it is also clear that refined sugars have a significant and rapid systemic impact (Myles 2014). Several studies have shown that consumption of high levels of refined sugars is associated with an increase in systemic cytokine profiles and inflammatory tone in humans (Aeberli et al. 2011, Sorensen et al. 2005), although some studies did not detect such an association (Kuzma et al. 2016). A recent study identified specific inflammatory markers associated with consumption of sugar-sweetened beverages, which included tumor necrosis factor receptor superfamily member 4 (TNFRSF4), IL-12, and the chemokine CXCL13, with some markers also

associated with type 2 diabetes (Ramne et al. 2020). There is evidence to suggest that although systemic inflammation may increase in response to refined sugar intake there is an allied reduction in efficacy of phagocytosis in circulating neutrophils (Sanchez et al. 1973). Although further work is necessary, the studies collectively suggest a paradigm whereby excessive intake of refined sugars in the Western diet stimulates systemic inflammation influencing increased adiposity and CVD risk, whereas diets rich in complex fibers (see below) have the potential to reduce systemic inflammation and LDL cholesterol, thereby reducing metabolic syndrome risk factors (Statovci et al. 2017).

Dietary fiber is any form of complex carbohydrate derived principally from plants, which is resistant to breakdown by human catalytic enzymes. Fiber therefore reaches the colon, where it is broken down by resident gut microbes to produce fermentation products, including short-chain fatty acids (SCFAs), lactate, and gas (Statovci et al. 2017). As it reaches the colon almost completely intact, fiber has the potential to stimulate alterations to microbial community structure, generally promoting growth of *Bifidobacterium* and *Lactobacillus* species among other microbial taxa.

SCFAs, which include butyrate, propionate, and acetate, are considered principal mediators of host–microbe interactions and have considerable potential to alter local immune responses and regulate epithelial cell homeostasis and barrier function. Numerous microbial species can produce acetate as an end product of fermentation, resulting in acetate being the most abundant SCFA in the colon (Blaak et al. 2020). Propionate can be produced by various Bacteroidetes via the succinate pathway or the Lachnospiraceae and other organisms via the acrylate pathway. The principal producers of butyrate include *Eubacterium rectale*, *Roseburia* species, and *Faecalibacterium prausnitzii* (Blaak et al. 2020). The production of these metabolites by colonic microorganisms is dynamic, and cross-feeding leads to alterations in community structure in the colon. For instance, production of acetate by *Bifidobacterium* or *Akkermansia* species can stimulate the growth of butyrate-producing organisms, allowing for syntrophy between co-abundant groups of organisms in the gut (Blaak et al. 2020).

SCFAs, in particular, butyrate, have been shown to improve gut barrier function in animal models through the promotion of tight junctions. Mechanistic studies have been carried out in mice following feeding with prebiotics and correlating resultant SCFA production with measures of barrier integrity. For instance, feeding fermentable fiber to mice was shown to increase SCFA production and enhance expression of tight-junction proteins (including ZO-1, ZO-2, occludin, and junctional adhesion molecule A) (Hung & Suzuki 2018). Similar results were seen in genetically obese *ob/ob* mice, with demonstrable increases in ZO-1 and occludin in prebiotic-fed animals that were functionally linked to the production of glucagon-like peptide 2 (GLP-2) (Cani et al. 2009). Effects on tight-junction proteins may be mediated through stimulation of AMP-activated protein kinase (AMPK) activity in epithelial cells (Peng et al. 2009), and local production of IL-10 and stimulation of IL-10 receptor alpha (IL-10RA) by colonocytes are also likely to play an important mechanistic role in the barrier response to SCFAs (Zheng et al. 2017). In humans, studies investigating gastrointestinal barrier function following regular consumption of sources of fermentable fiber or prebiotics have been equivocal with only some studies demonstrating an improvement in barrier function, perhaps suggesting differing effects of dietary fiber source (reviewed in Blaak et al. 2020).

The immunoregulatory effects of SCFAs have been well established using animal models. Butyrate, and to a lesser extent propionate and acetate, can engage GPCRs (GPR41, GPR43, and GPR109a) with resultant activation of MEK-ERK and p38 MAPK signaling pathways to facilitate the generation of extrathymic Foxp3$^+$ Treg cells to limit inflammation in the intestine or regulate physiological processes in colonocytes (Arpaia et al. 2013, Campos-Perez & Martinez-Lopez 2021, Smith et al. 2013). There is evidence that SCFAs also directly signal Th1 cells via GPR43

receptors to activate STAT3 and mTOR pathways and enhance production of the anti-inflammatory cytokine IL-10 (Sun et al. 2018). Similarly, SCFAs can promote production of IL-22 in $CD4^+$ T cells through the engagement of GPR41 and regulation via mTOR and STAT3 (Yang et al. 2020).

SCFAs also regulate aspects of innate immunity. Butyrate can influence dendritic cell maturation and induce a tolerogenic phenotype through the engagement of GPR43 and subsequent induction of retinaldehyde dehydrogenase (RALDH) (Tan et al. 2016) or induce retinoic acid production through engagement with GPR109a to promote a B cell IgA response (Wu et al. 2017). Ultimately, engagement of specific GPCRs results in regulation of local cytokine production with induction of IL-10 and IL-18 to promote local anti-inflammatory responses and homeostasis (Campos-Perez & Martinez-Lopez 2021, Singh et al. 2014). The dietary-driven production of SCFAs by the colonic microbiota also provides a conduit for regulation of systemic inflammation with gastrointestinal Treg cell responses being linked to regulation of airway inflammation in asthma (Statovci et al. 2017). In addition, diet-driven SCFAs are protective against allergic airway inflammation through a mechanism that promotes regulatory dendritic cell suppression of Th2 responses through activation of GPR41 (but not GPR43) by propionate (Trompette et al. 2014).

In humans, a diet supplemented with elevated fermentable fibers promotes an increase in microbial species capable of SCFA production and elevated detectable levels of SCFAs. Importantly, subtle changes in the chemical structure of dietary fibers can specifically alter microbiota responses in humans and change the proportion of butyrate and propionate (Deehan et al. 2020). Improved understanding of microbiota responses to different dietary fibers may be an avenue for rational, targeted dietary alteration of SCFAs. A recent meta-analysis suggests that elevated levels of dietary fiber in humans are associated with improvements in glucose control and cholesterol metabolism, but evidence is lacking for a role in the control of systemic inflammation, at least when C-reactive protein (CRP) is used as an inflammatory marker (Armet et al. 2020). In volunteers with type 2 diabetes, dietary-driven microbial production of SCFAs correlates with a clinical improvement in blood glucose control, an increase in GLP-1, and a reduction in acetylated hemoglobin (Zhao et al. 2018). A recent large-scale association study demonstrates a link between host genetic factors, production of butyrate by the microbiota, and improved glucose response. Interestingly, abnormal production or absorption of propionate was associated with increased type 2 diabetes risk (Sanna et al. 2019). Finally, a recent study provides proof-of-concept for the use of a low-fermentable fiber supplement as an adjunct to FMT for enhanced glucose control in obese individuals with type 2 diabetes (Mocanu et al. 2021), suggesting that appropriate dietary interventions may enhance the already promising metabolic effects of FMT seen in other studies (Aron-Wisnewsky et al. 2019).

4.4. Food Additives: Emulsifiers and Sweeteners

Sweeteners and emulsifiers are widely used in the food industry, and recent evidence indicates that these may be harmful to our endogenous microbiota, becoming risk factors for several disease conditions within the metabolic syndrome. Dietary emulsifiers, such as carboxymethylcellulose (CMC) and polysorbate-80 (p80), can alter the gut microbiota composition, resulting in a pro-inflammatory microbiota. Chronic exposure to emulsifiers results in erosion of the protective function of the mucus with increased bacterial adherence and increased levels of pro-inflammatory flagellin and LPS, leading to the development of metabolic syndrome and intestinal inflammation in mice (Chassaing et al. 2017). Recent studies have also shown that emulsifiers can exacerbate the development of small intestinal adenomas and colitis-associated cancer, targeting epithelial proliferation rather than inflammation in the adenoma model (**Figure 2**) (Viennois & Chassaing 2021, Viennois et al. 2017). The culture of 20 different well-known food additives

in a mini-bioreactor fermentation system confirmed that p80 and CMC deteriorate human microbiota composition and function, but several other emulsifiers, including maltodextrin, carrageenan, and gum compounds, also negatively impacted the composition and function of the microbiota. Other emulsifiers such as soy lecithin and mono- and diglycerides did not significantly affect the microbiota (Naimi et al. 2021). However, other studies have shown that soy lecithin increased pulmonary lipid peroxidation and platelet-activating factor bioactivity in asthmatics (Muehlmann et al. 2010) and promoted adiposity and inflammation in a model of high-fat-diet-induced obesity (Lecomte et al. 2016). Sweeteners such as sucralose may promote and exacerbate inflammation by altering the microbiota composition when consumed over six months (Bian et al. 2017). Similarly, exposure to saccharin, sucralose, or aspartame in mice altered the microbiota composition and function, leading to glucose intolerance, suggesting these can be risk factors for metabolic diseases such as diabetes (Suez et al. 2014). Contrary to these findings, saccharin intake altered microbiome composition and reduced inflammation in mice with acute and chronic colitis (Sunderhauf et al. 2020). Overall, much of our understanding of dietary additives comes from animal studies and microbiota because few studies have been carried out in humans.

5. IMPLICATIONS FOR DISEASE STATES OTHER THAN OBESITY/METABOLIC DISEASE

5.1. Inflammatory Bowel Disease

Epidemiological studies have identified the Westernized diet, processed foods, red meat, fat, and high sugar intake as risk factors for IBD. Consumption of vegetables, fruits, and dietary fibers has been associated with a reduced risk of developing Crohn's disease but not ulcerative colitis (UC) (Ananthakrishnan et al. 2018). Interestingly, a recent short-term crossover study in UC patients in the remission/inactive phase demonstrated that feeding with a low-fat- and high-fiber-containing diet improved quality of life, altered gut microbiota composition, and reduced markers of inflammation. Feeding patients an improved Standard American Diet (iSAD, supplemented with more fruits, vegetables, and fibers but still high in fat and red meat) also improved their quality of life, reduced the consumption of refined sugars, and presented a modest modulation of the intestinal microbiota (Fritsch et al. 2021). However, the authors were unable to determine whether the improvement was due to consumption of more fiber or less refined sugar or a change in fat type (Fritsch et al. 2021). The low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, which is known to reduce fermentable substrates in the colon, has been successful in improving symptoms in up to 70% of patients with irritable bowel syndrome coincident with alteration of microbiota composition (Staudacher et al. 2017). Similarly, a randomized controlled trial of patients with quiescent IBD placed on a four-week low-FODMAP diet also showed an improvement in gut symptoms and quality of life, especially in UC patients, but without improvement in clinical activity or markers of inflammation. Patients on the low-FODMAP diet showed a reduced abundance of *Bifidobacterium adolescentis*, *Bifidobacterium longum*, and *F. prausnitzii* but no overall alteration to microbial community structure in the gut (Cox et al. 2020). Although these bacteria are considered important for gut homeostasis and are already reduced in IBD, a further reduction due to the supplemented low-FODMAP diet did not appear to negatively affect these patients.

The ketogenic diet is characterized by high fat and low carbohydrate content, and recent studies indicate that it can be used to reduce glycemic responses associated with type 2 diabetes. It has been suggested that the ketogenic diet might target the microbiota to reduce inflammation by inhibiting accumulation of Th17 cells. However, ketogenic diets have also been shown to reduce gut microbial diversity (Rinninella et al. 2019a). There are currently no clinical studies

using this diet in IBD patients, but murine studies indicate that a ketogenic diet can reduce the development of DSS-induced colitis (Kong et al. 2021). Mice were fed a ketogenic diet for 16 weeks, which resulted in an increased Firmicutes:Bacteroidetes ratio, elevated Proteobacteria abundance, and an enrichment in *Akkermansia*, *Roseburia*, and Ruminococcaceae spp. Following a DSS challenge, mice fed the ketogenic diet displayed improved barrier function with reduced markers of inflammation, most likely by regulating innate lymphoid cells (ILC3) and their effector cytokines (including IL-17a, IL-22, and IL-18) and influencing monocyte chemotaxis (including CCL4 and CCL12). Following the induction of colitis, the ketogenic diet enriched *Akkermansia* and reduced levels of *Escherichia/Shigella*. FMT from mice fed the ketogenic diet to germ-free mice challenged with DSS resulted in an alleviation of inflammation and improved barrier function, thereby providing evidence for a functional role of the microbiota in eliciting diet-mediated improvements in disease score (Kong et al. 2021).

5.2. Infection

The interaction between diet and susceptibility to infection has recently emerged as an important association because of the potential role of nutrition as a modulator of both barrier function and immunity to pathogens in the intestine (Nobs et al. 2020). Obesity and type 2 diabetes are associated with an enhanced risk for mucosal infection and systemic inflammation potentially linked to intestinal barrier permeability (Thaiss et al. 2018). Commensal bacteria play a crucial role in preventing colonization by pathogens (a process known as colonization resistance) through direct mechanisms (nutrient competition, production of inhibitory metabolites, and influence upon pathogen virulence gene expression) or through indirect mechanisms mediated by the induction of the mucosal immune barrier response (Kreuzer & Hardt 2020).

Functional links between microbiota and pathogen resistance have been established. For instance, antibiotic-mediated damage of the intestinal microbiota prior to oral infection with *Listeria monocytogenes* increases the infectious load in mice, but resistance to infection can be restored through reestablishing the microbiota or specific members of the Clostridiales that have been associated with colonization resistance in this model (Becattini et al. 2017). Antibiotics also reduce resistance to oral *Salmonella* Typhimurium infection in mice with protection being restored through the provision of 15 rationally selected members of the gut microbiota (Brugiroux et al. 2016). Susceptibility to *Clostridium difficile* infection in the elderly is clearly linked to prior broad-spectrum antibiotic use, which perturbs members of the microbiota that produce secondary bile acids that are directly inhibitory to the pathogen. Reestablishing the microbiota (e.g., through FMT) restores secondary bile acid production and protects against *C. difficile* infection (Buffie et al. 2015).

Microbiota–host interactions may also influence virulence factor expression in pathogens. For instance, pathogenic enterohemorrhagic *E. coli* take advantage of *Bacteroides thetaiotaomicron* metabolism of host glycan to produce fucose; this increases fucose availability in the intestine, which induces virulence gene expression in the pathogen (Pacheco et al. 2012).

Several studies have examined the potential for components of a Western diet to influence susceptibility to infectious disease in animal model systems. Feeding a high-fat diet to mice significantly lowered resistance to *L. monocytogenes* infection, a finding that correlated with a reduction in markers of gut barrier function (including a reduction in expression of anti-listerial *Reg3g*) (Las Heras et al. 2019). The model also showed an altered microbiota and generalized increase in inflammatory markers but a reduction in expression of cytokines that are key to the inhibition of *L. monocytogenes* (notably IFN-γ). Interestingly, high-fat-fed mice were also susceptible to systemic (intraperitoneal) infection, reflecting systems-wide sensitivity to infection as a result of diet (Las Heras et al. 2019).

S. Typhimurium infection is also exacerbated in mice fed a high-fat diet (Wotzka et al. 2019). In this model dietary fat enhanced levels of bile in the gut, which promoted colonization by bile-resistant *S.* Typhimurium and was dependent upon the pathogen expressing the AcrAB/TolC bile acid locus. The effect was most pronounced in mice lacking commensal *E. coli*, and subsequent experiments demonstrated that commensal *E. coli* can enhance colonization resistance against the pathogen (Wotzka et al. 2019). Similarly, a Western-style diet alters the infection dynamics of *Citrobacter rodentium* in the mouse model. A Western-style high-fat, low-fiber diet actually enhanced early reduction of the pathogen but ultimately resulted in a more persistent infection. The findings were correlated with microbiota changes and SCFA profiles in the high-fat-diet-fed animals (An et al. 2021). Notably, a recent study used mouse models of hypoglycemia or obesity to show that the hyperglycemia that is associated with the metabolic syndrome/consumption of a Western diet, rather than obesity per se, is responsible for loss of barrier function, metabolic endotoxemia, and susceptibility to infection with *C. rodentium* (Thaiss et al. 2018).

Although a Western-style diet may enhance sensitivity to infection, at least in animal models, several studies have examined dietary interventions that might protect against infection. Studies on the role of carbohydrate (fiber) dietary supplementation have demonstrated varied results, with xylooligosaccharides and glucooligosaccharides providing enhanced protection against *L. monocytogenes* infection but inulin and pectin exacerbating infection (Ebersbach et al. 2010). Other potential interventions include β-1,4 mannobiose (a nondigestible disaccharide involved in IgA stimulation), which may have a use in protection against *Salmonella* infection in chickens (Ibuki et al. 2011). In addition to carbohydrates, some studies have examined the immunomodulatory effects of various fats. For instance, fish oils that are rich in omega-3 PUFAs improved host immune response against secondary infection with *L. monocytogenes* in an animal model (Cruz-Chamorro et al. 2011).

Dietary interventions have been proposed in the context of enhancing resistance to SARS-CoV-2 virus that causes COVID19. Diets such as the ketone diet that enhance R-β-hydroxybutyrate have demonstrated efficacy in protection against influenza virus infection and may have a role in preventing the damaging effects of the cytokine storm that is a hallmark of systemic coronavirus infection (Bradshaw et al. 2020).

6. CONCLUSIONS

Clearly, components of foods have an effect on the host that is almost pharmacological in nature and goes beyond a nutritional impact. The interplay between food components, the immune system, and microbiota is complex, but increased understanding of this interaction will bring exciting new developments in terms of personalized nutrition. Space did not permit the discussion of the impact of vitamins (many produced by the gut microbiota) or minerals (including salt) upon host immune processes, but these are covered elsewhere (Statovci et al. 2017). In addition to the developments described in this review, there have been fascinating discoveries in the area of gut–brain interactions (also mediated by the microbiota) that influence satiety, food impulses, and, potentially, food preferences. Allied to this are advances in our understanding of gut–liver and gut–lung interactions that hold the potential for dietary modulation of risk in ectopic disease and allergy. Finally, as we move toward an understanding of mechanisms using animal disease models, it is important to translate studies to humans to progress the advent of rational dietary modifications for health.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We acknowledge funding and support from Science Foundation Ireland (SFI) in the form of a center grant (APC Microbiome Ireland grant SFI/12/RC/2273). We also acknowledge funding of V.L.H. by the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement 641984, through funding of the List_MAPS consortium.

LITERATURE CITED

Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, et al. 2011. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *Am. J. Clin. Nutr.* 94:479–85

Al Nabhani Z, Dulauroy S, Lecuyer E, Polomack B, Campagne P, et al. 2019. Excess calorie intake early in life increases susceptibility to colitis in adulthood. *Nat. Metab.* 1:1101–9

An D, Oh SF, Olszak T, Neves JF, Avci FY, et al. 2014. Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. *Cell* 156:123–33

An J, Zhao X, Wang Y, Noriega J, Gewirtz AT, Zou J. 2021. Western-style diet impedes colonization and clearance of *Citrobacter rodentium*. *PLOS Pathog.* 17:e1009497

Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, et al. 2018. Environmental triggers in IBD: a review of progress and evidence. *Nat. Rev. Gastroenterol. Hepatol.* 15:39–49

Armet AM, Deehan EC, Thone JV, Hewko SJ, Walter J. 2020. The effect of isolated and synthetic dietary fibers on markers of metabolic diseases in human intervention studies: a systematic review. *Adv. Nutr.* 11:420–38

Aron-Wisnewsky J, Clement K, Nieuwdorp M. 2019. Fecal microbiota transplantation: a future therapeutic option for obesity/diabetes? *Curr. Diabetes Rep.* 19:51

Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, et al. 2013. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 504:451–55

Badeanlou L, Furlan-Freguia C, Yang G, Ruf W, Samad F. 2011. Tissue factor-protease-activated receptor 2 signaling promotes diet-induced obesity and adipose inflammation. *Nat. Med.* 17:1490–97

Beaumont M, Andriamihaja M, Armand L, Grauso M, Jaffrezic F, et al. 2017a. Epithelial response to a high-protein diet in rat colon. *BMC Genom.* 18:116

Beaumont M, Portune KJ, Steuer N, Lan A, Cerrudo V, et al. 2017b. Quantity and source of dietary protein influence metabolite production by gut microbiota and rectal mucosa gene expression: a randomized, parallel, double-blind trial in overweight humans. *Am. J. Clin. Nutr.* 106:1005–19

Becattini S, Littmann ER, Carter RA, Kim SG, Morjaria SM, et al. 2017. Commensal microbes provide first line defense against *Listeria monocytogenes* infection. *J. Exp. Med.* 214:1973–89

Begley M, Gahan CG, Hill C. 2005. The interaction between bacteria and bile. *FEMS Microbiol. Rev.* 29:625–51

Beyaz S, Mana MD, Roper J, Kedrin D, Saadatpour A, et al. 2016. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature* 531:53–58

Bian X, Chi L, Gao B, Tu P, Ru H, Lu K. 2017. Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. *Front. Physiol.* 8:487

Blaak EE, Canfora EE, Theis S, Frost G, Groen AK, et al. 2020. Short chain fatty acids in human gut and metabolic health. *Benef. Microbes* 11:411–55

Bradshaw PC, Seeds WA, Miller AC, Mahajan VR, Curtis WM. 2020. COVID-19: proposing a ketone-based metabolic therapy as a treatment to blunt the cytokine storm. *Oxid. Med. Cell Longev.* 2020:6401341

Brugiroux S, Beutler M, Pfann C, Garzetti D, Ruscheweyh HJ, et al. 2016. Genome-guided design of a defined mouse microbiota that confers colonization resistance against *Salmonella enterica* serovar Typhimurium. *Nat. Microbiol.* 2:16215

Buffie CG, Bucci V, Stein RR, McKenney PT, Ling L, et al. 2015. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature* 517:205–8

Caesar R, Reigstad CS, Backhed HK, Reinhardt C, Ketonen M, et al. 2012. Gut-derived lipopolysaccharide augments adipose macrophage accumulation but is not essential for impaired glucose or insulin tolerance in mice. *Gut* 61:1701–7

Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Backhed F. 2015. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. *Cell Metab.* 22:658–68

Campos-Perez W, Martinez-Lopez E. 2021. Effects of short chain fatty acids on metabolic and inflammatory processes in human health. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* 1866(5):158900

Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, et al. 2007. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 56:1761–72

Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, et al. 2009. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 58:1091–103

Cenac N, Garcia-Villar R, Ferrier L, Larauche M, Vergnolle N, et al. 2003. Proteinase-activated receptor-2-induced colonic inflammation in mice: possible involvement of afferent neurons, nitric oxide, and paracellular permeability. *J. Immunol.* 170:4296–300

Chassaing B, Van de Wiele T, De Bodt J, Marzorati M, Gewirtz AT. 2017. Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. *Gut* 66:1414–27

Chen J, Li J, Yiu JHC, Lam JKW, Wong CM, et al. 2017. TRIF-dependent Toll-like receptor signaling suppresses Scd1 transcription in hepatocytes and prevents diet-induced hepatic steatosis. *Sci. Signal.* 10(491):eaal3336

Cimen I, Kocaturk B, Koyuncu S, Tufanli O, Onat UI, et al. 2016. Prevention of atherosclerosis by bioactive palmitoleate through suppression of organelle stress and inflammasome activation. *Sci. Transl. Med.* 8:358ra126

Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, et al. 2012. Gut microbiota composition correlates with diet and health in the elderly. *Nature* 488:178–84

Costea PI, Hildebrand F, Arumugam M, Backhed F, Blaser MJ, et al. 2018. Enterotypes in the landscape of gut microbial community composition. *Nat. Microbiol.* 3:8–16

Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, et al. 2013. Dietary intervention impact on gut microbial gene richness. *Nature* 500:585–88

Cox SR, Lindsay JO, Fromentin S, Stagg AJ, McCarthy NE, et al. 2020. Effects of low FODMAP diet on symptoms, fecal microbiome, and markers of inflammation in patients with quiescent inflammatory bowel disease in a randomized trial. *Gastroenterology* 158:176–88.e7

Craciun S, Balskus EP. 2012. Microbial conversion of choline to trimethylamine requires a glycyl radical enzyme. *PNAS* 109:21307–12

Creely SJ, McTernan PG, Kusminski CM, Fisher FM, Da Silva NF, et al. 2007. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.* 292:E740–47

Cruz-Chamorro L, Puertollano E, de Cienfuegos GA, Puertollano MA, de Pablo MA. 2011. Acquired resistance to *Listeria monocytogenes* during a secondary infection in a murine model fed dietary lipids. *Nutrition* 27:1053–60

Dahl WJ, Rivero Mendoza D, Lambert JM. 2020. Diet, nutrients and the microbiome. *Prog. Mol. Biol. Transl. Sci.* 171:237–63

David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, et al. 2014. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505:559–63

Deehan EC, Yang C, Perez-Munoz ME, Nguyen NK, Cheng CC, et al. 2020. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. *Cell Host Microbe* 27:389–404.e6

Degirolamo C, Rainaldi S, Bovenga F, Murzilli S, Moschetta A. 2014. Microbiota modification with probiotics induces hepatic bile acid synthesis via downregulation of the Fxr-Fgf15 axis in mice. *Cell Rep.* 7:12–18

Depommier C, Everard A, Druart C, Plovier H, Van Hul M, et al. 2019. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* 25:1096–103

Devkota S, Wang Y, Musch MW, Leone V, Fehlner-Peach H, et al. 2012. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10$^{-/-}$ mice. *Nature* 487:104–8

Draper LA, Ryan FJ, Dalmasso M, Casey PG, McCann A, et al. 2020. Autochthonous faecal viral transfer (FVT) impacts the murine microbiome after antibiotic perturbation. *BMC Biol.* 18:173

Ebersbach T, Jorgensen JB, Heegaard PM, Lahtinen SJ, Ouwehand AC, et al. 2010. Certain dietary carbohydrates promote *Listeria* infection in a guinea pig model, while others prevent it. *Int. J. Food Microbiol.* 140:218–24

Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, et al. 2013. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *PNAS* 110:9066–71

Fan R, Kim J, You M, Giraud D, Toney AM, et al. 2020. α-Linolenic acid-enriched butter attenuated high fat diet-induced insulin resistance and inflammation by promoting bioconversion of n-3 PUFA and subsequent oxylipin formation. *J. Nutr. Biochem.* 76:108285

Fritsch J, Garces L, Quintero MA, Pignac-Kobinger J, Santander AM, et al. 2021. Low-fat, high-fiber diet reduces markers of inflammation and dysbiosis and improves quality of life in patients with ulcerative colitis. *Clin. Gastroenterol. Hepatol.* 19:1189–99.e30

Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, et al. 2016. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat. Med.* 22:1187–91

Gonzalez FJ, Jiang C, Patterson AD. 2016. An intestinal microbiota-farnesoid X receptor axis modulates metabolic disease. *Gastroenterology* 151:845–59

Gonzalez Olmo BM, Butler MJ, Barrientos RM. 2021. Evolution of the human diet and its impact on gut microbiota, immune responses, and brain health. *Nutrients* 13(1):196

Guban J, Korver DR, Allison GE, Tannock GW. 2006. Relationship of dietary antimicrobial drug administration with broiler performance, decreased population levels of *Lactobacillus salivarius*, and reduced bile salt deconjugation in the ileum of broiler chickens. *Poult. Sci.* 85:2186–94

Gulhane M, Murray L, Lourie R, Tong H, Sheng YH, et al. 2016. High fat diets induce colonic epithelial cell stress and inflammation that is reversed by IL-22. *Sci. Rep.* 6:28990

He Z, Hao W, Kwek E, Lei L, Liu J, et al. 2019. Fish oil is more potent than flaxseed oil in modulating gut microbiota and reducing trimethylamine-N-oxide-exacerbated atherogenesis. *J. Agric. Food Chem.* 67:13635–47

Heeney DD, Gareau MG, Marco ML. 2018. Intestinal *Lactobacillus* in health and disease, a driver or just along for the ride? *Curr. Opin. Biotechnol.* 49:140–47

Her JY, Lee Y, Kim SJ, Heo G, Choo J, et al. 2021. Blockage of protease-activated receptor 2 exacerbates inflammation in high-fat environment partly through autophagy inhibition. *Am. J. Physiol. Gastrointest. Liver Physiol.* 320:G30–42

Hou YC, Chu CC, Ko TL, Yeh CL, Yeh SL. 2013. Effects of alanyl-glutamine dipeptide on the expression of colon-inflammatory mediators during the recovery phase of colitis induced by dextran sulfate sodium. *Eur. J. Nutr.* 52:1089–98

Hung TV, Suzuki T. 2018. Dietary fermentable fibers attenuate chronic kidney disease in mice by protecting the intestinal barrier. *J. Nutr.* 148:552–61

Hyun E, Andrade-Gordon P, Steinhoff M, Vergnolle N. 2008. Protease-activated receptor-2 activation: a major actor in intestinal inflammation. *Gut* 57:1222–29

Ibuki M, Kovacs-Nolan J, Fukui K, Kanatani H, Mine Y. 2011. β 1–4 mannobiose enhances *Salmonella*-killing activity and activates innate immune responses in chicken macrophages. *Vet. Immunol. Immunopathol.* 139:289–95

Ilich JZ, Kelly OJ, Kim Y, Spicer MT. 2014. Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis. *Arh. Hig. Rada Toksikol.* 65:139–48c

Inagaki T, Moschetta A, Lee YK, Peng L, Zhao G, et al. 2006. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *PNAS* 103:3920–25

Islam KB, Fukiya S, Hagio M, Fujii N, Ishizuka S, et al. 2011. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. *Gastroenterology* 141:1773–81

Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. 2010. Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study. *Am. J. Gastroenterol.* 105:2195–201

Joyce SA, Kamil A, Fleige L, Gahan CGM. 2019. The cholesterol-lowering effect of oats and oat beta glucan: modes of action and potential role of bile acids and the microbiome. *Front. Nutr.* 6:171

Joyce SA, MacSharry J, Casey PG, Kinsella M, Murphy EF, et al. 2014. Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. *PNAS* 111:7421–26

Keewan E, Narasimhulu CA, Rohr M, Hamid S, Parthasarathy S. 2020. Are fried foods unhealthy? The dietary peroxidized fatty acid, 13-HPODE, induces intestinal inflammation in vitro and in vivo. *Antioxidants* 9(10):926

Kim CJ, Kovacs-Nolan JA, Yang C, Archbold T, Fan MZ, Mine Y. 2010. L-Tryptophan exhibits therapeutic function in a porcine model of dextran sodium sulfate (DSS)-induced colitis. *J. Nutr. Biochem.* 21:468–75

Kim KS, Hong SW, Han D, Yi J, Jung J, et al. 2016. Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science* 351:858–63

Kleessen B, Hartmann L, Blaut M. 2003. Fructans in the diet cause alterations of intestinal mucosal architecture, released mucins and mucosa-associated bifidobacteria in gnotobiotic rats. *Br J. Nutr.* 89:597–606

Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, et al. 2013. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* 19:576–85

Kong C, Yan X, Liu Y, Huang L, Zhu Y, et al. 2021. Ketogenic diet alleviates colitis by reduction of colonic group 3 innate lymphoid cells through altering gut microbiome. *Signal Transduct. Target. Ther.* 6:154

Korpela K, Salonen A, Virta LJ, Kekkonen RA, Forslund K, et al. 2016. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat. Commun.* 7:10410

Kreuzer M, Hardt WD. 2020. How food affects colonization resistance against enteropathogenic bacteria. *Annu. Rev. Microbiol.* 74:787–813

Kunisawa J, Hashimoto E, Inoue A, Nagasawa R, Suzuki Y, et al. 2014. Regulation of intestinal IgA responses by dietary palmitic acid and its metabolism. *J. Immunol.* 193:1666–71

Kuzma JN, Cromer G, Hagman DK, Breymeyer KL, Roth CL, et al. 2016. No differential effect of beverages sweetened with fructose, high-fructose corn syrup, or glucose on systemic or adipose tissue inflammation in normal-weight to obese adults: a randomized controlled trial. *Am. J. Clin. Nutr.* 104:306–14

Lang JM, Pan C, Cantor RM, Tang WHW, Garcia-Garcia JC, et al. 2018. Impact of individual traits, saturated fat, and protein source on the gut microbiome. *mBio* 9:e01604-18

Las Heras V, Clooney AG, Ryan FJ, Cabrera-Rubio R, Casey PG, et al. 2019. Short-term consumption of a high-fat diet increases host susceptibility to *Listeria monocytogenes* infection. *Microbiome* 7:7

Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, et al. 2013. Richness of human gut microbiome correlates with metabolic markers. *Nature* 500:541–46

Lecomte M, Couedelo L, Meugnier E, Plaisancie P, Letisse M, et al. 2016. Dietary emulsifiers from milk and soybean differently impact adiposity and inflammation in association with modulation of colonic goblet cells in high-fat fed mice. *Mol. Nutr. Food Res.* 60:609–20

Lee JY, Ye J, Gao Z, Youn HS, Lee WH, et al. 2003. Reciprocal modulation of Toll-like receptor-4 signaling pathways involving MyD88 and phosphatidylinositol 3-kinase/AKT by saturated and polyunsaturated fatty acids. *J. Biol. Chem.* 278:37041–51

Ley RE, Turnbaugh PJ, Klein S, Gordon JI. 2006. Microbial ecology: human gut microbes associated with obesity. *Nature* 444:1022–23

Li F, Jiang C, Krausz KW, Li Y, Albert I, et al. 2013. Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nat. Commun.* 4:2384

Li Z, Rava M, Bedard A, Dumas O, Garcia-Aymerich J, et al. 2017. Cured meat intake is associated with worsening asthma symptoms. *Thorax* 72:206–12

Liao CY, Song MJ, Gao Y, Mauer AS, Revzin A, Malhi H. 2018. Hepatocyte-derived lipotoxic extracellular vesicle sphingosine 1-phosphate induces macrophage chemotaxis. *Front. Immunol.* 9:2980

Liu TC, Kern JT, Jain U, Sonnek NM, Xiong S, et al. 2021. Western diet induces Paneth cell defects through microbiome alterations and farnesoid X receptor and type I interferon activation. *Cell Host Microbe* 29:988–1001.e6

Magne F, Gotteland M, Gauthier L, Zazueta A, Pesoa S, et al. 2020. The Firmicutes/Bacteroidetes ratio: a relevant marker of gut dysbiosis in obese patients? *Nutrients* 12(5):1474

Mah AT, Van Landeghem L, Gavin HE, Magness ST, Lund PK. 2014. Impact of diet-induced obesity on intestinal stem cells: hyperproliferation but impaired intrinsic function that requires insulin/IGF1. *Endocrinology* 155:3302–14

McCarty MF, DiNicolantonio JJ. 2015. An increased need for dietary cysteine in support of glutathione synthesis may underlie the increased risk for mortality associated with low protein intake in the elderly. *Age* 37(5):96

Meyer KA, Shea JW. 2017. Dietary choline and betaine and risk of CVD: a systematic review and meta-analysis of prospective studies. *Nutrients* 9(7):711

Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. 2012. Comparative meta-analysis of the effect of *Lactobacillus* species on weight gain in humans and animals. *Microb. Pathog.* 53:100–8

Mocanu V, Zhang Z, Deehan EC, Kao DH, Hotte N, et al. 2021. Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. *Nat. Med.* 27(7):1272–79

Muehlmann LA, Zanatta AL, Farias CL, Bieberbach EW, Mazzonetto AC, et al. 2010. Dietary supplementation with soybean lecithin increases pulmonary PAF bioactivity in asthmatic rats. *J. Nutr. Biochem.* 21:532–37

Myles IA. 2014. Fast food fever: reviewing the impacts of the Western diet on immunity. *Nutr. J.* 13:61

Naimi S, Viennois E, Gewirtz AT, Chassaing B. 2021. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome* 9:66

Nistal E, Caminero A, Herran AR, Perez-Andres J, Vivas S, et al. 2016. Study of duodenal bacterial communities by 16S rRNA gene analysis in adults with active celiac disease vs non-celiac disease controls. *J. Appl. Microbiol.* 120:1691–700

Nobs SP, Zmora N, Elinav E. 2020. Nutrition regulates innate immunity in health and disease. *Annu. Rev. Nutr.* 40:189–219

Ochi T, Feng Y, Kitamoto S, Nagao-Kitamoto H, Kuffa P, et al. 2016. Diet-dependent, microbiota-independent regulation of IL-10-producing lamina propria macrophages in the small intestine. *Sci. Rep.* 6:27634

Ohue-Kitano R, Yasuoka Y, Goto T, Kitamura N, Park SB, et al. 2018. α-Linolenic acid-derived metabolites from gut lactic acid bacteria induce differentiation of anti-inflammatory M2 macrophages through G protein-coupled receptor 40. *FASEB J.* 32:304–18

Pacheco AR, Curtis MM, Ritchie JM, Munera D, Waldor MK, et al. 2012. Fucose sensing regulates bacterial intestinal colonization. *Nature* 492:113–17

Passos ME, Alves HH, Momesso CM, Faria FG, Murata G, et al. 2016. Differential effects of palmitoleic acid on human lymphocyte proliferation and function. *Lipids Health Dis.* 15:217

Peng L, Li ZR, Green RS, Holzman IR, Lin J. 2009. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J. Nutr.* 139:1619–25

Pillon NJ, Chan KL, Zhang S, Mejdani M, Jacobson MR, et al. 2016. Saturated fatty acids activate caspase-4/5 in human monocytes, triggering IL-1β and IL-18 release. *Am. J. Physiol. Endocrinol. Metab.* 311:E825–35

Plovier H, Everard A, Druart C, Depommier C, Van Hul M, et al. 2017. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat. Med.* 23:107–13

Ramne S, Drake I, Ericson U, Nilsson J, Orho-Melander M, et al. 2020. Identification of inflammatory and disease-associated plasma proteins that associate with intake of added sugar and sugar-sweetened beverages and their role in type 2 diabetes risk. *Nutrients* 12(10):3129

Regnier M, Van Hul M, Knauf C, Cani PD. 2021. Gut microbiome, endocrine control of gut barrier function and metabolic diseases. *J. Endocrinol.* 248:R67–82

Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, et al. 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 341:1241214

Rinninella E, Cintoni M, Raoul P, Lopetuso LR, Scaldaferri F, et al. 2019a. Food components and dietary habits: keys for a healthy gut microbiota composition. *Nutrients* 11(10):2393

Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, et al. 2019b. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms* 7(1):14

Ryan PM, Stanton C, Caplice NM. 2017. Bile acids at the cross-roads of gut microbiome-host cardiometabolic interactions. *Diabetol. Metab. Syndr.* 9:102

Saez-Lara MJ, Robles-Sanchez C, Ruiz-Ojeda FJ, Plaza-Diaz J, Gil A. 2016. Effects of probiotics and synbiotics on obesity, insulin resistance syndrome, type 2 diabetes and non-alcoholic fatty liver disease: a review of human clinical trials. *Int. J. Mol. Sci.* 17(6):928

Sanchez A, Reeser JL, Lau HS, Yahiku PY, Willard RE, et al. 1973. Role of sugars in human neutrophilic phagocytosis. *Am. J. Clin. Nutr.* 26:1180–84

Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vich Vila A, et al. 2019. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Nat. Genet.* 51:600–5

Schirmer M, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, et al. 2016. Linking the human gut microbiome to inflammatory cytokine production capacity. *Cell* 167:1125–36.e8

Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, et al. 2014. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40:128–39

Skye SM, Zhu W, Romano KA, Guo CJ, Wang Z, et al. 2018. Microbial transplantation with human gut commensals containing CutC is sufficient to transmit enhanced platelet reactivity and thrombosis potential. *Circ. Res.* 123:1164–76

Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, et al. 2013. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 341:569–73

Sorensen LB, Raben A, Stender S, Astrup A. 2005. Effect of sucrose on inflammatory markers in overweight humans. *Am. J. Clin. Nutr.* 82:421–27

Souza CO, Teixeira AA, Biondo LA, Silveira LS, Calder PC, Rosa Neto JC. 2017. Palmitoleic acid reduces the inflammation in LPS-stimulated macrophages by inhibition of NFκB, independently of PPARs. *Clin. Exp. Pharmacol. Physiol.* 44:566–75

Statovci D, Aguilera M, MacSharry J, Melgar S. 2017. The impact of Western diet and nutrients on the microbiota and immune response at mucosal interfaces. *Front. Immunol.* 8:838

Staudacher HM, Lomer MCE, Farquharson FM, Louis P, Fava F, et al. 2017. A diet low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores *Bifidobacterium* species: a randomized controlled trial. *Gastroenterology* 153:936–47

Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, et al. 2014. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 514:181–86

Sun M, Wu W, Chen L, Yang W, Huang X, et al. 2018. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. *Nat. Commun.* 9:3555

Sunderhauf A, Pagel R, Kunstner A, Wagner AE, Rupp J, et al. 2020. Saccharin supplementation inhibits bacterial growth and reduces experimental colitis in mice. *Nutrients* 12(4):1122

Tan J, McKenzie C, Vuillermin PJ, Goverse G, Vinuesa CG, et al. 2016. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. *Cell Rep.* 15:2809–24

Tao L, Yi Y, Chen Y, Zhang H, Orning P, et al. 2021. RIP1 kinase activity promotes steatohepatitis through mediating cell death and inflammation in macrophages. *Cell Death Differ.* 28:1418–33

Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, et al. 2018. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* 359:1376–83

Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, et al. 2014. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat. Med.* 20:159–66

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027–31

Ufnal M, Zadlo A, Ostaszewski R. 2015. TMAO: a small molecule of great expectations. *Nutrition* 31:1317–23

Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, et al. 2011. The antibacterial lectin RegIIIγ promotes the spatial segregation of microbiota and host in the intestine. *Science* 334:255–58

Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, et al. 2011. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat. Med.* 17:179–88

Viennois E, Chassaing B. 2021. Consumption of select dietary emulsifiers exacerbates the development of spontaneous intestinal adenoma. *Int. J. Mol. Sci.* 22(5):2602

Viennois E, Merlin D, Gewirtz AT, Chassaing B. 2017. Dietary emulsifier-induced low-grade inflammation promotes colon carcinogenesis. *Cancer Res.* 77:27–40

Vrieze A, Van Nood E, Holleman F, Salojarvi J, Kootte RS, et al. 2012. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 143:913–16.e7

Wang X, de Carvalho Ribeiro M, Iracheta-Vellve A, Lowe P, Ambade A, et al. 2019. Macrophage-specific hypoxia-inducible factor-1α contributes to impaired autophagic flux in nonalcoholic steatohepatitis. *Hepatology* 69:545–63

Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, et al. 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472:57–63

Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, et al. 2006. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* 439:484–89

Winesett DE, Ulshen MH, Hoyt EC, Mohapatra NK, Fuller CR, Lund PK. 1995. Regulation and localization of the insulin-like growth factor system in small bowel during altered nutrient status. *Am. J. Physiol. Gastrointest. Liver Physiol.* 268:G631–40

Witjes JJ, Smits LP, Pekmez CT, Prodan A, Meijnikman AS, et al. 2020. Donor fecal microbiota transplantation alters gut microbiota and metabolites in obese individuals with steatohepatitis. *Hepatol. Commun.* 4:1578–90

Witkowski M, Weeks TL, Hazen SL. 2020. Gut microbiota and cardiovascular disease. *Circ. Res.* 127:553–70

Wolfe RR, Cifelli AM, Kostas G, Kim IY. 2017. Optimizing protein intake in adults: interpretation and application of the recommended dietary allowance compared with the acceptable macronutrient distribution range. *Adv. Nutr.* 8:266–75

Wotzka SY, Kreuzer M, Maier L, Arnoldini M, Nguyen BD, et al. 2019. *Escherichia coli* limits *Salmonella* Typhimurium infections after diet shifts and fat-mediated microbiota perturbation in mice. *Nat. Microbiol.* 4:2164–74

Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, et al. 2011. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334:105–8

Wu W, Sun M, Chen F, Cao AT, Liu H, et al. 2017. Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43. *Mucosal Immunol.* 10:946–56

Wu X, Poulsen KL, Sanz-Garcia C, Huang E, McMullen MR, et al. 2020. MLKL-dependent signaling regulates autophagic flux in a murine model of non-alcohol-associated fatty liver and steatohepatitis. *J. Hepatol.* 73:616–27

Yang W, Yu T, Huang X, Bilotta AJ, Xu L, et al. 2020. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat. Commun.* 11:4457

Yoon HS, Cho CH, Yun MS, Jang SJ, You HJ, et al. 2021. *Akkermansia muciniphila* secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. *Nat. Microbiol.* 6:563–73

Zhao L, Zhang F, Ding X, Wu G, Lam YY, et al. 2018. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science* 359:1151–56

Zheng L, Kelly CJ, Battista KD, Schaefer R, Lanis JM, et al. 2017. Microbial-derived butyrate promotes epithelial barrier function through IL-10 receptor-dependent repression of claudin-2. *J. Immunol.* 199:2976–84

Zhou Q, Pang G, Zhang Z, Yuan H, Chen C, et al. 2021. Association between gut *Akkermansia* and metabolic syndrome is dose-dependent and affected by microbial interactions: a cross-sectional study. *Diabetes Metab. Syndr. Obes.* 14:2177–88

Zhou W, Ramachandran D, Mansouri A, Dailey MJ. 2018. Glucose stimulates intestinal epithelial crypt proliferation by modulating cellular energy metabolism. *J. Cell Physiol.* 233:3465–75