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Nutrition Regulates Innate Immunity in Health and Disease

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Abstract

Nutrient content and nutrient timing are considered key regulators of human health and a variety of diseases and involve complex interactions with the mucosal immune system. In particular, the innate immune system is emerging as an important signaling hub that modulates the response to nutritional signals, in part via signaling through the gut microbiota. In this review we elucidate emerging evidence that interactions between innate immunity and diet affect human metabolic health and disease, including cardiometabolic disorders, allergic diseases, autoimmune disorders, infections, and cancers. Furthermore, we discuss the potential modulatory effects of the gut microbiota on interactions between the immune system and nutrition in health and disease, namely how it relays nutritional signals to the innate immune system under specific physiological contexts. Finally, we identify key open questions and challenges to comprehensively understanding the intersection between nutrition and innate immunity and how potential nutritional, immune, and microbial therapeutics may be developed into promising future avenues of precision treatment.

Contents

1. INTRODUCTION

Nutrition has a profound impact on human health, as the content, nature, and timing of consumption of specific nutrients are linked to metabolic and immune health and the development of major human diseases, including metabolic syndrome, autoimmunity, and cancer. The inflammatory mechanisms that compose innate immunity are strongly influenced by nutrition, and this interaction, when perturbed, can profoundly affect disease development. In this review, we discuss how the immune system, nutrition, and other signaling hubs such as the microbiota interact at the molecular level to orchestrate metabolic and immune homeostasis, and how altered nutrition–immune system interactions contribute to disease development and progression (**Figure 1**). We furthermore discuss the many unknowns and challenges in this developing field and highlight how research related to nutrition-based approaches may be harnessed in the future as a modality to impact immunity and immune system–related human disorders.

2. IMMUNITY AND METABOLIC DISEASE

Metabolic disorders resulting from malnutrition, or from excesses, deficiencies, or imbalances in food or specific nutrients, have been continuously rising in global prevalence and have reached epidemic proportions. It is estimated that over 1.9 billion adults are overweight or obese, whereas 462 million are underweight (216). These aberrations give rise to a variety of non-communicable

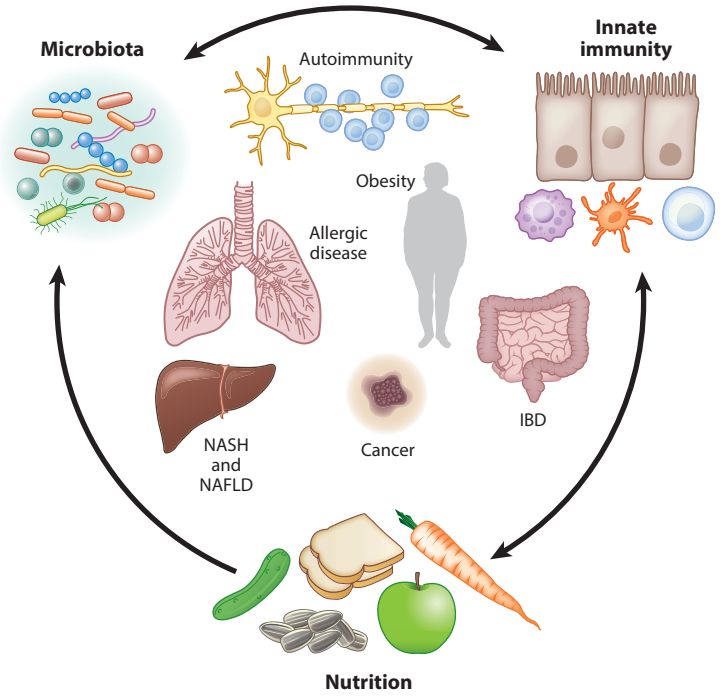

Figure 1

The interplay between nutrition, the microbiome, and innate immunity regulates many multifactorial diseases, including autoimmune disorders, cancers, allergic disease, and obesity. Abbreviations: IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

diseases and constitute the major cause of morbidity and mortality worldwide. Importantly, both innate immunity and metabolism are crucial for survival and have developed interdependently throughout evolution. A large body of research conducted over the last decade has illuminated that nutrients act on the host innate immune system to promote or inhibit inflammation, thereby controlling energy homeostasis and orchestrating metabolic health and disease. The intersection between diet and innate immunity occurs at the intestinal mucosal barrier, locally secreted host factors, gut-resident immune and nonimmune cells, and extraintestinal metabolically active tissues, among other levels, which is covered in Section 2.1.3. Additionally, a previously unappreciated mediator of this immune-metabolic cross talk is the gut microbiota, the composite of trillions of microorganisms occupying the gastrointestinal tract that have the capacity to increase or decrease energy extraction from nutrients or alter metabolic signaling and inflammation. Of note, dietary macro- and micronutrients alter leukocyte structure (121) and function (28), and their activation exerts metabolic switches at the cellular level (termed immunometabolism); however, these topics are beyond the scope of this article and are comprehensively reviewed elsewhere (103, 175).

2.1. Metabolic Syndrome

Metabolic syndrome (also termed cardiometabolic disease) comprises a group of closely related disorders including obesity, glucose intolerance culminating in adult-onset diabetes mellitus, hypercholesterolemia, nonalcoholic fatty liver disease (NAFLD), and hypertension. These disorders often co-occur, are considered risk factors of each other, and associate with similar sets of genetic

and environmental risk factors. Collectively, metabolic syndrome is increasingly recognized to involve aberrant immune processes, which contribute to its development and to the emergence of its devastating cardiovascular, neurodegenerative, and neoplastic consequences. According to the thrifty gene theory, the perpetuation of genes associated with obesity and insulin resistance conferred a survival advantage in prehistoric times, when energy storage and fat accumulation were essential during periods of prolonged starvation. Many of these genes are expressed by immune cells and are related to inflammation, as increased blood glucose levels provide energy to the immune system to overcome infections and major stressors (100). For instance, IkappaB kinase beta (IKK-β), a key mediator of inflammatory responses through the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), is also a driver of insulin resistance (1). In modern times, however, a chronic, low-grade inflammation derived from diets commonly consumed by industrialized societies (termed metabolic inflammation) is inadequate and often results in the development of or contribution to metabolic syndrome or its disease components. Such Western diets are typically characterized by an intake of high-fat and high-sugar products, a high proportion of processed food, and a low amount of fiber and their impact on innate immunity and metabolism is discussed in Sections 2.3 and 3–5 (**Figure 2**).

2.1.1. Monosaccharides. Elevated levels of glucose in blood (hyperglycemia) trigger nonenzymatic glycation of proteins and lipids, creating advanced glycated end products (AGEs). These compounds activate the pattern recognition receptor RAGE (receptor for advanced glycated end product), which activates NF-κB and stress kinases and induces production of reactive oxygen species (ROS). The latter stimulates the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome to produce interleukin 1 beta (IL-1β) and downstream proinflammatory cytokines (38). Moreover, hyperglycemia induced by various mechanisms prompted a breach of the intestinal barrier by disrupting the integrity of tight and adherens junctions and by transcriptional reprogramming of intestinal epithelial cells (181).

Fructose feeding also increased duodenal permeability in mice, which in turn promoted translocation of intestinal bacterial components, leading to higher expression levels of several Toll-like receptors (TLRs), induction of proinflammatory pathways, and increased numbers of macrophages in the liver (203).

2.1.2. Fatty acids. The effect of fatty acids on the innate immune system varies on the basis of their molecular structure. Saturated fatty acids (SFAs), commonly found in animal fat products such as whole-milk dairy products and fatty meats, elicit inflammation and insulin resistance, in line with their high abundance in the lipid A moiety of lipopolysaccharide (LPS). Conversely, unsaturated fatty acids, found in olive and vegetable oils, nuts, and avocados, possess anti-inflammatory properties, which are metabolically beneficial (102).

Elevated levels of fatty acids induce inflammation and reduce insulin sensitivity in rodents (69, 145). The proposed mechanisms linking fatty acids to activation of the innate immune system are manifold. SFAs activate proinflammatory responses in macrophages via TLR2, TLR4, and c-jun-N-terminal kinase (JNK) signaling pathways (132, 161). Hence, mice deficient in TLR4 were protected against high-fat-diet (HFD)-mediated insulin resistance (159, 165). Likewise, mice harboring a macrophage-specific JNK deletion and fed a HFD exhibited enhanced insulin sensitivity, reduced tissue infiltration by macrophages, and suppressed M1 proinflammatory macrophage polarization (66). Although not fully elucidated, evidence points to an indirect mechanism by which SFAs activate TLR4 (98, 161), including binding of SFAs to a TLR coreceptor (164), activating TLR4 by regulating receptor dimerization (215), or stimulating the release of noninfectious inflammatory signals sensed by TLRs (144, 147). Another pathway linking SFAs and TLR receptor

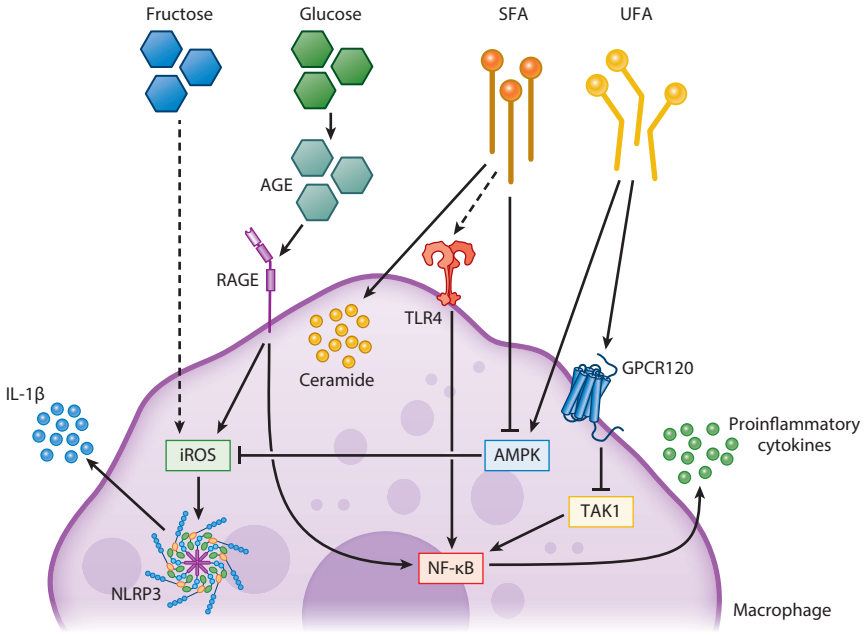

Figure 2

Macronutrients and their effects on macrophages. Monosaccharides and fatty acids can directly act on macrophages and modulate two main pathways, the TLR4/MyD88/NF-κB signaling pathway and the NLRP3 inflammasome, thus leading to metabolic inflammation and insulin resistance. Fructose and AGEs increase intracellular iNOS, which in turn activates the NLRP3 inflammasome, triggering IL-1β secretion. Glucose also induces NF-κB, which promotes production of proinflammatory cytokines. SFAs indirectly activate TLR4 and the NLRP3 inflammasome to promote inflammation and are metabolized into ceramide, which potentiates the aforementioned proinflammatory effects. UFAs oppose these actions by inhibiting the NLRP3 inflammasome and the NF-κB pathway, thus exerting an anti-inflammatory effect and ameliorating metabolic inflammation. Abbreviations: AGE, advanced glycated end product; AMPK, adenosine monophosphate-activated protein kinase; GPCR120, G-protein-coupled receptor 120; IL, interleukin; iNOS, induced nitric oxide synthase; iROS, induced reactive oxygen species; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; RAGE, receptor for advanced glycated end product; SFA, saturated fatty acid; TAK1, transforming growth factor beta-activated kinase 1; TLR4, Toll-like receptor 4; UFA, unsaturated fatty acid.

activation was observed when TLR4-dependent priming induced cellular metabolic alterations that were required for SFA-induced inflammation, such as induction of ceramide biosynthesis (69, 98). Inhibition of ceramide production attenuated insulin resistance in various metabolically active tissues in mice (69, 193). Additionally, SFAs may promote proinflammatory cytokine release and insulin resistance by driving NLRP3 inflammasome activation (211), which may be partially mediated by increased intracellular ceramide levels (197). As such, NLRP3-deficient mice were protected against HFD-induced obesity (176). Conversely, NLRP1 activation was shown to be metabolically beneficial, as mice deficient in NLRP1 exhibited exacerbated obesity and features of metabolic syndrome (126). Furthermore, a recent study suggested that a Western diet characterized by a high fat content could trigger epigenetic reprogramming in myeloid cells, which enhanced immune responses to TLRs and did not reverse after switching back to normal chow feeding, indicating that fatty acids can induce innate immune memory (25).

Contrary to SFAs, unsaturated fatty acids attenuate inflammation. Replacing SFAs with monounsaturated fatty acids in HFD-fed mice improved insulin sensitivity by inhibiting NLRP3 inflammasome activation (53). Omega-3 polyunsaturated fatty acids (PUFAs) decrease macrophage chemotaxis and shift macrophages toward an anti-inflammatory polarization state by stimulating G-protein-coupled receptor 120 (GPCR120), which subsequently results in the inactivation of transforming growth factor beta-activated kinase 1 (TAK1) and inhibition of downstream IKK-β/NF-κB and the JNK/activator protein 1 (AP1) signaling pathways (138). Additionally, omega-3 fatty acids inhibited NLRP3 inflammasome activation and attenuated HFD-induced insulin resistance, liver steatosis, and adipocyte hypertrophy (222), and their metabolites, protectins and resolvins, exhibited anti-inflammatory actions in vitro (6). As such, mice fed a HFD supplemented with omega-3 fatty acids showed decreased inflammation, improved insulin sensitivity, and improved glucose tolerance (138). Similarly, humans consuming omega-3 fatty acids exhibited an improvement in some inflammatory and metabolic markers (172, 186). Of note, because the amounts of omega-3 fatty acids required to exert anti-inflammatory properties may be exceedingly high, an alternative approach would be the use of GPCR120 agonists, which are metabolically effective in mice (139).

2.1.3. End-organ involvement. Consumption of a HFD drives structural and functional alterations to innate immune cells and their mediators in various metabolic organs (**Figure 3**). Although most studies depict diet-induced changes in concert with obesity and are therefore unable to reliably distinguish dietary effects from those associated with adiposity, some studies have successfully isolated the HFD as the sole contributor to innate immune modulation. For instance, low-grade endotoxemia is triggered shortly after a high-fat meal is consumed and does not require obesity as a prerequisite (46).

2.1.3.1. Adipose tissue. Macrophages play a major role in diet-induced inflammation of adipose tissue. HFD-induced obesity in mice was associated with recruitment of macrophages to adipose tissue and triggered a phenotypic switch to M1 macrophage polarization, thereby upregulating proinflammatory genes, such as those encoding for tumor necrosis factor alpha (TNF-α) and induced nitric oxide synthase (iNOS), and resulting in insulin resistance (71, 109, 151, 209, 220). Similar structural changes in human subcutaneous adipose tissue were also documented (209). The accumulation of macrophages in adipose tissue under a HFD was suggested to involve chemoattractants, such as chemokine ligand 2 (CCL2), as mice lacking CCL2 or its receptor chemokine receptor 2 (CCR2) showed reduced recruitment of macrophages to epididymal white adipose tissue (110), although other studies failed to replicate this finding (75, 84). Other chemoattractants suggested to mediate insulin resistance in mice with HFD-induced obesity include leukotriene B4 (106), galectin-3 (105), and semaphorin 3E (166). Similarly, the expression of netrin-1, a chemoattractant expressed by adipose tissue of human and mice with obesity, was inducible in macrophages in vitro by the SFA palmitate (154).

Innate lymphoid cells (ILCs) are classified into three major groups (types 1–3) on the basis of their expressed transcription factors, cell surface markers, and cytokine repertoire. ILC1 populations in mouse adipose tissue increase shortly after initiation of HFD, even before weight gain (9). These cells, in turn, produce interferon gamma (IFN-γ) to drive proinflammatory macrophage polarization, thereby leading to insulin resistance (143). However, once obesity has developed, prolonged HFD feeding (12 weeks to 8 months) is associated with decreased proportions of ILC1 populations. Likewise, humans with obesity display a lower frequency of ILC1 in their omental adipose tissue (9). However, ILC2s in white adipose tissue decreased in frequency in humans with obesity and in mice consuming a HFD. Maintenance of ILC2s in adipose tissue in mice was

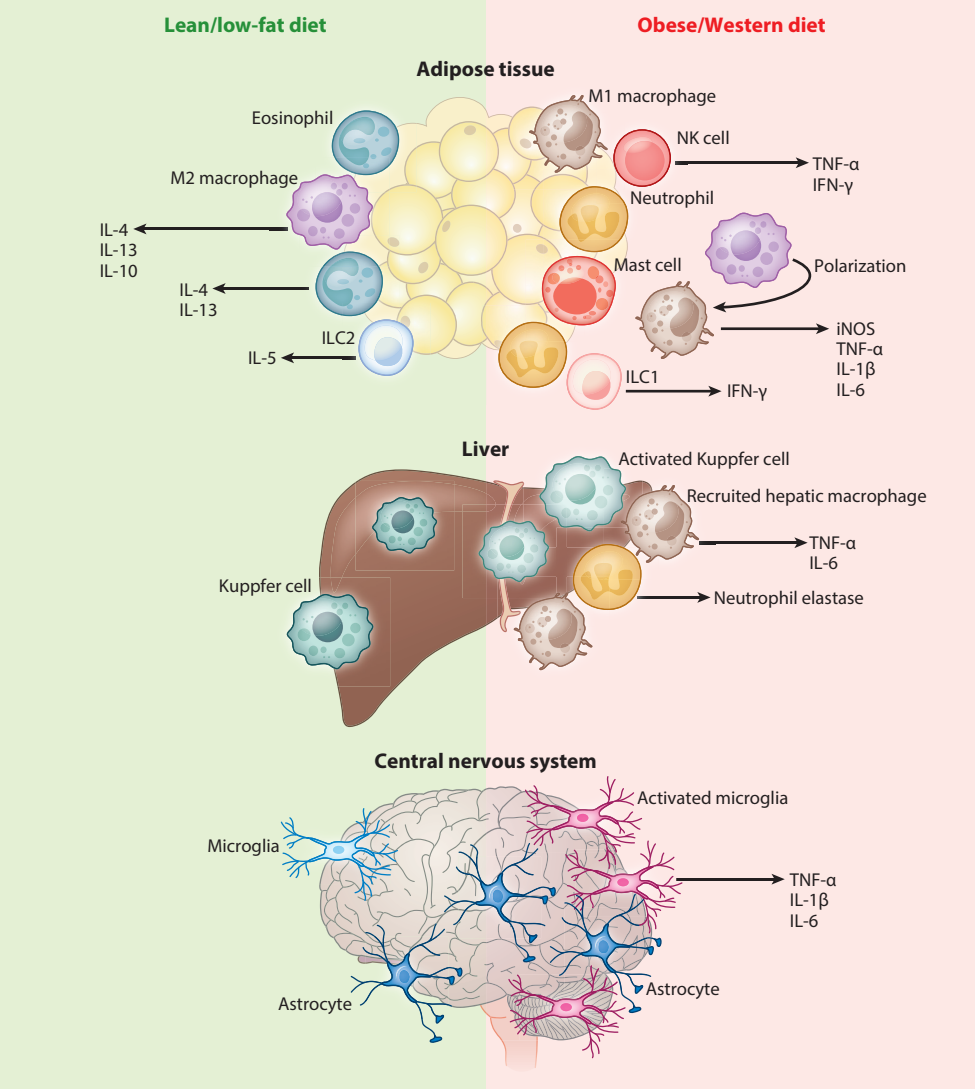

Figure 3

Western diet– and obesity-induced alterations to innate immunity in target organs. Diets rich in saturated fat and sugar drive histological changes in various organs, including metabolic organs such as adipose tissue, liver, and muscle, but also in structures in the central nervous system. These changes include recruitment of circulating bone marrow–derived innate immune cells and polarization of resident immune cells to their activated state, resulting in a composite proinflammatory phenotype. Abbreviations: IFN-γ, interferon gamma; IL, interleukin; ILC, innate lymphoid cell; iNOS, induced nitric oxide synthase; NK, natural killer; RHM, recruited hepatic macrophage; TNF-α, tumor necrosis factor alpha.

dependent on interleukin 33 (IL-33), and this axis promoted adipocyte beiging by the production of methionine-enkephalin peptides (13). Of note, the impact of ILC2s on metabolism varies according to their anatomical location, as ILC2s in the small intestine promote obesity (160).

Natural killer (NK) cells also increase in abundance in adipose tissue of humans with obesity (141) and HFD-fed mice (212), a process that depends on IL-6 and signal transducer and activator

of transcription 3 (Stat3) signaling (183). NK cells produce IFN-γ and TNF-α, which promote macrophage inflammation, and indeed their deletion in HFD-fed mice led to decreased accumulation of proinflammatory macrophages in epididymal adipose tissue and normalization of glucose in insulin tolerance (101, 142).

Other innate immune cell populations that infiltrate adipose tissue and are associated with metabolic disorders include mast cells, which characterize HFD-fed mice (107) and humans with obesity or type 2 diabetes mellitus (T2DM) (37, 107). Neutrophils accumulate in the intra-abdominal adipose tissue in mice early in the course of HFD feeding and precede the appearance of macrophages in the tissue (45). Conversely, adipose tissue eosinophils sustain alternatively activated M2 macrophages in an IL-4/IL-13-mediated pathway, and mice lacking eosinophils develop increased body fat, impaired glucose tolerance, and insulin resistance when fed a HFD (217).

Invariant natural killer T (NKT) cells are also negatively correlated with the degree of obesity in humans and mice (76, 112). They are prone to decrease in adipose tissue in response to HFD feeding and increase when HFD feeding is halted (111), although other observations show contradicting evidence (218).

2.1.3.2. Liver. A high-fat, high-sugar Western diet induces a unique inflammatory signature during NAFLD progression, as recently shown by single-cell RNA sequencing (95). This inflammatory program involves intricate interactions between immune and nonimmune cells, leading to nonalcoholic steatohepatitis (NASH) and stellate cell–mediated fibrosis (reviewed in 210). Specifically, HFD-induced obesity in mice drives polarization of Kupffer cells, specialized macrophages located in the liver, without increasing their numbers (204), and accumulation of bone marrow–derived circulating monocytes to the liver, termed recruited hepatic macrophages (RHMs). These cells secrete proinflammatory mediators, such as the cytokines TNF-α and IL-6, and contribute to the development of NAFLD (123, 137). The transition from NAFLD to NASH in mice fed a high-fat, high-cholesterol diet was dependent on TLR4 activation in Kupffer cells (223).

Neutrophils infiltrate the liver in HFD-fed mice and secrete neutrophil elastase, which exerts paracrine proinflammatory effects, including macrophage polarization and a TLR4-mediated proinflammatory gene expression profile that contributes to hepatic and adipose insulin resistance (178).

2.1.3.3. Muscle. HFD-fed mice as well as humans with obesity or glucose intolerance exhibit macrophage accumulation in skeletal muscle compared with their lean counterparts (52, 198). This process was proven to be CCL2 dependent in mice (52, 148) and resulted in the production of proinflammatory cytokines, such as TNF-α and IL-1β, subsequently leading to impaired insulin signaling and glucose metabolism in muscle (148).

2.1.3.4. Pancreas. In vitro studies showed that stimulation of beta islets by glucose led to beta cell apoptosis via upregulation of the Fas receptor (114). Additionally, glucose and palmitate triggered cytokine and chemokine release from these cells, which also occurred in vivo in HFD-fed mice (43, 74). The response of beta islets to palmitate was dependent on the TLR4/myeloid differentiation primary response 88 (MyD88) pathway and resulted in IL-1β production and subsequent NF-κB activation (42, 74). Of note, acute metabolic stress, such as streptozocin-induced hyperglycemia, increased IL-33 production by mesenchymal cells within beta islets, which in turn activated islet ILC2s to secrete IL-13 and colony-stimulating factor 2 and stimulated macrophage and dendritic cells (DCs) to produce retinoic acid, and ultimately resulted in insulin secretion.

This entire axis was suppressed in the presence of obesity, which hinders insulin production, and might explain glucose intolerance in obese states (30). Secreted cytokines, namely IL-8, prompted macrophage and neutrophil migration to the islets. Indeed, humans with T2DM showed increased numbers of pancreatic islet-associated macrophages, an observation replicated in HFD-fed mice (43).

2.1.3.5. Arterial vasculature. Mice bearing a genetic mutation rendering them susceptible to atherosclerosis and that were MyD88 deficient, were protected from the development of atherosclerotic plaques compared with MyD88-sufficient mice when fed a high-fat, high-cholesterol diet. MyD88, an adaptor protein downstream of the cluster of differentiation 14 (CD14)/TLR4 recognition complex, was pivotal for macrophage recruitment to the arterial wall and expression of chemokines (8).

2.1.3.6. Central nervous system. Hypothalamic inflammation, as well as inflammation in other brain structures, has a central role in the pathogenesis of obesity (64). In vitro studies showed that SFAs could activate microglia, the resident immune cells of the central nervous system (CNS), and prompt proinflammatory cytokine secretion (195). This process controls hyperphagia, weight gain, and leptin resistance and depends on the TLR4/MyD88/NF-κB signaling pathway, reminiscent of macrophage activation by SFAs in adipose tissue (see Section 2.1.2) (86, 194, 208). Additionally, SFAs exerted proinflammatory effects on astrocytes, which were inhibited in a dose-dependent manner by a polyunsaturated omega-3 fatty acid (65), although this result differed from that in another study (195). In vivo experiments with short-term HFD feeding led to neuroinflammation in rodents, manifesting in reactive gliosis and neuron injury markers, even before the onset of obesity (182). Substitution of the fatty acid component of the diet with unsaturated fatty acids in mice attenuated hypothalamic inflammation and improved systemic glucose homeostasis (26).

2.2. Caloric Restriction and Starvation

At the other end of the metabolic disease spectrum, conditions associated with caloric restriction or deficiencies in dietary intake and their metabolic aftermath also involve innate immune modulation. During starvation, the immune response is downregulated, preserving energy supplies for essential organ functions to allow the organism to survive. Of the many types of malnutrition, environmental enteropathy is a cryptic disorder that affects children living in areas of poor sanitation and hygiene and is characterized by chronic intestinal inflammation not fully remediable by nutrition. A recently developed mouse model for environmental enteropathy showed that both diet and the microbiota were required for the disorder to develop. Mice fed a malnourished diet supplemented with a mixture of the order *Bacteroidales* and *Escherichia coli* showed impaired intestinal barrier function and microbiota encroachment in vivo, and increased secretion of IL-6 and monocyte chemoattractant protein 1 (MCP-1) in cultured jejunal sections ex vivo. These malnourished mice were more prone to exacerbated infection with *Salmonella typhimurium* compared with control mice (14). Additionally, starvation resulted in downregulation of the brush border enzyme intestinal alkaline phosphatase, which led to a breach of the gut barrier. Enteral feeding, specifically with butyrate, maintained this enzyme's activity (60).

The innate immune system can be altered in the case of specific micronutrient deficiencies; for instance, vitamin A deprivation results in immune reprogramming, which includes a reduction in the frequency of ILC3s and their derived cytokines, predisposition to bacterial infections, and expansion of ILC2s in the small intestinal lamina propria (173). Protein malnutrition impaired

granuloma formation and the expression of iNOS, IFN-γ, and TNF-α in lungs of mice infected with *Mycobacterium tuberculosis*, which led to their accelerated demise (22).

As opposed to uncontrolled calorie restriction, which often results in devastating organ dysfunction stemming from micronutrient and macronutrient deficiencies, controlled calorie restriction promotes longevity in a variety of organisms. In *Caenorhabditis elegans* this process was mediated by modulating p38 mitogen-activated protein kinase signaling, a conserved innate immunity pathway (219). In mice, calorie restriction triggered compositional and functional microbiota alterations, manifesting as decreased LPS content. This resulted in increased infiltration of eosinophils into adipose tissue, type 2 cytokine signaling, and M2 macrophage polarization, thereby leading to white adipose tissue browning and subsequently to lower weight gain and improved glucose homeostasis, which was transferable by fecal microbiota transplantation (48, 49). Of note, mice with TLR4 deficiency were resistant to these favorable metabolic alterations (48). Additionally, calorie restriction led to a reduction in expression of NLRP3-associated transcripts in visceral and subcutaneous adipose tissues and in the subcutaneous adipose tissue in humans undergoing a yearlong intensive lifestyle intervention (197). Likewise, starvation increases production of beta-hydroxybutyrate. This ketone body suppressed the activation of the NLRP3 inflammasome and reduced the generation of proinflammatory cytokine in human monocytes in vitro. In vivo, mice harboring gain-of-function mutations rendering the NLRP3 inflammasome constitutively active and thereby mimicking NLRP3 inflammasome–mediated diseases showed attenuated inflammasome activation and proinflammatory cytokine production when fed a ketogenic diet (225). Likewise, ketogenic diet and beta-hydroxybutyrate conferred neuroprotection in a GPCR109A-dependent mechanism in a mouse model for stroke, possibly by modulating the function of monocytes and macrophages infiltrating the ischemic brain (152).

2.3. Role of the Microbiota

The gut microbiota encounters nutrients consumed by the host and closely interacts with innate immune cells through a thin mucosal layer, thus acting as an important hub in the host–diet cross talk. Interactions between the microbiota and nutrients are bidirectional, as bacteria differentially break down food into metabolites on the basis of their genetic repertoire and environmental stimuli, and dietary habits exert evolutionary forces on the microbiota and thereby shape their composition. Likewise, the microbiota and its surface structures and secreted factors drive inflammatory or tolerogenic signaling in host immune cells to regulate gut microbial ecology, and the same immune responses may also modulate host metabolism. Hence, many innate immune sensors, such as TLRs and inflammasomes, and their downstream responses, which are principally directed against invading microorganisms and pathogen-associated molecular patterns, play a considerable role in metabolic inflammation, and genetic polymorphisms in these sensors may predispose to altered risk for metabolic disorders (81). The contribution of the microbiota as a mediator in the diet–host cross talk is most strikingly demonstrated in antibiotic-treated or germ-free animals, which are protected against Western diet–induced obesity and metabolic disorders (4, 18). Herein, we present basic principles of the diet–microbiota–innate immunity interactions and highlight prominent examples of this tripartite relationship.

The assembly of gut microbiota is substantially affected by the dietary choices and metabolic state of the host (187). A microbiota consortium obtained from a host with obesity possesses a greater capacity to harvest energy from diet, compared with a consortium obtained from a lean host, and this trait was transmissible between hosts by fecal microbiota transplantation (191). Additional mechanisms by which the microbiota can induce obesity and metabolic derangements are metabolic signaling and inflammation. Hence, a diet that shifts the microbiota conformation to

increase its LPS content would generate low-grade chronic inflammation (metabolic endotoxemia), promoting insulin resistance. Indeed, treating HFD-fed mice with broad-spectrum antibiotics reduced TLR4 activation, ameliorated insulin signaling, and inhibited macrophage infiltration into the liver and adipose tissue (19). Correspondingly, specific pathogen-free mice fed SFA-rich lard exhibited increased adipose tissue inflammation and reduced insulin sensitivity, whereas germ-free and mice deficient in the TLR adaptor molecule MyD88 fed the same diet were protected from this perturbed metabolic phenotype (16). Additionally, HFD-fed mice showed increased levels of circulating activators of nucleotide binding oligomerization domain–containing 1 (NOD1), a sensor for bacterial peptidoglycan. Deletion of NOD1 in hematopoietic cells reduced macrophage proinflammatory polarization in adipose tissue and abrogated insulin resistance (23). Similarly, mice bearing genetic deletions of other pattern recognition receptors, such as TLR5 (201) and NLRP12 (190), exhibited gut microbiota alterations resulting in exacerbated features of metabolic syndrome upon HFD feeding. Other genetic deletions, such as NLRP3 (176), were protective against HFD-induced metabolic aberrations. These altered metabolic phenotypes could be transferred to wild-type mice by cohousing or fecal microbiota transplantation.

The intestinal mucosal barrier is the interface where most interactions between the host and the gut microbiota take place. An intricate reciprocal network of signals between the host and its resident commensals ensures that the inflammatory tone is adequate to inhibit systemic invasion by microorganisms but tolerant enough to avoid an overwhelming inflammatory response, which is detrimental to the host. This balance is achieved by sampling of microbial antigens by the innate immune system, leading to secretion of mucus, antimicrobial proteins, and immunoglobulin A. A breach of the intestinal barrier, which occurs in HFD consumption, may lead to translocation of bacteria or bacteria-derived compounds, resulting in metabolic endotoxemia (185). An example of host–microbiota interactions affected by dietary or microbiota-derived nutrients is activation of the NLRP6 inflammasome by taurine and its suppression by histamine and spermine, which controls antimicrobial peptide secretion and predisposes to dysbiosis and inflammation (104).

The microbiota metabolizes nutrients consumed by the host into a plethora of bioactive compounds, some of which modulate pivotal signaling pathways in the gut and metabolic organs and govern host metabolic homeostasis. Fermentable fiber is metabolized by the microbiota into short-chain fatty acids (SCFAs), which activate GPCRs, inhibit histone deacetylases, and serve as energy substrates (115). SCFAs affect host metabolism in various mechanisms, including regulating energy expenditure and mitochondrial function (57) and stimulating hormonal cues that affect food-seeking behavior (21). Importantly, fiber-derived SCFAs promoted mucus production and secretion and thereby enhanced intestinal barrier integrity and decreased intestinal permeability and endotoxemia, which prevented excessive weight gain, attenuated low-grade inflammation, and improved glucose metabolism (88). Furthermore, SCFAs sustained a healthy microbial growth, which stimulated IL-22 production possibly by ILC3s, thus promoting enterocyte proliferation and antimicrobial gene expression and preventing microbiota encroachment, which in turn protects against HFD-induced metabolic syndrome (234). SCFA receptors are present on immune cells, and GPCR43 activation by SCFAs in adipose tissue M2 macrophages, but not M1 macrophages, induced local TNF-α expression, which might be required for adequate remodeling of adipose tissue and its beneficial metabolic function (128). Further investigation is required to elucidate the full potential of SCFAs as direct mediators in metabolic inflammation. Furthermore, carnitine, a nutrient abundant in red meat, is metabolized by the gut microbiota into trimethylamine and then into trimethylamine *N*-oxide (TMAO) in the liver. TMAO, in turn, upregulates multiple macrophage scavenger receptors and promotes atherosclerosis (87, 207). The microbiota-derived tryptophan metabolites tryptamine and indole-3-acetate attenuate

proinflammatory responses in macrophages and hepatocytes (96). Finally, not only nutrients but also food additives can modulate innate immunity through the microbiota, as dietary emulsifiers altered the microbiome composition to promote metabolic endotoxemia, adiposity, and glucose intolerance in mice (24).

In conclusion, studying the numerous interactions between nutrients, the gut microbiota, and the host immune system may be challenging and hard to fathom; however, pinpointing the circuits that are amenable to manipulation can pave the way toward exploring novel therapeutic modalities to combat metabolic syndrome. Achieving these insights in the field of microbiota research will require the development of new technologies and the collaboration of a multidisciplinary team consisting of microbiologists, data analysts, algorithm programmers, and medical personnel.

2.4. Other Clinical Implications

Combating metabolic inflammation with anti-inflammatory agents has been proven effective in vivo. As such, salicylates alleviated hyperglycemia, hyperinsulinemia, and dyslipidemia in genetically obese rodents by improving insulin signaling (226), treatment with a neutralizing anti-mouse Notch ligand Delta-like 4 antibody ameliorated the development of atherosclerosis, insulin resistance, and fat accumulation in mice consuming a high-fat, high-cholesterol diet (56), and treatment with a monoclonal antibody against IL-1β reduced cardiovascular events in humans (155). Future research should include dietary interventions to achieve similar anti-inflammatory effects to boost host metabolism. An alternative approach would be to target the gut microbiota, either by administering prebiotics or probiotics or by transplanting fecal microbiota from a healthy donor, to exert an immunomodulatory effect on the host; however, translating recent discoveries regarding the cross talk between diet, innate immunity, and the microbiota to clinical practice still merits further study. In Sections 3, 4, and 6 we highlight examples of diet–innate immunity interactions affecting the pathogenesis of several key multifactorial diseases.

3. ALLERGIC DISEASE

There is increasing evidence that nutrition can influence the development of different allergic diseases, including food allergy, eczema, and asthma (130). Although many molecular mechanisms remain to be uncovered, there are indications that environmental factors, including nutrition of the pregnant mother as well as that of human infants, profoundly impact allergy development and exacerbate allergic inflammation. In the following two sections we discuss what is known about the intersection between nutrition, innate immunity, and allergic disease for asthma and food allergy.

3.1. Asthma

Asthma is a complex inflammatory disease of the airways characterized by chronic inflammation, mucus overproduction, and smooth muscle remodeling, which leads to bronchoconstriction and consequently reduced lung function. It has been significantly increasing in prevalence in the developed world over the last decades, and even in developing countries the number of people affected has recently increased (41). A factor likely contributing to this phenomenon is the increasing adoption of the Western lifestyle, which includes a Western diet. Concurrent with the increase in prevalence of asthma, there was also an increase in the proportion of obese individuals (131). In the United States there is indeed a significant association between the development of obesity and asthma in both adults and children (55). Furthermore, although there is a significant

association with atopy in adults, this not the case in children (55), suggesting that asthma pathogenesis in children is driven less by a classical T helper 2 cell–driven inflammatory response than by a different inflammatory profile such as Th17-driven neutrophilic asthma. How the molecular mechanisms in asthma development differ between adults and children and how nutrition affects disease development differently in relation to age remain to be investigated. There is also evidence that childhood asthma in turn can promote development of obesity later in life (127), although the role of nutrition in this context is unclear. A key factor driving both obesity and asthma in this context is the Western diet. Indeed, there are significant associations between the consumption of high-fructose corn syrup soft drinks and asthma development (31). In mice an obesogenic diet directly regulated the levels of many lung metabolites, including free fatty acids, complex lipids, and amino acids (168). Conversely, there is molecular evidence that a high-fiber diet leads to increased levels of free fatty acids such as acetate or propionate, which in turn limit allergic inflammation of airway tissue (117, 189). Mechanistically, propionate induced the development of more tolerogenic lung DCs by binding to GPCR41 (189), exemplifying the direct modulation of innate immunity by dietary components. Furthermore, SCFAs directly reduced the capacity of DCs to transport and present antigen to T cells (17) and promoted the generation of regulatory T cells (Tregs) (2), thereby dampening aberrant airway inflammation. Exposure to SCFAs in utero protected against asthma development (184). Conversely, children from obese mothers are more likely to develop asthma later in life (150). Taken together, these findings highlight the importance of nutrition for establishing tolerance in the airways before birth and in early development. Apart from SCFAs, other dietary components are emerging as potential drivers of asthma development, but identification of the underlying molecular mechanisms is still largely lacking. Both arginine- and vitamin-E-derived metabolites protected against airway hyperresponsiveness in mice (27, 149), but not much is currently known about potential effects of other vitamins or amino acids, warranting more research in this area.

3.2. Food Allergy

Another prime example in which nutrition modulates innate immunity in the context of allergic disease is food allergy. Aberrant responses to food-derived antigens have significantly increased over recent decades in Western countries (44), and changes in diet are thought to be a major contributing factor. At the molecular level mucosal type 1 conventional DCs promote oral tolerance to peanut allergen by responding to vitamin A derived from a high-fiber diet (179). In addition to vitamin A–derived retinoic acid, a high-fiber diet can protect against food allergy development by promoting SCFA-producing members of the microbiota, which in turn promote intestinal epithelial barrier integrity (179). Whereas a high-fiber diet prevents development of food allergy, a HFD promotes intestinal inflammation in a microbiota-dependent manner (73). This was enhanced with increased permeability of the intestinal barrier, suggesting that a HFD promotes a microbiota composition that breaks down the intestinal barrier, thereby promoting translocation of food-derived antigens and subsequent induction of a potent immune response.

4. AUTOIMMUNE/AUTOINFLAMMATORY DISEASE

The rise in autoimmune diseases in recent decades has been attributed to changes in lifestyle, including consumption of a Western diet (118). Disentangling the underlying interactions between nutrition and innate immunity and how they promote autoimmunity has thus received much attention in research. In the sections below we discuss the current knowledge on the interplay between diet and several key autoimmune diseases.

4.1. Psoriasis

There is increasing evidence that diet profoundly impacts the immune mechanisms underlying psoriasis, and diseases associated with obesity such as NAFLD can exacerbate psoriasis symptoms (199). Mechanistically, a HFD promoted production of chemokines CCL16 and CCL20 in keratinocytes, which in turn leads to the accumulation of dermal IL-17A-producing γδ T cells (129). IL-17A is a key cytokine in the pathogenesis of psoriatic inflammation (97). Although the dietary factors that exacerbate skin inflammation in obese individuals have not been definitively identified, there is evidence that free fatty acids could directly contribute to Th17-driven immune responses in skin (174). Indeed, omega-6 PUFAs, a class of lipid-derived mediators, have been implicated to promote accumulation of Th17 cells in skin (192), whereas for omega-3 PUFAs the opposite effect has been suggested (70). Although the role of such lipid mediators in psoriasis is being increasingly uncovered, how these molecules relate to nutrition is still largely unexplored.

4.2. Multiple Sclerosis

There is strong epidemiological evidence that multiple sclerosis (MS) is associated with a diet high in saturated animal fat, and conversely, high levels of PUFAs were protective against MS (40). How such specific dietary components influence CNS inflammation is still being unraveled, but emerging evidence indicates that diet can directly modulate disease pathogenesis in animal models of MS (39). A HFD exacerbated MS in mice by promoting IL-6- and CCL2-dependent infiltration of immune cells in the CNS (77). In addition to dietary lipids, high levels of glucose promoted CNS autoimmunity by driving Th17 differentiation (229). Along similar lines, sodium chloride directly supported Th17 polarization and subsequent Th17-dependent autoimmunity in mice (85); conversely, retinoic acid led to beneficial induction of Tregs (62). Whereas the effect of diet on T cells as the drivers of CNS inflammation is being increasingly investigated, the effects of dietary components on the innate immune response in this context remain largely unexplored. This is of particular importance, as induction of demyelination by T cells is critically dependent on innate immune cells such as DCs (80).

4.3. Systemic Lupus Erythematosus

Epidemiologically, lupus is strongly associated with metabolic syndrome (33); thus, how diet regulates innate immunity in autoimmune inflammation in this disease has recently developed as an important area of research. In general, diet modulates development of lupus in mice prone to autoimmunity (202). More specifically, in mouse models of lupus a HFD exacerbated disease in a TLR-7-dependent manner, leading to higher levels of anti-DNA autoantibodies, increased IgG/IgM glomerular deposition, and increased kidney histopathology (68). This was associated with increased levels of TNF and TLR7 expression in DCs (68), also a key factor in the pathogenesis of lupus in humans (79). Whereas a HFD promotes lupus development, a diet rich in starch prevents systemic translocation of specific commensal bacteria and thus inhibits development of autoimmune inflammation (228). This finding suggests that the permeability of the intestinal barrier is generally important for lupus pathogenesis. How the commensal microbiota mediates susceptibility to disease in response to other diets remains to be addressed, but the microbiota is likely to play a key role in the connection between lupus and metabolic syndrome. Furthermore, in support of the general concept that salt intake can promote autoimmunity, there is evidence that sodium chloride directly promotes Th17 responses in lupus patients while conversely suppressing Tregs (163). Although the underlying molecular mechanisms remain unclear, one can

speculate that salt intake could profoundly impact innate immunity in this context, which would then exacerbate the adaptive immune response.

4.4. Celiac Disease

The role of nutrition in celiac disease has only recently begun to be addressed, but there is now increasing evidence that dietary components in addition to gluten itself can influence development of gluten-induced inflammation. A key event in the development of celiac disease is the breakdown of intestinal tolerance to gluten. A recent study points toward reovirus as a potential trigger of this breach, as intestinal infection can prevent induction of peripheral Tregs, which in turn promote tolerance to gluten (10). This process is dependent on type I IFN secretion (10), but how the innate immune system regulates peripheral Treg induction and how antiviral immunity changes this interaction in this context remain to be investigated. It is clear, however, that secretion of IL-27 by a population of macrophages in the spleen is key to inducing IL-10-producing Tregs, which in turn promote tolerance to gluten (196). IL-10 is essential to prevent accumulation of cytotoxic innate $CD4^+$ T cells, which induce substantial epithelial damage in the intestine (29). This process likely impairs integrity of the epithelial barrier, which further exacerbates chronic inflammation by allowing translocation of commensal bacteria. This process contributes to a permanent change in the intestinal epithelial lymphocyte compartment, with an expansion of a gluten-sensitive γδ T cell subset that further promotes intestinal inflammation (119). How nutrition affects these molecular immune mechanisms remains to be elucidated, but it is likely that dietary effects on intestinal barrier integrity will be key modulators of disease.

4.5. Inflammatory Bowel Disease

Although the precise etiology of inflammatory bowel disease (IBD) is still unknown, it is increasingly clear that, apart from some genetic host traits, environmental factors, in particular the microbiota, are key triggers of chronic intestinal inflammation, driving the disease (214). Because nutrition profoundly impacts the composition and function of the microbiome as well as the immune system, the connection between diet and IBD is of great research interest. Epidemiological evidence indicates that PUFAs, omega-6 fatty acids, and meat promote IBD, whereas eating fiber, fruits, and vegetables is protective (72). Mice fed a HFD exhibited exacerbated disease, and this was associated with an increase in NKT cells and a decrease in colonic regulatory T cells (113) as well as Th17 cells (58). A likely key factor in this process, apart from HFD-induced changes in the microbiota, is direct hyperglycemia-induced impairment of the gut barrier. High levels of glucose impair intestinal barrier integrity and promote translocation of components of the microbiota (181), likely promoting colitis. This is potentially worsened by the impaired barrier-protecting Th17/22 response (58). Furthermore, recent evidence indicates that, in addition to adaptive components of the immune response, innate immunity is significantly altered by a HFD, which in turn influences susceptibility to colitis. These HFD-diet-induced changes to the intestinal microbiota include effects on ILC3s (3) and macrophages (82), all of which contribute to a dysregulated intestinal barrier immunity. Apart from high levels of fat and glucose, food rich in animal but not plant protein was detrimental for susceptibility to IBD in mouse models of disease (92). Mechanistically, this effect was strictly dependent on diet-induced changes of the microbiota and required the presence of monocyte-derived colonic macrophages but not the adaptive immune system (92). This finding highlights the importance of the innate immune compartment in regulating the host–microbiome interaction at mucosal surfaces and the response to diet in particular. At the epidemiological level a high-fiber diet is thought to be beneficial in an IBD

context, but experimental evidence indicates that in fact fermentable fibers can either exacerbate or ameliorate the disease in an NLRP3 inflammasome–dependent manner, depending on the type of fiber (170). A diet rich in the fiber inulin induced high levels of butyrate, which in turn promoted IL-1β-driven inflammation. These results highlight the complexity of immunomodulation by dietary components and underline the necessity to evaluate each one in a context-dependent manner.

5. INFECTION

The interaction between diet and susceptibility to infection has recently emerged as an important research topic, as nutrition modulates immunity to pathogens both at the local intestinal environment and systemically at other mucosal surfaces. A key aspect of resistance to pathogens that is controlled by nutrition is barrier integrity. Obese individuals are more susceptible to intestinal infection (also termed the leaky gut), and our laboratory recently showed that this is not due to metabolic derangements or diet-induced changes in the microbiota but rather to high levels of glucose (181). Hyperglycemia directly impairs intestinal barrier integrity and thus promotes systemic dissemination of pathogens and more severe disease (181). Glucose availability seems to regulate bacterial and viral infections differently; it is detrimental during bacterial sepsis but beneficial during severe influenza virus–mediated pneumonia (205). This suggests that diets significantly affecting glucose levels will also profoundly affect susceptibility to infection. In addition to glucose-mediated barrier defects, a HFD appears to lead to alterations in the intestinal epithelial cell compartment with an increase in goblet cells (99). Together, these effects translate to increased susceptibility to infection with bacterial pathogens including *Listeria monocytogenes* (99), *Citrobacter rodentium* (181), and *Salmonella typhimurium* (153). Apart from intestinal infection, a HFD has detrimental effects in a variety of other infectious disease contexts, including bacterial footpad infection with *Staphylococcus aureus* (50), infection with Lyme-disease-inducing *Burkholderia burgdorferi* (233), and infection with influenza virus (91). HFD-induced obesity was associated with impaired systemic innate and adaptive immune responses against the pathogen, including reduced neutrophil-mediated bacterial clearance, reduced macrophage cytokine production, and reduced levels of class-switched antibodies (50, 91, 233).

Although the underlying molecular mechanisms are still largely unclear, an additional potential explanation for HFD-mediated effects is that diets high in fat are also often very low in fiber. Indeed, low-fiber diets are highly associated with disseminated bacterial infection, as members of the microbiota start degrading the intestinal mucus barrier to replace fiber as a food source (35). Apart from their direct effects on intestinal barrier integrity, high-fiber diets directly promote beneficial host immune responses against viral infection, particularly the influenza virus (188). Mechanistically, fiber-derived fatty acids limit neutrophil-mediated lung immunopathology while promoting antiviral $CD8^+$ T cell responses (188). Diet-derived fatty acids were also important for ILC2-mediated protection from helminth infection (213). Helminth infection itself protected mice from diet-induced obesity, which was associated with changes in the gut microbiota (167), suggesting that parasite-induced and fatty-acid-dependent type-2 immune responses can overcome some of the systemic effects of obesogenic diets.

In addition to major dietary components, micronutrients have profound effects on innate immunity and susceptibility to infection. Levels of sodium chloride can directly promote resistance to viral infection by promoting type I interferon production of innate immune cells (230). Manganese, another salt component, can promote bacterial endocarditis by directly facilitating bacterial evasion of reactive oxygen-mediated killing of immune cells (78). A key host signaling module that regulates the innate immune response to diet is the aryl-hydrocarbon receptor

(AHR). AHR ligands directly regulate resistance to enteric infection by promoting ILC3 and Th17 responses (162) as well as promoting intestinal barrier integrity (120).

6. CANCER

It is now well established that diet profoundly affects the risk of developing cancer and that differences in diet partially explain differences in the prevalence of specific cancer types across different geographical regions (12). This effect is particularly strong for colon cancer, for which genetically similar populations can have strongly differing rates of cancer, with cancer biomarkers dependent on the amount of fat and fiber consumed (140). In addition, aberrant inflammation is seen as a key driving force of carcinogenesis (67); thus, investigating the underlying molecular mechanisms of the interactions between diet, innate immunity, and cancer development is strongly warranted. In following three sections we exemplify the dietary influences impacting colorectal cancer, liver cancer, and leukemia and the inflammatory responses associated with their pathogenesis. An increasing number of additional dietary influences on the relationship between nutrition and immune responses in cancer have been suggested but are beyond the scope of this review.

6.1. Colorectal Cancer

The rate of colorectal cancer is significantly associated with the consumption of red and processed meats (231), and the underlying molecular mechanisms have thus come under increased scrutiny in recent years. In mice there is strong evidence that this link likely depends on innate immunity, as a cancer-protective diet low in protein was found to depend on the presence of antigen-presenting cells and a subsequent antitumor $CD8^+$ T cell response (158). Although the precise molecular details remain unclear, the authors could show that the T cell–DC interaction is critical for the protective effect (158). In addition, a low-protein diet stimulated IFN-γ production by the tumor cells themselves, which further promoted immunosurveillance and thus cancer prevention (158). This concept of innate immune surveillance is emerging as a key element in preventing carcinogenesis. In intestinal stem cells responsiveness to IL-22 is essential for maintaining genomic integrity and inducing apoptosis (63). Production of IL-22 by ILC3s is strongly regulated by AHR ligands, and diets low in these metabolites thus predispose to colon carcinoma development in the context of genotoxic stress (63). This process also likely depends on the capacity of the microbiota to produce AHR ligands, and more work is necessary to delineate host–microbiome interactions in the maintenance of intestinal stem cell integrity.

Another dietary ingredient of meat products recently linked to the development of colorectal cancer is conjugated linoleic acid (CLA). CLA enhanced carcinogenesis in the colon by promoting an immunosuppressive environment dependent on transforming growth factor beta (TGF-β)-producing macrophages and T cells (122). TGF-β production depended on a macrophage-intrinsic role of peroxisome proliferator-activated receptor gamma (PPAR-γ), a key transcription factor regulating lipid metabolism (134). Thus, PPAR-γ acts as a signaling hub that integrates input signals from multiple dietary ligands to coordinate a comprehensive immunosuppressive response. Another key nutrient that controls colorectal cancer development in humans is folate consumption (83). In general, folate consumption correlates with reduced risk of carcinogenesis, but high levels of folate can lead to more aggressive tumor development in established neoplasms (83). This effect is likely due to an induction of immunosuppressive responses mediated by Tregs (221). Innate immunity likely plays a key role here by promoting or inhibiting antitumor T cell immunity in response to folate consumption; more research is necessary to unravel the mechanisms.

6.2. Liver Cancer

Obesity increases the risk for hepatocellular carcinoma (HCC) in humans (116), and these findings could be mirrored in mice in which a HFD promoted liver cancer development (146). Mechanistically, this process depended on secretion of IL-6 and TNF (146), as well as granulocyte colony stimulating factor, which induces recruitment of myeloid-derived suppressor cells (177) and thus generates the immunosuppressive environment necessary for tumor development. Conversely, a diet high in the soluble fiber inulin was beneficial for metabolic syndrome but still promoted HCC (169). Inulin-containing diet induced profound liver inflammation by promoting hepatocyte death and subsequent accumulation of neutrophils (169). This in turn promoted HCC in a TLR-4- and NLRC4-independent manner (169). Although the underlying innate immune mechanisms regulated by inulin remain unclear, this process depended strictly on fermenting bacteria, which produce SCFAs and thereby promote HCC (169).

6.3. Leukemia

Although the role of nutrition in the development of leukemias is still largely unclear, all-*trans* retinoic acid (ATRA) has been a key therapy for promyelocytic leukemia for several decades (32). Mechanistically, it induces differentiation of leukemia cells and thus inhibits further proliferation of cancerous cells (32). ATRA also inhibits inflammation in a mouse model of atherosclerosis, suggesting that it directly regulates innate immunity (232). Indeed, there is accumulating evidence that, in addition to acting on tumor cells, ATRA induces recruitment of NK cells (171), regulates ILCs (15), and controls macrophage function (200). Furthermore, there is evidence that $CD8^+$ T cell–mediated killing is also regulated by ATRA (224), which is likely due in part to enhanced anticancer innate immunity. ATRA therefore serves as a prime example of a vitamin-derived metabolite that is of high therapeutic relevance due to its modulation of innate immunity.

7. FUTURE DIRECTIONS IN THE FIELD

7.1. Interdependence Between Microbiota, Diet, and Innate Immunity

Many advances have been made in recent years to gain a molecular understanding of how diet substantially impacts disease at the epidemiological and molecular levels. In addition, other key environmental factors influencing health and disease, such as the microbiota, have been increasingly characterized, with groups of microbes or even individual species linked to specific disease phenotypes. However, despite the increased knowledge about key host factors such as cytokines and how they drive inflammatory disease and the more in-depth characterization of the microbiota, very little is known about how nutrition affects the interaction between innate immune mediators and the microbiome. How diet affects the function of the microbial ecosystem in the intestinal tract or on other mucosal surfaces remains largely unknown, and only very few studies have directly and mechanistically demonstrated how diet-induced change in the composition or function of the microbiota can impact disease development. Elucidating how these processes happen at the molecular level, including how specific dietary components directly change not only host–microbe but also microbe–microbe dynamic interactions and how this translates to global physiological effects such as weight gain and chronic inflammation, will be a key avenue of future research. For example, fiber-diet-induced SCFAs are beneficial in many disease contexts and detrimental in others. Although much is known about the impact of SCFAs on inflammation and what type of diet benefits their production by bacteria, it is not well understood to date which bacteria under what precise circumstances start producing butyrate or other SCFAs. Understanding how microbes respond to our diet at the individual and network levels will be an

important area of future research. Elucidating the detailed molecular diet–bacteria–metabolite axes and how they affect the host will be essential in gaining a better understanding of how environment influences disease. This will pave the way for therapeutically exploiting specific dietary components, potentially in combination with administration of microbiota configurations as discussed below.

Another key future development will have to be more rigorous experimental setups when conducting and interpreting experiments that explore the intersection between diet and disease. A HFD is often compared with a chow diet, which differs in multiple respects other than fat content. Such comparisons can lead to wrong interpretations about the effects of specific dietary components. Furthermore, differences in food intake or feeding rhythmicity induced by different diets (135) need to be controlled for if conclusions are to be drawn for metabolic or immune-mediated effects on disease, especially in animal models. In addition, because mice and humans have opposite diurnal cycles, translating findings about the impact of diet on specific immune or metabolic parameters in rodent models of disease needs to account for these differences in circadian host as well as microbiota responses. Another way to gain a better understanding of diet–microbiota–host interactions is to use mouse models that harbor a more human-like microbiota, such as wildling mice (133). Immune phenotypes from wildling mice more closely resemble those from humans (157); thus, wildling mice are a better model by which to study the impact of diet on inflammatory disease. Furthermore, transplantation of microbiota from human donors into germ-free mice combined with different diets will facilitate a better understanding of how diet affects host–microbiota interactions and how this influences disease development.

7.2. Therapeutically Exploiting the Intersection Between Innate Immunity and Nutrition

Despite the vast knowledge that has accumulated about the cross talk between innate immunity and metabolism, interventions based on immunomodulation to combat metabolic derangements have not been thoroughly tested in clinical trials. Although anti-inflammatory medications, such as salicylates, have successfully ameliorated features of metabolic syndrome in humans (54, 61), using nutrition to achieve anti-inflammatory effects still merits more research. Studies of human subjects usually measure features of metabolic syndrome as primary outcome, while inflammatory markers are overlooked or sampled from the blood instead of target organs.

Even with these limitations, some dietary constituents that exerted immunomodulatory effects on innate immune cells to alleviate metabolic inflammation in vitro and in vivo have been proven beneficial in humans (**Figure 4**). Such dietary regimens included calorie restriction (5) and supplementation with macronutrients, such as dietary fiber (20, 156) and unsaturated fatty acids (7, 124), and specific bioactive compounds, such as extra-virgin olive oil or nuts (47), tomato-based foods (59), and histidine (51). However, results have not been conclusive, and other studies failed to replicate the same favorable metabolic outcomes (11, 94, 108, 125, 136, 180). These discrepancies may emerge from the high heterogeneity among humans, as opposed to animal models, and future studies should try to better control for confounding variables, either endogenous (such as genetic makeup and individual parameters) or exogenous (such as environmental exposures and interaction with other dietary compounds). Another strategy to circumvent heterogeneity would be to integrate those numerous variables in the analysis. Indeed, recent studies by our laboratory and by other groups have demonstrated that metabolic responses to diet are highly variable and dependent on individual features, including the gut microbiota (90, 93, 227), suggesting that diet–microbiota–host immune system interactions can drive differential effects on host metabolism. Harnessing advanced bioinformatics and big data analysis poses a novel way to devise personalized dietary interventions, which are more likely to be effective.

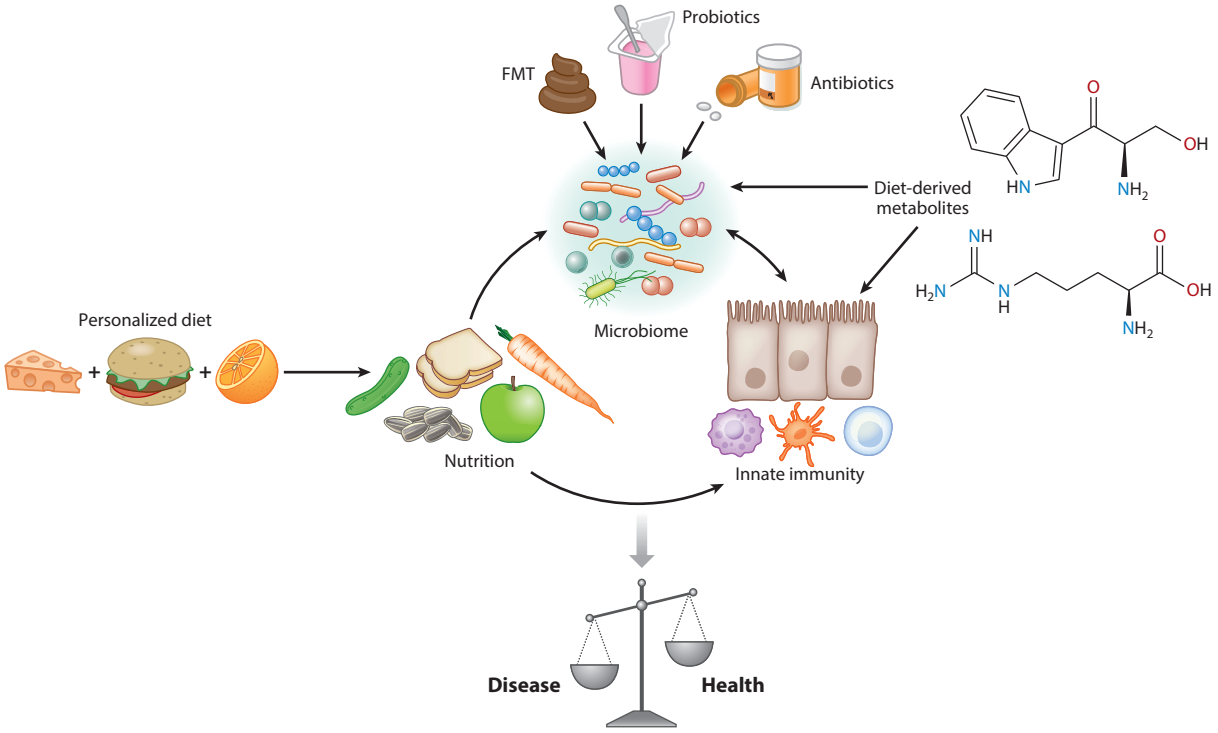

Figure 4

Nutrition or food-derived molecules such as metabolites can be harnessed as therapy for complex human diseases due to their potent effects on innate immunity and the microbiome, which in turn determines the balance between health and disease. Furthermore, direct modulation of the microbiome by FMT or with probiotics also presents itself as a promising avenue of future therapy development. Abbreviation: FMT, fecal microbiota transplantation.

We envision that adopting the concept of precision nutrition not only will allow for better dietary planning but will also pave the way toward devising interventions focused on altering easily modifiable individual features, such as the microbiota, in order to amplify the effect of diet on the host innate immune system. These interventions include prebiotics (36), probiotics (34), fecal microbiota transplantation (89), and antibiotics (206).

In conclusion, nutrition is a simple yet compelling therapeutic means to modify the host immune system and thereby improve metabolism. After various dietary compounds and their mechanisms in the host have been discovered, the main challenge ahead would be to translate this knowledge to health-promoting interventions in clinical practice. Increasing scientific rigor and utilizing advanced technologies in a multidisciplinary manner can bring a renaissance to this important aspect of human health.

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E.E. is a paid scientific consultant for DayTwo and BiomX. The other authors are not aware of any affiliations, memberships, funding or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

All authors researched data for the article; made substantial contributions to the discussion of content; and wrote, reviewed, and edited the manuscript before submission.

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