The Impact of Diet on Immunity and Respiratory Diseases

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Abstract

The Western world has witnessed a tremendous increase in the occurrence of allergy and autoimmunity in the second half of the 20th century. Extensive efforts have been made to explain this phenomenon and various hypotheses have been formulated. Among them, two concepts have attracted the most attention: the "hygiene hypothesis," identifying the reduced exposure to environmental microorganisms as a driving force behind the observed epidemiological trends; and the "diet hypotheses," pointing to the importance of changes in our dietary habits. In this review, we discuss the interplay between the Western diet, microbiota, and inflammatory conditions, with particular emphasis on respiratory diseases. This is followed by an in-depth overview of the immunomodulatory potential of different dietary fatty acids. We conclude by identifying the outstanding questions, which, if answered, could shed further light on the impact of dietary habits on immunity and interconnect it with postulates proposed by the hygiene hypothesis. Linking these two concepts will be an important step towards understanding how Western lifestyle shapes disease susceptibility.

Keywords: Western diet; microbiome; fatty acids

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In the past few decades dietary habits have undergone tremendous changes (1), and there is now a growing awareness of the impact this has had on our immune system, and consequently health and disease. In the Western world an increased consumption of energy-dense and processed foods has been observed, often called the "Western diet." This diet is generally high in animal protein, digestible sugars, starch, and fat content whereas dietary fiber content is low (1). The observed nutritional change in the Western world has coincided with a rise in the prevalence of inflammatory (including asthma and allergy) and autoimmune diseases (2, 3). Dietary ingredients are major determinants of gut microbial composition and consequently can shape the characteristics of immune responses. In this article, we discuss the impact of the Western diet on the gut microbiome and its effects on lung health and disease. In particular, the effects of fatty acids on immune responses, and their potential implications for respiratory health, are highlighted.

Diet and Gut Microbiome in Lung Health and Disease

Changes in dietary habits, such as consumption of a more "Westernized diet," are an important contributor to the global obesity epidemic. Obesity is, in the broadest sense, the result of an imbalance between energy intake and energy expenditure. This nutrient and metabolic surplus triggers a chronic low-grade systemic inflammatory response, and engages a set of molecules and signaling pathways similar to those involved in classic inflammation (4). However, obesity-induced systemic inflammation differs from classic inflammation in several key aspects. Obesity is a chronic disease and produces a tonic low-grade activation of the innate immune system. In addition, recurrent changes in postprandial nutrient quantity lead to fluctuations in circulating metabolic components (e.g., triacylglycerols, lipids, free fatty acids, and glucose), which induce immune activation (5–7). The structure and function of the gut microbiota are also heavily influenced by changes in dietary habits, which can consequently alter immune responses. Here we review how high dietary fat and low dietary fiber intake, as seen in the Western diet, alter the gut microbiome and can affect lung health and disease (Figure 1).

Dietary Fat Consumption and Systemic Inflammation

Changes in diet and subsequent modulation of host immunity and microbial ecology may alter host–microbial homeostasis, leading to gut dysbiosis. A balanced microbial community in the intestine is imperative for appropriate immune function and health, because dysbiosis of the gut microbiome has been associated with both local and chronic

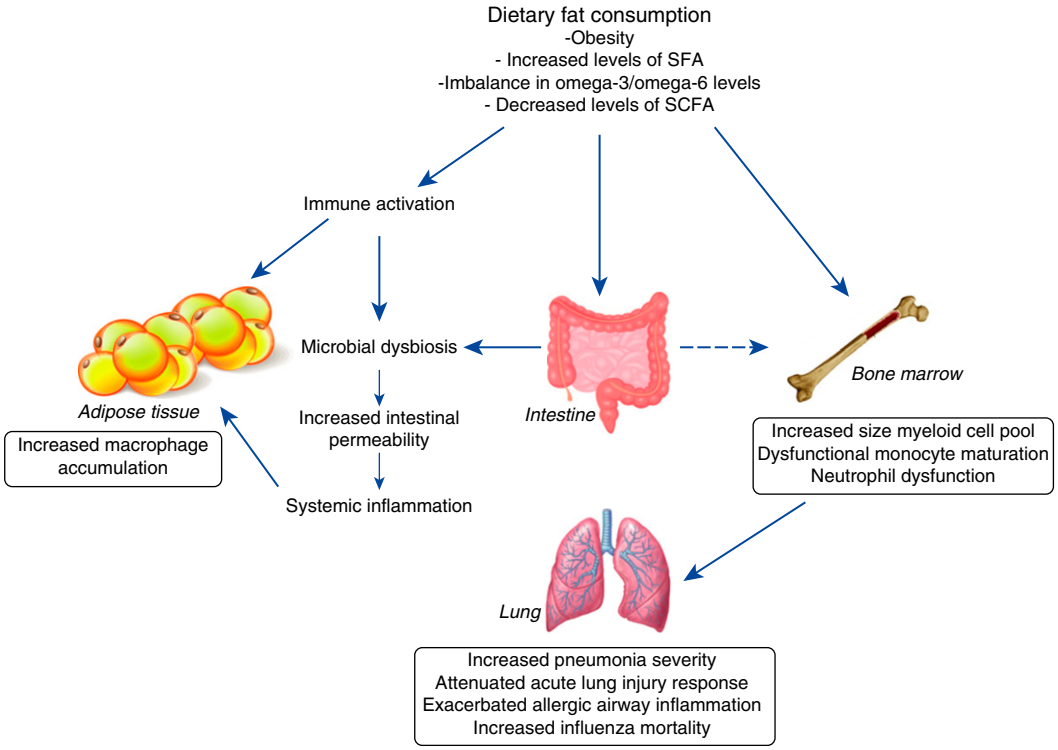

Figure 1. Immunomodulatory effects of dietary fat consumption on lung disease. Increased dietary fat consumption is associated with systemic inflammation that can lead to immune activation in associated tissues, such as the adipose tissue. This effect may be due to induction of obesity or through direct changes in fatty acid balance. Adipose tissue inflammation can be characterized by increased macrophage accumulation and the formation of so-called "crown-like structures." Systemic inflammation and immune activation can alter microbial composition in the intestine, leading to dysbiosis. Gut dysbiosis can increase intestinal permeability, thereby allowing bacteria to translocate to the circulation (and possibly the adipose tissue) and enhance systemic inflammation, which can in turn lead to adipose tissue inflammation. The complexity of the intestinal microbiota is strongly correlated with the size of the bone marrow myeloid pool. In addition, high-fat diet–induced obesity can alter the myeloid cell pool; however, whether there is a direct link between high-fat diet intake, gut microbiota, and size of the myeloid cell pool remains to be confirmed. Diet-induced obesity has been linked to dysfunctional monocyte maturation and neutrophil dysfunction in the bone marrow. This has been associated with increased pneumonia severity and attenuated acute lung injury in murine studies. SCFA = short-chain fatty acids; SFA = saturated fatty acids.

systemic disorders (8–10). High-fat diet intake has been shown to alter microbial composition in the intestine by increasing the ratio of *Firmicutes* to *Bacteroidetes* (11, 12). This shift has been associated with increased gut permeability and enhanced circulating LPS levels, which can induce systemic inflammation (13, 14). Interestingly, the type of dietary fat (either lard or fish oil) used in a high-fat diet induces different changes in the murine gut microbiome and consequently leads to differential activation of immune responses (15). For example, mice fed a lard-based high-fat diet showed increased Toll-like receptor (TLR) activation in the systemic circulation, increased crown-like structures, and accumulation of $CD45^+$ cells in white adipose tissue, which is indicative of increased white adipose tissue inflammation (15). Furthermore, high-fat diet–induced alterations in the gut microbiota have been linked to overexpansion of endotoxin-producing bacteria, thereby increasing gut permeability (13) and promoting translocation of live gram-negative bacteria through the intestinal mucosa to the circulation and mesenteric adipose tissue (16).

In addition to dietary-mediated microbial changes, changes in innate immunity, directly due to dietary constituents, are also capable of shaping the commensal microbiota. For example, pathogen-associated molecular patterns and danger-associated molecular patterns derived from intestinal microbiota and dietary factors (e.g., fatty acids, ceramides, high mobility group box 1 protein, fetuin, heat shock proteins, and modified low-density lipoprotein) have been proposed to activate TLRs during the development of obesity (17). Furthermore, high-fat diet feeding is suggested to reduce circulating butyrate levels in mice (18); however, additional studies are required to delineate whether this has an impact on immune activation.

Dietary Fat Consumption, Immune Modulation, and Respiratory Diseases

Clinical studies determining the effects of dietary fat consumption on immune modulation have reported that a high-fat meal challenge in healthy subjects increases circulating proinflammatory cytokine and neutrophil levels (7, 19, 20). The consequent effects on lung health and disease have been described. Wood and colleagues observed an increase in both TLR4 expression on induced-sputum cells and neutrophil counts in the sputum of subjects with asthma fed a high fat–containing meal (21). Gene expression profiling of sputum cells in healthy and

asthmatic subjects fed a high-fat diet, revealed increased expression of genes representing immune system processes (e.g., genes encoding for S100 calcium-binding protein P, S100 calcium-binding protein A16, myelin and lymphocyte protein, and mucin 1) in the subjects with asthma (22). These data suggest that multiple immune pathways are involved in the high-fat diet–induced airway inflammatory response in subjects with asthma. However, additional mechanistic studies are warranted to delineate the molecular mechanisms underlying this phenomenon.

Murine studies using high-fat diet feeding and associated obesity revealed developmental and inflammation-induced alterations in the immune response. High-fat diet feeding in mice induces modest changes in bone marrow composition. A slight increase in the percentage of lymphocytes is observed after chronic high-fat diet feeding (from 90 d on). However, a 40% increase in the total amount of nucleated cells was observed in diet-induced obese mice compared with low-fat diet controls, suggesting an overall increase in hematopoiesis (23). Moreover, the size of the bone marrow myeloid cell pool has been shown to correlate strongly with the complexity of the intestinal microbiota (24). Changes in microbiota composition, as observed in obesity, may therefore affect the cross-talk between hematopoiesis and microbiota, and potentially exacerbate inflammation or infection in the host. Evidence suggests that obesity as a consequence of high-fat diet feeding can lead to T-cell and macrophage dysfunction. Specifically, reduced cytokine expression in response to infection, observed in diet-induced obese mice, is linked to dysfunction in bone marrow macrophages and/or a defect in maturation of monocytes and a reduction in TLR2 expression on these cells (25). Furthermore, diet-induced obesity–mediated defects in development and functional responses of bone marrow–derived neutrophils have been demonstrated, leading to an attenuation of the pulmonary inflammatory response after induction of acute lung injury (26), whereas bacterial pneumonia severity is increased (27).

High-fat diet consumption leads to increased mortality in mice infected with influenza virus (28, 29), which is linked with a delayed antibody response (30). Obese individuals were shown to have a steep decline in antibody production to influenza vaccination compared with lean control subjects (31). However, the cellular mechanisms underlying this phenomenon at the B-cell level are unknown. In addition, selective impairment of dendritic cell functions and delayed recruitment of mononuclear cells to the lung during influenza infection have been observed in diet-induced obese mice (32). Moreover, Karlsson and colleagues demonstrated that increased morbidity and mortality during a secondary influenza infection are due to impairment in the ability to generate and maintain functional influenza-specific memory T cells (33).

Although the exact mechanisms underlying enhanced allergic airway responses in obesity require additional investigations, some studies suggest the involvement of innate lymphoid cells (ILCs). Airway responsiveness to methacholine was shown to be increased in mice after chronic high-fat diet feeding (24 wk) (34), and this response was mediated through a pathway that required NLR family, pyrin domain containing 3 protein, IL-17, and was facilitated by ILC3s (35). In addition, high-fat diet–induced obesity exacerbates house dust mite–induced airway inflammation, which was suggested to be mediated by ILC2s and ILC3s (36).

High-fat diet feeding and its associated obese state thus lead to numerous alterations in gut microbial composition and the immune response. Unfortunately, studies linking diet-induced intestinal dysbiosis to alterations in the immune response remain limited, and their effects on pulmonary health and disease is a scarcely investigated field of research that requires attention. Investigating the mechanisms underlying the impaired immune response seen after high-fat diet feeding by looking at host–microbiome interactions will provide the research community with useful insights to design more effective treatments and therapies.

Dietary Fiber Consumption

Fiber is an important component of our diet. In the typical "Western diet" dietary fiber content is low (37). There has been increased interest in the potential beneficial effects of a diet high in fiber. Dietary fiber is a substrate for intestinal microbes (38), and low dietary fiber intake leads to reduced levels of short-chain fatty acids (SCFAs). Analysis of the NHANES (National Health and Nutrition Examination Survey) database, a database that assesses the health and nutritional status of adults and children in the United States, revealed an association between low fiber intake and lower lung function (39), and increased dietary fiber intake has been associated with a 40–50% decrease in respiratory-related deaths (40, 41). Moreover, one study demonstrated that intake of a soluble fiber–containing meal decreases airway inflammation (sputum) and improves lung function in subjects with asthma (42).

Feeding mice a fiber-free diet has been shown to promote the expansion and activity of mucus-degrading bacteria in the colon, leading to increased susceptibility to infections as compared with fiber-fed controls (43). In contrast, high dietary fiber intake and its associated increase in SCFA levels are accompanied by shifts in microbial composition (elevated ratio of Bacteroidetes to Firmicutes) in the intestine (44, 45) and the airways (44). Together, these studies suggest that dietary fiber intake has considerable relevance for lung health. Beneficial effects of high-fiber diet intake on other inflammatory response were demonstrated in a variety of animal models, including colitis (46), allergic airway inflammation (44, 45), and food allergy (47), and it was suggested that these effects were also mediated by changes in SCFA levels.

A dietary basis for inflammatory diseases can, at least in part, be explained by interactions between dietary constituents and immune cells. Dietary fatty acids can differ in length (short, medium, and long chain), level of saturation (saturated and unsaturated), and their conformation, and can therefore have markedly contrasting functions. Below, we discuss the various types of fatty acids and their influence on immune responses and respiratory disease.

High-Fat Diet, Dietary Fatty Acids, and Susceptibility to Diseases

The Western diet is characterized by increased dietary fat content. Therefore, it has long been hypothesized that higher fat intake might be implicated in elevated risk for "lifestyle diseases." As discussed in the previous section, an important factor contributing to this is obesity. Alternatively, it might be speculated that a high-fat diet enhances disease susceptibility independently of obesity. In this view, increased free fatty acid release from the diet itself would result in modulation of the immune system

and influence the risk for disease development.

The effects of high-fat meals on inflammatory responses, independently of obesity, have been evaluated in studies involving human subjects. In the work by Wood and colleagues, nonobese patients with asthma received a high-fat or low-fat meal, and their lung function and airway inflammatory markers were assessed 4 hours later. Interestingly, patients who received a high-fat meal had increased TLR4 mRNA expression in their sputum cells, and this coincided with higher abundance of neutrophils (21). In a study by Nappo and colleagues, healthy subjects receiving a high-fat meal had elevated plasma levels of proinflammatory cytokines (tumor necrosis factor [TNF]-α and IL-6), as well as adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), 2–4 hours after the meal (19). Similarly, Blackburn and coworkers reported elevated levels of plasma IL-6 (7), and van Oostrom and colleagues noted an increase in plasma IL-6 and IL-8 together with elevated numbers of blood neutrophils in subjects receiving a high-fat meal (20). Exact mechanisms leading to these changes are unclear, although some authors suggested a possible role for increased glucose and fatty acid concentrations. The latter could act on TLR4 and stimulate innate immune cells to produce proinflammatory cytokines (20, 21). A similar observation was made in mice by Holland and colleagues, who demonstrated that mice infused with lard oil had higher levels of plasma IL-6 and TNF-α, and this effect was shown to be TLR4-dependent (48).

The effects of parental high-fat diet intake on the immune system of the offspring in animal models have also been investigated. One study concluded that a parental high-fat diet may imprint changes in microbiota composition in offspring mice, and that these changes may enhance susceptibility to inflammatory diseases, including allergy (49). Importantly, there were no differences in fasting blood glucose or body weight between pups born from high- and low-fat diet–fed parents, underlining that the observed effects were not confounded by diabetes or obesity (49). Transgenerational effects of a high-fat diet have also been postulated by Du and colleagues, who observed transient hair loss and an enhanced inflammatory status of the skin of mice born to mothers fed a high-fat diet. The authors linked these changes to an altered composition of breast milk, which was enriched in long-chain and saturated fatty acids (50).

Saturated Fatty Acids

Proinflammatory properties of saturated fatty acids *in vitro* are well described. They have been shown to trigger secretion of proinflammatory mediators from various cell types, including macrophages (51–54), adipocytes (55, 56), astrocytes (57), and aortic endothelial cells (58). These properties were demonstrated to depend on binding of saturated fatty acids to TLR4 (51, 52, 57, 59) or TLR4 and TLR2 (60, 61). Another receptor able to bind medium- and long-chain fatty acids, including saturated fatty acids, is G protein–coupled receptor 40 (GPR40) (62–64); however, the effects of saturated fatty acid–GPR40 interactions on the immune system at steady state or during inflammation are not known.

In vivo effects of saturated fatty acids in animal models are less well studied. Kleinridders and colleagues demonstrated that feeding mice a high-fat diet for 13 weeks, or administering palmitate by acute intracerebroventricular infusion, can induce leptin and insulin resistance and that these effects depend on the expression of myeloid differentiation primary response 88 in the central nervous system (65). Similarly, Posey and colleagues showed that intracerebroventricular infusion of palmitate recapitulates the effects of the high-fat diet and induces hypothalamic inflammation and insulin resistance in rats (66). Milanski and colleagues demonstrated that infusion of stearic and arachidonic acids induces proinflammatory gene expression in the hypothalamus (67). More recently, an interesting observation was made by Beyaz and colleagues, who observed that a high-fat diet enhanced self-renewal of intestinal stem cells and that this effect was recapitulated by *ex vivo* exposure of organoid cultures to palmitic acid (68). These data led to the postulation that saturated fatty acids might play a role in tumor initiation.

Finally, one study has shown that palmitic acid can induce inflammatory cardiomyocyte injury (69). The authors demonstrated that it interacted directly with the lymphocyte antigen 96 (known as the MD2 adapter protein) and activated TLR4 signaling. Importantly, MD2-deficient animals were protected from palmitic acid–induced myocardial injury (69).

There is a paucity of data regarding the *in vivo* effects of saturated fatty acids on lung disorders, using animal models. Similarly, epidemiological studies regarding association of saturated fatty acids with lung dysfunction are lacking. Further research is needed to establish the contribution of saturated fatty acids in various inflammatory conditions, including lung diseases, and to decipher the molecular pathways they engage. This might lead to the development of new therapeutic targets or dietary interventions with the potential to ameliorate inflammatory diseases.

Polyunsaturated Fatty Acids

Another constituent of dietary fats is polyunsaturated fatty acids, which can be further subdivided into omega-3 and omega-6 fatty acids. In the Western diet, consumption of omega-6 fatty acids is elevated, whereas that of omega-3 is reduced (1). Epidemiological studies have long suggested beneficial roles of a decreased omega-6/omega-3 ratio in various inflammatory disorders. A useful tool to study this in controlled settings was introduced by Kang and colleagues, who generated *fat-1* transgenic mice in which n-3 fatty acid desaturase converts omega-6 into omega-3 fatty acids (70). Using these mice, antiinflammatory properties of a decreased omega-6/omega-3 ratio were demonstrated in various models, including colitis (71), hepatitis (72), retinopathy (73), and epilepsy (74) as well as in models of lung diseases, such as acute lung injury (75) and allergic airway inflammation (76). In the colitis model, the improvement in disease score was associated with the induction of resolvins as well as the reduction of nuclear factor κ B activity and down-regulation of TNF-α, inducible nitric oxide synthase, and IL-1β expression (71). In the hepatitis model, it correlated with reduced hepatic gene expression of TNF-α, IL-1β, IFN-γ, and IL-6 (72). In retinopathy, *fat-1* mice had reduced expression of TNF-α (73). In the lung injury model, the beneficial role of an increased omega-3/omega-6 ratio was linked with reduction of macrophage inflammatory protein-2 and thromboxane B_2 levels (77). Finally, in allergic airway inflammation, this effect was associated with increased levels of

protectin D1 and resolving E1 and with reduced levels of proinflammatory cytokines (IL-1α, IL-2, IL-5, IL-9, IL-13, G-CSF [granulocyte-colony stimulating factor], KC [keratinocyte chemoattractant], and RANTES [regulated upon activation, normal T-cell expressed and secreted]) (76).

Consistently, some dietary interventions with omega-3 but not omega-6 fatty acids led to similar observations in various animal models of disease, such as colitis (78–80), neuroinflammation (81), insulin resistance (82), or atopic asthma (83, 84). However, it must be pointed out that not all omega-6 fatty acids have similar inflammatory properties. For example, γ-linolenic acid has been described to have antiinflammatory properties in various inflammatory conditions. A detailed description of γ-linolenic acid properties is beyond the scope of this review and has been covered elsewhere (85–87).

Monounsaturated Fatty Acids

Another class of unsaturated fatty acids is the monounsaturated fatty acids, including omega-7 and omega-9 fatty acids. Palmitoleic acid belonging to the omega-7 fatty acids was identified as an adipose tissue–derived lipid hormone stimulating muscle insulin action and suppressing hepatosteatosis (88). Its antiinflammatory properties *in vitro* were demonstrated by Macrae and colleagues, who showed that it suppressed palmitic acid–enhanced proinflammatory signaling (89). *In vivo*, its beneficial effects were underlined in a mouse model of nonalcoholic fatty liver disease (90). Finally, Kanwar and colleagues observed that milk fat enriched in conjugated linoleic acid (belonging to the omega-3 fatty acids) and vaccenic acid (belonging to the omega-7 fatty acids) suppressed allergic airway inflammation in a mouse model of asthma (91). Intriguingly, feeding mice with either conjugated linoleic acid or vaccenic acid alone was not effective in conferring this protection, but their combination recapitulated the effects of milk fat (91). With the exception of the latter study, there are no data regarding the roles of omega-7 fatty acids in animal models of lung disease. Likewise, epidemiological studies concerning the association of monounsaturated fatty acids with susceptibility to lung disorders are missing.

In vitro studies regarding omega-9 fatty acids suggest they have antiinflammatory properties. Oleic acid was shown to reverse palmitic acid–induced insulin resistance and inflammation in muscle cells (92). Also, it was demonstrated to inhibit cytotoxic T-cell binding to major histocompatibility complex class I targets (93). These data were supported by *in vivo* studies using animal models of Alzheimer's disease (94), type 2 diabetes (95), and sepsis (96), in which oleic acid was shown to exert antiinflammatory properties and reduce the severity of the studied conditions. The roles of omega-9 fatty acids during lung inflammation are not known. Controlled studies using animal models are lacking and epidemiological studies are scarce. From those, one study showed lack of any association between omega-9 fatty acids and asthma (97), whereas another found a positive correlation regarding this disease (98). Clearly, more studies are needed to clarify the effects of omega-9 fatty acids *in vivo*.

SCFAs

Although SCFAs may be found in certain foods, such as butter, some cheeses, and cow's milk, they are predominantly products of bacterial fermentation of complex polysaccharides found in dietary fibers. However, their roles in the context of high-fat diet–immunity cross-talk may be relevant because Western diet is characterized by decreased content of dietary fibers (1), and intake of high-fat diet may result in even lower levels of circulating SCFAs (18). SCFAs have been well documented to exert antiinflammatory properties *in vitro* (99–103). Furthermore, high-fiber diet feeding and SCFA supplementation have been shown to suppress inflammation in animal models of diseases, including colitis (46, 77, 104, 105), peanut allergy (47), as well as allergic airway inflammation (44, 45). The exact mechanisms behind the action of SCFA are diverse, as they have been shown to promote differentiation of regulatory T helper cells (77, 105–107), impair the capacity of dendritic cells to prime effector T-cell responses (44), and were demonstrated to trigger inflammasome activation (104). Increased short-chain fatty acid levels on high-fiber diet feeding may be related not only to direct digestion of the source of nutrients, but also to changes in microbiota composition observed after prolonged diet feeding. We and others showed that mice fed a high-fiber diet had an elevated ratio of Bacteroidetes to Firmicutes in the gut (44, 45) and the lungs (44). Of note, the Bacteroidetes phylum is known to be a potent producer of SCFAs (108).

Microbiota changes induced on high-fiber diet feeding could also contribute to the observed antiinflammatory effects independently of short-chain fatty acids. To study this issue, Tan and colleagues performed recolonization experiments, in which germ-free mice were transplanted with feces from mice fed either a high-fiber or low-fiber diet (referred to as high-fiber microbiota or low-fiber microbiota mice, respectively). Interestingly, high-fiber microbiota but not low-fiber microbiota animals were protected against peanut allergy, although both groups had comparable levels of SCFA, indicating that beneficial effects were not due to these metabolites (47). In summary, it is most likely that the antiinflammatory features of high-fiber diet feeding are due to a combination of several factors, including increased levels of circulating SCFAs (derived from fermentation of dietary fiber and further enhanced by shifts in microbiota composition in favor of SCFA-producing species) and changes in gut/lung microbiota composition independent of their capacity to produce SCFAs. Further research is needed to identify beneficial bacteria induced by a high-fiber diet at the species and strain levels, and to define their antiinflammatory metabolites besides SCFAs.

In summary, evidence from *in vitro* and *in vivo* studies using animal models indicates that fatty acids can directly modulate immune responses and influence disease susceptibility. In general, saturated and polyunsaturated omega-6 fatty acids are thought to be proinflammatory, whereas polyunsaturated omega-3, monounsaturated, and short-chain fatty acids are antiinflammatory. Despite these insights, the physiological contribution of pathways engaged by these fatty acids in homeostasis and in inflammatory diseases is unclear. Likewise, their importance in the maintenance of low-grade activation of the immune system in obesity is not established. More research is needed to shed light on these issues. Also, further unraveling of molecular pathways engaged by various fatty acids will be important for selection of

therapeutic targets with the potential to ameliorate inflammation. These might lead to the design of new, more effective therapies or dietary interventions against various inflammatory conditions.

Outlook and Perspectives

Major changes in dietary habits in industrialized countries during recent decades coincided with an increased occurrence of hypersensitivity and autoimmunity. Yet, it is still unclear whether there is a causative relationship between these two observations, because additional lifestyle changes occurred over this same period, such as increased cleanliness and reduced contact with our natural environment (largely covered by the "hygiene hypothesis" and its recent derivatives). Despite this, we summarized existing evidence that dietary changes have profound effects on our immune system and disease susceptibility. These effects might be achieved via the development of obesity, diet-induced alterations of the microbiota, or direct immunomodulatory properties of nutrients. These insights open up new avenues for future research and development. In particular, it is essential to identify beneficial and pathogenic bacterial species induced by specific dietary constituents and select metabolites with potential immunomodulatory effects. Furthermore, studying the characteristics of these bacteria, including optimal conditions for growth and survival in their ecological niche, will provide us with new insights into ways to manipulate them. Finally, their molecular characterization and screening for unique antigens might create new tools to target them pharmacologically.

Answers to these questions will be important to further define the impact of the "diet hypothesis" and interconnect it with other postulates, such as the "hygiene hypothesis." ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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