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Nutritional modulation of the microbiome and immune response

Ansen H.P. Burr[1,2,†], **Amrita Bhattacharjee**[1,†], **Timothy W. Hand**[1,*]

[1]R.K. Mellon Institute for Pediatric Research, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA 15224

[2]Medical Scientist Training Program, University of Pittsburgh/Carnegie Mellon University.

Abstract

The evolution of the immune system, diet, and the microbiome are interconnected. Dietary metabolites modulate the cells of the immune system, both directly and indirectly, via shifts in the composition of the intestinal microbiota and its products. As a result, overconsumption and malnutrition can have substantial effects on immune responses and inflammation. In resource-rich nations, diets high in processed foods, fat and sugar can contribute to chronic inflammatory conditions, which are on the rise worldwide. Conversely, in resource poor countries, malnutrition associated with food security can lead to immunodeficiencies and shifts in the microbiome that drive intestinal inflammation. Developing a deeper understanding of the relationship between diet, microbiota, and the immune system is of huge importance given its impact on inflammatory diseases and potential as an easily modifiable mediator of immunomodulation.

Introduction:

330 million years ago our ancestors evolved the ability to sustain themselves on a variety of different plants, in part, via the acquisition of an intestinal microbiome (1). The microorganisms of the microbiota (bacteria, archaea, fungi, protists and viruses) allowed herbivores to digest complex carbohydrates and they soon dominated the Earth. The acquisition of a complex microbiome also required evolution of host cellular and biochemical processes, including the adaptive immune system (2, 3). Adaptive immunity can mediate responses to repeat microbial encounters in an efficient manner, both protecting against invasive organisms and also fostering symbiosis with beneficial members of the microbiota (3, 4). Since the evolution of the host/microbiome relationship was driven by nutrition and this was intertwined with the evolution of the immune system, it is not surprising that diet and nutrition affect the immune response. Here we will review how diet affects immunity both directly, by modifying immune cells, and also indirectly, via inducing changes to either the microbiota or non-immune tissues. In particular, we will focus on how nutrition contributes to immune-mediated disease. We will address both overnutrition in High-income nations and undernutrition and malnutrition of Low-to-Middle-income settings. For clarity, we will not discuss at length the separate process where the host sequesters key nutrients and minerals from pathogens, which has been reviewed elsewhere

*To whom correspondence should be addressed: timothy.hand@chp.edu.

†Equal contribution

(5, 6). Additionally, we have focused on how specific nutrients modulate immune responses, as these studies more often provide mechanistic insights into interactions with specific cells.

Overnutrition and immunity

Recent advances in food production and distribution have reduced food insecurity and famine for billions of people. However, increasing caloric intake has been associated with a global rise of non-communicable diseases, such as cardiovascular disease, diabetes and cancer, which are the leading causes of death in High-income countries (HICs) (7). The 'Western' diet is characterized by increased consumption of total calories and a diet that is overly reliant on animal fat, refined grains and sugar and too little fruits and vegetables (8). Overnutrition has led to the staggering rise in global obesity rates, which have nearly tripled over the last 40 years (9, 10). The association of obesity and chronic inflammatory disease is well-established and extensively covered in previous reviews (11–15). Here, we will focus on how specific components of the Western Diet alter immune function acutely, contributing to inflammatory disease.

Dietary fat activates immunity and inflammation

Long-term high-fat diets (HFD) have been used in mice to induce obesity and the associated immune-metabolic shifts, such as low-grade adipose inflammation and insulin resistance (12). However, short-term consumption of high-fat diet in mice also results in altered immune function and inflammation, prior to the onset of obesity (16–18). The first site where the diet interacts with the host is the gastrointestinal epithelium and HFD has important effects on the constitution of this layer. The intestinal epithelium maintains a physical barrier between the microbiome and the host via tight junctions, which prevent intracellular entry of exogenous products (19). Feeding mice HFD for one week reduces the expression and alters the distribution of tight junction proteins, which is associated with increased intestinal permeability and bacterial product translocation (20, 21). This has been seen in humans as well, where high energy intake, in the form of excessive fat consumption, is correlated with higher levels of serum LPS levels, or endotoxemia (22). However, fatty acids can also support a healthy epithelium by driving increased 'stemness' and proliferative capacity in $Lgr5^{+}$ crypt base columnar stem cells (23). Therefore, the negative effects of HFD on barrier function are likely the result of immune activation in the intestine, rather than direct effects on the epithelium itself. Indeed, mice fed HFD for 4 weeks had increased expression of chemokines (CCL1, CCL2) and chemokine receptors (CCR2), leading to the infiltration of proinflammatory monocytes and lymphocytes to intestinal tissues (24). In specific contexts, innate immune responses can be directly induced by free fatty acids, which are elevated in the blood after high fat meals and directly activate TLR4 on adipocytes and macrophages and TLR2 on monocytes to induce cytokine production (25, 26). Further, saturated fatty acids, such as palmitate, can directly activate the NLRP3-ASC inflammasome in myeloid cells to support IL-1β processing (27). Cytokines and inflammatory lipid molecules produced by innate immune cells, such as TNFα, IL-1β IFNγ, iNOS, COX-2 and IL-6, increase intestinal permeability (28–30). As evidence for the immune-mediated effects of HFD, HFD-fed IFNγ-deficient mice show reduced intestinal permeability compared to controls, (31, 32). Therefore, HFD-induced increases in circulating bacterial products also

likely leads to the potent induction of inflammatory cytokines (21, 33). In support of this notion, germ-free mice, which lack a microbiome, have reduced expression of TNFα when fed a HFD (28). Thus, the over consumption of fat affects the intestinal barrier by directly activating macrophages, monocytes and T cells, leading to increased intestinal permeability and endotoxemia and further contributing to a systemic proinflammatory response. Short-term HFD feeding in mice also leads to a loss of hematopoietic stem cells in bone marrow and reduced hematopoietic reconstitution potential via disruption of TGFβ receptors in lipid rafts (34). Finally, dietary fat can have direct effects on adaptive immune cells where long-chain fatty acids, such as lauric acid, support the differentiation of T helper 17 (Th17) T cells and contribute to pathology in animal models of neuroinflammation (35).

Dietary fat and the microbiome

In addition to direct effects on host immune cells, HFD can quickly and reversibly change the composition of the microbiome. In mice, diets high in fat and sugar lead to a transient dysbiosis of the microbiota, characterized by reduced diversity and an expansion of opportunistic pathogens (36). Human microbiome studies have also associated increased *Proteobacteria* and *Firmicutes* and decreased *Bacteroidetes* to dyslipidemia, insulin resistance, and inflammation (37, 38). The importance of these associations is indicated my experiments where transfer of the microbiota from obese mice and humans to germ-free mice results in obesity in the recipient mice, while antibiotic treatment of obese mice reduces adipose inflammation and adiposity (21, 39, 40). Accordingly germ-free mice fed a HFD are resistant to the development of obesity (28). Conversely, there are members of the microbiota that suppress HFD-induced inflammatory responses, such as *Akkermansia muciniphilia,* which is negatively correlated with metabolic syndrome and has been shown to reduce systemic LPS and inflammation (41, 42). It is important to note that HFD-induced changes to the microbiome may also be indirectly affected by immune-mediated inflammation which is associated with the ‘blooming’ of *Enterobacteriaceae* that thrive in this environment (43, 44). For example, rats that are genetically susceptible to diet-induced obesity have an increase in LPS-producing *Enterobacteriaceae* which may enhance TLR signaling and HFD-induced inflammation (45). HFD and associated inflammation may also foster pathogen colonization as seen in murine *L. monocytogenes* infections, where HFD-induced microbiome changes are exacerbated and mice are more susceptible to infection due to a dysregulated immune response (46).

Food additives (sugar, salt and emulsifiers) increase inflammation

The Western diet is characterized by increased additives, such as emulsifiers, salt and sugar to make them more durable and hyper-palatable (8, 47). Sugar consumption has become dominant in the Western diet and it is estimated that an average person in the United States will consume over 70kg of sugar per year (48). High sugar consumption can have direct effects on host organs such as in models of Non-Alcoholic Fatty Liver Disease where excess dietary fructose leads to exacerbated hepatosteatosis (49). Sugar is also an important direct modifier of the immune response. For example, glucose is the preferred fuel source for Type 1 immunity, because it is important in the differentiation, proliferation and function of Th1 $CD4^+$ T cells, neutrophils, pro-inflammatory macrophages and activated dendritic cells (50–

53). Glucose is also the preferred substrate for proliferating $CD8^+$ T lymphocytes that need to use glycolysis so that components of the tricarboxylic acid cycle can be used for translation (54). High glucose intake also increases Th17 differentiation and exacerbates mouse models of colitis and autoimmune encephalomyelitis (55). Conversely, while glucose can support the proliferation of regulatory T cells (T_{regs}), Glut1 expression and glycolysis in these cells is associated with less potent suppression of inflammation (56). Accordingly, limiting sugar in the diet has shown substantial efficacy in the treatment of pediatric Inflammatory Bowel Disease (57). Glucose is also necessary for the proliferation and function of B cells as blocking glucose utilization decreases B cell number and antibody production in mice (58). Indeed, glycolysis-inhibitors, such as dimethyl fumarate and pyruvate kinase, have been found to improve autoimmune disease in mice and humans by downregulating aerobic glycolysis in activated lymphoid and myeloid cells (59, 60).

An additional issue, that compounds the effects of sugar consumption, is that processed foods often contain “acellular” sugar that, unlike sugar in fruits and vegetables, does not need to be digested and are immediately available to the host and microbiota. Gordon and colleagues, using gnotobiotic mice with a defined microbiome, reported that high sucrose diets led to an enrichment for enzymes for processing simple sugars (40). Such enzymes are often found in families of facultative anaerobic bacteria such as *Enterobacteriaceae* that bloom and contribute to intestinal inflammation (61). Processed foods are often deficient in fiber, so a high sugar diet may select against the symbiotic bacteria that help our digestion and select for bacteria that can best use simple sugars to proliferate quickly (61).

Other additives such as emulsifiers and salt have also sharply increased in the Western Diet, due to their preservative properties. Emulsifiers are detergents in food products, that, when fed to mice at low doses, leads to microbial encroachment and transferrable dysbiosis, which increases myeloperoxidase activity in the gut and results in endotoxemia (62). Excessive salt consumption is thought to contribute to the rise in hypertension and cardiovascular disease seen in high-income nations (63). Increasing salt concentration also has a direct effect on immune cells due to a salt sensing kinase (SGK1) on $CD4^+$ T cells that stabilizes IL-23R expression and enhances Th17 differentiation (64). These changes led to greater induction of Th17 cells *in vivo* with upregulation of pro-inflammatory cytokines GM-CSF, TNFα and IL-2 and worse autoimmunity in mice fed a high salt diet (65). SGK1 can also be activated downstream of the MTORC2 complex to increase Th2 differentiation and inhibit Th1 differentiation (66). Accordingly, high salt diets also exacerbate colitis in mouse models (67). In the future it will be important to determine the role of these food additives on immune-mediated disease in humans.

Fiber and short chain fatty acids are microbiome dependent immune regulators

The typical diet of HICs both overfeeds and undernourishes, in that there are too many calories but not the correct nutrients, including too little fiber. The evolution of the microbiome was driven by the necessity to digest complex polysaccharides into usable metabolites so it is intuitive that a lack of fiber would have negative effects on the health of

both the microbiome and host (68, 69). Similar to HFD and diets high in sugar, low fiber diets are associated with a low diversity and pro-inflammatory microbiota (70). The loss of diversity from a low fiber diet is pernicious since the loss of the bacterial strains may lead to a reduction in microbiome functionality that can only be restored from external sources (71). How reduced microbial diversity induces inflammation is not entirely clear, but we are beginning to understand some potential mechanisms. Reduced intestinal diversity is associated with domination of the microbiome by Gram negative bacteria (*Bacteroidetes*, *Proteobacteria, Verrucomicrobia*) which could lead to increased activation of the host immune response through increased levels of lipopolysaccharide (72). Indeed, in gnotobiotic mice with a defined consortium of bacteria, a fiber-free diet induced *Akkermansia muciniphilia* (a *Verrucomicrobia*) to consume and deplete the mucus barrier of the colon, leaving the host more susceptible to colonization and infection with the *Proteobacteria* pathogen, *Citrobacter rodentium* (73).

Perhaps the best studied mechanism via which low fiber diet and reduced microbiome diversity can contribute to inflammation is via a reduction in short chain fatty acids (SCFAs). SCFAs, namely acetate, propionate and butyrate, are metabolites produced by microbial digestion of complex carbohydrates. SCFAs are a major carbon source for epithelial cells of the intestine and are critical to the proper anaerobic function of the gut (74, 75). SCFAs also have important effects on immune cells, both by binding to G protein coupled receptors and Histone Deacetylases, which, in almost all cases, dampen inflammation (76). Thus, it has been posited that these metabolites act as a surrogate signal by which the immune system can measure microbiome health (4). Specifically, SCFAs dampen the inflammatory responses of myeloid cells both locally in the intestine and at peripheral sites such as the lung and bone marrow (77, 78). SCFAs have potent effects on adaptive immune cells as well. In particular, a lack of SCFA production, as is experienced by germ-free mice, leads to a substantial reduction in colonic T_{regs} (79–81). These SCFA-supported colonic T_{regs} are likely important for preventing inflammatory immune responses against innocuous antigens, derived either from diet, host or microbiota (79–84). However, SCFAs do not dampen immune responses indiscriminately. $CD8^+$ cytotoxic T cell responses are supported by SCFA signaling and a diet high in fiber was shown to reduce pathology and increase viral clearance in a mouse model of influenza infection (78, 85). SCFAs can also affect B cell responses. In support of the hypothesis that SCFAs drive host microbiota homeostasis, acetate production in the small intestine increases retinoic acid production by dendritic cells and thus can support class switch recombination to IgA (86). The direct effects of butyrate and propionate are more controversial, with different groups showing either augmentation or suppression of systemic antibody production which may be explained by differences in microbiome composition and experimental approach (87, 88).

In concert with the anti-inflammatory effects of fiber and SCFAs, both animal models and clinical studies generally support the notion that a diet high in fiber is protective against chronic inflammatory disease (76). For instance, a recent clinical study showed that a defined high fiber diet could improve outcomes of type 2 diabetic patients via shifts in the microbiota, as measured by hemoglobin A1C levels (89). Similar, though perhaps less significant effects have been seen in other studies (90, 91). The mechanism by which dietary

fiber is producing these positive effects is unknown and potentially quite complex given their pleiotropic effects on immune activation, metabolism and the microbiome.

Plant-based ligands for the Aryl Hydrocarbon Receptor (Ahr) activate IL-22 production in the intestine

Ahr is a transcription factor expressed in a variety of immune cells and in particular in the lymphocytes found at barrier surfaces. Ahr was initially studied for its response to toxins such as dioxin (92), but it is also activated by indole compounds, derived from the digestion of vegetables from the *Brassicaceae* family (cauliflower, broccoli, cabbage etc.) (93). One of the potent effects of Ahr activation is the production of IL-22 from innate lymphocytes at the intestinal surface (94). Ahr activation is necessary for IL-22 production from Innate Lymphoid cell type 3 (ILC3s) and Intraepithelial γδ T cells at the intestinal barrier (93–95). IL-22 signaling is important for keeping bacteria out of the base of the intestinal crypt via the induction of anti-microbial peptides, thereby protecting the Lgr5+ CBC stem cells and maintaining the regenerative capacity of the intestine in the face of genotoxic/inflammatory stress (96–98).

Thus, via multiple mechanisms the immune system is regulated by the proper digestion of plant products in the diet by the microbiota. Conversely, it is clear that the Western diet, which is low in plant products and high in fat and sugar, is contributing to dysbiosis of the gut microbiome and increased intestinal and systemic inflammation, contributing to substantial increases in chronic inflammatory diseases (Figure 1).

Undernutrition, malnutrition and immunity

In contrast to the diseases of overnutrition of HICs, many people in low- and middle-income countries. (LMICs) are subject to malnutrition and undernutrition. Despite recent laudable reductions in incidence, undernutrition and malnutrition continue to be a significant global public health concern and contribute to ~45% of mortality in children under five years old living in LMICs (99). Though they often coincide and thus the terms are used interchangeably, for the purposes of this review we will define undernutrition as insufficient caloric intake and malnutrition as insufficient quantities of specific nutrients and vitamins. Here we will first address how specific deficiencies in micronutrients affect immunity followed by a discussion of how under and malnutrition shape the immune response more generally.

Micronutrient deficiencies subvert immunity

Micronutrient (vitamins and mineral) deficits, can lead to immune dysfunction. For instance, Vitamin A deficiency can lead to immune dysfunction and increased susceptibility to infection (100). Vitamin A is absorbed from fruits and vegetables in the diet by the intestine and then enzymatically converted to retinoic acid (RA), which is a critical signal for multiple immune processes. During embryogenesis, RA supports the development of lymphoid tissue (101). Critically RA supports the differentiation of ILC3s, of which a sub-type, lymphoid tissue inducer cells, are important for the production of lymph nodes (102, 103). RA

production is modulated by the microbiome, specifically *Clostridia spp.,* which downregulates the expression of enzymes necessary for the production of RA, thereby curbing ILC3s and downstream anti-microbial peptide production (104). $CD103^+$ intestinal dendritic cells also require RA and the transcription factor it activates, RARα, for their development from precursors (105). Beyond development, RA is also critical for the activation of mucosal adaptive immune responses. Conversion of RA by $CD103^+$ DCs trafficking from the intestinal mucosa to the gut-draining lymph nodes induces homing markers, such as $\alpha_4\beta_7$ and CCR9, for gut homing on activated T cells and B cells (106, 107). RA also influences humoral immunity as RA produced by follicular dendritic cells in Peyer's patches induce B cell proliferation and the generation of IgA^+ B cells (108). The role of RA on $CD4^+$ T cell differentiation is more complex. A complete lack of RA signals and RARα activation leads to a substantial failure of signal transduction downstream of the T cell receptor, leading to deficits in T cell responses to infection (109). However, as RA production from $CD103^+$ DCs increases, it skews differentiation of $CD4^+$ T cells towards T_{regs}, contributing to the immune tolerance to innocuous food and microbiota-derived antigens(110–113). Thus, vitamin A deficiency represents a critical issue for the mucosal immune response, as it cannot adequately respond to infection and also lacks the ability to regulate responses to the microbiota, perhaps explaining why vitamin A deficiency is associated with increased incidence and severity of infection.

Zinc is a trace element that is essential for immunity and lack of adequate dietary zinc is common in sub-Saharan Africa and South Asia where it is associated with increased mortality (114). Even mild zinc deficiency is sufficient to induce an imbalance between Th1 cell and Th2 cell functions, as well as impair NK cell function (115). In contrast, zinc supplementation promotes survival and regulates inflammation. The zinc transporter, SLC39A8 (ZIP8), inhibits pro-inflammatory responses via zinc-mediated down-modulation of IKK activity (116), and reduces inflammation during sepsis (117).

Iron deficiency is the most common micronutrient deficiency in the world, affecting more than 25% people globally. Since iron is required for monocyte to macrophage differentiation and for macrophages to successfully ward off intracellular bacteria by the NADPH mediated oxidative burst, it is critical for innate immune responses to bacteria (118). Iron deficiency is also associated with lower CD4/CD8 T cell counts and defects in IgG mediated humoral immunity (119, 120). However, for both zinc and iron, the advantages imparted by oral supplementation are complex, as the microbiota, in particular the more pathogenic members, compete for and sequester iron (121). Additionally, high amounts of iron in the blood make the host prone to lethal bacteremia, which is in part, why iron is tightly regulated by the body (122). Therefore, attempts to restore levels of these metals must be undertaken carefully, particularly in LMICs where enteric bacterial infection is often endemic.

Undernutrition, the microbiome and childhood development

The intestinal microbiome has not only evolved with its host but also adapts in concert with the development of the host. Infants are first colonized with facultative anaerobes (*Enterobacteriaceae*), then *Bifidobacteria* and finally as children transition to solid food, *Clostridia* and *Bacteroides,* that assist in fiber digestion (123–125). During the first 1000

days of life these sequential changes in the composition of the juvenile gut microbiota are essential for healthy development and disturbances in the establishment of the microbiota may have deleterious effects (126). Undernourished children from LMICs exhibit a delayed maturation of the microbiome and maintain *Enterobacteriaceae* for longer periods of time (127). The effects of an 'immature' microbiome extend well beyond childhood as transfer of the microbiota from undernourished infants into germ-free mice leads to stunted growth, clearly indicating that the microbiome can contribute to development during early years of life (128).

The consequences of undernourishment are not limited to hunger, growth defects and delayed development of the microbiome. As discussed above, immune cells have specific requirements for food-derived metabolites and the development of the immune system is affected by metabolite deficiencies. Protein-energy malnutrition (PEM) affects the development of the immune system by decreasing hematopoiesis (129) and inducing thymic atrophy and thymocyte apoptosis, leading to an impairment in peripheral T cells (130). PEM can also affect T cell activation, as DCs from PEM mice are less competent for antigen presentation and eliciting T cell activation (131). Accordingly, children with undernutrition/malnutrition are at an increased risk of death due to infectious diseases such as influenza, diarrhea, pneumonia and malaria (132, 133). The effects of undernourishment can extend long after caloric intake is restored as altered nutritional and environmental conditions during early life can program cells to behave differently to the same stimuli later (134). For example, undernutrition in during development predisposes individuals to immune-related chronic inflammatory disorders such as type 2 diabetes, obesity and cardiovascular disease (135). Even intermittent fasting can have substantial effects on the distribution and function of both memory T cells and circulating inflammatory monocytes (136, 137). However the effects of more prolonged caloric restriction on long-lived tissue resident immunity is less well understood and may be critical to explaining the long-term pro-inflammatory effects of undernutrition.

Undernutrition and Environmental Enteric Dysfunction

Undernourishment and malnutrition do not occur in a vacuum. In LMICs, scarcity of food is driven by poverty, which goes hand-in-hand with lack of access to clean water and adequate sanitation. Intestinal infections caused by environmental contamination with pathogens can exacerbate the effects of undernutrition/malnutrition as these two conditions can function in a positive feedback loop. As mentioned above, undernourished individuals have a greater susceptibility to enteric pathogens and, in turn chronic inflammation and subsequent metabolic energy loss (138). Perhaps the best example of how malnutrition is both a cause and consequence of enteric dysfunction is the gastrointestinal disease Environmental Enteric Dysfunction (EED) (139). EED is most impactful in children, where it contributes to permanent stunting of both stature and brain development (138, 140). EED is characterized by villous blunting, lymphocytic infiltration, reduced absorptive capacity, and reduced barrier function (141). EED-associated malabsorption significantly exacerbates malnutrition because when diet is restored, nutrient uptake is still impacted, complicating diet-based health initiatives (142). While the etiology of EED is not known, it is possible that malnutrition and chronic inflammation combine to impede effective mucosal immunity,

leading to elongated infectious courses and loss of absorptive capacity in the small intestine (Figure 2). Tragically, reduced mucosal immunity in areas where EED is endemic may also contribute to a reduced efficacy of oral vaccination, further complicating public health efforts to reduce infection and restore impaired pediatric development (143–146).

Conclusion

The diet that humans evolved to eat is hard to define. For humans, culture, customs and technology make observing our 'natural' diet very difficult, but nonetheless it is likely that few if any people eat the diet of our evolutionary ancestors (147). Additionally much of what we eat, is modified by the microbiota and our response to any given diet is shaped by our individualized and malleable microbiomes (148). While the immune system and microbiome are adaptable to the diet, there are limits, and unfortunately, the diet of HICs is testing the boundaries of both systems and contributing to chronic disease on a massive scale. For example, it seems that the immune system has mechanisms to detect whether the microbiota is properly digesting dietary plant products via the measurement of microbiome-derived SCFAs. One potentially unfortunate outcome from this mechanism is that a Westernized diet low in plant products may 'fool' the immune system into thinking that the microbiome is not functioning, leading to unnecessary inflammation. Alternatively, in LMICs the combined effects of malnutrition and undernutrition lead to inhibited development of protective mucosal immunity. As a result, chronic inflammation and malabsorption in LMICs can lead to developmental delays that are difficult to restore and have health effects that extend well past the pediatric developmental period. As we seek to increase wealth and food security in LMICs worldwide it will be important to not repeat our errors in shifting to a hyper-processed, high sugar and low fiber diet which might exchange one set of problems for another.

Finally, though this review has focused on the negative effects of consuming diet that is ill-suited for health, we should not lose sight of the tremendous opportunity we have to augment immunity with deeper knowledge of diet and metabolites. Indeed, there is evidence that anti-microbial immunity can be both aided and inhibited by nutrition levels and macronutrients (149, 150). A deeper understanding of the interacting network that connects diet, the microbiome and the immune system will be important so that we can design diets to better resolve disease.

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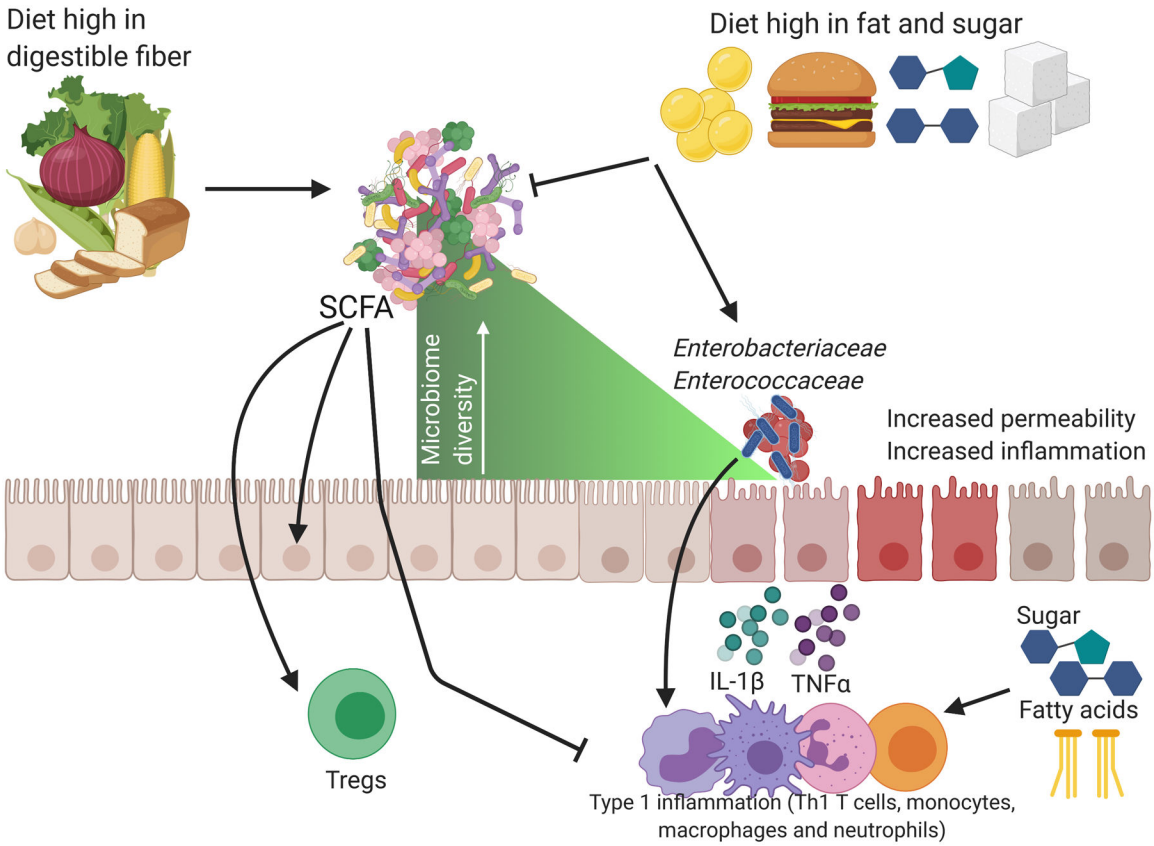

Figure 1. The Westernized diet drives mucosal inflammation

Diets high in fiber support microbiome diversity and the production of short-chain fatty acids (SCFAs) which act as an energy source for the intestinal epithelium, decrease oxygen in the intestinal lumen, increase colonic Tregs and suppress inflammatory immune cells. Conversely diets high in fat and sugar contribute to reduced microbiome diversity and activate inflammatory type 1 immune cells (Th1 T cells, monocytes, macrophages and neutrophils) to produce cytokines such as IL-1β and TNFβ. These immune cells increase inflammation in the intestine which allows for 'blooms' of *Enterobacteriaceae* and *Enterococcaceae*, a loss of microbiome diversity and increased permeability through the opening of tight junctions. Figure created using biorender.com.

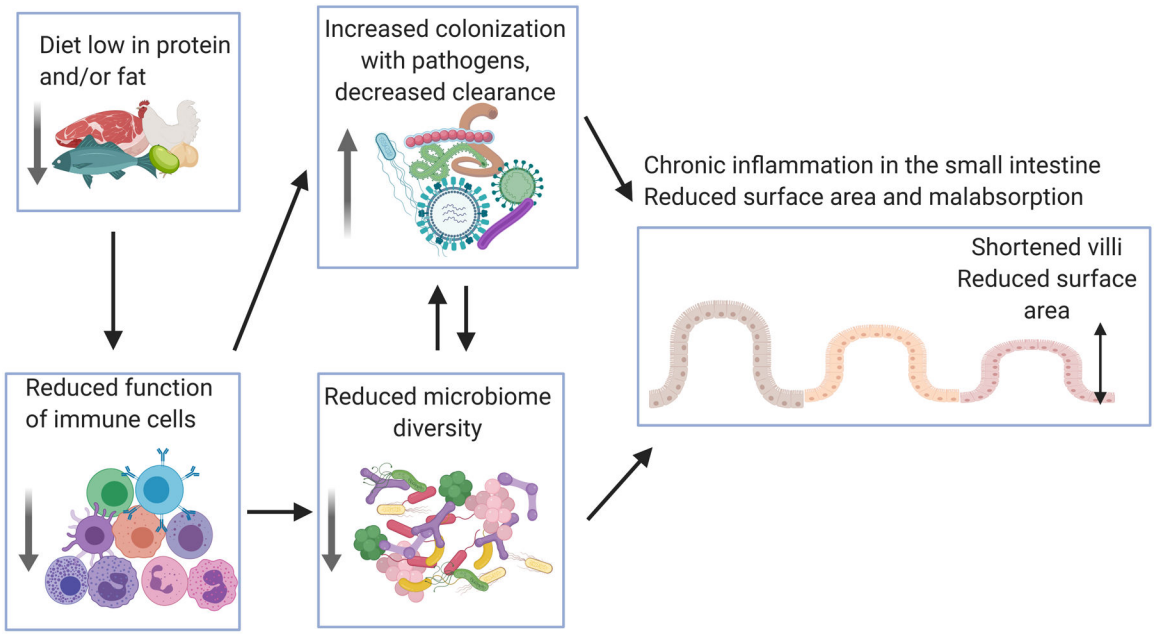

Figure 2. Proposed mechanism for the development of Environmental Enteric Dysfunction

Insufficient protein and fat in the diet can reduce the effectiveness of the immune response, leading to improper control of intestinal infection and a loss of a healthy diverse microbiome. Together malnutrition, chronic infection and microbiome dysbiosis lead to intestinal inflammation, reduced epithelial surface area and malabsorption exacerbating the effects of malnutrition. Figure created using biorender.com.