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Food, Immunity, and the Microbiome

Running title: Diet and microbiome

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Abstract

There is increasing evidence that ingested diet-borne components areinvolved in the pathogenesis of disorders such as inflammatory bowel diseases, atherosclerosis, and type−2−diabetes. Nutrients can have short- and long-term effects in shapingthecompositionof the microbiota. Western diets (enriched in fat, phosphatidylcholine, and L-carnitine)promote inflammation and atherosclerosis through specific fatty acids and degradation products such astrimethylamineN-oxide. Other dietary factors such as carbazoles or tryptophan-enriched proteinshave anti-inflammatory properties—partly via activation of aryl hydrocarbon receptors. The microbiota and its metabolic machinery produce a myriad of metabolites that serveas important messengers between the diet, microbiota, and host. Short-chain fatty acids affect immune responses and epithelial integrity via G-protein coupled receptors and epigenetic mechanisms. By increasing our understanding of interactions between diet, immunity, and the microbiota, we might develop food-based approaches to prevent or treat many diseases. There is now scientific evidence to support theadage “we are what we eat”, and this process begins in early life.

The human gastrointestinal tract harbors more than 100 trillion bacteria that,together with archaea, fungi, and viruses, form the gut microbiota.The cumulative collection of genetic information extractable from the microbiota is astonishingly diverse [1-4]The microbiota colonizes our intestine with increasing densities, reaching up to 10^{11} bacteria/g of luminal content in the colon. Not surprisingly,the human microbiome includesa huge amount of genetic information—100-fold more genes than the human genome. With thisenormous pool of genetic information, the microbiota may influence human life at many levels,far beyond host immunity and metabolic functions.

Studieson the human microbiota have been catalyzed by the availability of feasible diagnostic tools.Most studies have tried to categorize the microbiota according to operational taxonomic units, based sequence analysesof variable regions of bacterial 16S ribosomal DNA genes. More elaborate metagenomic studies aim to generate a map of the entire metagenome, from which functional properties can be inferred. High degrees ofbacterial richness and diversity have been associated with good health.[5]

As we have increased our knowledge about the dynamics of microbial compositions, we have identified numerous variables that can be used to determine the composition of the microbiota. Diet has emerged probably as the most relevant factor. By the time children reach 3 years of age, their microbiota resemble that of adults; studies have shown that besides mode of childbirth, severe illnesses and antibiotic therapy, and particularly the diet, affect colonization patterns of the infant's microbiota in early life.[4, 6, 7]Although the effects of breast- vs. formula-feeding seem to be important, the greatest change in microbial composition occurs with the introduction of solid foods, again pointingtodiet as a central determinant of the microbiota.[8-10]Recent studies have demonstrated that certain diets may

induce short-term reversible and others long-term effects which may persist throughout life.[5, 11]

The microbiota is an important factor in human development and maintenance of the immune response. Diet determines its dynamics and composition, and the triad diet−microbiota−immunity isrequired for human development and health. Recent increases in the incidence of insulin resistance, type 2 diabetes, inflammatory bowel disease (IBD), asthma, and various cancers havebeen linked to changes in diet, immunity, and microbiota.[12]Diets such as a Mediterranean diet have been proposed to provide health benefits.[13]We review the effects of food on the microbiome and thereby on host immunity, discussing pathways that might mediate the beneficial or detrimental effects of various diets and food components.

Diet and the Microbiome

There are different effects of diet on the structure of the intestinal microbiota.[14, 15]There is growing evidence that recent lifestyle changes, most notably high-fat andhigh-sugar Western diets, have had substantial effects on taxonomic, genetic, and metabolic features of our microbiota.[16, 17]These manipulations of the microbiota might contribute to the growing epidemics of chronic diseases such as allergy, IBD, atherosclerosis or obesity and type 2 diabetes.[18]

The first evidence for the effectsof diet on the human GI microbiota came from a study that compared the microbiomes of rural African and Italian children.[19]Analyses of stools from African children showed a significant depletion in *Firmicutes* and *Enterobacteriaceae* (*Shigella* and *Escherichia*), and significantly more short-chain fatty

acids (SCFA), compared to Italian children. The *Bacteroides* enterotype observed in children from Florence correlated with consumption of animal protein, a variety of amino acids, and saturated fats; meat consumption, a feature of the Western diet, was likely to have contributed to this enterotype. The authors concluded that a Western lifestyle, which also includes clean water and refrigerated western foods, resulted in the dominance of *Bacteroides*, whereas an African lifestyle, characterized by home-made vegetarian, high-fiber containing foods,resulted in the dominance of *Prevotella* in the microbiota. However, it is not clear whether these findings are clinically relevant, and the concept of enterotypes has not been fully established.[20]

Zimmer et al compared microbial compositions in fecal samples from vegetarians and vegans with those of similar number of omnivores.[21]They reported that proportions of *Bacteroides spp., Bifidobacterium spp., Escherichia coli*, and *Enterobacteriaceae spp*. Were significantly lower in samples from vegans than from omnivores. Proportions of *E coli biovars, Klebsiella spp., Enterobacter spp., other Enterobacteriaceae, Citrobacter spp*., and *Clostridium spp*. did not differ between the groups. The proportions of these microbes in vegetarians were between those of vegans and omnivores.[21]

Preclinical studies have also shown that different diets affect the microbiota. A high-fat diet (HFD) alters the composition of the intestinal microbiome of mice independently of obesity.[22]Placing mice onHFDs reduced proportions of *Bacteroidetes* and increased those of *Firmicutes* and *Proteobacteria.* Turnbaugh et al transplanted fresh or frozen adult human fecal preparations into germ-free C57BL/6 mice. These so-called humanized mice were stably colonized and had the same levels of bacterial diversity astheir donors, demonstrating the ability of the microbiota to establish a stable ecosystem in a competitive

environment.[16] Switching these mice from a low-fat, plant polysaccharide-based diet to a high-fat, high-sugar-containing (Western) diet altered their microbial structures within 24 hours. The microbiota had changes in predominant metabolic pathways and patterns of gene expression.These findings indicate that changes in the microbiota occur due when certain bacteria are able tobloom in a new environment.[16]

Walker at al also provide evidence that dietary modifications can have rapid effects on the microbiota.[23] The short-term effects of controlled macronutrients were studied in 14 overweight men who received diets either entirely of animal or plant productsfor 10 weeks.Diets high in resistant starch (the plant product diet), an important non-digestible carbohydrate, increased proportions of *Firmicutes* bacteria related to *Ruminococcus bromii* within 3−4 days, although these changes could be rapidly reversed.[23]Short-term dietary interventions are ably to modify the microbiota substantially and rapidly, as shown by David et al.[17] Here, an animal-based diet changed the microbiota in only a single day. The most significant changes observed were within the clusters *Bilophilawadsworthia, Alistipesputredinis*, and *Bacteroides sp*., which are all involved in bile resistance.These findings support the link between dietary saturated milk fats, bile acids, and outgrowth of inflammatory bacteria such as *Bilophila wadsworthia*. They also show that the human gut microbiome can adapt rapidly to herbivorous and carnivorous diets.

Exercise and age can also affect the relationship between microbiota, immunity, and metabolism. Clarke et al studied the effects of exercise and diet on the intestinal microbiota by analyzing fecal samples from male professional rugby players and healthy male controls (non-athletes). Healthy male control groupswith different BMIs (BMI < 25 vs > 28), were included to control for age, diet, and level of physical activity. Exercise increased the

diversity of the microbiota as well as protein consumption, which was significantly higher in athletes compared to controls. There was a positive correlation between protein intake and microbial diversity.[24]

Studies of the microbiota of an elderly population showed that they have greater levels of inter-individual variation than among younger adults.[25]Claesson et al correlated microbial composition with measures of frailty, co-morbidities, inflammation, and nutritional status, indicating the relevance of the GI microbiota to human health.[5] In this study, residents of a long-term facility had increased proportions of *Prevotella, Ruminococcus, Alistipes,* and *Oscillobacter*, compared to non-residents. However, as for many studies comparing the microbiomes of different populations,[26] correlations do not indicate causation—it could be that poor health in this elderly population affected their GI microbiome.

Recent studies have associated the intestinal microbiota with the efficiency in producing energy from diet, which might affect body weight, development of obesity, and related disorders such as non-alcoholic fatty liver disease.[27, 28]Most studies have focused on the effects of dietary excess and obesity-related disorders on the microbiota; [29]this topic is not covered bythis article (for reviews, see[30-32]). Although many studies have provided evidence for the effects of diet on the microbiota, more high-quality studiesare needed to determine how these changes affect human health.There are many confounding factors to analyses of the human microbiota, and it is difficult to determine which differences have clinical relevance. Relationships among food, immunity, and the microbiota are presented in Figure 1.

Mechanisms of Inflammatory Diets

Epidemiologic features of many chronic inflammatory disorders have changed dramatically in the last 30 years. Disorders such as IBD, rheumatoid arthritis, metabolic syndrome, andatherosclerosis, are characterized by continuous low-grade systemic inflammation, of unknown causes. Genetic factors contribute, to various degrees, to some of these diseases, such as IBD.[33]Epidemiologic studies, however, have indicated that environmental factors such as dietalso have important roles. Diet can directly affect inflammatory processes and the immune system, and also through mechanisms involving the microbiota. The definition of gut healthvaries and depends on ethnic, genetic, geographical, and dietary factors that maintain a delicate balance between food, the microbiota, and immunity. Disruption of this homeostasis balance can initiate metabolic and/or inflammatory diseases.[34]

Western diets have long been assumed to promote inflammatory processes. Rural Africans consume substantially more fiber than people in Western countries and rarely develop diseases such as allergy, asthma, colon cancer, or cardiovascular diseases.[35]The Western diet comprises refined grains, alcohol, salt, certain oils, corn-derived fructose, fatty domesticated meats, and other foods, frequently consumed in caloric excess. It can be further characterized by increased consumption of energy-dense, processed foods and reduced consumption of vegetables and fruits.

Several of these constituents, such as fructose, have been associated with development of chronic inflammatory disorders.[36, 37]Excessive consumption of sodium has long been associated with conditions such as arterial hypertension.[38]However, excessive sodium consumption also affects intestinal immunity and inflammation, by induction of interleukin-17 (IL17)-producing T helper cells, although this study did not explore the role of

the microbiota in this process.[39]In contrast, a Mediterranean diet, characterized by high consumption of vegetables, olive oil, and fruits, is associated with lower ratesof cardiovascular diseases and asthma.[13, 40]There is increasing evidence that the composition of the gut microbiota, as affected by various diets,is related to disease development.[41]

Metabolites of dietary phospholipid phospatidylcholine (PC)

There have been recent major advances in our understanding of the relationship amongthe metabolome, the microbiota, and cardiovascular disease.[42] Researchers searched for cardiovascular risk factors using a metabolomic approach, and identified metabolites derived from dietary phospholipid phospatidylcholine (PC): choline, trimethylamine (TMA) N-oxide, and betaine. PC(also called lecithin) is enriched in foods such as red meat, eggs, milk, and certain fish. It is converted towards choline and TMA by enzymes produced the gut flora.[43]TMA is further metabolized by hepatic flavin monoxygenases (FMO) to TMA N-oxide (TMAO).[44]Wang et al demonstrated that generation of TMAO requires themicrobiota, does not occurin germ-free mice, and can be prevented by administration of antibiotics.[42]Then, in a large series of patients, they showed that levels of choline, betaine, and TMAO correlated with all cardiovascular disease phenotypes. This was the first published link among diet, the microbiota, and an inflammatory disease (atherosclerosis can be considered an inflammatory disorder).

In support of this observation, atherosclerosis-prone *ApoE*$^{-/-}$mice develop significantly more atherosclerotic plaques than wild-type mice when placed on diets enriched in PC. In humans, Wang et alobserved an association between circulatingconcentrations of TMAO and hepatic expression of a flavin-containing monooxygenase 3 (FMO3, a transmembrane drug-metabolizing enzyme); there could be

inter-individual differences in TMAO levels based on expression of FMO3.[42]Mouse FMO3 has 10-fold higher specificity than FMO1for TMA, and mice that overexpress FMO3 have increased levels of TMAO.[45]Diets enriched in choline and TMA increased formation of peritoneal macrophage foam cells, macrophage cholesterol content, numbers ofaortic macrophages, and expression of the scavenger receptor CD36 in mice.

Increasing our understanding of the relationship among food, microbiota, and disease could lead to treatments that involve functional foods or pre- or probiotics.[46]Interestingly, certain methanogens, which are variably present in human gut, use only methyl compounds including TMA as substrates. One of these strains, *Methanomassiliicoccus luminyensis10* can deplete TMA by reducing it with H2 for methanogenesis.[47]

In a study of 4007 participants, levels of TMAO correlated with major adverse cardiovascular events—even after adjustment for conventional risk factors.[48] In the same study, levels of TMAO were substantially reduced by administration of broad-spectrum antibiotics tohealthy participants who consumed 2 hard-boiled eggs. A recent study by the same authors associated increased plasma levels of choline and betaine with major adverse cardiac events, although when levels of TMAO were also increased.[49]It is unclear whether these events are associated with genetic factors. A recent study suggested that nutritional factors might have stronger effects than genetic factors in determining TMAO levels.[50]

There are high levels of another TMA, L-carnitine,in red meat. It also processed by the gut microbiota, results in increased levels of TMAO, and is associated with atherosclerosis.[51]A continuous diet high in L-carnitine caused large changes in the coecal microbiota of mice, leading to increased plasma levels of TMAO and atherosclerosis. This

process was microbiota-dependent and in humansincreased plasma levels of L-carnitine correlated with cardiovascular events—again only in association with increased levels of TMAO. Interestingly, vegans and vegetarians produced less TMAO from L-carnitinethanomnivores.[51]Dietary L-carnitine also promoted atherosclerosis in *ApoE*$^{-/-}$ mice.[51]Many studies have therefore associated dietary PC and L-carnitine consumption with the activities of the microbiotaand cardiovascular disease. These types of findings offer exciting new insights as tohow a Western diet might promote cardiovascular and other diseases.

Fat

The Western diet might have other features that contribute to its inflammatory effects— especially high fat content. Fatty acids promote inflammation through diverse mechanisms, including direct actions on immune cells, toll-like receptors (TLRs), and cytokine signaling, as well as by affecting intestinal permeability.[52-54]Even in healthy subjects, a high-fat Western diet was correlated with endotoxemia and may contribute to a state of systemic low-grade inflammation.[55, 56]A HFD induced intestinal inflammation, increasing ileal production of tumor necrosis factorand adiposity, only in conventionally raised specific-pathogen free mice, but not germ-free mice.[57]A HFD, but not a low-fat diet, resulted in severe pulmonary damage and mortality in mice with combined disruption of*Tlr2* and *Tlr4*. This phenotype was transmissible to wild-type mice upon either cohousing or fecal transplantation; antibiotics prevented pulmonary disease, indicating the involvement of certain pathobionts.[58]

The Western diet is commonly enriched in polyunsaturated fatty acids such as n−6. A diet rich in polyunsaturated fatty acids led to intestinal inflammation in older mice,demonstrated by increased influx of neutrophils and macrophages, and was associated dysbiosis, with depletion of *Bacteroidetes* and *Firmicutes*.[59]A 3-week diet of saturated milk-derived fatty acids, but not polyunsaturated fat or a low-fat diet, increased formation of taurin-conjugated bile acids (e.g. taurocholic acid) in *Il10*$^{-/-}$ mice which develop spontaneous colitis.[60]These alterations in bile composition increased the availability of organic sulphur in the intestinal lumen, leading to expansion of the low-abundance, sulphite-reducing pathobiont *Bilophila wadsworthia*in vitro and in vivo. This resulted in increased susceptibility and severity of colitis in IL10-deficient, but not wild-type, mice via an increased T-helper 1 cell response. Interestingly, mono-colonization of germ-free IL10-deficient mice with *B wadsworthia* led to colitis only in association with the consumption of milk fatty acids. These findings support the association of certain dietary fats contained in Western diets with dysbiosis and development of colitis, and indicate the diet-induced expansion of certain pathobionts.[60]

Pups from female mice fed HFDs during gestation and lactation had worse outcomes in various models of immune-mediated inflammation.[61]For example, they had increased colonic inflammatory responses, higher circulating concentrations of endotoxin, and alterations to the microbiome. These findings indicate that an altered microbiota can be inherited.

Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) is overexpressed on the surface of ileal mucosa in patients with Crohn's disease and acts as a receptor for adherent invasive *E coli* (AIEC).Wild-type mice and mice that overexpress

CEACAMs 3, (5), 6, or 7, when placed onHFDs, developed alterations to their intestinal microbial community structures,with increases in mucus-degrading *Ruminococcus torques* and *Bacteroides* and *Prevotella*species.[62]Findings were paralleled by changes in intestinal permeability and goblet cell number and activation of different immune pathways, allowing AIEC to adhere. Therefore, diet cannot only affect the microbiota but also changes its behavior toward a disease promoting directionparticularly in genetically susceptible hosts.

Overall, Western diets have been shown to affect immunity, promote inflammation, and alter the microbiota and metabolomevia different pathways, with major health implications (Table 1, Figure 2).

Protective Interactions Among Diet, Immunity, and the Microbiota

Diets enriched in vegetables and fruits seem to contribute to GIhomeostasis and have anti-inflammatory effects. Aryl hydrocarbon receptor (AhR), a transcription factor expressed byimmune cells, epithelial cells, and some tumor cells, is an important receptor for certain dietary components.There are multiple exogenous and endogenous AhR ligands—some come from foods such as broccoli, others include phytochemicals, natural chemicals,and bacterial metabolites. Ligand binding activates the AhR, causing its translocation into the nucleus, where it dimerizes with the AhR nuclear translocator. This heterodimer regulates many genes that control immunity and inflammation, such as *IL22*.

Two studies demonstrated how dietary-derived AhR ligands affect local immunity and the microbiota.[63, 64] Specific components of certain vegetables of the family Brassicaceae (for example, broccoli or cabbage) are physiologic ligands of the AhR. Li et al showed that AhR signaling helps maintain intraepithelial lymphocytes, and that AhR-

deficiency increased epithelial vulnerability and immune activation in mice. AhR-deficient mice had alterations to the composition of their microbiota, and decreased intestinal production of granzymes A and B, C-type lectins, and matrix metalloproteinase 7, accompanied by a 4-fold increase in the proportion of *Bacteroidetes*. Interestingly, absence of AhR ligands increased severity of colitis in mice; when these mice were placed on diets enriched in AhR ligands, observed alterations were partly reversed.

Kiss et al demonstrated that activation of AhR by dietary ligands is required for post-natal expansion of certain innate lymphoid cells and the development of intestinal lymphoid follicles.[64]Mice deficient in AhR had an impaired immune response and were highly susceptible to infection with *Citrobacter rodentium*. AhR ligands increased numbers of IL22-producing RORγt^{+} intestinal lymphoid cells. These cells help coordinate intestinal epithelial innate immune functions such as the production of anti-microbial peptides and mucus and maintenance of epithelial integrity. Numerous studies have shown that AhR is required for production of IL22, supporting the importance of this relationship.[65]The studies of Li et al and Kiss et al provide evidence that some sort ofdietary pattern recognition receptors mightexist that link diet with intestinal immunity and the microbiota.

AhR expression is decreased in intestinal tissue of patients with IBD, and activation of AhR signaling by specific agonists reduces colitis.[66]The pathway between AhR ligands and IL22 may be of major interest beyond the field of intestinal immunity. Administration of IL22 reduced metabolic defects and restored mucosal immunity tomice on HFDs, as well as in leptinreceptor-deficient (*db/db*) mice.[67]Commensal bacteria such as *Clostridia* have the potential to protect against food allergen sensitization, by inducing production of IL22.[68] So, dietary factors that activate the AhR have the capacity to affect expression of cytokines

(particularly IL22), synthesis of mucins, production of antimicrobial peptides, and consequently shape the composition of the intestinal microbial community (see Figure 3).

AhR binding ofspecific ligands such as 6-formylindolo(3,2-b) carbazole increases natural killer cell activation,including production of interferon-γand cytolytic activity.[69]Administration of AhR ligands to miceincreased the ability of natural killer cells to control growth of a murine lymphoma cell line (RMA-S cells) and RMA-S-induced tumor formation. Another fascinating aspect of AhR is that some of its ligands are bacterial metabolites.[70] 1,4-dihydroxy-2-naphthoic acid, a precursor tovitamin K2 produced from *Proprionibacterium freudenreichii*and isolated from Swiss-type cheese, activated AhR in vitro and in mice,increasing synthesis of antimicrobial peptides,altering gut microbiota and reducing dextran sulfate sodium-induced colitis. Bacterial pigments, namely phenazines (*Pseudomonas aeruginosa)* and naphthoquinone phthiocol (*Mycobacterium tuberculosis)*, are also directactivators of AhR that control anti-bacterial responses.[71]The AhR is therefore unique in that it is not only a dietary pattern recognition receptor, but also as a pathogen-associated molecular pattern receptor.

The essential amino acid tryptophan is another nutrient that might have anti-inflammatory activities. As found in various vegetables and fish, tryptophan is metabolized by the microbiota, e.g. *Lactobacilli,* to indole-3-aldehyde, another AhR agonist.[72]Switching the diet from sugar to tryptophan as major energy source resulted in expansion of *Lactobacilli* that produce the AhR ligandindole-3-aldehyde. This interaction was accompanied by induction of IL22, which affected the microbiota, providing resistance to colonization by *Candida albicans* and protecting the mucosa against inflammation.

Beside the well-established function of angiotensin-converting enzyme 2 (ACE2) in the renin-angiotensin-system (RAS), ACE2 also regulates intestinal amino acid homeostasis and expression of antimicrobial peptides, affecting the gut microbiome. ACE2-dependent changes in epithelial immunity and the gut microbial communities might depend on dietary tryptophan.[73]Tryptophan might exert anti-inflammatory effects via additional pathways such, as after conversion to kynurenine by indoleamine 2,3-dioxygenase (IDO). Both kynurenine and IDO have immunomodulatory functions that include promotion of regulatory T cells and regulation of immune tolerance.[74]

Not unexpectedly, the tryptophan metabolite kynurenineisanothertryptophan-derived ligand of the AhR. Kynurenine is produced by cancer cells and suppresses anti-tumor immune responses.[75]Tryptophan metabolites such as kynurenic acid and niacin also interact with certain G-protein coupled receptors (GPCRs). Beside carbazoles or indole-3-aldehyde, several other plant products, such as flavonoids and polyphenols, also bind the AhR—although with lower affinity.[76, 77] The AhR might therefore be considered as to be a major anti-inflammatory factor that integrates dietary (dietary pattern recognition receptors), microbial, metabolic, and endogenoussignals to alter the composition of the microbiome and elicitprotective immune reactions (Table 1 and Figure 3).

Short-chain Fatty Acids(SFCAs)

One mechanism by which the gut microbiota promote GI homeostasis is likely to involve production of the SCFAs acetate, butyrate, and propionate. These molecules serve as messengers that link dietary fiber to the commensal microbiota and the host. Although there is little evidence for how certain commensals contribute to production of various

metabolites, including SCFAs, diet substantially affects fecal SCFA content.Contingent on a fiber-rich diet, African children have much higher fecal concentrations of SCFAs than European adolescents.[19]Dietary fibers come from the indigestible part of plant foods and contain either insoluble fiber, such as cellulose or lignin, or soluble fiber, such as galacto- or fructo-oligosaccharides. Only soluble fibers are digested by microbiota-derived enzymes into large quantities. Notably, SCFAs provide approximately 5%−10% of total energy to healthy people. SCFAs diffuse passively and distribute systemically, are recovered via mono-carboxylic-acid transporters. However, they might mostly act as signaling molecules by binding to various GPCRs, such as GPR41 (free fatty acid receptor 3, FFAR3) and GPR43 (FFAR2), or GPR109A.[78, 79] GPCRs are found in many different cell types, including gut epithelial cells, adipocytes, and immune cells such as macrophages or dendritic cells.

SCFAs, Nicotinic Acid, GPCRs, and the Intestinal Immune System

SFCAs, along with other metabolites produced in the intestine, help maintain gut homeostasis and epithelial integrity by processes that might include mucus production, secretion of immunoglobulin A, and tissue repair. The acetate-producing commensal *Bacteroides thetaiotaomicron* induces goblet cell proliferation and mucus production.[80]Similar functions have been shown for other protective commensals, such as *Faecalibacterium prausnitzii*. An intact mucus layer is required for intestinal function; its disruption is likely to initiate intestinal disorders such as ulcerative colitis, as well as extra-intestinal diseases.

SCFAs also havemany anti-inflammatory activities, such as suppression of inflammatory cytokines and chemokines,[81]and reduce production of adhesion molecules,

probably by pathways that lead to inactivation of NFκB.[82] Furthermore, SCFAs may directly interfere with inflammasomes and cytokines such as IL18 or IL22, which have important roles in maintaining epithelial integrity.[83] Depletion of acetate-producing *Bifidobacteria* increased susceptibility to enteropathogenic infections and promoted excessive intestinal inflammation in mice.[10]

GPCRs can sense metabolites to activate signaling pathways, and research into their roles in GI homeostasis and intestinal immunity is moving rapidly.[84]They frequently signal via arrestinβ2[85], and GPR43, GPR109A (HCAR2), and GPR120 have anti-inflammatoryeffects. Mice deficient in GPR43 have exacerbated inflammatory reactions in several organs including the intestine,[86] an effect probably mediated by lack of acetate.GPR120 binds Ω-3 fatty acids to protect against inflammation and has metabolically beneficial effects.[85]

Ω-3 fatty acids are key components of healthy diets such as the Mediterranean diet and suppress inflammation in humans.[87] It remains to be established if and how Ω-3 fatty acids affect the microbiota.Activation of GPR109A, areceptor for butyrate and nicotinic acid (niacin), a vitamin, and a degradation product of tryptophan, can prevent colonic inflammation and tumorigenesis.[88]Activation of GPR109A resulted in increased expression of anti-inflammatory molecules in macrophages and dendritic cells, induced development of regulatory T cells,and stabilized the gut barrier by upregulating IL18.[88]Therefore, GRP109A seems to interact with bacteria-derived metabolites to prevent or reduce inflammation. Findings from studies ofnicotinic acid are exciting, as it blocks production of inflammatory cytokines, activation of macrophages,[89] and atherosclerosis in mice and humans.[90]

SCFAs and Systemic Immunity

Butyrate induces differentiation of colonic regulatory T cells and prevents development ofcolitis in mice following administration of$CD4^+CD45RB^{hi}$cells.Interestingly, there is a correlation between butyrate content in the gut and numbers of regulatory T cells.[91]Butyrate increased acetylation ofhistone H3 at the promoter of the gene encoding the forkhead transcription factor FOXP3, providing some interesting clues for potential mechanisms. In addition, butyrate and propionate each facilitate development of regulatory T cells outside the thymus; this activity involved their ability to inhibit histone deacetylases (HDAC), an anti-inflammatory effect.

Acetate does not induce development of regulatory Tcells or inhibit HDAC.[92]These findings support those from a study showing that SCFAs control the developmentof colonic regulatory T cellsin a GPR43-dependent manner.[93]Butyrate might regulate intestinal macrophage function by preventing production of inflammatory cytokines, also in an HDAC-dependent manner.[94]By these mechanisms, SCFAs could help maintain tolerance to the intestinal microbiota and reduce the responsiveness of lamina propria mononuclear cells. Induction of regulatory T cells might be one mechanism by whichSCFAs promote tolerance to the microbiota. Mice fed high-fiber dietsundergo alterations to the intestinal microbiota and are then protected from allergic airway inflammation.[95]The SCFA propionate regulates allergic inflammation, bone marrow hematopoiesis, dendritic cell and macrophage functions, via GPCRs—in the case of the high-fiber diet, viaGPR41.

So,SCFAs are not only an important energy source, but also act as signaling molecules, particularlyin the intestine, where they maintain energy balance and epithelial

integrity. GPCRs are activated in response to nutrients beyond SCFAs, such as tryptophan or tryptophan metabolites such as nicotinic acid, Ω-3 fatty acids, and kynurenic acid (see Figure 3). Nonetheless, the picture is far from complete, as certain GPCRs such as GPR91 have inflammatory activityupon binding to succinate.[96]

Under-nutrition, Immunity, and Alterations to the Microbiota

Just as obesity is associated with changes to the microbiota,[32]so is malnutrition.Severe acute malnutrition is a life-threatening form of under-nutrition that occurs primarily in third world countries. Kwashiorkor is an aggressive form of severe acute malnutrition characterized by generalized edema, skin rash, and anorexia; it is a consequence of deficiencies in nutrient intake,along with unknown environmental factors.[97]Recent studies have suggested that an immature gut microbiome contributes to development of kwashiorkor as in children with this disease the microbiome failed to mature over time and was characterized by a reduced overall gene content.[98]Ready-to-use therapeutic food (RUTF), a homogenous mixture of lipid-rich and water-soluble food components, has been used to treat kwashiorkor.RUTF not only reduces symptoms of kwashiorkor but also has significant effects on the gut microbiota.

Kwashiorkor-like features can be induced in gnotobiotic mice by transplantation of frozen stool samples from children with kwashiorkor and then placing the mice on asterilized typical Malawian diet. Mice that developed kwashiorkor-like symptoms had higher numbers of *Bilophila wadsworthia*and *Clostriduum innocuum* than mice fed a Malawian diet that did not develop kwashiorkor-like symptoms. These findings are of interest because *Bwadsworthii* has been identified as potential pathobiont in other studies.[60]

The findings have also been supported by studies of children inBangladesh. In these children,severe acute malnutrition was also associated with an immaturity of the microbiata.[99] Importantly, nutritional interventions produced partial clinical improvement and only partially ameliorated microbiota immaturity. An immature microbiota was also observed in children with less-severe malnutrition and correlated with anthropometric parameters. In a study of the effects of adjunct antibiotic therapy in children with kwashiorkor,[100] the combination of RUFT and antibiotics was superior to that of RUTF and placebo in improving recovery and reducing mortality. Despite various explanations for this outcome (e.g. the immunocompromised state of kwashiorkor children), the findings indicate that the intestinal microbiota make important contributes to certain forms of malnutrition.

So, a balanced dietthat continuously includes diverse nutrients, such as SCFAs and AhR ligands, might be a prerequisite for a potent immune response, a healthy microbiota, and intact barrier function. Little is understood about how food, the immune system, and the intestinal microbiota interact, especially under conditions of under-nutrition. One consequence of prolonged under-nutrition appears to be inflammatory disease, which could develop because the immature microbiota lacks the ability to sense and respond to metabolites such as SCFAs or nicotinic acid, nutrients such as AhR ligands, and tryptophan or retinoic acids. Microbial responses to factors such as bile acids could also be impaired in the immature microbiota, leading to expansion of pathobionts and inflammation.Similar changes in the microbiome might be associated with other diseases characterized by cachexia and malnutrition.

Conclusions

There is a fascinating relationship among food, immunity, and the microbiota. Many dietary components affect these interactions.We do not know how dietary modification of commensals affects the core microbiome, orhow this produces functional consequences. We know that bacterial metabolites such as SCFAs, metabolites generated from food by bacteria (TMAO), and dietary components alone affect the functions of many human systems and tissues.

Many commensals and their metabolites are required to obtain nutrients from food and maintain gut health and homeostasis. These are likely to have evolved as we adapted to new dietary and microbial signals, resulting in a complex mutualistic network between human cells and microbes. This network is a challenge to study, due to technical limitations.Nonetheless, the field of microbiota research is growing rapidly.

Studies ofI BD have suggested that analysis of stool samples might not be adequate to study the intestinal microbiome—rectum biopsy samples seem to bemore appropriate.[101]This could also hold true for many other diseases in which currently the microbiome is investigated. Furthermore, as we associate changes in the microbiome with features of diseases, it is not clear which causes the other.In studies of obesity or malnutrition, it is not clear whether associated changes in the microbiota occurred before, during, or as a result of these disorders.

Interventional studies have established that dietary factors have strong effects on the microbiota. However, it will be important to optimize clinical studies to gain deeper mechanistic insights.Such studies could lead to development of functional foods, with beneficial and even therapeuticeffects on the microbiota and immune system. Foods might one day be used in clinical medicine to prevent and treat diseases. The effects of food on the microbiota and immune system isone of the most exciting areas of science—we now

know that microbiota-derived and dietary factors operate together to determine gut health and beyond. You are what you eat is finally supported by scientific evidence.

Table 1: Effects of various diets on microbiota and immunity

	Foods (Food Components)	Microbiota-dependent	Involved pathways	Effect on Immunity
INFLAMMATORY	red meat, eggs, milk (contain phosphatidylcholine, L-carnitine)	+ [1]	TMA TMAO	atherosclerosis ↑ (pro-inflammatory cytokines, forward cholesterol transport)
	high fat diet	+ [1]	intestinal permeability ↑ TLRs	endotoxemia intestinal cytokine expression ↑ intestinal and systemic inflammation↑
	milk-derived fat	+ [2]	expansion of pathobionts (e.g. *Bilophilawadsworthia*)	pro-inflammatory cytokines ↑ Th1-driven inflammation ↑
	salt	?	p38 / MAPK pathway	Th17-driven inflammation ↑

	Foods (Food Components)	Microbiota-dependent	Involved pathways	Effect on Immunity
ANTI-INFLAMMATORY	cruciferous vegetables (carbazoles)	+ [2]	AhR ligands	IL-22 ↑, maintenance of intraepithelial lymphocytes and innate lymphoid cells
	vegetables, fish (tryptophan)	+ [2]	AhR ligands [3] GPCRs [4]	IL-22 ↑, mucosal protection from inflammation
	soluble fiber (complex carbohydrates)	+ Generation of SCFA	GPCRs (Gpr41, Gpr43, Gpr109a)	mucus production ↑ IgA production ↑ pro-inflammatory cytokines ↓ Tregs↑
	mediterrenian diet (enriched in ω-3 fatty acids)	?	Gpr120	pro-inflammatory cytokines ↓

[1] *eithershown in germfreemiceor after prolongedantibiotictherapy*
[2] *dietresults in an alteredmicrobiota*
[3] *tryptophanmetabolizedbymicrobiota (e.g. lactobacilli) toindole-3 aldehydeandkynurenine (bothAhRligands)*
[4] *tryptophanmetaboliteskynurenicacidandniacinbindto GPCRs*

Abbravations

AhR ..... arylhydrocarbonreceptor
GPCRs ..... G-protein coupledreceptors
MAPK ..... mitogen-activatedproteinkinase
SCFA..... shortchainfattyacids
Th ..... T helpercell
TLRs..... Toll like receptors
TMA..... Trimethylamine
TMAO..... Trimethylamine N-Oxide
Tregs ..... regulatory T cells

Figure Legends

Figure 1. Network of Food, Immunity, and the Microbiota

Foods, mainly plant-, fruit-, and animal-derived carbohydrates and proteins and fats, rapidly affect the composition and metabolic capacities of our commensal microbiota (green arrow). From the perspective of the microbiota, altered environmental conditions place selective pressure on various species, leading to competition for the most fit to survive and replicate. Microbes produce signals that manipulate the host's eating behavior, generating cravings or dysphoria for certain nutrients (dashed blue arrow). The microbiota signals either through microbiota-immanent molecules, such as TLR ligands or inflammasomes or NOD activators, or through products derived from its enzymatic machinery such as SCFAs or TMA (black arrow). From the perspective of the host, thefood supply is scarce and linked with geographical, seasonal, and ethnical parameters. Evolution has produced a highly optimized mutualistic system in which the maximum capacity of energy is extracted from a given amount of food while intestinal homeostasis is maintained. Consequently, animals have evolved mechanisms to modify the microbiota for their own benefit, such as via the mucus barrier andAMPs. Many of the involved mechanisms are produced by the intestinal mucosal immune system (red arrow). It is important to mention that the intestinal immune system can maintain a state of local and systemic unresponsiveness towards orally administered food and microbial antigens. Finally, certain food-derived signals are able to directly engage with host receptors such as the aryl hydrocarbon receptor (green dashed line).

Abbreviations: AMPs, anti-microbial peptides; NOD, nucleotide oligomerization domain; SCFAs, short-chain fatty acids; TLR, toll-like receptor; TMA, trimethylamine

Figure 2. Inflammatory Mechanisms of Food Components

(A) Certain dietary components candirectly activate inflammatory pathways. Free fatty acids (FFA) induce lysosomal instability, leading to release of cathepsin B and activation of NFkB. Palmitic acid activates IL1β and IL18 through a pathway involving TLR2 and the NALP3

inflammasome. Palmitic acid also increases intestinal permeability, resulting in endotoxemia in the portal and systemic circulation. Sodium chloride enhances differentiation of IL17-producing CD4+ T cells (T-helper 17 cells) through a pathway involving p38 MAPK, NFAT5, and SGK1.

(B) Other dietary components induce inflammation indirectly, after modification by the commensal microflora. Ingested PC or L-carnitine is converted to TMA by bacterial enzymes. TMA is further processed by hepatic flavin monooxygenases to TMAO, which promotes atherosclerosis and activates macrophages.

(C) Certain diets alter the intestinal microbiota to one that promotes inflammation. In genetically susceptible animals (those with defects in inflammasome function or animalsthat overexpress CEACAMs), these alterations to the microbiota can promote initiation or aggravation of intestinal inflammation, via various mechanisms. Milk-derived saturated fats promote taurin-conjugation of bile acids—important sourcesof organic sulfur, supporting the development of sulphite-reducing pathobionts such as *Bilophila wadsworthia*. These can promote inflammation.

Abbreviations: CEACAM, carcinoembryonic antigen-related cell adhesion molecule; FMO, flavin monooxygenases; IL, interleukin; NALP3, NOD-like receptor family, pyrin domain containing 3; NFAT5, nuclear factor of activated T-cells 5; NF-κB, nuclear factor kappa B; SGK1, serine/threonine-protein kinase 1; Th, T helper cell

Figure 3. Anti-inflammatory Effects of Food Components

(A) The aryl hydrocarbon receptor (AhR) provides an important link between the intestinal immune system and food-derived ligands. AhR activating ligands include indolo[3,2-b] carbazole or 6-formylindolo[3,2-b]carbazole, which come from cruciferous vegetables, flavonoids, and polyphenols, (B) as well as bacterial-derived molecules, such as phenazins and naphtoquinon phthiocol, and microbial metabolic products such as 1,4-dihydroxy-2-naphthoic acid. AhR ligands activate chaperone-bound AhRs, which dimerize with the AhR nuclear translocator (Arnt) to regulate gene expression. AhR signaling is required for the generation and maintenance of intestinal immune cells including specialized intraepithelial

lymphocytes and CD4-RORγδ+ innate lymphoid cells. AhR-induced production of IL22 could have immunomodulatory and metabolic effects. (C) Tryptophan is another important anti-inflammatory molecule in food. It's uptake is regulated by intestinal ACE2 (independent of its functions in the renin-angiotensin system). Tryptophan is converted to indole-3-aldehyde (another ligand of AhR) by bacterial enzymes. Tryptophan is required for generation of nicotinamide (also vitamin B3 or niacin). Nicotinamide can activate the mTOR pathway, includig p70S6 kinase and anti-microbial peptides, to produce anti-inflammatory effects. Within the cell, tryptophan is converted to kynurenine (another AhR ligand) by indoleamine 2,3-dioxygenase (IDO). (D) Soluble dietary fiber (complex carbohydrates, CCH) is cleaved into SCFAs by bacterial glycoside hydrolases. The SCFAs acetate, proprionate, and butyrate have anti-inflammatory effects. SCFAs bind GPCRs such as GPR41, GPR43, or GPR109A, which activate the transcription factor arrestin-β2. Interestingly, GPCRs can be activated by other ligands such as niacin (GPR109A) and Ω-3fattyacids (GPR120). Butyrate is a natural inhibitor of the histone deacetylases 6 and 9, and could promote development of peripheral regulatory T cells through epigenetic mechanisms.

Abbreviations: AA, amino acids; ACE2, angiotensin-converting enzyme; FOXP3, forkhead box P3; GPCRs, G-protein coupled receptors; HA/Nam, nicotinamide; HDAC, histone deacetylase; IE, intraepithelial; ILCs, intestinal lymphoid cells; mTOR, mechanistic target of Rapamycin; Treg, regulatory T cells

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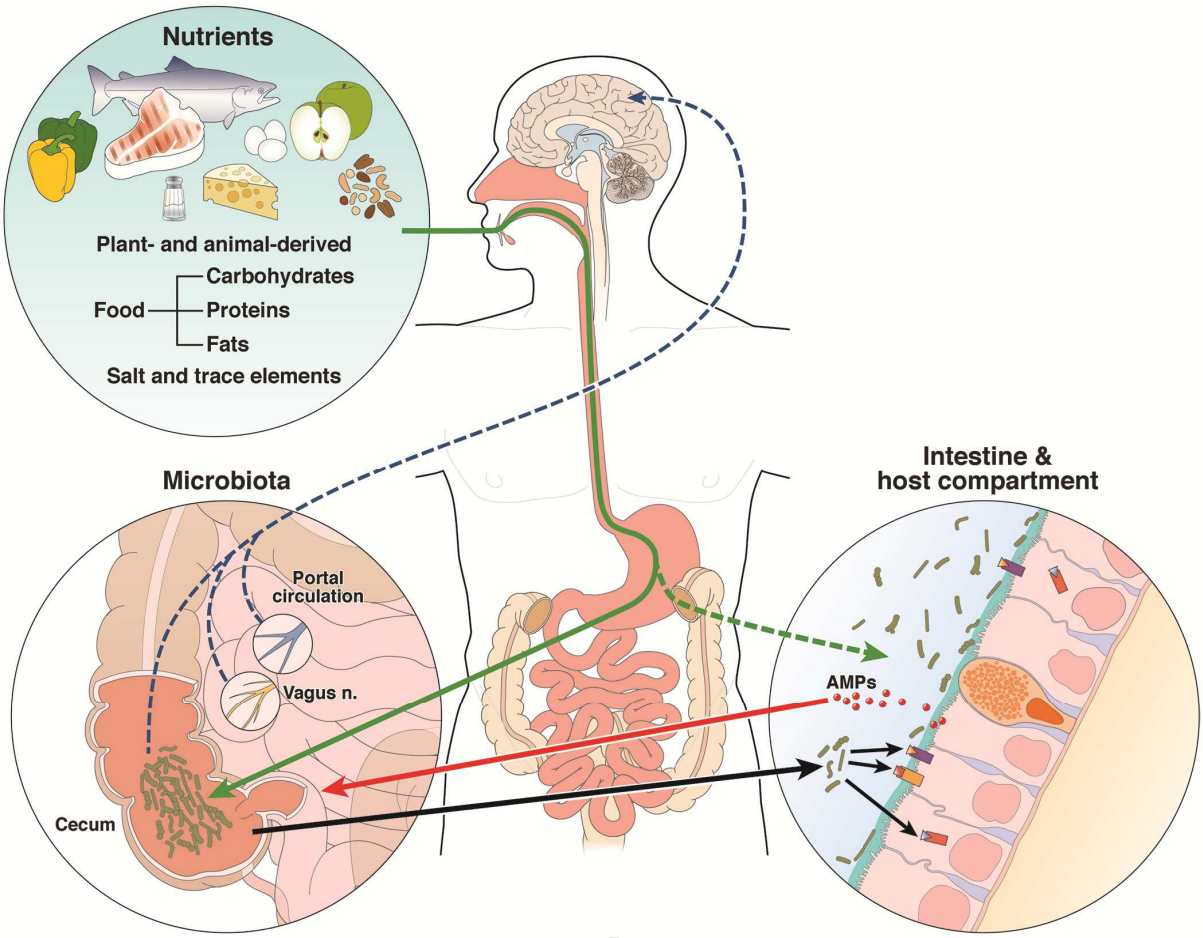
Nutrients
Plant- and animal-derived
Food
Carbohydrates
Proteins
Fats
Salt and trace elements
Microbiota
Portal circulation
Vagus n.
Cecum
Intestine & host compartment
AMPs