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Food Processing, Dysbiosis, Gastrointestinal Inflammatory Diseases, and Antiangiogenic Functional Foods or Beverages

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food processing, dysbiosis, eubiosis, mast cells, hypoxia, angiogenesis, kynurenine pathway, transglutaminase 2, inflammatory bowel disease, celiac disease

Abstract

Foods and beverages provide nutrients and alter the gut microbiota, resulting in eubiosis or dysbiosis. Chronic consumption of a diet that is high in saturated or *trans* fats, meat proteins, reducing sugars, and salt and low in fiber induces dysbiosis. Dysbiosis, loss of redox homeostasis, mast cells, hypoxia, angiogenesis, the kynurenine pathway, transglutaminase 2, and/or the Janus kinase pathway are implicated in the pathogenesis and development of inflammatory bowel disease, celiac disease, and gastrointestinal malignancy. This review discusses the effects of oxidative, carbonyl, or glycative stress–inducing dietary ingredients or food processing–derived compounds on gut microbiota and gastrointestinal epithelial and mast cells as well as on the development of associated angiogenic diseases, including key signaling pathways. The preventive or therapeutic potential and the biochemical pathways of antiangiogenic or proangiogenic foods or beverages are also described. The outcomes of the interactions between disease pathways and components of food are critical for the design of foods and beverages for healthy lives.

1. INTRODUCTION

During digestion and absorption, the human gastrointestinal tract extracts nutrients from ingested foods or beverages for basic nutrition and health. Some foods and beverages are rich in anti-inflammatory bioactive compounds, and others are rich in proinflammatory compounds. Regular ingestion of foods rich in anti-inflammatory bioactive compounds can favor dominance of beneficial gut microbiota that break down food components into metabolites that help maintain homeostasis. Conversely, regular consumption of a diet rich in proinflammatory compounds favors dysbiosis and dominance of gut microbiota that release disease-promoting metabolites, which can result in adverse health consequences for the host. The main risk factors for dysbiosis are diet; age; metabolic syndrome; stress; antibiotics; parenteral and enteral nutrition; irritable bowel syndrome; chronic inflammatory conditions such as ulcerative colitis and Crohn's disease; bacterial pathogens such as exogenous lipopolysaccharide, rotavirus, and *Clostridium difficile*; autism, stroke, and brain injury.

Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, *Fusobacterium*, and Saccharibacteria are major phyla of the oral and esophageal microbiota (Lv et al. 2019). Gram-positive bacteria, including *Streptococcus* species, are closely associated with the normal esophageal microbiota, whereas gram-negative and anaerobic bacteria species dominate in the abnormal esophageal microbiota (Lv et al. 2019). Human saliva is a rich source of oral epithelial cells that express Toll-like receptors (TLRs) (Swaminathan et al. 2013). Chronic or daily exposure of tooth surfaces to fermentable carbohydrates, especially sucrose and fructose, from energy-dense foods (**Table 1**) is a risk factor for caries and periodontitis. Reducing sugars increase oxidative stress and production of AGEs (advanced glycation end-products), which may also trigger a hyperinflammatory and angiogenic response in leukocytes.

Caries and periodontal diseases are risk factors for rheumatoid arthritis, obesity, and diabetes. Periodontal pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* activate

Table 1 Classification of foods according to processing degree

Fresh and minimally processed foods	Ingredients	Processed foods	Additives
Fresh fruits	Preservatives	Ready-to-eat, ready-to-drink, and ready-to-heat foods such as breakfast cereals	Carboxymethyl cellulose
Vegetables	Sweeteners		Carrageenan
Meat	Flavors and spices		Trehalose
Eggs	Flavor enhancers	Infant formula	Sucralose
Grains	Fat replacers	Baby foods	Saccharin
Legumes	Nutrients	Yogurts	Aspartame
Chilled, frozen, or dried fruits	Emulsifiers	Cheese	Neotame
Fruit juices without added sugar	Stabilizers and thickeners	Kombucha	Acesulfame K
	Binders	Pickles	Splenda potassium
	Texturizers	Sauerkraut	Polysorbate 80
	pH control agents and acidulants	Miso	Titanium dioxide
		Sausages	Glycerol monolaureate
	Leavening agents	Instant soups	Sucrose esters
	Anticaking agents	Snacks	Maltodextrin
	Humectants	Smoked and salted meats	Color additives
	Firming agents	Carbonated drinks	Nitrite
	Dough strengtheners	Fried foods	Nitrate
	Enzyme		Fat substitutes

Table based on data from the US Food and Drug Administration (see FDA 2010, 2019).

epithelial TLRs. TLRs promote cell proliferation, invasiveness, and angiogenesis in a variety of cancers. TLR2, TLR3, TLR4, TLR5, TLR7, and TLR9 are expressed in oral cancer cells and appear to reflect certain prognostic markers of oral tumors (Ikehata et al. 2018). The binding of bacterial lipopolysaccharide (LPS) to TLRs activates signal transduction pathways involving the Toll/interleukin (IL)-1 receptor (TIR) domain with coupling to adaptor molecules such as myeloid differentiation factor 88 (MyD88) or the TIR domain–containing adaptor inducing interferon (IFN)-β-related adaptor molecule (TRAM). These changes can lead to activation of the MyD88-dependent pathway (used by TLRs except TLR3) or the MyD88-independent TRAM pathway (Rich et al. 2014). LPS can induce a TLR4 inflammatory response through the MyD88-dependent pathway, which in turn promotes the expression of proinflammatory transcription factors such as nuclear factor κB (NF-κB). NF-κB induces inflammatory mediators, including cytokines and chemokines, that exacerbate the progression of chronic inflammatory disease. Activation of the MyD88-independent pathway produces type 1 IFN (Rich et al. 2014). Activated TLRs initiate signaling pathways that cause the release of cytokines and chemokines, which recruit immune cells that, in turn, induce cytokine production. The production of angiogenic mediators and growth factors potentially influences tumor progression. Prolonged exposure to energy-dense foods and beverages causes oxidative stress, leading to chronic inflammation. This inflammation provides a microenvironment for cytokines and inflammatory mediators that can initiate cancers and their progression, invasion, and metastasis. Oral cancer accounts for 10% of head and neck tumors, with a low 5-year survival rate (Rich et al. 2014).

Salivary proteins and proline-rich proteins precipitate tannins or plant polyphenols, including the epigallocatechin gallate (Bennick 2002). The interaction between salivary proteins and tannins occurs at the region of phenolic antioxidant properties, and the antioxidant capacity of the tannins may be impaired (Soares et al. 2019).

Emulsifiers, including surfactants and amphiphilic biopolymers, have contact with salivary proteins and teeth, but there is little information about the outcome of their interactions. Interactions between emulsifiers and the gut microbiota are discussed in Section 3 below.

After mastication, food is transported through the esophagus to the stomach. The interaction between foods, beverages, or additives and the esophagus is short; however, chronic consumption of an unhealthy diet can affect the health and physiology of the esophagus. Chronic consumption of beverages or foods such as alcohol, high-fat foods, fried foods, smoked foods, pickled foods, coffee, chocolate, beer, and wine, or spicy foods can induce gastroesophageal reflux symptoms during the first hour after intake and predispose individuals to esophageal cancer (Katada et al. 2016, Surdea-Blaga et al. 2019). The 5-year survival rate for esophageal cancer is less than 20% (Lv et al. 2019).

The esophagus has far fewer microbes than the colon. Dysbiosis in the esophagus leads to the accumulation of LPS, which binds to microorganism-associated molecular patterns such as TLRs and NOD (nucleotide oligomerization domain)-like receptors. The resultant complexes induce the release of proinflammatory cytokines and chemokines such as IL-17 and IL-23 through the LPS/TLR4/NF-κB pathway (Lv et al. 2019).

The gastric microbiome is composed mostly of *Helicobacter pylori*; however, *Lactobacillus* species are also present. *H. pylori* alters the gastric microbiota and reduces diversity (Hunt & Yaghoobi 2017). There is a strong positive correlation between *H. pylori* and periodontal disease, multiple sclerosis, asthma, nonalcoholic fatty-liver disease, insulin resistance, and type 2 diabetes and a negative correlation between *H. pylori* and asthma or celiac disease (CD) (Bravo et al. 2018).

In the gastric mucosa and fecal microbiota of male C57BL/6 mice fed a high-fat diet, sequencing of the 16S rRNA gene identified dysbiosis with a reduction of beneficial bacteria such as *Bifidobacterium* species and *Akkermansia muciniphila* (He et al. 2018). A high-fat diet induces

dysbiosis, and an increase in LPS levels initiates the TLR/MyD88/NF-κB inflammatory pathway and angiogenesis-dependent inflammation.

A meta-analysis of the effect of red, processed, or white meat consumption on the risk of gastric cancer showed that consumption of red meat increased risk by 47% and that consumption of salty, processed red meat increased risk by 57% (Kim et al. 2019). White meat was associated with a 20%-decreased risk of gastric cancer (Kim et al. 2019). Salted, smoked, and pickled foods such as kimchi or miso or preserved foods rich in preformed *N*-nitroso compounds are associated with an increased risk of stomach cancer (Nan et al. 2005).

Chronic alcohol consumption reduces the *H. pylori* population in the stomach. Abusive ethanol consumption induces acute gastric ulcer and H_2O_2-induced gastric epithelial cell damage through the MAPK/NF-κB signaling pathway; increases the levels of proinflammatory cytokines including tumor necrosis factor α (TNF-α), IL-1β, IL-6, and IL-18; and increases myeloperoxidase activity in gastric tissue (C. Zhang et al. 2019).

Dysbiosis in the stomach is dynamic and correlates with an increase in the abundance of lactic acid bacteria, including *Streptococcus*, *Lactobacillus*, *Bifidobacterium*, and *Lactococcus*. These bacteria supply lactate, a fuel source for cancer cells that promotes inflammation, angiogenesis, and cancer metastasis that has been observed in gastric cancer patients (Vinasco et al. 2019).

3. FOODS, BEVERAGES, AND INTESTINAL DYSBIOSIS

In the small intestine, proteases (e.g., trypsin, chymotrypsin), lipases, or amylases break down proteins, fats, or carbohydrates, respectively, into smaller components from which nutrients are absorbed and enter the circulation. The intestinal barrier is multilayered and composed of integral membrane proteins, junctional proteins, and cell cytoskeleton structure. The integral membrane proteins include the occludin and claudin families. The junctional complex proteins include zonula occludens (ZO)-1, ZO-2, and ZO-3. Zonulin modulates intercellular tight junctions that are involved in the trafficking of macromolecules. Adherens junctions strengthen the intestinal barrier.

The movement of solutes and lipophilic products from the intestinal bolus across the intestinal epithelium is regulated either between epithelial cells via the tight junction region or across the apical membrane of epithelial cells (**Figure 1**). Large hydrophobic molecules cross the epithelium by passive permeability. Lipophilic and small hydrophilic molecules cross the membrane via the transcellular route. Small hydrophilic molecules cross the membrane through the transcellular route via aqueous pores.

Food or beverage ingredients can increase or decrease intestinal permeability. Alcohol, glucose, sucrose, and fructose from energy-dense Western foods; high-fat, high-meat-protein, high-reducing-sugar foods; high-fructose-corn-syrup–sweetened carbonated drinks; savory and sweet snacks; and foods containing artificial sweeteners, additives, and low levels of plant-based proteins and fiber increase intestinal membrane permeability (Bischoff et al. 2014). This greater permeability can be detrimental if large amounts of antinutrients or toxins are increasingly being absorbed.

Within the healthy colon, Bacteroidaceae (genus: *Bacteroides*) and Prevotellaceae (genus: *Prevotella*) are prevalent. Along with Lachnospiraceae (genus: *Blautia*), Ruminococcaceae (species *Faecalibacterium prausnitzii*), Peptostreptococcaceae (genus: *Romboutsia*), and Eubacteriaceae (species: *Eubacterium cylindroides*), these bacteria produce glycoside hydrolases that break down complex plant polysaccharides to monosaccharides and short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. Enzymes from eubiotic microflora hydrolyze complex polyphenols such as ellagitannins into bioavailable phenolic acids or other low-molecular-weight compounds such as urolithins and low-molecular-weight phenolic acids, including benzoic, hippuric, and vanillic

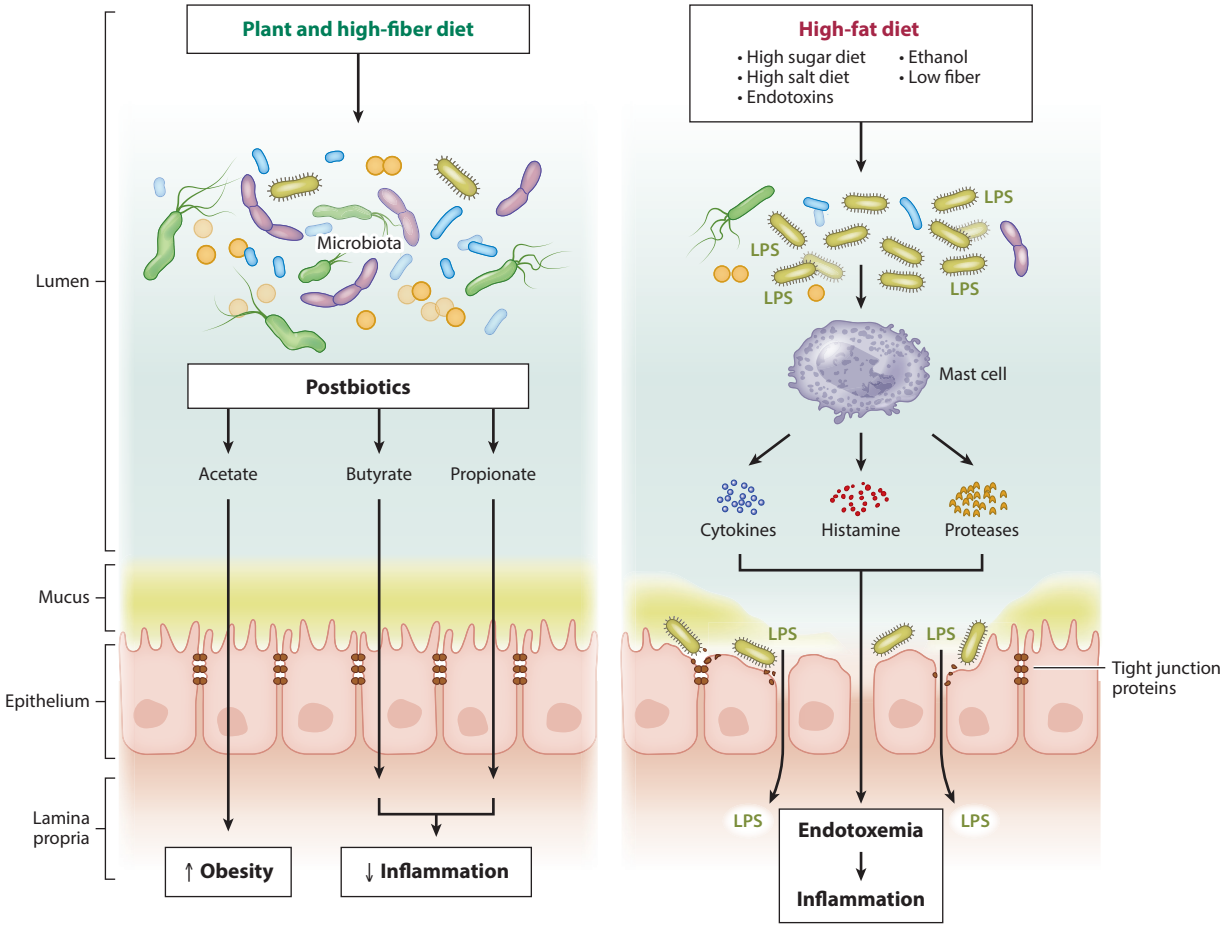

Figure 1

Interactions between dietary components and gut microbiota. The gut microbiota metabolizes prebiotics into short-chain fatty acids or other acids as postbiotics, such as acetate, propionate, or butyrate. Acetate induces hunger and can favor the development of obesity. Propionate and butyrate are anti-inflammatory and can lead to homeostasis. Regular consumption of high-fat, high-sugar, endotoxin-rich, low-fiber foods, and/or ethanol leads to dysbiosis, from which lipopolysaccharides (LPSs) can translocate into the circulation to cause low-level endotoxemia and low-grade inflammation. Figure adapted from Yang et al. (2017) and Boeckxstaens (2015).

acid metabotypes, some of which have potent anti-inflammatory activity (Tomás-Barberán et al. 2017).

Diet is a major environmental risk factor for dysbiosis (**Table 2**). Consumption of a Western diet consistently disrupts the gut microbiota homeostasis; overactivates intestinal mucosal mast cells (MCs) (David et al. 2014), a process described more fully in Section 5; and correlates with dysbiosis development, progression to low-grade inflammation in the gut, and development of metabolic disorders (Chiba et al. 2019).

Dysbiosis is strongly associated with a weakened immune system through the induction of indoleamine 2,3-dioxygenase 1 (IDO1) (Laurans et al. 2018). Dysbiosis is also associated with irritable bowel syndrome, inflammatory bowel disease (IBD), CD, food allergies, type 1 and type 2 diabetes, insulin resistance, cancer, cardiovascular diseases, and neurological disorders (Yap &

Table 2 Mechanisms of inhibition of gastrointestinal angiogenesis by functional foods

Inhibitor (food source)	Food sources	OS, NS	Dysbiosis	MC activation	Hypoxia angiogenesis	Tight junction	TG2	JAK	KYN	Reference(s)
PHENOLICS										
Epigallocatechin gallate	Tea	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Ushiroda et al. 2019
Curcumin	Turmeric	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yang et al. 2012, Mafra et al. 2019
Resveratrol	Grape	Yes	Yes	Yes	Yes	No	No	No	No	Zhao et al. 2018, Yang et al. 2019
Quercetin	Onion, apple, raspberry	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Kempuraj et al. 2006, Zhao et al. 2017
Proanthocyanidins	Cocoa, cherries, berries, beans	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Strat et al. 2016
Hydroxytyrosol	Olive oil	Yes	No	Yes	No	No	No	No	No	Persia et al. 2014
SAPONINS AND TERPENES										
Betulinic acid	Birch tree, olive oil	Yes	No	Yes	Yes	No	No	Yes	No	Wu et al. 2019
Glycyrrhizin	Licorice	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Di Paola et al. 2009, Qiu et al. 2019
Ginsenosides	Ginseng	Yes	Yes	Yes	No	Yes	No	No	No	Sun et al. 2007
Perillyl alcohol	Citrus	Yes	Yes	Yes	Yes	No	No	No	No	Ma et al. 2016
Farnesol	Lemongrass, peach, tomato, chamomile	Yes	No	No	No	Yes	No	Yes	No	Fang et al. 2019
Tangeretin or nobiletin	Citrus	Yes	No	Yes	Yes	Yes	No	Yes	No	Hagenlocher et al. 2017
CARBOHYDRATES										
Inulin	Artichoke, chicory, garlic, onion	Yes	Yes	Yes	Yes	Yes	No	No	No	Pasqualetti et al. 2014, Chen et al. 2017
Oligosaccharides	Cereals, banana, asparagus, oats	No	No	No	No	No	No	No	No	NA
Polydextrose	Synthetic	Yes	Yes	Yes	Yes	No	No	No	No	Witaicenis et al. 2010
Fucoidan	Brown seaweed, wakame	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Rui et al. 2017, Li et al. 2018
Glucosamine/ chondroitin sulfate	Shell of shellfish/shark cartilage	Yes	No	Yes	Yes	Yes	No	No	No	Bak et al. 2014, Navarro et al. 2015
β-Glucan	Barley, yeast, mushrooms	Yes	Yes	Yes	Yes	Yes	No	No	No	Agostini et al. 2015, Botschuijver et al. 2017, Chen et al. 2019
VITAMINS										
Vitamin B_3	Whole grains, poultry, fish)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Bekier et al. 1974
Vitamin B_6	Pork, poultry, whole grains, oats, eggs, soy	Yes	Yes	Yes	Yes	No	No	No	Yes	Vitellio et al. 2019

(*Continued*)

Table 2 (*Continued*)

Inhibitor (food source)	Food sources	OS, NS	Dysbiosis	MC activation	Hypoxia angiogenesis	Tight junction	TG2	JAK	KYN	Reference(s)
Vitamin B_{12}	Fish, meat, poultry, eggs, milk	Yes	No	No	Yes	No	No	No	No	van de Lagemaat et al. 2019
Vitamin C	Citrus, kiwi, berries	Yes	No	Yes	Yes	No	Yes	No	No	Blaszczak et al. 2019
Vitamin D	Milk, fatty fish, egg yolks, liver	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Wang et al. 2019
Vitamin E	Vegetable oils, nuts, seeds	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Mazière et al. 2001, Li et al. 2017
Vitamin K_2	Natto, hard cheeses, liver, egg yolks	Yes	Yes	Yes	Yes	No	Yes	No	No	Ponziani et al. 2017
POLYPEPTIDES AND AMINO ACIDS										
Bowman–Birk inhibitor	Legumes	Yes	No	Yes	Yes	Yes	No	No	No	Ware et al. 1997, Losso 2008
Kunitz trypsin inhibitor	Legumes	Yes	No	Yes	Yes	No	No	No	No	Shakiba et al. 2007
Lactoferrin/ lactoferricin	Milk	Yes	No	No	Yes	No	No	No	No	Gonzalez de Mejia & Dia 2010
Lunasin	Legumes	Yes	No	Yes	Yes	No	Yes	No	No	Gonzalez de Mejia & Dia 2010
Carnosine	Muscle	Yes	Nov	Yes	Yes	Yes	Yes	No	Yes	Shen et al. 2008, Hipkiss 2009, Iovine et al. 2014
Glycine	Meat, fish, eggs	Yes	No	No	No	Yes	No	No	No	Li et al. 2016
PROBIOTICS, POSTBIOTICS, AND OTHERS										
Probiotics	Yogurt	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Zhu et al. 2018, Cancello et al. 2019
Butyrate/ propionate	Milkfat, cheese, yogurt, butter	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	D'Argenio et al. 1994, Wang et al. 2018
Ω-3 fatty acids	Mackerel, salmon, herring	No	Yes	No	No	No	No	No	No	Y. Zhang et al. 2019
α-Lipoic acid	Red meat, organ meat, broccoli, Brussels sprouts	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Lin et al. 2006, Trivedi & Jena 2013

Abbreviations: JAK, Janus kinase; KYN, kynurenine; MC, mast cell; NS, nitrosative stress; OS, oxidative stress; TG2, transglutaminase 2.

Mariño 2018). A weakened immune system, allergy, diabetes, and cardiovascular diseases are all risk factors for the body's inability to fight the so-called cytokine storm that is a characteristic of the ongoing coronavirus disease 2019 (COVID-19) pandemic (Gheblawi et al. 2020).

Nonstarch carbohydrate polymers with 10 or more monomeric units can resist digestion by enteric enzymes in the upper gastrointestinal tract and are either fermented by the gut microbiota in the large intestine or remain as they are and are excreted. The fermentation of complex dietary fiber generates SCFAs, including butyrate, propionate, and acetate. Butyrate is the preferred energy source for colonocytes and enterocytes, maintains mucosal integrity, inhibits histone deacetylase, suppresses inflammation, and inhibits angiogenesis (Serpa et al. 2010). More than

90% of SCFAs are absorbed in the gut or used by the microbiota. Small amounts of propionate and acetate are found in the peripheral circulation. Excessive acetate can induce obesity (**Figure 1**).

Additives, including emulsifiers, coating and thickening agents, noncaloric sweeteners, and colorants, can induce dysbiosis, colitis, and metabolic syndrome in humans and animals (Chassaing et al. 2017, Laudisi et al. 2019). Trehalose is a GRAS (generally recognized as safe) food additive that resists digestion and absorption in the small intestine. Foods, including pasta, ground beef, and ice cream, can have between 2% and 11.25% trehalose. Several studies have shown that since the approval and introduction of trehalose, in countries where it is consumed, the incidence of pathogenic *Clostridium difficile* and the number of deaths associated with it have significantly increased (Abt 2018, Collins et al. 2018). Trehalose promotes the growth of *C. difficile* in the large intestine and causes debilitating and sometimes fatal colitis.

Carrageenans are widely used in the food industry for their gelling and thickening properties and their ability to stabilize emulsions. Carrageenan-induced colitis and toxicity are associated with a significant decrease in the anti-inflammatory bacterium *A. muciniphila* (Shang et al. 2017).

Titanium dioxide (TiO_2), or food additive E171, enhances and brightens the color of white foods such as dairy products, candy, frosting, and the powder on doughnuts. It is used in more than 900 commonly consumed food products at between 0.7 and 5.9 mg per kilogram of body weight (or more) per day throughout many people's life span (Pinget et al. 2019). TiO_2 induces dysbiosis and the reduction of colonic mucin 2 gene, leading to increased expression of inflammatory cytokines that are markers of IBD.

Food additives (**Table 1**) induce dysbiosis, reduce the mucin layer and production of mucus, increase tight junction permeability, and promote leaky gut and inflammatory LPS translocation to trigger systemic inflammation and obesity (Furuhashi et al. 2020). Maltodextrin is used as a coating to protect products during spray-drying; however, it decreases mucus production and has other deleterious effects on intestinal barrier integrity (Laudisi et al. 2019).

Trimethylamine-*N*-oxide (TMAO) is a dysbiosis-derived metabolite of dietary choline, phosphatidylcholine, or L-carnitine from red meat. TMAO is a major risk factor for coronary artery disease. However, the US Food and Drug Administration has recently concluded that emulsifiers commonly used in the United States, including lecithin, mono- and diglycerides, carboxymethyl cellulose, P80, stearoyl lactylates, sucrose esters, and polyglycerol polyricinoleate, do not raise safety concerns at the current specified level of use (Shah et al. 2017).

The acetate and lactate paradox suggests that despite numerous reports of the potential health benefits of fermented foods for improving lactose malabsorption or eradicating *H. pylori*, there is very limited clinical evidence of these foods' effectiveness in improving dysbiosis and gastrointestinal health and disease (Dimidi et al. 2019). Fermentation products such as acetic acid fuel ulcerative colitis (UC) and obesity. Lactic acid sustains the proliferation of cancer cells, promotes angiogenesis, and directly contributes to various cancers, including gastric and colorectal tumor growth and progression, because high lactate promotes higher expression of hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) under normoxic conditions (Goodwin et al. 2019).

4. HYPOXIA, ANGIOGENESIS, AND GASTROINTESTINAL INFLAMMATORY DISEASES

The lamina propria (**Figure 1**) serves as an important physical barrier preventing unwanted materials and organisms from gaining access to the body. The lamina propria is highly vascularized and juxtaposed with an anaerobic lumen where trillions of metabolically active anaerobic microbes live. This physiological condition has resulted in a steep gradient of oxygen along the healthy

intestinal mucosa between the oxygen-rich lamina propria and the gut lumen; in the lumen of the small and large intestines, partial pressure of oxygen values lower than 10 mm Hg have been recorded (Zheng et al. 2015). This unique condition of transient periods of low oxygen levels has been termed physiologic hypoxia. Hypoxia triggers several signaling processes governed by HIFs, which play an important role in the development of IBD. The stability of oxygen-dependent HIFs (HIF-1α, HIF-2α, or HIF-3α) is determined by the prolyl hydroxylases (PHD1, PHD2, and PHD3) and asparaginyl hydroxylase (FIH) (Epstein et al. 2001). HIF-α subunits are unstable under normoxic conditions, but bacterial LPS can activate HIFs under normoxic conditions (Blouin et al. 2004). LPS is elevated in several IBDs. Reactive oxygen species (ROS) and reduced cellular iron inhibit PHDs under normoxic conditions and activate HIFs (Cash et al. 2007).

Physiologic hypoxia prevents the oxygen-sensing hydroxylases PHD1–3 and FIH from repressing HIFs. As a result, HIF-1α remains active and translocates to the nucleus, where it binds to constitutive HIF-1β (Manresa & Taylor 2017). The HIF-α–HIF-1β dimer then binds to a hypoxia-response element, becomes active, and increases the expression of target genes, including VEGF, erythropoietin, and glycolytic enzymes, involved in helping cells adapt to hypoxia while promoting angiogenesis and angiogenesis-dependent diseases (Semenza 2003).

PHD1 expression is upregulated at both the mRNA and protein expression levels, which are correlated with IL-8 and TNF-α in patients with UC and Crohn's disease (Van Welden et al. 2013). Altered PHD1 leads to increased HIF-1α, which in turn activates NF-κB in intestinal epithelial cells; NF-κB increases the production of TNF-α (Kennel et al. 2018). Inflammation-dependent angiogenesis is a characteristic of IBD wounds and is driven by angiogenic factors, including HIF-1α, VEGF, transforming growth factor β1 (TGF-β1), and IL-8 (Danese et al. 2007). Tissue hypoxia induces inflammation, and hypoxic microenvironments containing high levels of HIF-1α and HIF-2α are found in inflamed intestinal tissues (Eltzschig & Carmeliet 2011). HIF activation is a characteristic of solid tumors, including esophageal, gastric, and intestinal cancers. The activities of HIF-1 depend on the HIF-1α subunit level, which is regulated by oxygen, nitric oxide (NO), ROS, and mechanistic target of rapamycin. Hypoxia signaling, oxygen-sensing hydroxylase, and angiogenesis inhibition are targets for IBD management or treatment (Colgan 2016). Hypoxia causes MC degranulation (Krystel-Whittemore et al. 2015) and activates transglutaminase 2 (TG2) (Penumatsa et al. 2014).

5. FOODS, BEVERAGES, AND GASTROINTESTINAL MAST CELLS

MCs (**Figure 1**) are long-lived granulocytes derived from bone marrow myeloid cell progenitors ($CD34^+$). Growth and survival of MCs are influenced by stem cell factors and cytokines (IL-3, IL-4, IL-9, IL-10, IL-33, CXCL12, TGF-β, nerve growth factor) (Reber et al. 2015). MCs are located at the boundaries between the external environment and the internal tissues and are found in large numbers at mucosal surfaces of the lungs, gastrointestinal tract, and skin; around blood vessels; near nerves; and in dental pulp, glands, smooth muscle cells, and the conjunctiva. In the esophagus, regardless of age, the number of MCs increases from the upper end of the esophagus to the lower end (Aminova & Grigorenko 2015). Degranulating MCs are often seen in upper and lower esophageal tissues from old and senile people (Aminova & Grigorenko 2015). MCs make up 1–5% of mononuclear cells in the lamina propria and submucosa. In the stomach, MCs are confined to the upper fundic and pyloric glands. In healthy intestinal mucosa, MCs regulate barrier function and act on blood flow, peristalsis, and immune function.

MCs are classified according to their protease, tryptase, or chymase content. MC_Ts are tryptase rich and chymase poor; MC_Cs express chymase and little or no tryptase; and MC_{TC}s contain tryptase, chymase, and carboxypeptidase. Human mucosal MCs are MC_Ts, and human submucosal MCs are tryptase and chymase rich (MC_{TC}s). In human small intestine, approximately 98%

of MCs are MC_Ts, and MC_Ts account for approximately 13% of submucosal MCs (Reber et al. 2015). MC_Ts activate protease-activated receptor 2, which degrades tight junction proteins, including occludin, ZO-1, claudin, and mucin 2, ultimately leading to increased intestinal permeability (Jacob et al. 2005).

Physiologically, intestinal MCs regulate tissue homeostasis (epithelial secretion and barrier functions, blood flow, and vascular permeability; smooth muscle functions and peristalsis; recruitment of immune cells; and bacterial phagocytosis) and mediate diseases (diarrhea, impaired epithelial and endothelial barriers, chronic inflammation, pain) (Bischoff 2016). Immune stimuli [immunoglobulin (Ig)E, IgG, free-chain Ig, antigen], interleukins (IL-4, IL-6, IL-9, IL-10), cytokines (TNF-α and IFN-γ), and other molecules (C3a, C5a) can trigger MC activation. Nonimmune stimuli, including neurotransmitters (acetylcholine, dopamine, serotonin, epinephrine, histamine), neuropeptides (substance P, histamine-releasing peptide, bradykinin), hormones (e.g., estradiol), growth factors [VEGF, TGF-β, fibroblast growth factor 2 (FGF-2), platelet-derived endothelial growth factor], biological agents (bacterial challenge, LPS, peptidoglycan, *Mycobacterium*), and physicochemicals (NO, thermal, pH, trauma, hypoxia, free radicals), can also trigger MC activation (Wouters et al. 2016).

Activation of MCs is a normal physiological process that regulates vascular homeostasis, innate and adaptive immune functions, and angiogenesis and mediates detoxification (Bischoff 2016). Overactivation of MCs is associated with several chronic diseases, including allergy, asthma, gastrointestinal disorders, malignancies, and metabolic and cardiovascular disorders. A high-fat diet activates mucosal MCs and increases the release of MC-preformed inflammatory mediators, including proteases and histamine, and newly synthesized inflammatory mediators, including cytokines, chemokines, prostaglandin D2, and leukotrienes. LPS, saturated fats, or *trans*-fatty acids can induce a TLR4 inflammatory response through the MyD88-dependent pathway, which promotes the expression of proinflammatory NF-κB.

MCs are at the intersection between gut microbiota and allergic/nonallergic inflammatory diseases (De Zuani et al. 2018). MC–microbiota interactions can promote or inhibit MC activation. Activated MCs can protect the host by killing bacteria. In one study, bacterial insult–induced degranulation of MCs led to the release of β-hexosaminidase, which inhibited *Listeria monocytogenes* in vitro and protected the host against *Staphylococcus epidermidis* infection in vivo (Campillo-Navarro et al. 2017). In another study, human chymase released by activated MCs was anti-inflammatory and degraded virulent Hsp70, IL-33, and HMGB1 released by *Trichinella spiralis* infection (Roy et al. 2014).

Under pathological conditions in the gastrointestinal tract, activated MCs secrete prestored proteases, peptidases, histamine, cytokines, chemokines, and growth factors that act by initiating and maintaining inflammation in UC (Albert-Bayo et al. 2019). Excessive histamine can lead to food allergies. Secreted proteases include tryptases, chymases, cathepsin G, cathepsins L and S, carboxypeptidase A3, dipeptidyl peptidase I/cathepsin C, and TNF-α, among which tryptases and chymases are almost entirely MC specific (Caughey 2016). MCs link proinflammatory food or beverage ingredients with gastrointestinal inflammatory diseases. High intake of a high-fat diet or fructose-rich beverages induces dysbiosis and LPS-associated endotoxemia, which activate MCs (Hagenlocher et al. 2017). Chronic alcohol use promotes increases in polyp-associated MCs and MC-mediated inflammation that can lead to carcinogenesis (Wimberly et al. 2013). Activated MCs also promote erosion of the colonic mucosal lining and increase gut permeability (Hussain et al. 2019). MCs play a critical role in gastrointestinal angiogenesis through VEGF, FGF-2, placenta-derived growth factor, IL-6, and tryptase and chymase stored in MC granules (Ammendola et al. 2014). Inhibition of MC activation stimulators or downstream effectors such as proteases (tryptase, chymase), histamine, cytokines, chemokines, and growth factors associated with disease pathways

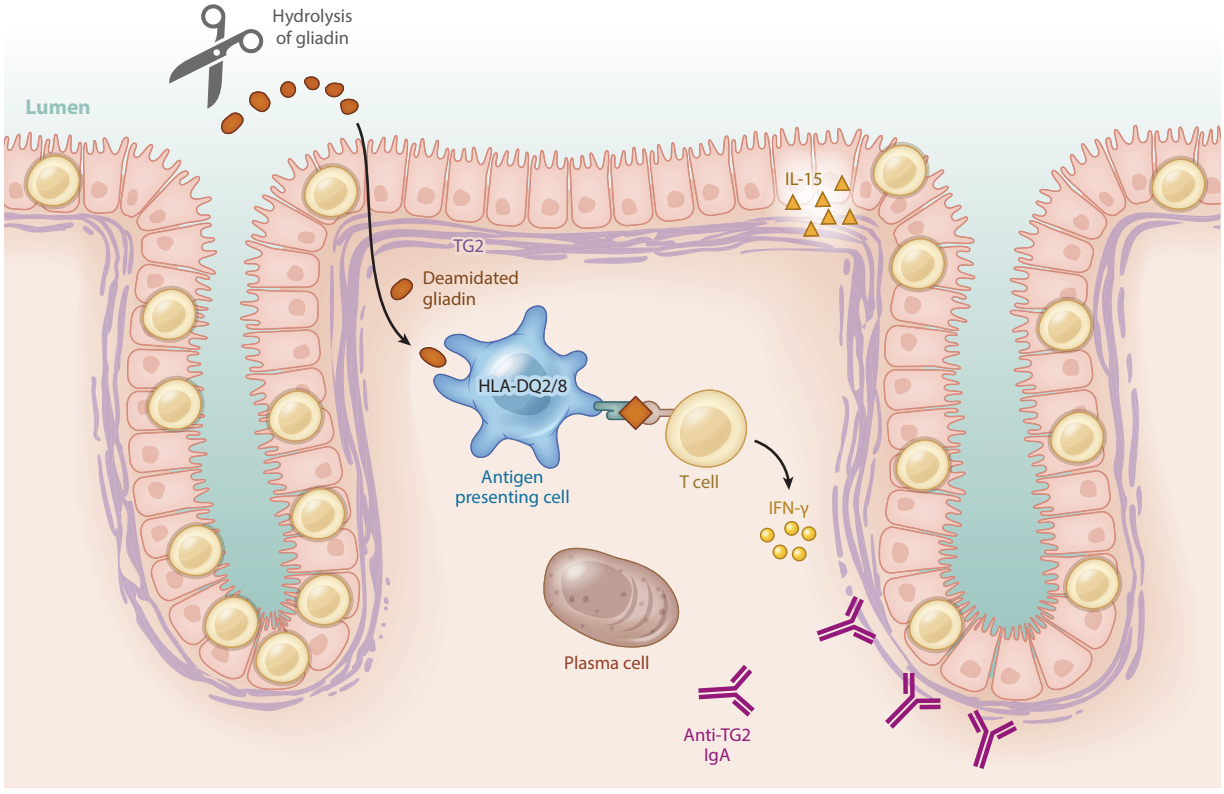

Figure 2

Gliadin-induced celiac disease. Hydrolysis of gliadin in the small intestine generates proangiogenic peptide sequences 31–43 and 57–68, which can trigger celiac disease at any location in the small intestine. Abbreviations: IFN, interferon; Ig, immunoglobulin; IL, interleukin; TG2, transglutaminase 2. Figure adapted with permission from Sollid & Khosla (2011).

represents a new approach to address all the inflammatory and tumor pathological conditions of the digestive tube in which MCs are involved.

6. TRANSGLUTAMINASE 2– AND DIET-INDUCED GASTROINTESTINAL INFLAMMATORY DISEASES

TG2 plays a critical role in the pathogenesis of CD and is associated with the progression of UC, Crohn's disease, and colon cancer (**Figure 2**). CD is an autoimmune disease, a T cell–mediated enteropathy, that occurs in genetically predisposed individuals who, following the ingestion of gluten-rich products, develop inflammatory damage in the small intestine. Individuals who carry the human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 haplotype are more susceptible to CD development than noncarriers. The disease affects 1% of people worldwide. Gliadin from wheat, rye, or barley triggers CD (Sollid & Khosla 2011). Hydrolysis of gliadin in the small intestine generates proangiogenic peptide sequences 31–43 and 57–68 (p31–43 and p57–68), which can trigger CD at any location in the small intestine. p31–43 or p57–68 is responsible for the synergism of the innate and adaptive immunological response observed in CD. The innate immune response to p31–43 or p57–68 is marked by increased production of IFN-γ, which triggers the production of TNF-α and IL-15 (Ludvigsson et al. 2013) and overexpression of NF-κB via a TLR2- and

TLR4-dependent pathway. This process causes the secretion of proinflammatory cytokines such as IP-10/CXCL10 and overexpression of COX-2 in CD (Fernandez-Jimenez et al. 2014). Elevated levels of IL-6, IL-1β, and IL-8 are commonly found in the serum of CD patients (Cinova et al. 2007). Production of these inflammatory biomarkers stems from the action of TG2 and is primarily responsible for the destruction of the intestinal mucosa, causing the major symptoms of CD. In CD, oxidative stress mediates most of the cytotoxic effects induced by gliadin peptides and increases TG2 levels, whereas nitrosative stress contributes to the impairment of tight junctions.

TG2 is calcium dependent and is activated by an increase in intracellular calcium, which occurs when p31–43 or p57–68 presents to intestinal cells. Wheat, rye, or barley gliadin is a preferred substrate for TG2 because it contains many glutamine residues susceptible to deamidation or transamination.

If a gluten-free diet is not implemented early on, CD increases the patient's intestinal permeability and carries the risk of long-term intestinal and extraintestinal inflammatory diseases and conditions, including nonalcoholic fatty-liver disease, arthritis, fatigue, headache, anemia, mouth sores, muscle aches, depression, rashes, neuropathy, short stature, delayed puberty, osteoporosis, infertility, and neurodegeneration (Hoffmanová et al. 2015). These side effects can occur in asymptomatic patients. In the small intestine, gliadin binds to the chemokine receptor CXCR3, expressed on intestinal epithelium followed by the release of zonulin, which leads to an opening in the enterocytes of tight junction proteins as well as to increased paracellular permeability (Sturgeon & Fasano 2016).

CD, UC, Crohn's disease, and juvenile (type 1) diabetes share high TG2 expression and anti-TG2 levels. The association between CD and UC is stronger than that between CD and Crohn's disease (Casella et al. 2010). The association of TG2 with CD and intestinal dysbiosis is very strong, and dysbiosis is not completely restored by a gluten-free diet (Kumar et al. 2017). Individuals with active CD have a prevalence of proinflammatory gram-negative bacteria such as Firmicutes, Proteobacteria, *Staphylococcus*, and *Clostridium* and low levels of anti-inflammatory bacteria such as *Bifidobacterium* and *Lactobacillus* (Verdu et al. 2015). Blood samples from 120 confirmed active CD patients had higher levels of TLR4 mRNA and TLR9 mRNA compared with 120 age- and sex-matched healthy controls, whereas higher levels of TLR4 mRNA and TLR2 mRNA were observed in the duodenal mucosa of CD patients compared with healthy controls (Ghasiyari et al. 2018). These results suggest that dysbiosis through the TLR2/4/MyD88/TRIF/MAPK/NF-κB pathway can be an important trigger in the pathogenesis of CD and, along with genetic HLA haplotypes and environmental factors, can exacerbate the inflammatory response in the small bowel mucosa of CD patients (Palová-Jelínková et al. 2013, Ghasiyari et al. 2018).

TG2 is present in various cancers and cancer cell lines, including the colon cancer microenvironment, and has been associated with tumor development and progression, invasion, and chemoresistance, and with the epithelial-to-mesenchymal transition (Ayinde et al. 2017). Colon cancer TG2 mRNA expression was associated with earlier relapse and worse prognosis in patients with metastatic disease (Miyoshi et al. 2010).

7. THE KYNURENINE PATHWAY, OXIDATIVE STRESS, AND DIET-INDUCED GASTROINTESTINAL INFLAMMATORY DISEASES

Tryptophan is an essential amino acid that is obtained through the diet, with a recommended daily allowance between 250 and 425 mg/day for adults. Tryptophan is metabolized into two pathways, the methoxyindole and kynurenine pathways. Approximately 5% of ingested tryptophan is converted into serotonin and melatonin through the methoxyindole or 5-hydroxytryptamine

pathway. Serotonin deficiency has been associated with a deficiency in melatonin and disturbances in circadian rhythms, mood, and sleep. The remaining 95% of ingested tryptophan is metabolized by IDO1, IDO2, or tryptophan 2,3-dioxygenase (TDO) through the kynurenine pathway. IDO1 can be found in the gut, brain, blood, spleen, kidney, and lung and can be induced by exogenous LPS from contaminated foods or by dysbiosis-induced LPS accumulation. IDO2 can be found in the kidney. TDO can be found in the liver, kidney, or brain.

Under physiological conditions, IDO1 expression occurs at a low level, mostly in the cells of the lamina propria (Ciorba 2013). Inflammatory cytokines, including IFN-γ, IFN-β, TNF-α, IL-1β, IL-2, amyloid peptides, TGF-β, and LPS, can stimulate IDO1 secretion (Ciorba 2013). IDO1 gene and protein levels are elevated in the inflamed intestinal mucosa of IBD patients (Ferdinande et al. 2008). IDO1 mRNA and IDO2 mRNA are expressed in colon cancer and contribute to colon cancer–mediated immunosuppression that results in poor prognosis (Löb et al. 2009).

In pigs, in vivo administration of 100 μg LPS (*E. coli* O111:B4) per kilogram of body mass ($n = 20$) induced increased plasma concentrations of proinflammatory cytokines and tryptophan metabolites, including kynurenine, kynurenic acid, and quinolinic acid, starting 1 h post stimulation and reaching peak levels 6 h post administration (Wirthgen et al. 2014). The kynurenine pathway was activated. IL-10 was also elevated in the plasma after 3 h and was part of the anti-inflammatory immune response. The ratio of kynurenine to tryptophan, a marker of IDO activation, was high. High IDO is indicative of neurological disorders and is a marker of increased mortality in cancer, sepsis, and trauma.

Increased tryptophan metabolites through the kynurenine pathway are associated with increased activity of IBD. An analysis of serum tryptophan in 535 IBD patients showed lower levels in CD patients versus UC patients versus controls (Nikolaus et al. 2017). The levels of mRNA encoding IDO1 in colonic biopsies, serum quinolinic acid, and IL-22 were higher in IBD patients than in controls (Nikolaus et al. 2017).

Kynurenic acid and picolinic acid are neuroprotective but are poorly transported across the blood–brain barrier (Németh et al. 2006). Quinolinic acid crosses the blood–brain barrier; can develop in the central nervous system; is anxiogenic, excitotoxic, and neurotoxic; induces oxidative stress and chronic induction of quinolinic acid inside and outside the gastrointestinal tract and represents a major link among the gut microbiome, allergies, and the brain, including all neurologic disorders (van der Leek et al. 2017, Dehhaghi et al. 2019). Patients with chronic pain ($n = 17{,}834$) were evaluated for common abnormal biomarkers; elevated quinolinic acid was observed in 29% ($n = 5{,}107$) of the participants, and elevated pyroglutamate, a biomarker of glutathione depletion, was observed in 19% ($n = 3{,}314$) (Gunn et al. 2020).

8. THE JANUS KINASE AND GASTROINTESTINAL INFLAMMATORY DISEASES

The Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling pathway is critical in the pathogenesis of IBD and autoimmune CD because many of the inflammatory cytokines associated with the development and progression of these diseases use this pathway for signaling. Cytokine signaling induces phosphorylation of the JAKs (JAK1, JAK2, or JAK3), which autophosphorylate and phosphorylate their cytokine receptors, the STAT proteins (O'Shea & Plenge 2012, Villarino et al. 2015). The latter form homo- or heterodimers, migrate into the nucleus, and activate transcription of inflammatory cytokines. Inhibition of JAKs interferes with several key cytokines, including IL-2, IL-6, IL-12, IL-23, and IFN-γ, that are associated with the pathogenesis of IBD.

9. OXIDATIVE OR CARBONYL STRESS, DYSBIOSIS, MAST CELL ACTIVATION, AND GASTROINFLAMMATORY DISEASES

Beverages rich in fructose or other reducing sugars and processed at high temperatures are sources of α-dicarbonyls, which, in turn, are precursors of AGEs. The levels of α-dicarbonyl methylglyoxal (MGO) in 13 brands of carbonated commercial soft drinks and other beverages were between 700 μg per 100 mL and 11,100 μg per 100 mL (Tan et al. 2008). The highest levels of MGO and glyoxal (GO) in coffee were 716.7 μg per 100 mL and 554.6 μg per 100 mL, respectively, whereas soymilk had 587.5 μg per 100 mL of MGO and 500 μg per 100 mL of GO (Wang et al. 2017). Most herbal drinks, including teas and herbal teas, had less than 80 μg per 100 mL MGO or GO. In juices, the highest level was less than 300 μg per 100 mL for MGO or GO (Wang et al. 2017). Reactive dicarbonyls as well as AGEs induce oxidative and glycative stress (Lin et al. 2016).

Dietary sources of 3-deoxyglucosone include balsamic vinegar (2,622 mg/L), honey (1,641 mg/L), jams/jellies (1,061 mg/kg), candies (1,011 mg/kg), bread (619 mg/kg), fruit juices (410 mg/L), and cookies (385 mg/kg) (Degen et al. 2012). Dietary intake of 3-deoxyglucosone has been estimated to be between 20 and 160 mg/day and MGO has been estimated at between 5 and 20 mg/day (Degen et al. 2012).

Dicarbonyls are precursors of AGEs, which bind to the transmembrane receptor of AGEs (RAGE) on the cell surface of intestinal tract cells and activate NADPH oxidase, which in turn enhance ROS generation (**Figure 3**). RAGE also activates several proinflammatory pathways, including the JAK or Ras pathway (**Figure 3**) (Piperi et al. 2017). The prevalence of metabolic syndrome is very high in Western countries, associated with epigenetics, and highly correlated with dysbiosis. Consumption of AGE-rich foods has been associated with dysbiosis; dietary restriction of AGE-rich foods is associated with a significant reduction in the relative abundance of *Prevotella copri* and *Bifidobacterium animalis* and with an increased relative abundance of *Alistipes indistinctus*, *Clostridium citroniae*, *Clostridium hathewayi*, and *Ruminococcus gauvreauii* (Yacoub et al. 2017).

Chronic consumption of alcohol induces dysbiosis, with an increase in the gram-negative bacteria Actinobacteria and Proteobacteria and a decrease in both Bacteroidetes and Firmicutes (Bull-Otterson et al. 2013). As a result, the intestinal flora release a large number of endotoxins, which disrupt the tight junctions and increase the translocation of LPS and pathogens from the intestinal lumen into the portal blood, elevating LPS levels and triggering significant inflammation and liver injury.

Female Ossabaw swine fed a Western high-fat, high-fructose, high-cholesterol diet developed obesity and severe microbiota dysbiosis, with an abundance of Gammaproteobacteria, including *Desulfovibrio*, Succinivibrionaceae, *Succinivibrio*, Enterobacteriaceae, and Desulfovibrionaceae, as well as of the gram-negative Bacteroidetes family Prevotellaceae (Panasevich et al. 2018). The presence of these bacteria was associated with increased intestinal tight junction permeability through the induction of enterocyte membrane expression and localization of TLR4 and CD14 (Guo et al. 2013).

Regular consumption of *trans*-fatty acids decreases the abundance of beneficial bacteria such as Bacteroidetes, Lachnospiraceae, and Bacteroidales S24–7; induces dysfunction of gut microbiota; and increases obesity in animal models (Ge et al. 2019, Hua et al. 2020). The Western diet is strongly correlated with the onset, rising incidence, and progression of UC in most patients (Ho et al. 2019).

Consumption of high-fructose corn syrup–rich soft drinks has shown a significant association with UC risk. Alcohol consumption has no significant association with UC or CD risk, but alcohol

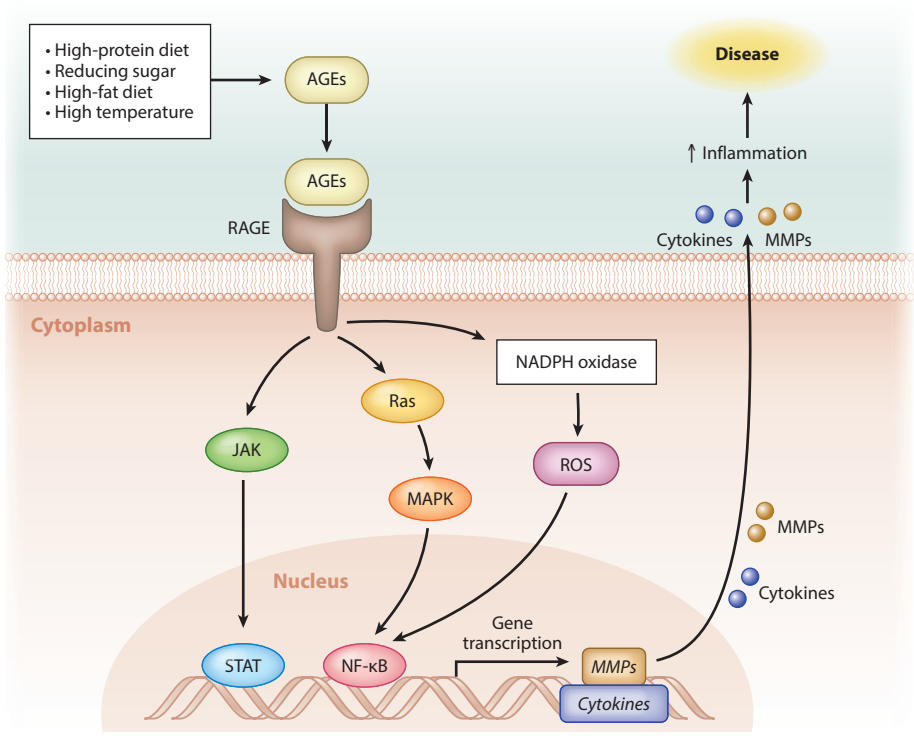

Figure 3

Potential mechanism of inflammation induced by food-derived AGEs. AGEs bind to RAGE, which can activate several pathways, including the ROS/NF-κB, Ras/MAPK/NF-κB, or JAK-STAT pathway. ROS can induce dysbiosis. Abbreviations: AGEs, advanced glycation end-products; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; RAGE, receptor of AGEs; ROS, reactive oxygen species. Figure adapted from Piperi et al. (2017).

consumption by UC patients may worsen the symptoms of the disease. Alcohol reduces folate; damages DNA; induces DNA methylation; and generates ROS, which, in the absence of powerful antioxidants, can activate signaling molecules involved in inflammation, metastasis, angiogenesis, and cancer progression (Na & Lee 2017).

10. THERAPEUTIC APPROACHES TO GASTROINTESTINAL INFLAMMATORY DISEASES

For the past 80 years, pharmacological and/or surgical intervention has been the fundamental approach to the treatment of gastrointestinal inflammatory diseases (Keane et al. 2017). Drugs that stabilize MCs include fludarabine, IFN, and tyrosine kinase inhibitors; however, most of them carry side effects (Ramsay et al. 2010). Most of these drugs irreversibly inhibit TNF-α, IL-12/23 p40, JAKs, or $\alpha_4\beta_7$ (Wong & Cross 2019). These drugs do not focus on ameliorating intestinal microflora composition and sometimes do not prevent long-term complications. Fecal transplantation is also being investigated. Active flares and associated systemic effects are found in approximately 50% of UC patients (Keane et al. 2017). Few therapies target primarily mucosal healing. A nontoxic approach that targets inflammation and mucosal healing would be ideal for the treatment of gastrointestinal inflammatory diseases.

11. ANTIANGIOGENIC FUNCTIONAL FOODS OR BEVERAGES AND GASTROINTESTINAL INFLAMMATORY DISEASES

Whole foods or diets rich in antiangiogenic bioactive compounds present a unique opportunity to develop a cost-effective strategy for the prevention and treatment of gastrointestinal inflammatory diseases because antiangiogenic functional foods or beverages can target and inhibit the different pathways associated with oxidative stress, dysbiosis, hypoxia, MC activation, intestinal inflammation, leaky gut, endotoxemia, systemic inflammation, and metabolic syndrome and can reestablish homeostasis. Unlike drugs, antiangiogenic functional foods or beverages are reversible inhibitors of the same pathways that most of the drugs target. Antiangiogenic functional foods or beverages also address mucosal healing.

The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Blue Zone diets are among the best and most varied sources of antiangiogenic compounds to address diet-induced dysbiosis (Losso 2016). The Blue Zone includes populations in Loma Linda, California; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece; and Okinawa, Japan, whose dietary habits and lifestyle allow them to live a decade longer and have less cancer, heart disease, dementia, and obesity than the general US population (Losso 2016). The Blue Zone diets are based on minimally processed foods and mostly plant-based proteins; they include beans, herbs, meat up to once a week, and moderate consumption of wine and dairy products.

Pectin inhibits the interaction of salivary proteins and polyphenolics by forming a soluble protein/polyphenol/pectin complex, whereas gum arabic competes with protein for phenolic binding (Soares et al. 2012). The Mediterranean diet, which is rich in antiangiogenic compounds and has a very low carbohydrate component, protects against esophageal reflux (Surdea-Blaga et al. 2019). There is a strong inverse correlation between wine consumption and *H. pylori* population, in contrast to beer consumption (Brenner et al. 1999). In East Africa, an affordable probiotic starter culture incorporating *Lactobacillus rhamnosus* yoba 2012, a variant of *L. rhamnosus* GG, enables communities to make their own probiotic fermented foods and reduces *H. pylori*–associated gastric pathology and production of lactic acid in vivo (Westerik et al. 2018). However, because lactic acid fuels cancer progression and metastasis and acetic acid fuels obesity and UC, it is desirable to select for probiotic *Lactobacillus* species that produce less lactic acid or convert acetic acid into butyric acid.

Resveratrol at 0.5 g/day for 6 weeks or 1 g/day for 8 days improves oxidative stress; levels of plasma C-reactive protein, TNF-α, and NF-κB p65; and quality of life of patients with IBD (Nunes et al. 2018). Higher consumption of green tea is associated with a significantly higher relative abundance of *Bifidobacterium* (Seura & Fukuwatari 2019).

Intestinal homeostasis can be reestablished or maintained through supplementation of exogenous dietary antiangiogenic postbiotics such as butyrate, propionate, and protocatechuic acid in food formulations or as dietary supplements. The rationale is that dysbiosis reduces the levels of bacteria that can produce sufficient levels of the desirable SCFAs butyrate and propionate for the host. Exogenous butyrate is a strong antiangiogenic postbiotic that can address all the pathways associated with diet, dysbiosis, and gastrointestinal inflammatory diseases (**Table 2**). However, technologies to deliver exogenous butyrate to the small intestine are needed. Alternatively, tributyrin can be used.

Table 2 presents a nonexhaustive list of antiangiogenic dietary compounds with demonstrated efficacy against the pathways that link dysbiosis to chronic inflammatory diseases. The food sources of these antiangiogenic compounds are also listed. For the general population, regular consumption of an antiangiogenic diet that follows nutritional recommendations and includes dietary supplements decreases the risk of dysbiosis and associated diseases. For individuals at

higher risk of developing gastrointestinal inflammatory diseases because of genetic predisposition and/or lifestyle, an antiangiogenic diet, including nutraceuticals may reduce the incidence of disease. Antiangiogenic functional foods or beverages can also be used as diet and therapy adjuvants to improve survival rate and quality of life for sick people or hospital patients.

12. FUTURE DIRECTIONS

Dysbiosis is and will remain a major problem for human overall health. Regular consumption of minimally processed whole foods rich in antiangiogenic bioactive compounds is a nonpharmacological approach that will promote or reestablish homeostasis, eubiosis, and overall health. The effects of antiangiogenic functional foods or beverages on the gut microbiome–cardiovascular axis and gut microbiome–brain axis need to be investigated. We hypothesize that the severity of several chronic diseases, including COVID-19, in some patients has a strong correlation with dysbiosis. Minimally processed antiangiogenic foods that modulate the gut microbiome will be a part of a larger strategy to improve the body's defense against chronic, inflammatory, life-threatening diseases. Plant geneticists need to develop technologies to increase the levels of antiangiogenic compounds in foods. Food scientists must design undergraduate and graduate curricula that encompass a better understanding of the human body and disease, dietary compounds, pharmacokinetics, and delivery systems that will enable researchers to better address the gut microbiome. Clinical trials of antiangiogenic functional foods or beverages are and will be needed. Food science has a major role in human health.

DISCLOSURE STATEMENT

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